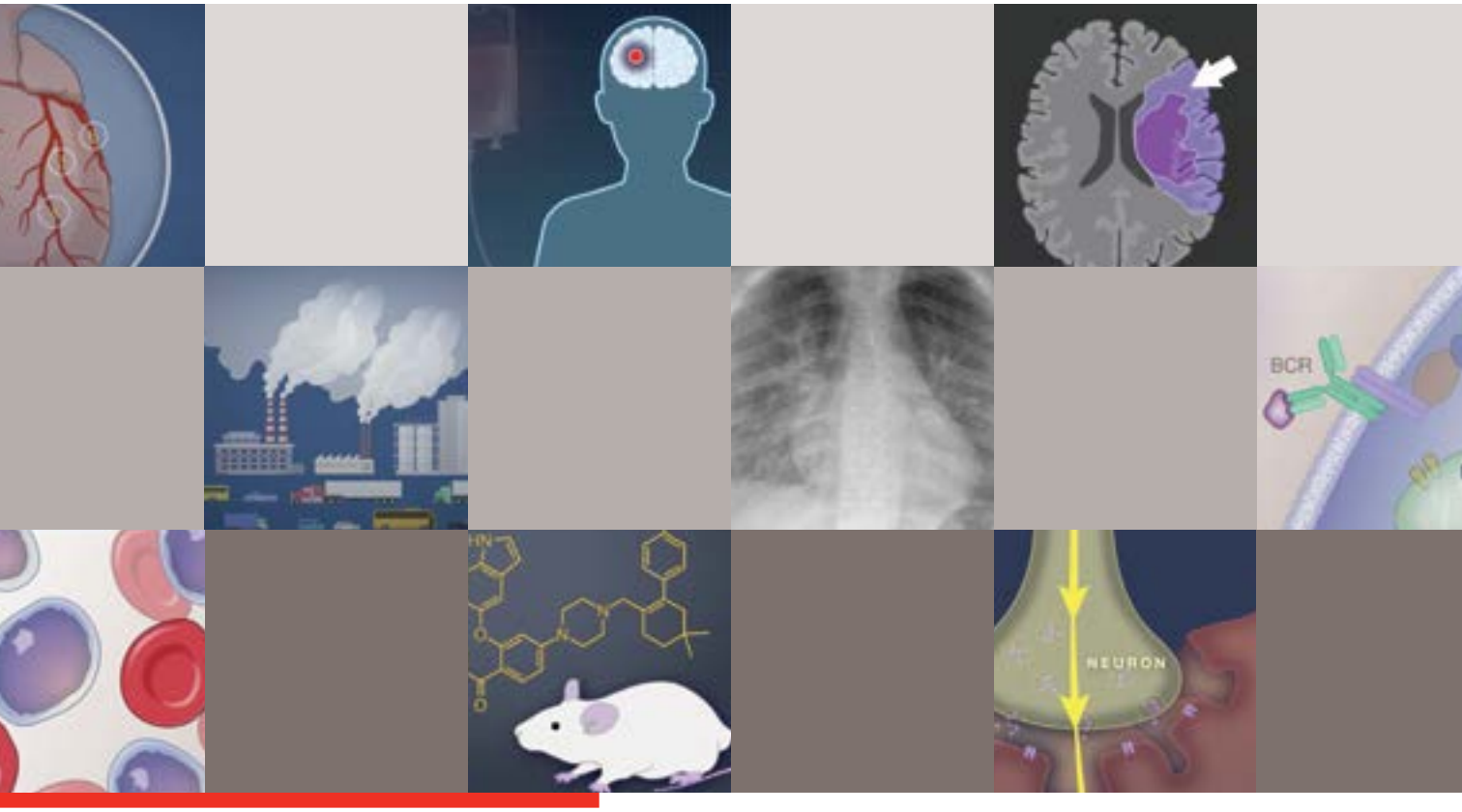
The NEW ENGLAND JOURNAL of MEDICINE



Notable Articles of 2019

A collection of articles selected by NEJM editors

NEJM GROUP

The NEW ENGLAND JOURNAL of MEDICINE

December 2019

Dear Reader,

The news headlines started to appear at the end of the summer and steadily increased. In August, the U.S. Food and Drug Administration and the Centers for Disease Control and Prevention said they were investigating reports of pulmonary symptoms possibly related to e-cigarettes. By the fall, deaths began to be reported.

We know that physicians need the best information in order to advise patients and to identify these vaping-related illnesses. In early September, we published a report on pulmonary illness related to e-cigarette use in Illinois and Wisconsin. The 53 cases described in this report had patterns of pneumonitis that included acute eosinophilic pneumonia, organizing pneumonia and lipoid pneumonia, among others. Products that contained THC were the most commonly reported e-cigarette product exposure. 2019 will be remembered for emergence of vaping-related disease and this article was the first to describe the clinical details.

We have published several other notable articles this year. One, published in April, described heart and lung transplants from HCV infected donors. This study found that treatment with an antiviral regimen for 4 weeks, initiated within a few hours after transplantation, prevented the establishment of HCV infection. Were the results of this trial sufficient to encourage more widespread use of HCV-mismatched transplantation? It is still too early to say, but the results were very encouraging. Another, a trial of ibrutinib and venetoclax for first-line treatment of CLL, showed impressive results: every patient had a response and almost all had a complete response.

These are just a couple of the practice-changing articles published in 2019 that are improving patient care. One of the pleasures of my new role as editor-in-chief has been the chance to see all of the best medical research arrive in our inbox. I hope you enjoy reading it as much as I do.

Sincerely,

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

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Early or Delayed Cardioversion in Recent-Onset Atrial Fibrillation

N.A.H.A. Pluymaekers, E.A.M.P. Dudink, J.G.L.M. Luermans, J.G. Meeder, T. Lenderink, J. Widdershoven, J.J.J. Bucx, M. Rienstra, O. Kamp, J.M. Van Opstal, M. Alings, A. Oomen, C.J. Kirchhof, V.F. Van Dijk, H. Ramanna, A. Liem, L.R. Dekker, B.A.B. Essers, J.G.P. Tijssen, I.C. Van Gelder, and H.J.G.M. Crijns, for the RACE 7 ACWAS Investigators*

ABSTRACT

BACKGROUND

Patients with recent-onset atrial fibrillation commonly undergo immediate restoration of sinus rhythm by pharmacologic or electrical cardioversion. However, whether immediate restoration of sinus rhythm is necessary is not known, since atrial fibrillation often terminates spontaneously.

METHODS

In a multicenter, randomized, open-label, noninferiority trial, we randomly assigned patients with hemodynamically stable, recent-onset (<36 hours), symptomatic atrial fibrillation in the emergency department to be treated with a wait-and-see approach (delayed-cardioversion group) or early cardioversion. The wait-and-see approach involved initial treatment with rate-control medication only and delayed cardioversion if the atrial fibrillation did not resolve within 48 hours. The primary end point was the presence of sinus rhythm at 4 weeks. Noninferiority would be shown if the lower limit of the 95% confidence interval for the between-group difference in the primary end point in percentage points was more than −10.

RESULTS

The presence of sinus rhythm at 4 weeks occurred in 193 of 212 patients (91%) in the delayed-cardioversion group and in 202 of 215 (94%) in the early-cardioversion group (between-group difference, −2.9 percentage points; 95% confidence interval [CI], −8.2 to 2.2; P=0.005 for noninferiority). In the delayed-cardioversion group, conversion to sinus rhythm within 48 hours occurred spontaneously in 150 of 218 patients (69%) and after delayed cardioversion in 61 patients (28%). In the early-cardioversion group, conversion to sinus rhythm occurred spontaneously before the initiation of cardioversion in 36 of 219 patients (16%) and after cardioversion in 171 patients (78%). Among the patients who completed remote monitoring during 4 weeks of follow-up, a recurrence of atrial fibrillation occurred in 49 of 164 patients (30%) in the delayed-cardioversion group and in 50 of 171 (29%) in the early-cardioversion group. Within 4 weeks after randomization, cardiovascular complications occurred in 10 patients and 8 patients, respectively.

CONCLUSIONS

In patients presenting to the emergency department with recent-onset, symptomatic atrial fibrillation, a wait-and-see approach was noninferior to early cardioversion in achieving a return to sinus rhythm at 4 weeks. (Funded by the Netherlands Organization for Health Research and Development and others; RACE 7 ACWAS ClinicalTrials.gov number, NCT02248753.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Crijns at the Department of Cardiology, Maastricht University Medical Center, P. Debyelaan 25, 6229 HX Maastricht, the Netherlands, or at hjgm.crijns@mumc.nl.

*A complete list of investigators in the RACE 7 ACWAS trial is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Pluymaekers and Dudink contributed equally to this article.

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The RACE to Treat Atrial Fibrillation in the Emergency Department

Jeff S. Healey, M.D., and William F. McIntyre, M.D.

Atrial fibrillation is an increasingly common reason for presentation to the emergency department, representing nearly 0.5% of all such visits.[1] Appropriate patient care must consider the relief of symptoms, the safety of discharge from the emergency department, the plan for follow-up care, and the use of resources. However, there is great variation in the management of this condition, including the use of cardioversion.[2-5]

Pluymaekers and colleagues[4] now report in the *Journal* the results of the RACE 7 ACWAS randomized noninferiority trial involving 437 patients with recent-onset (<36 hours) atrial fibrillation who presented to 17 emergency departments in the Netherlands. The majority of the patients in this trial had a history of atrial fibrillation, but none had episodes that had lasted more than 48 hours. The patients were randomly assigned to undergo either immediate cardioversion (early-cardioversion group) or a wait-and-see approach with medication (delayed-cardioversion group). The primary end point was sinus rhythm at 4 weeks after the initial emergency department visit.

In the early-cardioversion group, approximately equal numbers of patients underwent electrical or pharmacologic cardioversion, with flecainide being the most commonly used agent in the latter approach. In the delayed-cardioversion group, rate-control medications were used to achieve a heart rate of less than 110 beats per minute and relief of symptoms. Then patients were discharged home, with an outpatient visit scheduled for the following day and a referral for cardioversion (as close as possible to 48 hours after symptom onset) if there had been no resolution of atrial fibrillation.

At the 4-week evaluation, sinus rhythm (as determined on 12-lead electrocardiography [ECG]) was present in 91% of the patients in the delayed-cardioversion group and in 94% in the early-cardioversion group, findings that met the criteria for the noninferiority of the wait-and-see approach. In the delayed-conversion group, 69% of the patients had spontaneous conversion and 28% underwent cardioversion within 48 hours. In the early-cardioversion group, nearly 95% of the patients left the emergency department in sinus rhythm (16% after spontaneous conversion while waiting for the procedure and 78% after cardioversion). The median duration of the stay in the emergency department was 120 minutes in the delayed-cardioversion group and 158 minutes in the early-cardioversion group. There were no significant between-group differences in the patients' quality of life[6] or clinical outcomes at 4 weeks. Among the 335 patients for whom ambulatory ECG recordings were available, nearly a third had a recurrence of atrial fibrillation within 4 weeks, and the time until a first recurrence was similar in the two groups. Fewer than 2% of the patients required hospitalization, 7% required repeat visits to the emergency department because of atrial fibrillation, and cardiovascular complications occurred in 4%.

RACE 7 was a well-designed and well-executed trial with results that can be applied to a sizable population, since 30% of the patients with atrial fibrillation who presented to the emergency department at the two sites that maintained systematic screening logs ultimately were eligible to participate in the trial. Patients were excluded because they presented more than 36 hours after symptom onset (35% of the patients), they had episodes that lasted more than 48 hours (18%), or their condition was hemodynamically unstable (11%), along with multiple other individual and administrative reasons. The findings suggest that rate-control therapy alone can achieve prompt symptom relief in almost all eligible patients, with good quality of life and a low risk of complications, while facilitating rapid discharge from the emergency department. The trial's inclusion criteria identified a large group of patients who had more than a two-thirds chance of a spontaneous return to sinus rhythm, in whom unnecessary cardioversions were averted. In this pragmatic trial, the wait-and-see strategy reduced the median length of stay in the emergency department to 2 hours, as compared with the 3 to 10

hours expected from observational studies.[2,3,7] However, for these results to be broadly applicable, defined treatment algorithms[7] and access to prompt follow-up are needed, which may not be practical in all settings.

The results of this trial greatly simplify the current controversy regarding the safety of cardioversion between 12 and 48 hours after the onset of atrial fibrillation.[8,9] For most patients with recent-onset atrial fibrillation, the wait-and-see approach may become the preferred strategy, unless they have a history of persistent atrial fibrillation or there are barriers to implementing this approach. Early cardioversion remains an option for patients who have had atrial fibrillation for more than 36 hours if they are receiving long-term anticoagulation, have been classified as low risk on transesophageal echocardiography, or have a low risk of stroke and atrial fibrillation with a duration of 36 to 48 hours.[8] Early cardioversion remains an option for any patient with hemodynamic instability.

Within 1 year after a visit to the emergency department for atrial fibrillation, 5 to 10% of patients will die from any cause, and 10 to 20% will have a stroke, embolism, or myocardial infarction or be hospitalized for heart failure.[10] Although observational studies suggest that sinus rhythm at the time of discharge from the emergency department is associated with an improved prognosis,[5] such reports have confounding factors, since patients in sinus rhythm tend to be healthier. In RACE 7, cardiovascular complications were infrequent and similar in the two trial groups.

Since the early-cardioversion strategy did not significantly increase the rate of sinus rhythm at 4 weeks, it is implausible that such treatment would improve long-term outcomes, a finding that is consistent with the results comparing long-term rate control with pharmacologic rhythm control.[11] However, long-term prognosis can be improved with oral anticoagulation and risk-factor modification,[10,12] which can be initially addressed in the emergency department visit and then effectively managed with routine specialist follow-up.[12,13] Therapy to prevent recurrent hospitalization for atrial fibrillation[11,14] is another key component of long-term care, since most patients who present to the emergency department have recurrent atrial fibrillation.[10,12] The management of atrial fibrillation in the emergency department is not only a sprint to eliminate symptoms and facilitate safe discharge but also the start of a marathon to improve long-term outcomes for patients.

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

From the Population Health Research Institute, McMaster University, Hamilton, ON, Canada.

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ORIGINAL ARTICLE

Heart and Lung Transplants from HCV-Infected Donors to Uninfected Recipients

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*A complete list of the members of the DONATE HCV Trial Team is provided in the Supplementary Appendix, available at NEJM.org.

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ABSTRACT

BACKGROUND

Hearts and lungs from donors with hepatitis C viremia are typically not transplanted. The advent of direct-acting antiviral agents to treat hepatitis C virus (HCV) infection has raised the possibility of substantially increasing the donor organ pool by enabling the transplantation of hearts and lungs from HCV-infected donors into recipients who do not have HCV infection.

METHODS

We conducted a trial involving transplantation of hearts and lungs from donors who had hepatitis C viremia, irrespective of HCV genotype, to adults without HCV infection. Sofosbuvir–velpatasvir, a pangenotypic direct-acting antiviral regimen, was preemptively administered to the organ recipients for 4 weeks, beginning within a few hours after transplantation, to block viral replication. The primary outcome was a composite of a sustained virologic response at 12 weeks after completion of antiviral therapy for HCV infection and graft survival at 6 months after transplantation.

RESULTS

A total of 44 patients were enrolled: 36 received lung transplants and 8 received heart transplants. The median viral load in the HCV-infected donors was 890,000 IU per milliliter (interquartile range, 276,000 to 4.63 million). The HCV genotypes were genotype 1 (in 61% of the donors), genotype 2 (in 17%), genotype 3 (in 17%), and indeterminate (in 5%). A total of 42 of 44 recipients (95%) had a detectable hepatitis C viral load immediately after transplantation, with a median of 1800 IU per milliliter (interquartile range, 800 to 6180). Of the first 35 patients enrolled who had completed 6 months of follow-up, all 35 patients (100%; exact 95% confidence interval, 90 to 100) were alive and had excellent graft function and an undetectable hepatitis C viral load at 6 months after transplantation; the viral load became undetectable by approximately 2 weeks after transplantation, and it subsequently remained undetectable in all patients. No treatment-related serious adverse events were identified. More cases of acute cellular rejection for which treatment was indicated occurred in the HCV-infected lung-transplant recipients than in a cohort of patients who received lung transplants from donors who did not have HCV infection. This difference was not significant after adjustment for possible confounders.

CONCLUSIONS

In patients without HCV infection who received a heart or lung transplant from donors with hepatitis C viremia, treatment with an antiviral regimen for 4 weeks, initiated within a few hours after transplantation, prevented the establishment of HCV infection. (Funded by the Mendez National Institute of Transplantation Foundation and others; DONATE HCV ClinicalTrials.gov number, NCT03086044.)

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Organs from Hepatitis C Virus–Positive Donors

Emily A. Blumberg, M.D.

Organs that are suitable for donation to the more than 113,000 persons who are waiting for transplants in the United States are in short supply; in 2018, only 36,500 persons received transplants.[1] Many potential recipients die before transplantation, and in 2018, a total of 12,225 persons were removed from the waiting list because of death or progressive illness that rendered them too sick to undergo transplantation. Given these dismal outcomes, substantial efforts have been made to find new approaches to expand the pool of donor organs that were previously considered to be unacceptable. This expansion includes the use of organs obtained from donors with hepatitis C virus (HCV) infection in candidates for transplantation who do not have HCV infection — so-called HCV-mismatched transplantation.

There are several reasons why transplantation programs are more willing to consider HCV-positive donors than they were previously. The potential pool of HCV-positive donors is substantial, in large part because of the current opioid epidemic in the United States.[2] These donors are typically younger than donors without HCV infection, and they have fewer coexisting conditions that are associated with decreased recipient and organ survival. Moreover, a sustained viral response and cure are now achievable with the increased availability of direct-acting antiviral agents, which have expanded efficacy against diverse HCV genotypes, favorable safety profiles, limited drug interactions, and pharmacokinetic properties that allow for administration of these agents irrespective of the patient's renal function. The published results of research involving limited numbers of HCV-mismatched transplantations have been favorable and have encouraged acceptance of a broad pool of donors.[3-7] Consensus guidelines of the American Society of Transplantation have provided support for further research in this area.[2]

As now reported in the *Journal*, Woolley and colleagues[8] have expanded on this experience with a large series of HCV-mismatched heart and lung transplantations. The investigators administered a short (4-week) course of a pangenotypic antiviral regimen to preemptively treat recipients of organs from HCV-infected donors. Some recipients had enteric feeding tubes for expedited drug delivery in the early period after transplantation. Early results are promising, with a 100% sustained viral response and generally excellent patient and allograft outcomes.

This trial has some unique features that must be considered. The median donor age was surprisingly young, and HCV-positive donors were younger than those without HCV infection. Both HCV-negative and HCV-positive donors in this trial were younger than the mean age in the current donor pool in the United States. As anticipated, the availability of HCV-positive organs resulted in transplantation in candidates who were less critically ill and who had a lower priority on the waiting list for transplantation. Consequently, the shorter lengths of stay in the intensive care unit and hospital and the relative preservation of renal function probably reflect recipient factors rather than donor factors. Whether longer-term results will be equally encouraging is unknown. Nevertheless, this article clearly provides support for further consideration of the use of organs from HCV-positive donors, even for candidates for heart and lung transplantation.

Are the results of this trial sufficient to encourage more widespread use of HCV-mismatched transplantation? The early results are very encouraging, but there is still a lot to learn. Data regarding long-term outcomes are limited; one of the longest follow-up periods reported is 1 year for 20 recipients.[4] It is unknown whether an increase in the incidence of cardiovascular disease, which was previously reported in recipients of organs from HCV-positive donors, will be a late complication.[9] In addition, what is known about the sustained viral response may need to be reconsidered in light of a recent anecdotal report of a recipient of a mismatched lung transplant who had a severe relapse after treatment for transplant-related HCV infection.[10] The effect of relapse may be minimized by the use of a longer

course of effective treatment at the time of relapse. Immune activation related to de novo viral infection may lead to other unintended consequences, including organ rejection, other infections, and metabolic complications, especially if organ donation is expanded to critically ill candidates. Finally, patient consent assumes a level of understanding about HCV infection that may not currently exist.

Successful outcomes in HCV-mismatched transplantation, with cure of HCV infection, have been predicated on rapid access to effective antiviral therapy. Woolley et al. guaranteed early treatment for their patients regardless of insurance coverage, and most investigators have provided free direct-acting antiviral agents in the early period after transplantation. These drugs are expensive, and it is uncertain who will bear that cost in nonresearch settings. It is unknown whether cheaper short-course therapy, as used in the current trial, will be consistently effective in all recipients regardless of the organ transplanted and the timing of initiation of treatment. However, if the experience of Woolley et al. is borne out by other investigators, a short course of treatment would substantially reduce the cost of transplantation. To ensure prompt and equitable access to these potentially lifesaving organs, it is imperative that transplantation centers determine how antiviral agents will be provided in advance of acceptance of organs from HCV-positive donors.

Approximately 2.4 million persons in the United States have HCV infection, with the highest incidence among injection-drug users, and organs obtained from these persons account for nearly a third of donor organs in many areas of the country. The time has come to consider expanding the use of HCV-mismatched transplantation under controlled conditions. Increasing numbers of successful outcomes in single-center studies provide support for further research with larger-scale multicenter trials. These are exciting times for the field of transplantation, since the ability to use organs from HCV-positive donors may substantially increase the donor pool and thus increase access to organs for patients who might otherwise have died while waiting.

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

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Thrombolysis Guided by Perfusion Imaging up to 9 Hours after Onset of Stroke

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ABSTRACT

BACKGROUND

The time to initiate intravenous thrombolysis for acute ischemic stroke is generally limited to within 4.5 hours after the onset of symptoms. Some trials have suggested that the treatment window may be extended in patients who are shown to have ischemic but not yet infarcted brain tissue on imaging.

METHODS

We conducted a multicenter, randomized, placebo-controlled trial involving patients with ischemic stroke who had hypoperfused but salvageable regions of brain detected on automated perfusion imaging. The patients were randomly assigned to receive intravenous alteplase or placebo between 4.5 and 9.0 hours after the onset of stroke or on awakening with stroke (if within 9 hours from the midpoint of sleep). The primary outcome was a score of 0 or 1 on the modified Rankin scale, on which scores range from 0 (no symptoms) to 6 (death), at 90 days. The risk ratio for the primary outcome was adjusted for age and clinical severity at baseline.

RESULTS

After 225 of the planned 310 patients had been enrolled, the trial was terminated because of a loss of equipoise after the publication of positive results from a previous trial. A total of 113 patients were randomly assigned to the alteplase group and 112 to the placebo group. The primary outcome occurred in 40 patients (35.4%) in the alteplase group and in 33 patients (29.5%) in the placebo group (adjusted risk ratio, 1.44; 95% confidence interval [CI], 1.01 to 2.06; P=0.04). Symptomatic intracerebral hemorrhage occurred in 7 patients (6.2%) in the alteplase group and in 1 patient (0.9%) in the placebo group (adjusted risk ratio, 7.22; 95% CI, 0.97 to 53.5; P=0.05). A secondary ordinal analysis of the distribution of scores on the modified Rankin scale did not show a significant between-group difference in functional improvement at 90 days.

CONCLUSIONS

Among the patients in this trial who had ischemic stroke and salvageable brain tissue, the use of alteplase between 4.5 and 9.0 hours after stroke onset or at the time the patient awoke with stroke symptoms resulted in a higher percentage of patients with no or minor neurologic deficits than the use of placebo. There were more cases of symptomatic cerebral hemorrhage in the alteplase group than in the placebo group. (Funded by the Australian National Health and Medical Research Council and others; EXTEND ClinicalTrials.gov numbers, NCT00887328 and NCT01580839.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Donnan at Florey Institute of Neuroscience and Mental Health, University of Melbourne, Royal Melbourne Hospital, 300 Grattan St., Parkville, VIC 3050, Australia, or at geoffrey.donnan@unimelb.edu.au.

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

Drs. Davis and Donnan contributed equally to this article.

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EDITORIALS

Image-Guided Intravenous Alteplase for Stroke — Shattering a Time Window

Randolph S. Marshall, M.D.

The era of time-based treatment with intravenous alteplase in patients with acute stroke may finally be drawing to a close. As the only approved pharmacologic treatment for acute stroke, and one that has been used since 1995, alteplase is still limited to patients whose stroke began within 4.5 hours before the infusion.[1] Several attempts have been made to show the safety and efficacy of unrestricted thrombolysis beyond 4.5 hours, but they failed. The time window was based on sound preclinical evidence. An influential experiment in rodents showed that a 15-minute occlusion of the middle cerebral artery produced selective neuronal necrosis in the deep gray matter but spared the cortex. Longer occlusions produced increasingly larger infarct volumes in the cortex, but after 180 minutes, volumes of infarction were no different from those produced after 24 hours of occlusion.[2] This report of findings in rodents was followed by a report of clinical data showing that a shorter time to treatment within the sanctioned interval of 4.5 hours from stroke onset produced better functional outcomes.[3] Faced with these time constraints and the promise of better outcomes with earlier treatment, a generation of stroke practitioners championed earlier stroke recognition, faster transport to stroke centers, and more efficient stroke diagnostic protocols in the emergency department.[4] The battle cry of "Time is brain!"[5] reigned unopposed, until now.

In this issue of the *Journal*, Ma et al. report the results of the Extending the Time for Thrombolysis in Emergency Neurological Deficits (EXTEND) trial, in which 225 patients with specific imaging features were randomly assigned to receive standard doses of intravenous alteplase or placebo between 4.5 and 9.0 hours after the onset of stroke.[6] Although the study was terminated after only two thirds of the intended population were enrolled, the likelihood of a good outcome (a score of 0 or 1 on the modified Rankin scale at 90 days [indicating no or minimal deficits, respectively]) was 44% higher in the alteplase group than in the placebo group (adjusted risk ratio, 1.44; 95% confidence interval, 1.01 to 2.06; P=0.04). The success of this trial is attributable to an image-guided approach to patient selection that had already brought success to mechanical thrombectomy performed many hours after the onset of stroke symptoms. Patients were eligible for the EXTEND trial if they had a mismatch between the core volume of infarction and the volume of potentially salvageable brain tissue in the ischemic penumbra. This trial represents a major successful step in using an image-guided approach to extend the seemingly immutable time limit for pharmacologic thrombolysis in patients with acute stroke.

It is actually logical that success in extending the treatment window for stroke emerged for thrombolysis only after it had been shown for mechanical thrombectomy. While thrombolysis was stuck in a time window of 4.5 hours, remarkably good outcomes with thrombectomy were being shown at 6 hours, 16 hours, and 24 hours.[7] Patients treated at later times do better than those in the earlier time window.[7] The reason for this "late window paradox" is heterogeneity in the population of patients with acute

stroke that was not apparent from animal models or standard imaging in patients with acute stroke: up to 50% of patients with large-vessel occlusions have infarct cores that grow slowly, probably because of collateral flow in the penumbra.[8] The EXTEND investigators hypothesized that there would be no reason that revascularization with a pharmacologic agent could not produce the same reperfusion and functional outcomes as mechanical revascularization. With the selection of patients who have relatively small infarct cores and large penumbras, pharmacologic thrombolysis could now perform as well as mechanical thrombectomy in the late time window.

The EXTEND trial has clinical implications as well as limitations. As of 2013, only 6.5% of patients hospitalized for ischemic stroke in the United States received intravenous thrombolysis treatment.[9] Extending the time window for treatment could result in greater numbers of patients eligible to receive treatment for acute stroke. Perhaps more importantly, stroke centers with imaging capability to detect a mismatch between the size of the ischemic core and the penumbra could treat patients with stroke many hours after the onset of stroke symptoms and treat those who awaken with a stroke, without the need for an interventionalist to be present. Furthermore, because the image analysis software is available commercially and is automated for computed tomography and magnetic resonance imaging, primary stroke centers could provide this service.

The current trial by Ma et al. will need to be validated. It was stopped early owing to the publication of results of another clinical trial, which was not truly equivalent to the EXTEND trial because it targeted patients who were likely to be eligible for thrombolysis at the standard times and did not use penumbra-based image guidance.[10] Further randomized clinical trials that compare intravenous thrombolysis with thrombectomy in the late time window among patients selected on the basis of penumbra-based imaging are warranted. Alternative thrombolytic agents such as tenecteplase are also being tested. Despite the work to be done, the EXTEND trial shattered an important barrier to the treatment of acute stroke.

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

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Early Neuromuscular Blockade in the Acute Respiratory Distress Syndrome

The National Heart, Lung, and Blood Institute PETAL Clinical Trials Network*

ABSTRACT

BACKGROUND

The benefits of early continuous neuromuscular blockade in patients with acute respiratory distress syndrome (ARDS) who are receiving mechanical ventilation remain unclear.

METHODS

We randomly assigned patients with moderate-to-severe ARDS (defined by a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen of <150 mm Hg with a positive end-expiratory pressure [PEEP] of ≥8 cm of water) to a 48-hour continuous infusion of cisatracurium with concomitant deep sedation (intervention group) or to a usual-care approach without routine neuromuscular blockade and with lighter sedation targets (control group). The same mechanical-ventilation strategies were used in both groups, including a strategy involving a high PEEP. The primary end point was in-hospital death from any cause at 90 days.

RESULTS

The trial was stopped at the second interim analysis for futility. We enrolled 1006 patients early after the onset of moderate-to-severe ARDS (median, 7.6 hours after onset). During the first 48 hours after randomization, 488 of the 501 patients (97.4%) in the intervention group started a continuous infusion of cisatracurium (median duration of infusion, 47.8 hours; median dose, 1807 mg), and 86 of the 505 patients (17.0%) in the control group received a neuromuscular blocking agent (median dose, 38 mg). At 90 days, 213 patients (42.5%) in the intervention group and 216 (42.8%) in the control group had died before hospital discharge (between-group difference, −0.3 percentage points; 95% confidence interval, −6.4 to 5.9; P=0.93). While in the hospital, patients in the intervention group were less physically active and had more adverse cardiovascular events than patients in the control group. There were no consistent between-group differences in end points assessed at 3, 6, and 12 months.

CONCLUSIONS

Among patients with moderate-to-severe ARDS who were treated with a strategy involving a high PEEP, there was no significant difference in mortality at 90 days between patients who received an early and continuous cisatracurium infusion and those who were treated with a usual-care approach with lighter sedation targets. (Funded by the National Heart, Lung, and Blood Institute; ROSE ClinicalTrials.gov number, NCT02509078.)

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*A full list of the investigators in the Re-evaluation of Systemic Early Neuromuscular Blockade (ROSE) trial and the Prevention and Early Treatment of Acute Lung Injury (PETAL) network is provided in the Supplementary Appendix, available at NEJM.org.

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EDITORIAL

Early Paralytic Agents for ARDS? Yes, No, and Sometimes

Arthur S. Slutsky, C.M., M.D., and Jesús Villar, M.D., Ph.D.

Lung-protective ventilation, which includes low tidal volumes and limitation of plateau pressures, is the standard approach in patients with acute respiratory distress syndrome (ARDS).[1] Almost a decade ago, the ARDS et Curarisation Systematique (ACURASYS) trial[2] showed that in patients with moderate-to-severe ARDS, a strategy of 48 hours of deep sedation with muscle paralysis induced by an intravenous infusion of cisatracurium resulted in a lower incidence of barotrauma and higher adjusted overall survival at 90 days than deep sedation alone. These results were unexpected, since the intervention was performed only for the first 2 days, yet the Kaplan–Meier survival curves were virtually superimposable for about 18 days before they separated. The reason for the lower mortality in the intervention group was uncertain, but it was thought to be because the use of cisatracurium led to decreased ventilator-induced lung injury and biotrauma (i.e., the release of mediators in the lung and translocation of these mediators into the systemic circulation).[3,4] Perhaps because of this uncertainty, along with concerns about long-term neuromuscular function after treatment with cisatracurium, the addition of a paralytic agent to a lung-protection strategy was not widely adopted by the critical care community.

For these reasons, and because current clinical practice has changed since the ACURASYS trial was conducted, the Reevaluation of Systemic Early Neuromuscular Blockade (ROSE) trial was performed to reexamine the benefits of cisatracurium-induced paralysis in patients early after the onset of ARDS. Patients with moderate-to-severe ARDS were assigned either to a 48-hour continuous infusion of cisatracurium with deep sedation or to a usual-care approach with light sedation and without routine neuromuscular blockade. The trial, the results of which are now reported in the *Journal*,[5] was stopped early for futility. The results were markedly different from those of the ACURASYS trial. In the ROSE trial, there was no between-group difference in the number of patients with barotrauma, and mortality at 90 days was virtually identical in the two groups (42.5% of patients in the intervention group and 42.8% in the control group died).

Why should the results of two well-performed trials differ so greatly? As shown in Table 1, there were a number of differences between the trials that could plausibly explain the different results. However, we postulate that one of these factors — the difference in sedation levels — is the major reason. Many patients who are admitted to an intensive care unit receive some sedation to treat anxiety or agitation and to facilitate care. Deeper sedation is also often used when the patient is "fighting the ventilator" (so-called patient–ventilator dyssynchrony). Dyssynchrony is common during mechanical ventilation and is associated with prolonged duration of mechanical ventilation and increased mortality.[6]

In 2013, Akoumianaki et al.[7] identified a previously unrecognized form of dyssynchrony in patients with ARDS. They called this dyssynchrony reverse triggering, because a breath delivered by the ventilator triggered a contraction of the diaphragm, which initiated a spontaneous breath — the reverse of what happens during assisted ventilation. Because the second breath can occur before a complete exhalation, the pa-

Table 1. Comparisons of the ACURASYS and ROSE Trials.*

Variable	ACURASYS Trial	ROSE Trial	Commentary
No. of centers (location)	20 ICUs (Europe)	48 hospitals (United States)	It is unlikely that different practices across the Atlantic would explain the different results of the two trials.
No. of patients (intervention group vs. control group)	340 (178 vs. 162)	1006 (501 vs. 505)	Estimates for sample-size calculations were different.
Trial design for group assignment	Double blind	Unblinded	Potential effect should be minimal.
ARDS definition	American–European consensus	Berlin criteria	It is unlikely that this difference had a major effect on the characteristics of patients enrolled in the trials.
Criteria for moderate-to-severe ARDS	Pao_2:FIO_2 <150 mm Hg with PEEP ≥5 cm of water	Pao_2:FIO_2 <150 mm Hg with PEEP ≥8 cm of water	ROSE allowed enrollment of patients with Pao_2:FIO_2 of 150–200 mm Hg after initial assessment but before randomization.
Median time from ARDS diagnosis to trial inclusion (IQR) — hr	16 (6–29)	8 (4–16)	Earlier inclusion time in ROSE may have resulted in enrollment of some patients who might have died before they could have been enrolled in ACURASYS.
Intervention vs. control strategies	Cisatracurium infusion plus deep sedation vs. deep sedation	Cisatracurium infusion plus deep sedation vs. light sedation	No routine neuromuscular blocking agents were allowed in the control groups.
Mechanical-ventilation approach	Lung-protective ventilation with low PEEP	Lung-protective ventilation with high PEEP	In the first 7 days, PEEP levels were higher by about 2–3 cm of water in ROSE than in ACURASYS.
Monitoring of patient–ventilator dyssynchrony	Not reported	Not reported	Ideally, future studies should assess dyssynchronies.
ICU-acquired paresis and long-term outcomes	No difference between groups	No difference between groups	Patients in the control group in ROSE had higher mean levels of activity to day 6 than patients in the intervention group.
Serious adverse events	Pneumothorax more frequent in the control group (11.7% vs. 4%)	Rates of overall barotrauma did not differ between groups	There were more acute cardiovascular events in the intervention group in ROSE than in the control group.

* Shown are comparisons between the ARDS et Curarisation Systematique (ACURASYS)[2] and Reevaluation of Systemic Early Neuromuscular Blockade (ROSE)[5] trials, which assessed the use of neuromuscular blocking agents in patients with moderate-to-severe acute respiratory distress syndrome (ARDS). ICU denotes intensive care unit, IQR interquartile range, Pao_2:FIO_2 the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, and PEEP positive end-expiratory pressure.

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tient can receive a much larger tidal volume (called breath stacking) than with the initial ventilator breath. This can worsen ventilator-induced lung injury because of pulmonary overdistention, and it can potentially cause diaphragmatic muscle-fiber damage and increased work of breathing — all of which lead to poorer outcomes.[7]

There are a number of important attributes of reverse triggering. First, it is very difficult to recognize at the bedside without measurement of esophageal pressure or diaphragmatic electrical activity, and these techniques are not routinely performed in a clinical setting.[7] Second, although the prevalence of reverse triggering is unknown, it is thought to be relatively common (it occurred in 30% of patients with ARDS in one study[8]). Third, contrary to expectations, the incidence of reverse triggering increases with deeper sedation levels. We postulate that in the ACURASYS trial, deep sedation in the control group led to breath stacking, increased ventilator-induced lung injury, and higher mortality. The intervention group was protected from this effect because cisatracurium prevented the diaphragmatic contraction that would have occurred in response to the reverse triggering mechanism.[8]

What, then, are the implications of the results of these trials? First, we recommend that neuromuscular blocking agents not be used routinely in patients with moderate-to-severe ARDS. We would draw this conclusion regardless of whether the hypothesis of reverse triggering is correct. The ROSE trial is more current than the ACURASYS trial, is much larger, and shows some acute, serious cardiovascular events with cisatracurium use. Second, from a physiological perspective, there is a rationale to consider neuromuscular blocking agents in any patient with ARDS (or, indeed, in any patient) who, despite carefully implemented ventilatory and sedation strategies, has a ventilatory pattern that confers a predisposition to ventilator-induced lung injury (e.g., breath stacking); neuromuscular blocking agents may also be considered in patients with increased respiratory drive that could generate potentially injurious transpulmonary pressure swings.[9] Third, we suggest that patient–ventilator dyssynchronies may have a greater effect on clinical outcomes than generally recognized. A recent trial that examined the effects of lung-recruitment maneuvers and high positive end-expiratory pressure in patients with moderate-to-severe ARDS unexpectedly showed that this strategy resulted in higher mortality than a strategy of low positive end-expiratory pressure.[10] It is likely that dyssynchrony in the form of breath stacking, albeit not necessarily reverse triggering, contributed to this higher mortality.[10]

Therapeutic strategies in ARDS should ideally be tailored to the specific underlying disease or injury mechanism at any given point in time, rather than being applied uniformly to all patients. Early paralytic agents for ARDS? Given their long-term neuromuscular safety profile in the ROSE trial, we suggest that paralytic agents can sometimes be used, when physiologically and clinically indicated.

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Ibrutinib and Venetoclax for First-Line Treatment of CLL

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ABSTRACT

BACKGROUND

Ibrutinib, an inhibitor of Bruton's tyrosine kinase, and venetoclax, an inhibitor of B-cell lymphoma 2 protein, have been approved for patients with chronic lymphocytic leukemia (CLL). Preclinical investigations have indicated potential synergistic interaction of their combination.

METHODS

We conducted an investigator-initiated phase 2 study of combined ibrutinib and venetoclax involving previously untreated high-risk and older patients with CLL. All patients had at least one of the following features: chromosome 17p deletion, mutated *TP53*, chromosome 11q deletion, unmutated *IGHV*, or an age of 65 years or older. Patients received ibrutinib monotherapy (420 mg once daily) for 3 cycles, followed by the addition of venetoclax (weekly dose escalation to 400 mg once daily). Combined therapy was administered for 24 cycles. Response assessments were performed according to International Workshop on Chronic Lymphocytic Leukemia 2008 criteria. Minimal residual disease was assessed by means of multicolor flow cytometry in bone marrow (sensitivity, 10^{-4}).

RESULTS

A total of 80 patients were treated. The median age was 65 years (range, 26 to 83). A total of 30% of the patients were 70 years of age or older. Overall, 92% of the patients had unmutated *IGHV*, *TP53* aberration, or chromosome 11q deletion. With combined treatment, the proportions of patients who had complete remission (with or without normal blood count recovery) and remission with undetectable minimal residual disease increased over time. After 12 cycles of combined treatment, 88% of the patients had complete remission or complete remission with incomplete count recovery, and 61% had remission with undetectable minimal residual disease. Responses were noted in older adults and across all high-risk subgroups. Three patients had laboratory evidence of tumor lysis syndrome. The adverse-event profile was similar to what has been reported with ibrutinib and venetoclax.

CONCLUSIONS

In this study, combined venetoclax and ibrutinib was an effective oral regimen for high-risk and older patients with CLL. (Funded by AbbVie and others; ClinicalTrials.gov number, NCT02756897.)

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EDITORIALS

Ibrutinib and Venetoclax — Doubling Down on CLL

Adrian Wiestner, M.D., Ph.D.

Chronic lymphocytic leukemia (CLL) is a clonal expansion of mature B cells in blood, bone marrow, and lymphoid tissues that usually manifests as a high lymphocyte count in the circulating blood. Cell expansion is driven by constitutive B-cell receptor signaling and sustained by overexpression of the antiapoptotic protein B-cell lymphoma 2 (BCL2) (Fig. 1A).[1,2] Microbial and autoantigens have been implicated in activating B-cell receptor signaling in CLL cells. Furthermore, many types of B-cell receptors that are expressed by CLL cells also bind to epitopes within their structural domains, promoting cell-autonomous signaling. B-cell receptor signaling mainly occurs in lymphoid tissues and sends growth and survival signals to the leukemic cells. Overexpression of BCL2 is due to both tumor–microenvironment interactions and genetic mechanisms. The deletion of chromosome arm 13q, the most common genetic abnormality in CLL, leads to loss of microRNAs mir-15a and mir-16-1, which act as inhibitors of BCL2 expression.

Drugs that target B-cell receptor signaling and BCL2 have emerged as breakthrough therapies in CLL, and they are rapidly replacing chemoimmunotherapy.[3,4] Ibrutinib inhibits Bruton's tyrosine kinase, an essential component of B-cell receptor signal transduction; this inhibition shuts off tumor proliferation and reduces tumor bulk. Oral ibrutinib is continued indefinitely, as limited by adverse events or until disease progression. Most responses to ibrutinib are partial, but with continuous therapy, they are quite durable.[3,5] In a recent study of ibrutinib as first-line therapy, the estimated progression-free survival at 2 years was 87%.[3] Venetoclax, a selective and potent BCL2 inhibitor, induces apoptosis. Like ibrutinib, it is also orally administered and highly effective in CLL across conventional risk groups.[6] With venetoclax, many patients have a complete response and can remain in remission after stopping therapy.[4] An important adverse event with venetoclax is tumor lysis syndrome. Gradual dose escalation, premedication, and frequent laboratory surveillance are used to safely initiate venetoclax therapy. Progressive disease during treatment with ibrutinib or venetoclax monotherapy has been associated with acquired mutations in *BTK* and *BCL2*, respectively.[7,8] Preclinical studies provide a strong rationale for combining ibrutinib and venetoclax, and it is hoped that the combination can prevent the emergence of drug resistance.[9]

In this issue of the *Journal*, Jain et al.[10] report results from an investigator-initiated study of the combination of ibrutinib and venetoclax for first-line therapy of CLL. (The treatment plan is shown in Fig. 1B.) The results are impressive. First, every patient had a response, almost all had a complete response, and in most no residual disease was detected by means of flow cytometry (Fig. 1C and 1D). Second, there appears to be no added toxicity from combining the two drugs. Third, initiation of venetoclax was facilitated by a period of administration of ibrutinib alone that reduced tumor bulk and the risk of tumor lysis syndrome. Finally, and most surprisingly, the published report does not include a Kaplan–Meier curve! Here, assessment of minimal residual disease (MRD) has replaced the

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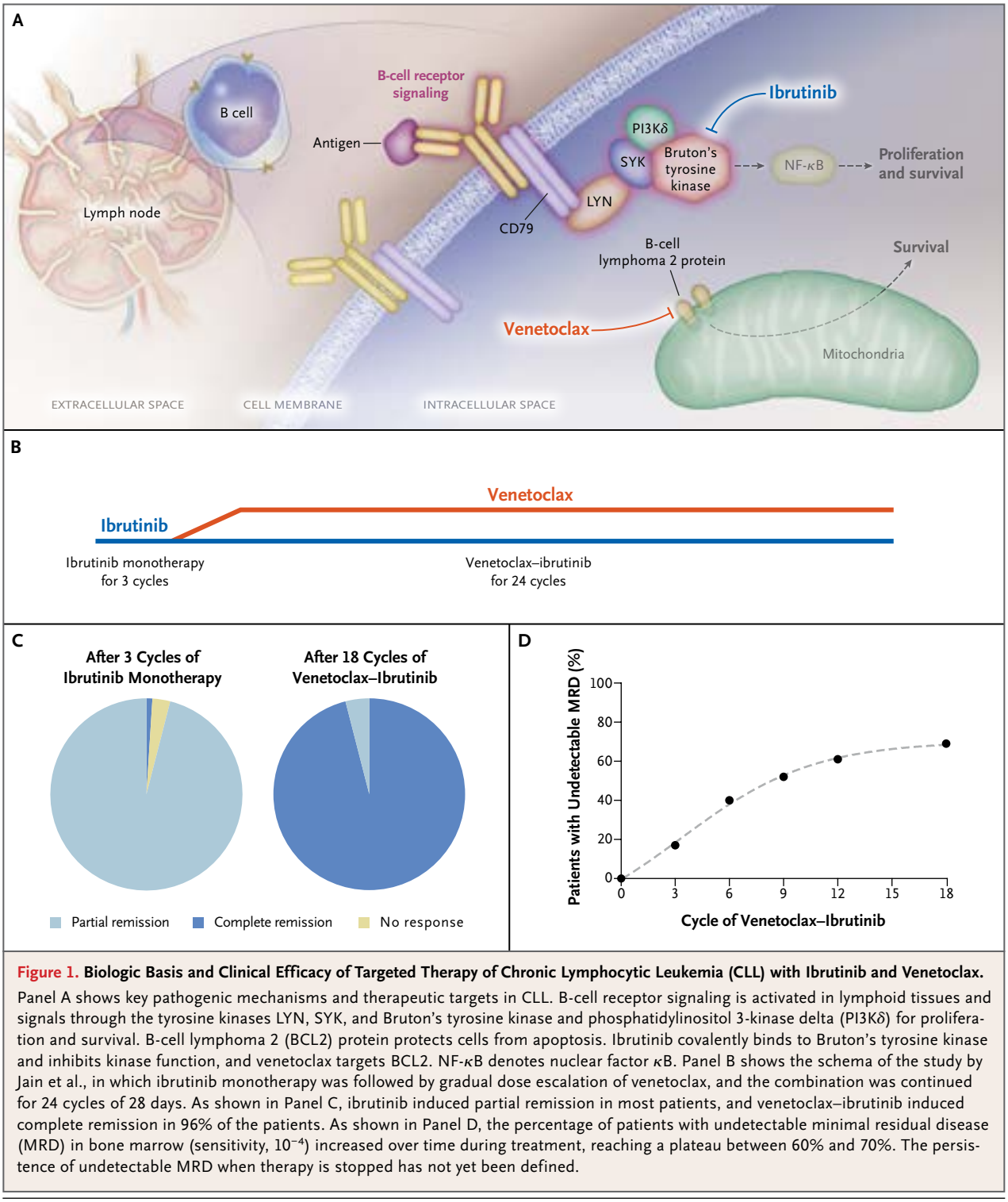

Figure 1. Biologic Basis and Clinical Efficacy of Targeted Therapy of Chronic Lymphocytic Leukemia (CLL) with Ibrutinib and Venetoclax.

Panel A shows key pathogenic mechanisms and therapeutic targets in CLL. B-cell receptor signaling is activated in lymphoid tissues and signals through the tyrosine kinases LYN, SYK, and Bruton's tyrosine kinase and phosphatidylinositol 3-kinase delta (PI3Kδ) for proliferation and survival. B-cell lymphoma 2 (BCL2) protein protects cells from apoptosis. Ibrutinib covalently binds to Bruton's tyrosine kinase and inhibits kinase function, and venetoclax targets BCL2. NF-κB denotes nuclear factor κB. Panel B shows the schema of the study by Jain et al., in which ibrutinib monotherapy was followed by gradual dose escalation of venetoclax, and the combination was continued for 24 cycles of 28 days. As shown in Panel C, ibrutinib induced partial remission in most patients, and venetoclax–ibrutinib induced complete remission in 96% of the patients. As shown in Panel D, the percentage of patients with undetectable minimal residual disease (MRD) in bone marrow (sensitivity, 10^{-4}) increased over time during treatment, reaching a plateau between 60% and 70%. The persistence of undetectable MRD when therapy is stopped has not yet been defined.

progression-free survival curve of old, indicating a possible shift in focus away from traditional clinical-trial end points and toward even more stringent measures of clinical efficacy that may be central to regulatory decisions.

Undetectable MRD, defined as less than 1 CLL cell among 10,000 leukocytes (sensitivity, 10^{-4}) on flow cytometry, can predict progression-free and overall survival.[11] However, in patients who received ibrutinib monotherapy, the correlation between MRD assessment and progression-free survival has not been shown. Monotherapy with ibrutinib or venetoclax on a continuous dosing schedule has been investigated in patients with CLL with chromosome 17p deletion. With ibrutinib, deep remissions were uncommon.[12] With venetoclax, 48% of the patients who could be evaluated had undetectable MRD.[6] Nevertheless, progression-free survival at 24 months was similar: 63% with ibrutinib and 54% with venetoclax.[6,12]

The rate of remission with undetectable MRD with the ibrutinib–venetoclax combination appears to plateau in the high 60% range, as it did with combined venetoclax and rituximab in relapsed CLL. At the time of reporting, most patients were still receiving combination therapy. Patients with undetectable MRD after 24 cycles will stop all therapy, and patients with detectable MRD can continue ibrutinib. If we extrapolate from previous studies with venetoclax, undetectable MRD will probably predict a long period of progression-free survival after treatment discontinuation. Similarly, on the basis of experience with single-agent ibrutinib in first-line therapy, patients with detectable MRD who continue ibrutinib can be expected to do well. Extended follow-up of this important study will provide many more insights into targeted therapy of CLL. Important questions include the following: Can treatment ever be safely stopped? Are there subgroups with a poor prognosis that require additional therapy? What is the nature and mechanism of ibrutinib and venetoclax resistance? And does substituting a different BTK inhibitor for ibrutinib preserve activity with a lower risk of toxic effects?

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ORIGINAL ARTICLE

Targeting Huntingtin Expression in Patients with Huntington's Disease

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ABSTRACT

BACKGROUND

Huntington's disease is an autosomal-dominant neurodegenerative disease caused by CAG trinucleotide repeat expansion in *HTT*, resulting in a mutant huntingtin protein. IONIS-HTT_{Rx} (hereafter, HTT_{Rx}) is an antisense oligonucleotide designed to inhibit *HTT* messenger RNA and thereby reduce concentrations of mutant huntingtin.

METHODS

We conducted a randomized, double-blind, multiple-ascending-dose, phase 1–2a trial involving adults with early Huntington's disease. Patients were randomly assigned in a 3:1 ratio to receive HTT_{Rx} or placebo as a bolus intrathecal administration every 4 weeks for four doses. Dose selection was guided by a preclinical model in mice and nonhuman primates that related dose level to reduction in the concentration of huntingtin. The primary end point was safety. The secondary end point was HTT_{Rx} pharmacokinetics in cerebrospinal fluid (CSF). Prespecified exploratory end points included the concentration of mutant huntingtin in CSF.

RESULTS

Of the 46 patients who were enrolled in the trial, 34 were randomly assigned to receive HTT_{Rx} (at ascending dose levels of 10 to 120 mg) and 12 were randomly assigned to receive placebo. Each patient received all four doses and completed the trial. Adverse events, all of grade 1 or 2, were reported in 98% of the patients. No serious adverse events were seen in HTT_{Rx}-treated patients. There were no clinically relevant adverse changes in laboratory variables. Predose (trough) concentrations of HTT_{Rx} in CSF showed dose dependence up to doses of 60 mg. HTT_{Rx} treatment resulted in a dose-dependent reduction in the concentration of mutant huntingtin in CSF (mean percentage change from baseline, 10% in the placebo group and –20%, –25%, –28%, –42%, and –38% in the HTT_{Rx} 10-mg, 30-mg, 60-mg, 90-mg, and 120-mg dose groups, respectively).

CONCLUSIONS

Intrathecal administration of HTT_{Rx} to patients with early Huntington's disease was not accompanied by serious adverse events. We observed dose-dependent reductions in concentrations of mutant huntingtin. (Funded by Ionis Pharmaceuticals and F. Hoffmann–La Roche; ClinicalTrials.gov number, NCT02519036.)

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Oligonucleotide Treatment for Huntington's Disease

Kenneth H. Fischbeck, M.D., and Nancy S. Wexler, Ph.D.

Huntington's disease is a severe autosomal-dominant neurodegenerative disorder that involves chorea, cognitive decline, and psychological problems such as depression, delusions, and impulsive behavior. Nowhere are the manifestations more striking than around Lake Maracaibo in northwestern Venezuela, where the disease is almost epidemic. The Huntington's disease kindreds in Venezuela encompass more than 18,000 persons spanning 10 generations. DNA samples from nearly 4000 patients and family members in this area were used to map the Huntington's gene to chromosome 4 in 1983[1] and to identify the disease gene in 1993.[2] Subsequent studies in this population have discovered modifiers of age at onset.[3] A new prospective treatment specifically targeting the messenger RNA (mRNA) encoding the mutant protein has been tested in patients with Huntington's disease, as now reported in the *Journal* by Tabrizi et al.[4]

Huntington's disease is caused by a trinucleotide repeat expansion that results in an expanded polyglutamine tract in the disease protein, huntingtin. The mutant protein is toxic and prone to aggregation in cell culture, animal models, and human brains. Remarkably, disease manifestations are reversed when the mutant gene is turned off or suppressed in transgenic mice,[5,6] which suggests that this approach could be effective in humans. Oligonucleotides targeting mutant huntingtin mRNA for degradation did not result in adverse effects when delivered intrathecally in nonhuman primates, and they reduced huntingtin levels throughout the brain.[6] Although complete loss of normal huntingtin results in embryonic lethality in mice,[7] partial reduction in levels later in life has an acceptable safety profile. This allows a non–allele-specific approach, in which the treatment would be suitable for all patients. Importantly, the levels of huntingtin protein can be assessed in the spinal fluid and correlate well with levels in the brain, thus providing a measure of the biologic effect of the treatment.

The trial reported by Tabrizi et al. involved 46 patients who were randomly assigned to receive placebo or one of five doses of the oligonucleotide HTT_{Rx} and followed at nine centers in the United Kingdom, Germany, and Canada. The patients received four injections into the spinal fluid at 4-week intervals, with a 4-month follow-up. The trial agent was not associated with dose-limiting adverse events; the most common adverse effects were related to the lumbar punctures. There was a dose-dependent increase in the concentration of HTT_{Rx} and a decrease in levels of mutant huntingtin protein in the spinal fluid. Remarkably, the reduction in the levels of mutant huntingtin was in a range that is expected to have therapeutic benefit on the basis of studies in animals. This is a pathbreaking trial that strongly supports further development of HTT_{Rx} as a treatment for Huntington's disease. A confirmatory phase 3 trial is now under way (ClinicalTrials.gov number, NCT03761849), with a plan to follow 660 patients worldwide for up to 2 years. Now, 26 years after the discovery of the etiologic gene, a path to modifying Huntington's disease seems clear, with implications for other neurodegenerative diseases that have a known genetic cause. The next step is to determine whether HTT_{Rx} has a clinical effect in a larger number of patients followed over a longer period of time. The current trial was of insufficient size and duration to show a significant difference in clinical measures between patients given the active agent and those who received placebo. However, an analysis after the trial showed a correlation of such measures with levels of the mutant protein in the spinal fluid, indicating that reducing the protein level could be beneficial.

The phase 3 trial that has just begun is appropriately designed to determine whether this intervention has a clinically meaningful effect. The ultimate challenge will be to bring safe, effective, and affordable treatment not only to patients in North America and Europe but also to patients with Huntington's disease throughout the world. For those in Venezuela who donated the samples that made this promising approach possible, the treatment should be free.

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

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A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease

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ABSTRACT

BACKGROUND

Deoxygenated sickle hemoglobin (HbS) polymerization drives the pathophysiology of sickle cell disease. Therefore, direct inhibition of HbS polymerization has potential to favorably modify disease outcomes. Voxelotor is an HbS polymerization inhibitor.

METHODS

In a multicenter, phase 3, double-blind, randomized, placebo-controlled trial, we compared the efficacy and safety of two dose levels of voxelotor (1500 mg and 900 mg, administered orally once daily) with placebo in persons with sickle cell disease. The primary end point was the percentage of participants who had a hemoglobin response, which was defined as an increase of more than 1.0 g per deciliter from baseline at week 24 in the intention-to-treat analysis.

RESULTS

A total of 274 participants were randomly assigned in a 1:1:1 ratio to receive a once-daily oral dose of 1500 mg of voxelotor, 900 mg of voxelotor, or placebo. Most participants had sickle cell anemia (homozygous hemoglobin S or hemoglobin Sβ^0-thalassemia), and approximately two thirds were receiving hydroxyurea at baseline. In the intention-to-treat analysis, a significantly higher percentage of participants had a hemoglobin response in the 1500-mg voxelotor group (51%; 95% confidence interval [CI], 41 to 61) than in the placebo group (7%; 95% CI, 1 to 12). Anemia worsened between baseline and week 24 in fewer participants in each voxelotor dose group than in those receiving placebo. At week 24, the 1500-mg voxelotor group had significantly greater reductions from baseline in the indirect bilirubin level and percentage of reticulocytes than the placebo group. The percentage of participants with an adverse event that occurred or worsened during the treatment period was similar across the trial groups. Adverse events of at least grade 3 occurred in 26% of the participants in the 1500-mg voxelotor group, 23% in the 900-mg voxelotor group, and 26% in the placebo group. Most adverse events were not related to the trial drug or placebo, as determined by the investigators.

CONCLUSIONS

In this phase 3 randomized, placebo-controlled trial involving participants with sickle cell disease, voxelotor significantly increased hemoglobin levels and reduced markers of hemolysis. These findings are consistent with inhibition of HbS polymerization and indicate a disease-modifying potential. (Funded by Global Blood Therapeutics; HOPE ClinicalTrials.gov number, NCT03036813.)

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

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EDITORIALS

A Targeted Agent for Sickle Cell Disease — Changing the Protein but Not the Gene

Alexis Thompson, M.D., M.P.H.

Affecting an estimated 100,000 Americans and millions worldwide, sickle cell disease is among the most common inherited blood disorders in humans and is associated with profound complications and premature death.[1,2] The pathophysiology of sickle cell disease begins with a single amino acid substitution in the β-globin chain that creates mutant hemoglobin S (HbS) that can polymerize in red cells under certain conditions. HbS polymerization results in a very complex cascade of processes that include erythrocyte sickling, intravascular hemolysis with release of cell-free hemoglobin, increased adhesion of red cells to the endothelium of blood vessels, activation of platelets, production of inflammatory cytokines, and ultimately vascular occlusion.[3,4] Early detection, ideally by means of newborn screening, and preventive measures such as penicillin prophylaxis have saved lives in regions where these measures are available and consistently applied. For nearly 20 years, hydroxyurea was the only disease-modifying therapy for sickle cell disease approved by the Food and Drug Administration (FDA). Although studies have shown that hydroxyurea is effective in reducing admissions for pain and acute chest syndrome, use of the agent remains low.[5,6] Clearly, additional safe, effective, and ideally, targeted agents are needed.

Vichinsky et al.[7] now report in the *Journal* the findings from the HOPE (Hemoglobin Oxygen Affinity Modulation to Inhibit HbS Polymerization) trial, a phase 3, multicenter, international, double-blind, randomized trial of voxelotor in children and adults with sickle cell disease. As an inhibitor of HbS polymerization, voxelotor increases hemoglobin–oxygen affinity and has been shown to reduce red-cell sickling, hemolysis, and anemia in murine models and early-stage clinical trials.[8,9] In accordance with its stated mechanism of action, voxelotor, if effective, should ameliorate fundamental aspects of sickle cell disease.

The HOPE trial examined the responses to two dose levels of voxelotor as compared with placebo (assigned in a 1:1:1 randomization scheme) over a period of 24 weeks. The participants were stratified according to age, hydroxyurea use, and geographic region. More participants who received the 1500-mg daily dose of voxelotor had a hemoglobin response (defined as an increase in hemoglobin level of >1.0 g per deciliter at 24 weeks) and reduced marker levels of hemolysis than those who received placebo, and fewer acute episodes of anemia occurred in the 1500-mg voxelotor group than in the placebo group during the trial period. Subgroup analyses suggested a potential benefit for voxelotor in both adults and adolescents, patients receiving voxelotor alone or in combination with hydroxyurea, and patients with few or frequent vaso-occlusive episodes. The investigators concluded that the increase in hemoglobin level and reduction in hemolysis observed with voxelotor support its use as a new, potentially disease-modifying therapy for sickle cell disease.

The difference between the 1500-mg once-daily dose of voxelotor and placebo with respect to the primary efficacy end point in the trial, a modest increase in hemoglobin level, was statistically significant, and the increase tended to

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occur fairly early in the treatment course. The clinical significance of this response was the associated reduction in hemolysis, a consequence of sickle cell disease that is associated with chronic organ injury. A trend toward a cumulative reduction in the incidence of vaso-occlusive pain episodes with voxelotor as compared with placebo may be emerging in an extended follow-up analysis out to 72 weeks. Follow-up studies are needed to examine this very important, clinically relevant end point.

The occurrence of adverse events during the treatment period was common in this trial, but more serious grade 3 or greater events were balanced across all trial groups and included reports of gastrointestinal complications (diarrhea, nausea, and abdominal pain), headache, and rash. Relatively small numbers of patients discontinued the trial drug because of adverse events. Adverse events related to sickle cell disease were also fairly similar across the trial groups.

As described in a thoughtful review by Eaton and Bunn,[10] HbS polymerization is the root cause of sickle cell disease and its complications, and approaches to treating sickle cell disease that ultimately inhibit polymerization can and should have a therapeutic effect. But can increasing oxygen affinity of hemoglobin cause harm if it results in tissue hypoxia? The predicted benefit of antisickling agents does not require complete inhibition of HbS polymerization. In the HOPE trial, the observed hemoglobin occupancy with voxelotor was sufficient to maintain 26% of HbS in the oxygenated state. This modest inhibition of polymerization should increase delay time without deleterious shifts in the oxygen-binding curve, allowing red cells to transit through the microcirculation with less sickling and therefore improved oxygen delivery. At the dose levels studied, voxelotor did not appear to impair tissue oxygenation, a finding that is supported by the maintenance of baseline serum erythropoietin levels, a surrogate end point in the trial.

This trial has several new and meritorious features. It is a phase 3, randomized, controlled trial of a rationally designed agent for sickle cell disease, a condition for which there have been limited disease-modifying therapies. Voxelotor seemed to have a relatively safe profile at the dose levels studied. The data presented support the achievement of the stated primary end point in the HOPE trial, which was to reduce anemia and hemolysis. The hemoglobin response and reduction in hemolysis observed with an orally administered, once-daily medication with side effects that minimally affect lifestyle may make voxelotor a promising advancement in the management of sickle cell disease if approved by the FDA.

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Ambient Particulate Air Pollution and Daily Mortality in 652 Cities

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ABSTRACT

BACKGROUND

The systematic evaluation of the results of time-series studies of air pollution is challenged by differences in model specification and publication bias.

METHODS

We evaluated the associations of inhalable particulate matter (PM) with an aerodynamic diameter of 10 μm or less (PM_{10}) and fine PM with an aerodynamic diameter of 2.5 μm or less ($PM_{2.5}$) with daily all-cause, cardiovascular, and respiratory mortality across multiple countries or regions. Daily data on mortality and air pollution were collected from 652 cities in 24 countries or regions. We used overdispersed generalized additive models with random-effects meta-analysis to investigate the associations. Two-pollutant models were fitted to test the robustness of the associations. Concentration–response curves from each city were pooled to allow global estimates to be derived.

RESULTS

On average, an increase of 10 μg per cubic meter in the 2-day moving average of PM_{10} concentration, which represents the average over the current and previous day, was associated with increases of 0.44% (95% confidence interval [CI], 0.39 to 0.50) in daily all-cause mortality, 0.36% (95% CI, 0.30 to 0.43) in daily cardiovascular mortality, and 0.47% (95% CI, 0.35 to 0.58) in daily respiratory mortality. The corresponding increases in daily mortality for the same change in $PM_{2.5}$ concentration were 0.68% (95% CI, 0.59 to 0.77), 0.55% (95% CI, 0.45 to 0.66), and 0.74% (95% CI, 0.53 to 0.95). These associations remained significant after adjustment for gaseous pollutants. Associations were stronger in locations with lower annual mean PM concentrations and higher annual mean temperatures. The pooled concentration–response curves showed a consistent increase in daily mortality with increasing PM concentration, with steeper slopes at lower PM concentrations.

CONCLUSIONS

Our data show independent associations between short-term exposure to PM_{10} and $PM_{2.5}$ and daily all-cause, cardiovascular, and respiratory mortality in more than 600 cities across the globe. These data reinforce the evidence of a link between mortality and PM concentration established in regional and local studies. (Funded by the National Natural Science Foundation of China and others.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Kan at P.O. Box 249, 130 Dong-An Road, Shanghai 200032, China, or at kanh@fudan.edu.cn.

Drs. Liu and R. Chen and Drs. Gasparrini and Kan contributed equally to this article.

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Do We Really Need Another Time-Series Study of the $PM_{2.5}$–Mortality Association?

John R. Balmes, M.D.

The link between particulate pollution and mortality was originally recognized in the context of severe episodes of poor air quality in the 20th century, such as the London Fog of 1952.[1] These episodes showed clear evidence that the number of deaths increased in association with high levels of particulate matter (PM). The policy response to the increasing evidence of the effects of air pollution on public health was for governments to develop air-quality regulations. In the United States, the Clean Air Act of 1970 mandated that the Environmental Protection Agency (EPA) develop national ambient air-quality standards (NAAQS) to protect even the most vulnerable members of the general population from adverse health effects.[2] An NAAQS for PM was initially established in 1971.

The current primary NAAQS for PM applies to particles with an aerodynamic diameter of 2.5 μm or less ($PM_{2.5}$) — particles that are small enough to be deposited in the alveoli. A secondary NAAQS applies to particles with an aerodynamic diameter of 10 μm or less (PM_{10}) — particles that can be deposited in large airways. The epidemiologic evidence in support of the adoption of an NAAQS for $PM_{2.5}$ was largely from time-series studies.[3] Time-series analyses include daily measures of health events (e.g., daily mortality), regressed against concentrations of PM (e.g., 24-hour average $PM_{2.5}$) and weather variables (e.g., daily average temperature) for a given geographic area. The population serves as its own control, and confounding by population characteristics is negligible because these are stable over short time frames. Time-series studies can be confounded by time-varying factors such as influenza epidemics and temperature; however, statistical methods to reduce such confounding have been developed.[3]

Many time-series studies have been conducted in cities in various countries around the world. Efforts have been made to include larger regions in time-series analyses to increase the generalizability of the reported associations.[4] A meta-analysis has shown that the $PM_{2.5}$–mortality association remains robust in pooled analyses.[5] Multiple longitudinal cohort studies of the association between long-term $PM_{2.5}$ exposure and mortality, in which individual-level covariates were included in the analyses, have generally shown even stronger associations, providing important support for the evidence from time-series studies.[6] Moreover, experimental data from exposure studies in animals and controlled exposure studies in humans have increasingly provided mechanistic evidence in support of the epidemiologic findings.

Given the abundance of evidence in support of an association between short-term $PM_{2.5}$ exposure and mortality, what is the contribution of the time-series study by Liu et al. in this issue of the *Journal*?[7] First, this study included almost 60 million deaths from 652 cities in 24 countries, thereby greatly increasing the generalizability of the association and decreasing the likelihood that the reported associations are subject to confounding bias. In observations consistent with previous studies, all-cause (nonaccidental), cardiovascular, and respiratory mortality were associated with short-term exposures to both PM_{10} and $PM_{2.5}$. The strength of the associations was reduced but remained significant in two-pollutant models that addressed potential confounding by gaseous pollutants.

Perhaps the most interesting result of the study by Liu et al. is from their concentration–response analysis. On the basis of studies of exposure to multiple combustion sources of $PM_{2.5}$ (outdoor air pollution, secondhand tobacco smoke, and active tobacco smoking) and cardiovascular mortality, Pope et al. proposed that the shape of the concentration–response relation is curvilinear, with a lesser slope at higher exposure levels.[8] Although other studies have reported evidence of such curvilinearity, the current study of PM data from many regions around the world provides the strongest evidence to date that higher levels of exposure may be associated with a lower per-unit risk. Regions that have lower exposures had a higher per-unit risk. This finding has profound policy implications, especially

given that no threshold of effect was found. Even high-income countries, such as the United States, with relatively good air quality could still see public health benefits from further reduction of ambient PM concentrations (i.e., below the current NAAQS).

The Clean Air Act requires a periodic review of the weight of evidence of adverse health effects of regulated air pollutants by an external body of scientists, called the Clean Air Scientific Advisory Committee (CASAC). Controlled exposure studies in humans, toxicologic studies in animals, and epidemiologic studies are included in the weight-of-evidence reviews by CASAC. In the context of the current review of the NAAQS for PM and the Trump Administration's view of inconvenient scientific evidence as anathema,[9] Anthony Cox, the current chair of CASAC, has characterized the abundant observational epidemiologic evidence from time-series and cohort studies of the $PM_{2.5}$–mortality association as not proving causality. Rather than relying on the weight-of-the-evidence approach that the EPA has traditionally used to infer causation, Cox wants to rely on studies that use a theoretical approach called "manipulative causality."[10] This theory restricts epidemiologic evidence that may be considered acceptable to assess causality to results from intervention studies or studies that have been analyzed with the use of causal inference statistical methods. The effort to exclude all observational epidemiologic data that have not been analyzed in a manipulative causality framework not only makes no sense, it would set a dangerous precedent for environmental policy.

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

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Complete Revascularization with Multivessel PCI for Myocardial Infarction

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ABSTRACT

BACKGROUND

In patients with ST-segment elevation myocardial infarction (STEMI), percutaneous coronary intervention (PCI) of the culprit lesion reduces the risk of cardiovascular death or myocardial infarction. Whether PCI of nonculprit lesions further reduces the risk of such events is unclear.

METHODS

We randomly assigned patients with STEMI and multivessel coronary artery disease who had undergone successful culprit-lesion PCI to a strategy of either complete revascularization with PCI of angiographically significant nonculprit lesions or no further revascularization. Randomization was stratified according to the intended timing of nonculprit-lesion PCI (either during or after the index hospitalization). The first coprimary outcome was the composite of cardiovascular death or myocardial infarction; the second coprimary outcome was the composite of cardiovascular death, myocardial infarction, or ischemia-driven revascularization.

RESULTS

At a median follow-up of 3 years, the first coprimary outcome had occurred in 158 of the 2016 patients (7.8%) in the complete-revascularization group as compared with 213 of the 2025 patients (10.5%) in the culprit-lesion-only PCI group (hazard ratio, 0.74; 95% confidence interval [CI], 0.60 to 0.91; P=0.004). The second coprimary outcome had occurred in 179 patients (8.9%) in the complete-revascularization group as compared with 339 patients (16.7%) in the culprit-lesion-only PCI group (hazard ratio, 0.51; 95% CI, 0.43 to 0.61; P<0.001). For both coprimary outcomes, the benefit of complete revascularization was consistently observed regardless of the intended timing of nonculprit-lesion PCI (P=0.62 and P=0.27 for interaction for the first and second coprimary outcomes, respectively).

CONCLUSIONS

Among patients with STEMI and multivessel coronary artery disease, complete revascularization was superior to culprit-lesion-only PCI in reducing the risk of cardiovascular death or myocardial infarction, as well as the risk of cardiovascular death, myocardial infarction, or ischemia-driven revascularization. (Funded by the Canadian Institutes of Health Research and others; COMPLETE ClinicalTrials.gov number, NCT01740479.)

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*A complete list of the COMPLETE trial steering committee members and investigators is provided in the Supplementary Appendix, available at NEJM.org.

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EDITORIALS

A More COMPLETE Picture of Revascularization in STEMI

Lars Køber, M.D., and Thomas Engstrøm, M.D.

Up to half of patients presenting with acute ST-segment elevation myocardial infarction (STEMI) have multivessel coronary artery disease, and American College of Cardiology–American Heart Association–European Society of Cardiology guidelines have a class IIb recommendation for the treatment of nonculprit lesions.[1-4] Four intermediate-sized trials have shown that complete revascularization is safe and reduces the risk of repeat revascularization.[5-8] Until now, a general strategy of complete revascularization has not been shown to reduce the risk of hard outcomes, such as death and recurrent myocardial infarction. In addition, it has been suggested that identification of nonculprit lesions relevant for complete revascularization should be based on fractional flow reserve (FFR) measurements.

Mehta and colleagues now report in the *Journal* the results of the COMPLETE (Complete versus Culprit-Only Revascularization Strategies to Treat Multivessel Disease after Early Percutaneous Coronary Intervention [PCI] for STEMI) trial, a large, randomized trial comparing complete revascularization with treatment of the culprit lesion only in patients presenting with STEMI.[9] A total of 4041 patients who had nonculprit lesions with at least 70% stenosis of the vessel diameter or an FFR measurement of 0.80 or less were randomly assigned, in a 1:1 ratio, to undergo either complete revascularization or treatment of the infarct-related artery only. Patients underwent randomization up to 72 hours after the index PCI procedure. Treatment of nonculprit lesions could be performed during the index admission or after discharge, a choice that was made by investigators before randomization. There was a low crossover rate (<5%) between the two treatment groups.

The risk of the first coprimary composite outcome (death from cardiovascular causes or recurrent myocardial infarction) was a quarter lower in the complete-revascularization group than in the culprit-lesion-only PCI group. This benefit was driven by a reduction in new myocardial infarction. Cardiovascular mortality was similar in the two groups (2.9% and 3.2%), as was all-cause mortality (4.8% and 5.2%). The risk of the second coprimary outcome, which included ischemia-driven revascularization in addition to the other two events, was 50% lower in the complete-revascularization group than in the culprit-lesion-only PCI group.

Among patients who were randomly assigned to undergo complete revascularization, one third had the second procedure after hospital discharge. Subgroup analyses that were based on the intended timing of the second procedure showed no interaction with the primary outcomes, which indicates that complete revascularization may be safely postponed until after hospital discharge in selected patients. The risk of adverse events (including stroke, major bleeding, and acute kidney injury) was similar in the two groups, which supports the safety of an additional procedure.

Comparing the COMPLETE trial with previous trials provides important information (Table 1). Although the patients in the COMPLETE trial had an age and sex distribution similar to that of the patients in the other trials, they had a lower yearly risk of the primary outcomes but still had more events than did the patients in all

Table 1. Comparison of the COMPLETE Trial with Previous Trials of Complete Revascularization.*

Variable	PRAMI	CvLPRIT	DANAMI-3–PRIMULTI	Compare-Acute	COMPLETE
No. of patients	465	296	627	885	4041
Mean age — yr	62	65	63	61	62
Male sex — %	78	81	81	77	80
Median follow-up — mo	23	12	27	12	36
Median time from randomization to second procedure — days	0 (same time as index procedure)	<2	2	0 (same time as index procedure)	1 (during admission); 23 (after discharge)†
FFR measurement of nonculprit lesions obtained	No	No	Yes	Yes	Yes (in <1% of patients)
Events with treatment of culprit lesion only — no./total no. of patients					
Death	16/231	10/146	11/313	10/590	106/2025
Cardiovascular death	10/231	7/146	9/313	6/590	64/2025
Myocardial infarction	20/231	4/146	16/313	28/590	160/2025
Revascularization	46/231	16/146	52/313	103/590	160/2025
Events with complete revascularization vs. treatment of culprit lesion only — hazard ratio (95% CI)					
Cardiovascular death or myocardial infarction	0.36 (0.18–0.73)	NA	0.80 (0.45–1.45)	NA	0.74 (0.60–0.91)
Death	NA	0.38 (0.12–1.20)	1.40 (0.63–3.00)	0.80 (0.25–2.56)	0.91 (0.69–1.20)

* Shown are data from the following trials: PRAMI (Preventive Angioplasty in Acute Myocardial Infarction),[5] CvLPRIT (Complete versus Lesion-Only Primary Percutaneous Coronary Intervention [PCI] Trial),[6] DANAMI-3–PRIMULTI (Third Danish Study of Optimal Acute Treatment of Patients with ST-Segment Elevation Myocardial Infarction [STEMI]: Primary PCI in Multivessel Disease),[7] Compare-Acute,[8] and COMPLETE (Complete versus Culprit-Only Revascularization Strategies to Treat Multivessel Disease after Early PCI for STEMI).[9] CI denotes confidence interval, FFR fractional flow reserve, and NA not available in the publication.

† Investigators specified before randomization whether they intended to perform the second procedure during the index hospitalization or after hospital discharge. Among the patients who underwent complete revascularization, the intended timing of the second procedure was during the index hospitalization for 1285 patients and after hospital discharge for 596 patients.

the other trials together, a finding that shows the importance of having properly sized trials with long-term follow-up.

Is functional assessment with FFR of nonculprit lesions unnecessary? In the COMPLETE trial, almost all nonculprit lesions were treated on the basis of angiographic findings, but nearly 60% of the lesions had at least 80% stenosis of the vessel diameter on visual estimation and 38% were in the left anterior descending coronary artery. Thus, most lesions were angiographically significant, and FFR may still have an important role in diagnosing lesions of intermediate severity.

Should the results of the COMPLETE trial, in combination with the results of previous randomized trials, change the guidelines to support complete revascularization in all patients with STEMI and multivessel disease? Patients participating in trials are different from sicker patients seen in the clinical setting, and extrapolation of the results to patients with a greater risk of complications may not be safe. Among patients in the COMPLETE trial, the mean SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) score — a score used to predict the risk associated with revascularization by taking into account the complexity of coronary artery disease, with scores ranging from 0 (no disease) to more than 50 (multiple very complex lesions) — was relatively low, conferring an increased chance of successful revascularization. More complex nonculprit lesions (associated with higher SYNTAX scores) may be different physiologically and may

be less suitable for routine treatment. Also, some patients may benefit more from firm adherence to high-potency dual antiplatelet therapy with either prasugrel or ticagrelor. In the COMPLETE trial, one quarter of the patients received clopidogrel, which may not be the most effective therapy in patients with acute coronary syndromes.[10]

Should the consistent lack of benefit with respect to all-cause mortality discourage the strategy of routine complete revascularization? Since this strategy appears to be safe and reduces the risk of the composite outcome of cardiovascular death or recurrent myocardial infarction, as well as the risk of future revascularization, it appears to be appropriate to recommend complete revascularization for patients similar to those included in the COMPLETE trial. We hope that the investigators will be able to obtain data from longer follow-up in order to evaluate whether the tendency toward a small reduction in all-cause mortality becomes significant over time. Better selection of high-risk patients may also refine the determination of who is most likely to benefit from complete revascularization. Regardless, in light of the results of the well-planned and well-executed trial by Mehta et al., the guidelines should recommend a strategy of full revascularization in patients with STEMI and multivessel disease, at least in those who have suitable nonculprit lesions.

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

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ORIGINAL ARTICLE

Pulmonary Illness Related to E-Cigarette Use in Illinois and Wisconsin — Preliminary Report

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ABSTRACT

BACKGROUND

E-cigarettes are battery-operated devices that heat a liquid and deliver an aerosolized product to the user. Pulmonary illnesses related to e-cigarette use have been reported, but no large series has been described. In July 2019, the Wisconsin Department of Health Services and the Illinois Department of Public Health received reports of pulmonary disease associated with the use of e-cigarettes (also called vaping) and launched a coordinated public health investigation.

METHODS

We defined case patients as persons who reported use of e-cigarette devices and related products in the 90 days before symptom onset and had pulmonary infiltrates on imaging and whose illnesses were not attributed to other causes. Medical record abstraction and case patient interviews were conducted with the use of standardized tools.

RESULTS

There were 53 case patients, 83% of whom were male; the median age of the patients was 19 years. The majority of patients presented with respiratory symptoms (98%), gastrointestinal symptoms (81%), and constitutional symptoms (100%). All case patients had bilateral infiltrates on chest imaging (which was part of the case definition). A total of 94% of the patients were hospitalized, 32% underwent intubation and mechanical ventilation, and one death was reported. A total of 84% of the patients reported having used tetrahydrocannabinol products in e-cigarette devices, although a wide variety of products and devices was reported. Syndromic surveillance data from Illinois showed that the mean monthly rate of visits related to severe respiratory illness in June through August of 2019 was twice the rate that was observed in the same months in 2018.

CONCLUSIONS

Case patients presented with similar clinical characteristics. Although the features of e-cigarette use that were responsible for injury have not been identified, this cluster of illnesses represents an emerging clinical syndrome or syndromes. Additional work is needed to characterize the pathophysiology and to identify the definitive causes.

ONLINE ONLY

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EDITORIAL

Vaping-Induced Lung Injury

David C. Christiani, M.D., M.P.H.

A number of environmental agents are known to cause acute or subacute inhalation injury to the lung parenchyma. Indeed, emergency response guidelines for medical personnel describe toxic inhalation pneumonitis as a heterogeneous group of chemically induced injuries to the lung parenchyma as well as to the upper respiratory tract. The manifestations of such injury depend on the characteristics (e.g., solubility, composition) and the amount of the toxic compound or compounds inhaled.[1] Much of what we know about toxic inhalation syndromes derives from high levels of exposure in either occupational settings (e.g., exposure to metals, solvents, acids, bases, ozone, phosgene, or chlorine dioxide) or community settings where fires or accidents may occur (e.g., factory explosions, derailments of chemical-bearing train cars, and overexposure to household cleaning agents). Depending on the type of chemical agent and the amount of material inhaled, patients may experience symptoms ranging from minor respiratory tract discomfort to acute airway injury and damage to the parenchyma with pneumonitis, alveolar edema, respiratory failure, and death. A common pathophysiological pathway includes inflammation, edema of airways with epithelial sloughing, alveolar inflammation, and edema with hypoxemia.[2]

Layden et al.[3] now report in the *Journal* a cluster of cases from Illinois and Wisconsin in which patients presented with acute, severe respiratory distress after using e-cigarette (vaping) products. Two letters also published in the *Journal* add further support to vaping-induced respiratory distress: a 6-case cluster from Utah[4] and a report of imaging changes seen in a range of cases.[5] The Centers for Disease Control and Prevention reported in late August 2019 that at least 215 acute, severe respiratory distress cases have been identified, spanning 25 states, and as of this writing at least 2 deaths have occurred.[6] Although more investigation is needed to determine the vaping agent or agents responsible, there is clearly an epidemic that begs for an urgent response.

The cases demonstrate a heterogeneous collection of pneumonitis patterns that include acute eosinophilic pneumonia, organizing pneumonia, lipoid pneumonia, diffuse alveolar damage and acute respiratory distress syndrome (ARDS), diffuse alveolar hemorrhage, hypersensitivity pneumonitis, and the rare giant-cell interstitial pneumonitis. Though the precise manifestations of the respiratory injury may be diverse, there are clues to the precipitants that warrant attention. About 80% of the persons who vaped and became ill reported having used both nicotine products and tetrahydrocannabinol (THC) or cannabidiol (CBD) products. Active infection (which would include live bacterial contamination of e-cigarette fluids) does not appear to explain the clinical presentation, but acute toxic lung injury does seem to fit. Mixing of multiple ingredients with primary compounds and potential contaminants may result in in vitro (or even in vivo) production of new agents that may be toxic. E-cigarette fluids have been shown to contain at least six groups of potentially toxic compounds: nicotine, carbonyls, volatile organic compounds (such as benzene and toluene), particles, trace metal elements according to flavor,[7] and bacterial endotoxins and fungal glucans.[8] Two flavorants alone, diacetyl and 2,3-pentanediol, have been shown to perturb gene expression pathways related to cilia and cytoskeletal processes in normal human bronchial epithe-

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Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

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ABSTRACT

BACKGROUND

Type 2 diabetes mellitus is the leading cause of kidney failure worldwide, but few effective long-term treatments are available. In cardiovascular trials of inhibitors of sodium–glucose cotransporter 2 (SGLT2), exploratory results have suggested that such drugs may improve renal outcomes in patients with type 2 diabetes.

METHODS

In this double-blind, randomized trial, we assigned patients with type 2 diabetes and albuminuric chronic kidney disease to receive canagliflozin, an oral SGLT2 inhibitor, at a dose of 100 mg daily or placebo. All the patients had an estimated glomerular filtration rate (GFR) of 30 to <90 ml per minute per 1.73 m^2 of body-surface area and albuminuria (ratio of albumin [mg] to creatinine [g], >300 to 5000) and were treated with renin–angiotensin system blockade. The primary outcome was a composite of end-stage kidney disease (dialysis, transplantation, or a sustained estimated GFR of <15 ml per minute per 1.73 m^2), a doubling of the serum creatinine level, or death from renal or cardiovascular causes. Prespecified secondary outcomes were tested hierarchically.

RESULTS

The trial was stopped early after a planned interim analysis on the recommendation of the data and safety monitoring committee. At that time, 4401 patients had undergone randomization, with a median follow-up of 2.62 years. The relative risk of the primary outcome was 30% lower in the canagliflozin group than in the placebo group, with event rates of 43.2 and 61.2 per 1000 patient-years, respectively (hazard ratio, 0.70; 95% confidence interval [CI], 0.59 to 0.82; P=0.00001). The relative risk of the renal-specific composite of end-stage kidney disease, a doubling of the creatinine level, or death from renal causes was lower by 34% (hazard ratio, 0.66; 95% CI, 0.53 to 0.81; P<0.001), and the relative risk of end-stage kidney disease was lower by 32% (hazard ratio, 0.68; 95% CI, 0.54 to 0.86; P=0.002). The canagliflozin group also had a lower risk of cardiovascular death, myocardial infarction, or stroke (hazard ratio, 0.80; 95% CI, 0.67 to 0.95; P=0.01) and hospitalization for heart failure (hazard ratio, 0.61; 95% CI, 0.47 to 0.80; P<0.001). There were no significant differences in rates of amputation or fracture.

CONCLUSIONS

In patients with type 2 diabetes and kidney disease, the risk of kidney failure and cardiovascular events was lower in the canagliflozin group than in the placebo group at a median follow-up of 2.62 years. (Funded by Janssen Research and Development; CREDENCE ClinicalTrials.gov number, NCT02065791.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Perkovic at the George Institute for Global Health, University of New South Wales Sydney, Level 5, 1 King St., Newtown, NSW 2042, Australia, or at vperkovic@georgeinstitute.org.au.

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

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EDITORIALS

Clinical Credence — SGLT2 Inhibitors, Diabetes, and Chronic Kidney Disease

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

The number of people who die from kidney disease every year has risen over the past decade and is now estimated at 5 million to 10 million worldwide. The increase in rates of obesity — along with associated rates of type 2 diabetes, hypertension, and cardiovascular disease — has principally driven the elevated mortality. More than 660,000 Americans have reached the point of requiring intervention for end-stage kidney disease, with 468,000 receiving dialysis and more than 193,000 undergoing kidney transplantation, leading to a major public health and economic burden.[1] Hence, the development of new treatments that may prevent or delay the progression of chronic kidney disease, as well as treat type 2 diabetes, is an important goal.

Tight control of glucose levels and blood pressure slows but does not prevent the onset of diabetic nephropathy.[2] The standard approach for retarding the onset of diabetic nephropathy and stabilizing renal function has been blockade of the renin–angiotensin–aldosterone system, particularly with inhibitors of angiotensin-converting enzyme. This approach was first used in the early 1990s in patients with type 1 diabetes[3]; randomized trials subsequently established that such drugs were also effective in type 2 diabetes.[4] Newer classes of agents have also been tried but have not been successful.

Inhibitors of sodium–glucose cotransporter-2 (SGLT2) were initially approved as a new class of hypoglycemic agents that lowered blood glucose levels in patients with type 2 diabetes by enhancing urinary glucose excretion through the inhibition of SGLT2 in the proximal convoluted tubule, where glucose is reabsorbed. SGLT2 inhibitors reduce the renal threshold of glucose from 180 mg per deciliter (10 mmol per liter) to 40 to 120 mg per deciliter (2 to 7 mmol per liter), thereby effectively lowering blood glucose levels. In 2015, EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients)[5] changed the landscape in diabetes management by showing a lower risk of cardiovascular death among the 4687 patients who received empagliflozin than among the 2333 controls (172 patients [3.7%] vs. 137 patients [5.9%]) (hazard ratio, 0.62; 95% confidence interval [CI], 0.49 to 0.77). Patients in the empagliflozin group also had a lower risk of death from any cause (269 patients [5.7%] vs. 194 patients [8.3%]) (hazard ratio, 0.68; 95% CI, 0.57 to 0.82) and a lower risk of hospitalization for heart failure (126 patients [2.7%] vs. 95 patients [4.1%]) (hazard ratio, 0.65; 95% CI, 0.50 to 0.85). Recently, the CANVAS Program (Canagliflozin Cardiovascular Assessment Study)[6] showed similar cardiovascular benefits, indicating a class effect of SGLT2 inhibitors. Further support for that finding was noted in the CVD-REAL (Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors)[7] and the Health Improvement Network (THIN) trials.[8] As a result, SGLT2 inhibitors are now widely used in patients with type 2 diabetes both to improve glycated hemoglobin levels and to reduce cardiovascular risk.

Recent studies have hinted that medications designed to treat diabetes could also confer renoprotection through a mechanism that differs

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from those affecting glucose homeostasis.[3,4,7] Among these drugs, the SGLT2 inhibitors appeared to be the most promising.

In the *Journal*, Perkovic et al.[9] now report the primary results of the double-blind, randomized CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial, in which 4401 patients with type 2 diabetes and albuminuric chronic kidney disease received 100 mg of canagliflozin or placebo added to renin–angiotensin–aldosterone blockade and baseline diabetic therapy after a 2-week run-in period. All the participants met the criteria of having an estimated glomerular filtration rate (GFR) of 30 to <90 ml per minute per 1.73 m^2 of body-surface area and a urinary albumin-to-creatinine ratio of more than 300 (with albumin measured in milligrams and creatinine in grams). Sixty percent of the patients had an estimated GFR of 30 to 60 ml per minute per 1.73 m^2. The primary outcome was a composite of end-stage kidney disease (dialysis for at least 30 days, transplantation, or a sustained estimated GFR of less than 15 ml per minute per 1.73 m^2 for 30 days), doubling of the serum creatinine level for at least 30 days, or death from renal or cardiovascular disease. Secondary outcomes included cardiovascular outcomes (death, heart failure, myocardial infarction, or stroke). The trial was halted early (median follow-up, 2.62 years) after a planned interim analysis indicated that the primary outcome had been met.

The relative risk of the primary outcome was nearly 30% lower in the canagliflozin group than in the placebo group. There was also a 20 to 30% lower relative risk of deleterious cardiovascular outcomes. The glycated hemoglobin levels were reduced more by canagliflozin than by placebo, as were blood pressure and body weight. The slope of the decline in the estimated GFR was slower in the canagliflozin group than in the placebo group. Rates of two targeted adverse events, fractures and lower-limb amputations, were similar in the two groups; diabetic ketoacidosis was more frequent in the canagliflozin group than in the placebo group, despite the overall low rates (2.2 vs. 0.2 per 1000 patient-years).

The underlying mechanisms of canagliflozin activity are probably both renal and systemic. SGLT2 inhibition increases glucose and sodium delivery to the distal renal tubule, which is sensed by the juxtaglomerular apparatus as increased glomerular perfusion. This leads to increased vasoconstriction of the afferent arteriole, which decreases glomerular perfusion and intraglomerular pressure. Although these effects decrease the estimated GFR in the short term, as was seen during the first weeks of the CREDENCE trial, over time that effect stabilizes. The level of angiotensin II in the circulation decreases, as does the level of atrial natriuretic peptide, with a subsequent decrease in inflammation and an increase in intrarenal oxygenation. Decreased body weight and sympathetic output, decreased uric acid, and perhaps an increase in glucagon may also contribute.[10] Other hypoglycemic agents, such as inhibitors of dipeptidyl peptidase-4, also suppress oxidative stress, lessening fibrosis and apoptosis, which may retard progression.[4]

Overall, the importance of CREDENCE,[9] a well done and large clinical trial, cannot be overstated. The investigators estimated that among 1000 patients treated for 2.5 years, 22 would need to be treated with canagliflozin to prevent the composite primary outcome of end-stage kidney disease, doubling of the serum creatinine level, or renal or cardiovascular death. In addition, among the same number of patients, canagliflozin treatment would prevent 22 hospitalizations for heart failure and 25 composite events of cardiovascular death, myocardial infarction, or stroke. Such data are certain to be welcomed by patients with diabetes and chronic kidney disease and by the clinicians who treat them.

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

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ORIGINAL ARTICLE

Large-Scale Assessment of a Smartwatch to Identify Atrial Fibrillation

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ABSTRACT

BACKGROUND

Optical sensors on wearable devices can detect irregular pulses. The ability of a smartwatch application (app) to identify atrial fibrillation during typical use is unknown.

METHODS

Participants without atrial fibrillation (as reported by the participants themselves) used a smartphone (Apple iPhone) app to consent to monitoring. If a smartwatch-based irregular pulse notification algorithm identified possible atrial fibrillation, a telemedicine visit was initiated and an electrocardiography (ECG) patch was mailed to the participant, to be worn for up to 7 days. Surveys were administered 90 days after notification of the irregular pulse and at the end of the study. The main objectives were to estimate the proportion of notified participants with atrial fibrillation shown on an ECG patch and the positive predictive value of irregular pulse intervals with a targeted confidence interval width of 0.10.

RESULTS

We recruited 419,297 participants over 8 months. Over a median of 117 days of monitoring, 2161 participants (0.52%) received notifications of irregular pulse. Among the 450 participants who returned ECG patches containing data that could be analyzed — which had been applied, on average, 13 days after notification — atrial fibrillation was present in 34% (97.5% confidence interval [CI], 29 to 39) overall and in 35% (97.5% CI, 27 to 43) of participants 65 years of age or older. Among participants who were notified of an irregular pulse, the positive predictive value was 0.84 (95% CI, 0.76 to 0.92) for observing atrial fibrillation on the ECG simultaneously with a subsequent irregular pulse notification and 0.71 (97.5% CI, 0.69 to 0.74) for observing atrial fibrillation on the ECG simultaneously with a subsequent irregular tachogram. Of 1376 notified participants who returned a 90-day survey, 57% contacted health care providers outside the study. There were no reports of serious app-related adverse events.

CONCLUSIONS

The probability of receiving an irregular pulse notification was low. Among participants who received notification of an irregular pulse, 34% had atrial fibrillation on subsequent ECG patch readings and 84% of notifications were concordant with atrial fibrillation. This siteless (no on-site visits were required for the participants), pragmatic study design provides a foundation for large-scale pragmatic studies in which outcomes or adherence can be reliably assessed with user-owned devices. (Funded by Apple; Apple Heart Study ClinicalTrials.gov number, NCT03335800.)

From the Division of Cardiovascular Medicine (M.V.P.), Stanford Center for Clinical Research (K.W.M., A.R., N.T.), the Quantitative Sciences Unit (H.H., A.G., V.B., J.L., S.E.G., M.D.), Information Resources and Technology (T.F., G.H.), Department of Medicine (S.D.), and the Center for Digital Health (M.P.T.), Stanford University, Stanford, Apple, Cupertino (L.C., D.N., A.B., S.D.), and the Veterans Affairs Palo Alto Health Care System, Palo Alto (M.P.T.) — all in California; the University of Colorado School of Medicine, Aurora (J.S.R.); the Division of Cardiovascular Disease, Cooper Medical School of Rowan University, Camden, NJ (A.M.R.); the Lankenau Heart Institute and Jefferson Medical College, Philadelphia (P.K.); StopAfib.org, American Foundation for Women's Health, Decatur, TX (M.T.H.); and the Duke Clinical Research Institute, Duke University, Durham, NC (C.B.G.). Address reprint requests to Dr. Perez or Dr. Turakhia at Stanford Center for Clinical Research, 1070 Arastradero Rd., Palo Alto, CA 94304, or at mvperez@stanford.edu or mintu@stanford.edu.

*A complete list of the Apple Heart Study Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Watched by Apple

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After taking over media, social communication, and the consumer economy, the forces of digital innovation are moving into the worlds of medical practice and medical research. Both the power and the limitations of digital innovation in medicine are evident in a report by Perez and colleagues, "Large-Scale Assessment of a Smartwatch to Identify Atrial Fibrillation," published in this issue of the *Journal*.[1] The study was sponsored by Apple, and in 8 months it managed to enroll some 419,000 participants through the use of a smartphone application (app). Having an iPhone and an Apple Watch were entry requirements, so the study participants were in fact customers of the sponsor. Not surprisingly, most of the enrollees were young: 52% were younger than 40 years of age and only 6% were 65 or older, which may be the opposite of a desirable age profile for a study of atrial fibrillation.[2] Irregular rhythms were identified initially by the watch's optical sensor and interpreted by algorithm. In 0.52% of participants, rhythm patterns suggestive of atrial fibrillation were detected, which led to more conventional monitoring with an electrocardiography (ECG) patch sent by mail. There was documentation of atrial fibrillation in slightly over a third of those who returned the patch. Most of the irregular rhythms detected by smartwatch as possible atrial fibrillation were confirmed as such by the ECG patch, with a positive predictive value for a subsequent irregular tachogram of 0.71.

The main message from the Apple Heart Study lies not in the technology tested, which is rapidly evolving and changing. The lessons lie in how the study was done and why it was done. People have been wearing fitness monitors for many years, but now we're seeing the appeal of a watch with an app that can detect arrhythmias that may justify medical evaluation and treatment.[3] There is now wide public awareness that atrial fibrillation is a common cause of stroke.[4] Over 400,000 people downloaded the app and enrolled in the study, not because of any health problem but because they were curious and wanted the reassurance of high-tech, zero-effort heart monitoring. In fact, of the 219,179 participants younger than 40, over 99.8% received no notifications of an irregular pulse. It's difficult to draw any conclusions about the true frequency of atrial fibrillation, since only 21% of those with irregular pulse notifications based on monitoring by the smartwatch subsequently returned the ECG patch for analysis. In a study with easy, app-based enrollment, the percentage of people who dropped out was high and full follow-through with the research protocol was low. The study tried to exclude enrollees with a history of atrial fibrillation, but some of the detections were in patients who later admitted to a previous diagnosis of atrial fibrillation.

The results of the Apple Heart Study could be very valuable. The study challenges us to reassess the relation of atrial fibrillation to stroke. The data on that relation have been based on traditional, less-sensitive approaches, such as ECG and shorter-term monitoring of patients with symptoms. Patients with atrial fibrillation detected the "old-fashioned" way clearly have an increased risk of stroke (with the magnitude of increase depending on their $CHADS_2$ or CHA_2DS_2-VASc score).[5] But whether brief episodes of atrial fibrillation that may be detected by longer-term monitoring carry similar risks is not at all clear. Indeed, a study from a large registry suggests that patients with brief episodes of atrial tachycardia or atrial fibrillation detected by pacemakers or defibrillators may not have an increased risk of stroke or other adverse cardiovascular events.[6] This issue will require more research and probably large, controlled trials of anticoagulation in low-risk, but worried, populations. We certainly want to avoid the risks of anticoagulation if there are no benefits in patients with brief, isolated bouts of arrhythmia.

Technological progress commonly allows miniaturization, and we will be seeing more and more wearable, implantable, and even ingestible devices for detecting, monitoring, and treating diseases ranging from diabetes to seizure disorders.[7] Easy-to-use, wearable devices will facilitate research and allow more immediate, reliable patient reports than are available with traditional

interviews. Nonetheless, obtaining long-term participant commitment and compliance may become a greater challenge, as the results of the Apple Heart Study suggest.

In addition, the initial enthusiasm for new technologies can be overtaken by suspicion about who will be using the personal data and to what ends. People feel strongly about the right to privacy of their personal health data. When patients meet and get to know a medical research team, trust can grow. It is far more difficult to trust in freestanding device technologies and the billion-dollar companies behind them. As more of our health data become more accessible and move to the cloud, which few of us really understand, suspicion and worry grow even stronger. Again and again we have seen privacy violations, sometimes because of negligent security and sometimes because of deliberate and deceptive misuse of personal data. The uncomfortable fact is that our personal health data have considerable financial value to those who want to use them in the myriad marketplaces connected to our $3.7 trillion health economy. As we implement novel technology for improving human health, physicians need to help protect the interests of patients against the use of technology that ignores the greater good.

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

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