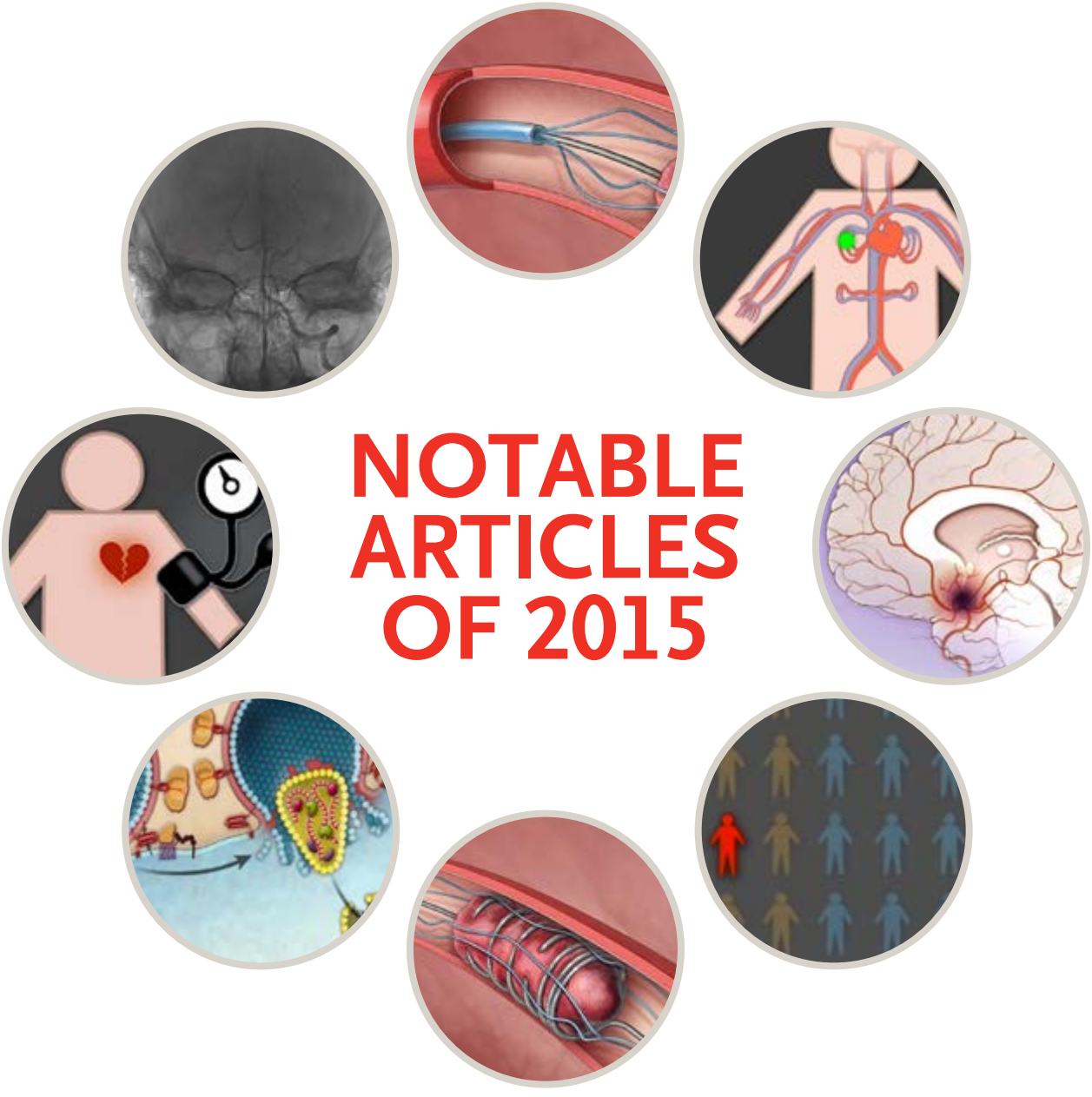
The NEW ENGLAND JOURNAL of MEDICINE



NOTABLE ARTICLES OF 2015

A collection of memorable research
of the past year as selected by NEJM editors

NEJM GROUP

The NEW ENGLAND JOURNAL of MEDICINE

January 2016

Dear Reader,

The face of medicine is constantly changing. In the past year, a number of studies published in the *New England Journal of Medicine* challenged our ways of thinking. A trial on peanut allergy, published in February, indicates that allergen avoidance is not the way to prevent allergy in young children. The SPRINT trial on intensive blood pressure management, published in November, redefines blood-pressure target goals. A third study, published in December, found that continuous chest compressions during CPR don't improve survival rates.

At NEJM we work to identify, vet, and publish the research that makes a difference in medicine. Each year, from the thousands of submissions we receive, we publish about 200 research articles. We choose these because we think these articles will change the face of medicine. This digital collection represents the cream of the crop, the dozen studies from 2015 that we think will have the biggest influence on medicine. We hope that you enjoy this collection and that you will continue to join us as we log medicine's journey.

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ORIGINAL ARTICLE

A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke

O.A. Berkhemer, P.S.S. Fransen, D. Beumer, L.A. van den Berg, H.F. Lingsma, A.J. Yoo, W.J. Schonewille, J.A. Vos, P.J. Nederkoorn, M.J.H. Wermer, M.A.A. van Walderveen, J. Staals, J. Hofmeijer, J.A. van Oostayen, G.J. Lycklama à Nijeholt, J. Boiten, P.A. Brouwer, B.J. Emmer, S.F. de Bruijn, L.C. van Dijk, L.J. Kappelle, R.H. Lo, E.J. van Dijk, J. de Vries, P.L.M. de Kort, W.J.J. van Rooij, J.S.P. van den Berg, B.A.A.M. van Hasselt, L.A.M. Aerden, R.J. Dallinga, M.C. Visser, J.C.J. Bot, P.C. Vroomen, O. Eshghi, T.H.C.M.L. Schreuder, R.J.J. Heijboer, K. Keizer, A.V. Tielbeek, H.M. den Hertog, D.G. Gerrits, R.M. van den Berg-Vos, G.B. Karas, E.W. Steyerberg, H.Z. Flach, H.A. Marquering, M.E.S. Sprengers, S.F.M. Jenniskens, L.F.M. Beenen, R. van den Berg, P.J. Koudstaal, W.H. van Zwam, Y.B.W.E.M. Roos, A. van der Lugt, R.J. van Oostenbrugge, C.B.L.M. Majoie, and D.W.J. Dippel, for the MR CLEAN Investigators*

ABSTRACT

BACKGROUND

In patients with acute ischemic stroke caused by a proximal intracranial arterial occlusion, intraarterial treatment is highly effective for emergency revascularization. However, proof of a beneficial effect on functional outcome is lacking.

METHODS

We randomly assigned eligible patients to either intraarterial treatment plus usual care or usual care alone. Eligible patients had a proximal arterial occlusion in the anterior cerebral circulation that was confirmed on vessel imaging and that could be treated intraarterially within 6 hours after symptom onset. The primary outcome was the modified Rankin scale score at 90 days; this categorical scale measures functional outcome, with scores ranging from 0 (no symptoms) to 6 (death). The treatment effect was estimated with ordinal logistic regression as a common odds ratio, adjusted for prespecified prognostic factors. The adjusted common odds ratio measured the likelihood that intraarterial treatment would lead to lower modified Rankin scores, as compared with usual care alone (shift analysis).

RESULTS

We enrolled 500 patients at 16 medical centers in the Netherlands (233 assigned to intraarterial treatment and 267 to usual care alone). The mean age was 65 years (range, 23 to 96), and 445 patients (89.0%) were treated with intravenous alteplase before randomization. Retrievable stents were used in 190 of the 233 patients (81.5%) assigned to intraarterial treatment. The adjusted common odds ratio was 1.67 (95% confidence interval [CI], 1.21 to 2.30). There was an absolute difference of 13.5 percentage points (95% CI, 5.9 to 21.2) in the rate of functional independence (modified Rankin score, 0 to 2) in favor of the intervention (32.6% vs. 19.1%). There were no significant differences in mortality or the occurrence of symptomatic intracerebral hemorrhage.

CONCLUSIONS

In patients with acute ischemic stroke caused by a proximal intracranial occlusion of the anterior circulation, intraarterial treatment administered within 6 hours after stroke onset was effective and safe. (Funded by the Dutch Heart Foundation and others; MR CLEAN Netherlands Trial Registry number, NTR1804, and Current Controlled Trials number, ISRCTN10888758.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Dippel at the Department of Neurology H643, Erasmus MC University Medical Center, PO Box 2040, Rotterdam 3000 CA, the Netherlands, or at d.dippel@erasmusmc.nl.

Drs. Berkhemer, Fransen, and Beumer and Drs. van Zwam, Roos, van der Lugt, van Oostenbrugge, Majoie, and Dippel contributed equally to this article.

*A complete list of investigators in the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) is provided in the Supplementary Appendix, available at NEJM.org.

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EDITORIALS

Interventional Thrombectomy for Major Stroke — A Step in the Right Direction

Werner Hacke, M.D., Ph.D.

Intravenous thrombolytic therapy is the only proven treatment for acute ischemic stroke, but its use is limited by a brief time window of up to 4.5 hours after the onset of symptoms[1] and a recanalization rate of less than 50%. Large clots in vessels such as the distal internal carotid artery or the first segment of the middle cerebral artery respond poorly to intravenous thrombolysis.[2] The need for a treatment for patients who do not have a good response to intravenous treatment alone remains pressing.

On the basis of compelling anecdotal experience, stroke specialists had hoped that transvascular recanalization would be an alternative to or a follow-on treatment after intravenous therapy for severe strokes with large-vessel occlusion. However, three randomized, controlled trials of intraarterial treatment, all reported in the *Journal*, have had negative or ambiguous results.[3-5] These trials were criticized for their use of older recanalization devices, which were associated with lower recanalization rates than those found with newer devices such as retrievable stents[6]; for the long interval between the onset of stroke and intervention; and for disappointingly low recruitment rates, which suggested that many suitable patients had been treated outside the trials. Moreover, subgroup analyses suggested that there was a benefit for patients treated in shorter time windows.[7,8] Perhaps most important, two of the trials did not require evidence of an occluded vessel before randomization, thereby making intracerebral treatment futile from the start.

The lessons of these studies were that trials of intraarterial treatment should enroll patients with severe strokes, have proof of proximal vessel occlusion, initiate treatment as early as possible, and use modern thrombectomy devices.[9] The results of the first such trial now appear in the *Journal*.[10] The Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands (MR CLEAN) included patients with severe stroke and proximal-vessel occlusion. Almost 90% of the patients received intravenous thrombolysis first, and almost all the devices used were of the retrievable-stent variety, which have a track record of successful recanalization. Thrombectomy improved outcomes, with an absolute difference of 13.5 percentage points in the rate of functional independence, as assessed with the use of the modified Rankin scale. Most other prespecified clinical end points and the rate of recanalization favored transvascular treatment, although the recanalization rate with transvascular treatment was a little lower than expected. There were no significant differences in mortality or the occurrence of symptomatic intracranial hemorrhage.

Readers may wonder how the trialists from a country with only 16.8 million inhabitants succeeded in enrolling 500 patients in just over 3 years, whereas other trials from much larger regions with similarly advanced medical systems struggled with recruitment. The well-established network of investigator-initiated stroke trials in the Netherlands contributed to the success of the trial, as did the relatively short distances between the 15 intervention centers in the country. In my view, however, the most important reason for success was the decision by the Dutch government to pay for the use of thrombectomy devices only in the context of a randomized trial,

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thereby precluding treatment outside the trial. This policy may be difficult to implement in other health systems, but imagine what progress the medical-device field would see if this strategy were the rule.

Finally, what does this first positive thrombectomy trial mean for interventional treatment? Is there any doubt left, or should thrombectomy now become the new standard treatment for severe stroke with proximal large-vessel occlusion up to 6 hours after stroke onset? Several similar trials are ongoing; it is premature to conclude that there is no longer equipoise regarding thrombectomy. We need and will get results from other well-designed trials, not only to confirm or refute the results of MR CLEAN but also to look at effects in subgroups (according to stroke severity, occlusion site, or time to treatment initiation), for which most single trials are underpowered. MR CLEAN is the first step in the right direction.

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

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ORIGINAL ARTICLE

Tenofovir-Based Preexposure Prophylaxis for HIV Infection among African Women

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ABSTRACT

BACKGROUND

Reproductive-age women need effective interventions to prevent the acquisition of human immunodeficiency virus type 1 (HIV-1) infection.

METHODS

We conducted a randomized, placebo-controlled trial to assess daily treatment with oral tenofovir disoproxil fumarate (TDF), oral tenofovir–emtricitabine (TDF-FTC), or 1% tenofovir (TFV) vaginal gel as preexposure prophylaxis against HIV-1 infection in women in South Africa, Uganda, and Zimbabwe. HIV-1 testing was performed monthly, and plasma TFV levels were assessed quarterly.

RESULTS

Of 12,320 women who were screened, 5029 were enrolled in the study. The rate of retention in the study was 91% during 5509 person-years of follow-up. A total of 312 HIV-1 infections occurred; the incidence of HIV-1 infection was 5.7 per 100 person-years. In the modified intention-to-treat analysis, the effectiveness was −49.0% with TDF (hazard ratio for infection, 1.49; 95% confidence interval [CI], 0.97 to 2.29), −4.4% with TDF-FTC (hazard ratio, 1.04; 95% CI, 0.73 to 1.49), and 14.5% with TFV gel (hazard ratio, 0.85; 95% CI, 0.61 to 1.21). In a random sample, TFV was detected in 30%, 29%, and 25% of available plasma samples from participants randomly assigned to receive TDF, TDF-FTC, and TFV gel, respectively. Independent predictors of TFV detection included being married, being older than 25 years of age, and being multiparous. Detection of TFV in plasma was negatively associated with characteristics predictive of HIV-1 acquisition. Elevations of serum creatinine levels were seen more frequently among participants randomly assigned to receive oral TDF-FTC than among those assigned to receive oral placebo (1.3% vs. 0.2%, P=0.004). We observed no significant differences in the frequencies of other adverse events.

CONCLUSIONS

None of the drug regimens we evaluated reduced the rates of HIV-1 acquisition in an intention-to-treat analysis. Adherence to study drugs was low. (Funded by the National Institutes of Health; VOICE ClinicalTrials.gov number, NCT00705679.)

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*A complete list of members of the Vaginal and Oral Interventions to Control the Epidemic (VOICE) Study Team is provided in the Supplementary Appendix, available at NEJM.org.

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EDITORIALS

Preventing HIV in Women — Still Trying to Find Their VOICE

Michael S. Saag, M.D.

The development and widespread use of potent antiretroviral therapy has transformed HIV infection from a near-certain death sentence to a chronic manageable condition, whereby patients who adhere fully to their medication regimen can have an almost normal life span.[1] Moreover, those who take their medications as prescribed generally do not transmit the virus to others.[2] If we could identify all persons infected with HIV, get them into care, successfully initiate antiretroviral therapy, and achieve and sustain suppression of the virus to undetectable levels, all patients would in theory have a near-normal life span and not transmit the virus to others — and the epidemic would end.[3] Despite the success of antiretroviral therapy in dramatically prolonging life expectancy, we have not seen much progress in preventing new infections. In most areas around the world, including the United States, the number of new persons infected last year was roughly the same as in years before.[4] Most experts indicate that "treatment as prevention" is an important approach, but we cannot treat our way out of the epidemic. Rather, multiple approaches to prevention are required.

One such approach is the use of preexposure prophylaxis, whereby antiretroviral agents are used, either through systemic administration or as topical microbicides such as vaginal gels. Well-conducted, randomized studies have had mixed results. In a study conducted in resource-rich countries, involving men who have sex with men, preexposure prophylaxis reduced transmission by 44% overall and by 92% among those who took their medications regularly.[5] In contrast, in a study conducted among women in sub-Saharan Africa (the Preexposure Prophylaxis Trial for HIV Prevention among African Women [FEM-PrEP]), the use of preexposure prophylaxis was ineffective, probably because of low levels of adherence to the medication regimen.[6] The use of vaginal gels as microbicides has also had mixed efficacy outcomes.

In this issue of the *Journal*, Marrazzo and colleagues report the findings of the Vaginal and Oral Interventions to Control the Epidemic (VOICE) trial, a placebo-controlled, randomized study of preexposure prophylaxis that was provided as oral antiretroviral therapy or as a vaginal gel to women living in sub-Saharan Africa.[7] The study assessed five treatment groups (oral tenofovir alone, oral tenofovir with emtricitabine, oral placebo, vaginal tenofovir gel, and vaginal placebo gel). Although it was planned for a 36-month maximum follow-up, the data and safety monitoring board recommended terminating treatment in the oral tenofovir and tenofovir gel study groups early, owing to futility. The oral tenofovir–emtricitabine group continued to completion, but the treatment showed no efficacy. Therefore, the study yielded results similar to those of the FEM-PrEP trial. The likely reason for the lack of efficacy can be gleaned from the pharmacokinetic data: approximately 30% of plasma samples in the VOICE study had detectable drug at the pharmacokinetic time points, which indicates that the majority of women in the trial were not taking their assigned medications regularly.

It is well established that medications don't work if they are not taken, which probably explains why no difference in efficacy was observed between the active-drug and placebo groups. On closer inspection, however, the striking finding

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in the VOICE trial is the disconnect between reported adherence and actual adherence to the regimen. Although approximately 30% of plasma samples collected from the women had detectable drug, 90% and 88% of the women indicated that they had not missed a dose when asked by either a study interviewer or a computerized questionnaire, respectively. More striking, the medication reconciliation, in which returned unused tablets were counted to determine missed doses, revealed that 86% of medication was "taken." This means that a large number of participants actively removed unused medications from their allotment before returning to the study site in order to create the appearance of compliance with the protocol.

The question that emerges is this: why did the participants go to such lengths to create the appearance that they were taking medications when they were not? To the study team's credit, they investigated this question through a series of qualitative interviews with VOICE participants after the study results became known.[8,9] In a recently published report, van der Straten and colleagues identified several factors associated with poor adherence to the protocol.[8] A common theme stemmed from fear of taking the medicine, because of concern either about adverse effects or about being falsely labeled as having HIV infection. The drugs used in the VOICE study are well known as anti-HIV agents. Despite detailed education provided by the study team, many of the participants feared that such potent treatment must have serious toxicity when used in uninfected people. In addition, because it is common knowledge within the community that antiretroviral therapy is associated with HIV infection, many women in the study were afraid that if they were seen taking HIV medications, they would be labeled as being infected. As a result, many of the women concealed their use of the products or hid the products out of a fear of stigma. The strong presence of stigma was identified among male partners and community members interviewed as part of the study, validating the concerns among the VOICE participants that their taking HIV pills would lead to gossip and rumor in the community, workplace, and household. Infurther work, the researchers specifically studied participants with low levels of drug in the blood versus those with high levels.[9] The group with low levels had significantly more fear of the drug side effects and had less trust in the clinic and its staff. In contrast, those with high drug levels developed strategies to overcome concerns about stigma, valued advice from nurses, and were more likely to believe that the products worked.[9]

At first glance, the VOICE study appears to indicate that preexposure prophylaxis doesn't work in women in Africa and that we should move on to explore other approaches to the prevention of HIV transmission in high-risk settings. On further review, the study indicates that much more work is needed, not so much in the realm of understanding the biologic basis of preexposure prophylaxis as a preventive treatment but rather in the realm of understanding behavioral barriers in the setting of strong social stigma.

The "Declaration of Sentiments," penned by Elizabeth Cady Stanton at the Women's Rights Convention in Seneca Falls, New York, in 1848, starts with the following statement: "When, in the course of human events, it becomes necessary for one portion of the family of man to assume among the people of the earth a position different from that which they have hitherto occupied . . . ."[10] This declaration represented the formal beginning of the women's rights movement in the United States. As in the fight for women to find their voice in the United States against strong social stigma so long ago, victory in the battle to prevent HIV will require the women at risk for infection to find "a position different from that which they have hitherto occupied" in order for them to find their VOICE.

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

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ORIGINAL ARTICLE

Randomized Trial of Peanut Consumption in Infants at Risk for Peanut Allergy

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ABSTRACT

BACKGROUND

The prevalence of peanut allergy among children in Western countries has doubled in the past 10 years, and peanut allergy is becoming apparent in Africa and Asia. We evaluated strategies of peanut consumption and avoidance to determine which strategy is most effective in preventing the development of peanut allergy in infants at high risk for the allergy.

METHODS

We randomly assigned 640 infants with severe eczema, egg allergy, or both to consume or avoid peanuts until 60 months of age. Participants, who were at least 4 months but younger than 11 months of age at randomization, were assigned to separate study cohorts on the basis of preexisting sensitivity to peanut extract, which was determined with the use of a skin-prick test — one consisting of participants with no measurable wheal after testing and the other consisting of those with a wheal measuring 1 to 4 mm in diameter. The primary outcome, which was assessed independently in each cohort, was the proportion of participants with peanut allergy at 60 months of age.

RESULTS

Among the 530 infants in the intention-to-treat population who initially had negative results on the skin-prick test, the prevalence of peanut allergy at 60 months of age was 13.7% in the avoidance group and 1.9% in the consumption group (P<0.001). Among the 98 participants in the intention-to-treat population who initially had positive test results, the prevalence of peanut allergy was 35.3% in the avoidance group and 10.6% in the consumption group (P=0.004). There was no significant between-group difference in the incidence of serious adverse events. Increases in levels of peanut-specific IgG4 antibody occurred predominantly in the consumption group; a greater percentage of participants in the avoidance group had elevated titers of peanut-specific IgE antibody. A larger wheal on the skin-prick test and a lower ratio of peanut-specific IgG4:IgE were associated with peanut allergy.

CONCLUSIONS

The early introduction of peanuts significantly decreased the frequency of the development of peanut allergy among children at high risk for this allergy and modulated immune responses to peanuts. (Funded by the National Institute of Allergy and Infectious Diseases and others; ClinicalTrials.gov number, NCT00329784.)

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*A complete list of members of the Learning Early about Peanut Allergy (LEAP) Study Team is provided in the Supplementary Appendix, available at NEJM.org.

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EDITORIALS

Preventing Peanut Allergy through Early Consumption — Ready for Prime Time?

Rebecca S. Gruchalla, M.D., Ph.D., and Hugh A. Sampson, M.D.

Kids can't take peanut butter to school. Some airlines no longer serve peanuts because of fear of anaphylaxis among passengers. These developments are just the tip of the iceberg as the prevalence of peanut allergy among children continues to increase worldwide, especially in westernized countries. In the United States alone, the prevalence has more than quadrupled in the past 13 years, growing from 0.4% in 1997 to 1.4% in 2008[1] to more than 2% in 2010.[2] Peanut allergy has become the leading cause of anaphylaxis and death related to food allergy in the United States.[3]

In 2000, largely in response to outcomes reported in infant feeding trials conducted in Europe and the United States, the American Academy of Pediatrics (AAP) recommended that parents refrain from feeding peanuts to infants at risk for the development of atopic disease until the children reached 3 years of age.[4] However, since the number of cases of peanut allergy continued to rise, many investigators and clinicians began questioning this advice. In 2008, after reviewing the published literature, the AAP retracted its recommendation, stating that there was insufficient evidence to call for early food avoidance.[5] Shortly thereafter, Du Toit et al.[6] noted that the prevalence of peanut allergy among Jewish children in London who were not given peanut-based products in the first year of life was 10 times as high as that among Jewish children in Israel who had consumed peanut-based products before their first birthday. In addition, subsequent studies that evaluated the early introduction of other allergenic foods, including egg[7] and cow's milk,[8] showed that earlier introduction of egg and milk into an infant's diet was associated with a decrease in the development of allergy.

But since these studies were observational, we needed data from controlled trials to provide reliable clinical guidance regarding the best time to introduce allergenic foods (e.g., milk, egg, peanuts, and tree nuts) to infants at high risk for the development of allergies (i.e., those from atopic families). Du Toit et al.[9] now address this question in the *Journal* in their landmark study, Learning Early about Peanut Allergy (LEAP). The investigators hypothesized that early introduction of peanut-based products (before 11 months of age) would lead to the prevention of peanut allergy in high-risk infants. More than 500 infants at high risk for peanut allergy were randomly assigned to receive peanut products (consumption group) or to avoid them (avoidance group). Approximately 10% of children, in whom a wheal measuring more than 4 mm developed after they received a peanut-specific skin-prick test, were excluded from the study because of concerns that they would have severe reactions. At 5 years of age, the children were given a peanut challenge to determine the prevalence of peanut allergy. The results are striking — overall, the prevalence of peanut allergy in the peanut-avoidance group was 17.2% as compared with 3.2% in the consumption group.

The trial was designed to examine two groups — children who had negative results on the peanut skin-prick test at enrollment (nonsensitized) and those who had "mild" sensitization at enrollment (wheals with mean diameters of 1 to 4 mm in response to the test). In these two groups the

results on the prevalence of peanut allergy were equally striking. Among the children who initially had a negative result on the skin-prick test, the prevalence of peanut allergy was 13.7% in the avoidance group and 1.9% in the consumption group, and among those who had mild sensitization the prevalence was 35.3% in the avoidance group versus 10.6% in the consumption group. Thus, early consumption was effective not only in high-risk infants who showed no indication of peanut sensitivity at study entry (primary prevention) but also in infants who had slight peanut sensitivity (secondary prevention).

Du Toit et al. carefully defined their high-risk population, which included children with severe eczema, egg allergy, or both. Moreover, they determined whether these infants were sensitized to peanut at study entry and then challenged those in the peanut-consumption group to ensure that these children were unresponsive before sending them home to consume peanut-based products on a regular basis.

Given the results of this prospective, randomized trial, which clearly indicates that the early introduction of peanut dramatically decreases the risk of development of peanut allergy (approximately 70 to 80%), should the guidelines be changed? Should we recommend introducing peanuts to all infants before they reach 11 months of age? Unfortunately, the answer is not that simple, and many questions remain unanswered: Do infants need to ingest 2 g of peanut protein (approximately eight peanuts) three times a week on a regular basis for 5 years, or will it suffice to consume lesser amounts on a more intermittent basis for a shorter period of time? If regular peanut consumption is discontinued for a prolonged period, will tolerance persist? Can the findings of the LEAP study be applied to other foods, such as milk, eggs, and tree nuts?

These questions must be addressed, but we believe that because the results of this trial are so compelling, and the problem of the increasing prevalence of peanut allergy so alarming, new guidelines should be forthcoming very soon. In the meantime, we suggest that any infant between 4 months and 8 months of age believed to be at risk for peanut allergy should undergo skin-prick testing for peanut. If the test results are negative, the child should be started on a diet that includes 2 g of peanut protein three times a week for at least 3 years, and if the results are positive but show mild sensitivity (i.e., the wheal measures 4 mm or less), the child should undergo a food challenge in which peanut is administered and the child's response observed by a physician who has experience performing a food challenge. Children who are nonreactive should then be started on the peanut-containing diet. Although other studies are urgently needed to address the many questions that remain, especially with respect to other foods, the LEAP study makes it clear that we can do something now to reverse the increasing prevalence of peanut allergy.

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

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ORIGINAL ARTICLE

Association of Improved Air Quality with Lung Development in Children

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ABSTRACT

BACKGROUND

Air-pollution levels have been trending downward progressively over the past several decades in southern California, as a result of the implementation of air quality–control policies. We assessed whether long-term reductions in pollution were associated with improvements in respiratory health among children.

METHODS

As part of the Children's Health Study, we measured lung function annually in 2120 children from three separate cohorts corresponding to three separate calendar periods: 1994–1998, 1997–2001, and 2007–2011. Mean ages of the children within each cohort were 11 years at the beginning of the period and 15 years at the end. Linear-regression models were used to examine the relationship between declining pollution levels over time and lung-function development from 11 to 15 years of age, measured as the increases in forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) during that period (referred to as 4-year growth in FEV_1 and FVC).

RESULTS

Over the 13 years spanned by the three cohorts, improvements in 4-year growth of both FEV_1 and FVC were associated with declining levels of nitrogen dioxide ($P<0.001$ for FEV_1 and FVC) and of particulate matter with an aerodynamic diameter of less than 2.5 μm ($P=0.008$ for FEV_1 and $P<0.001$ for FVC) and less than 10 μm ($P<0.001$ for FEV_1 and FVC). These associations persisted after adjustment for several potential confounders. Significant improvements in lung-function development were observed in both boys and girls and in children with asthma and children without asthma. The proportions of children with clinically low FEV_1 (defined as <80% of the predicted value) at 15 years of age declined significantly, from 7.9% to 6.3% to 3.6% across the three periods, as the air quality improved ($P=0.001$).

CONCLUSIONS

We found that long-term improvements in air quality were associated with statistically and clinically significant positive effects on lung-function growth in children. (Funded by the Health Effects Institute and others.)

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EDITORIAL

Cleaner Air, Bigger Lungs

Douglas W. Dockery, Sc.D., and James H. Ware, Ph.D.

In the latter half of the 20th century, Los Angeles had, by many measures, higher levels of photochemical air pollutants than any other major city in the United States (Fig. 1). To address this problem, the California Air Resources Board and its partners became leaders in quantifying the health effects of air pollutants and in aggressively implementing pollution-control strategies.

Even with these actions, air-pollution levels remained high. In 1993, "Health Advisories" were issued on 92 days.[1] In that year, the prospective Children's Health Study was launched to examine the effects of air pollution on lung growth in children. Fourth-grade children were recruited from 12 communities in southern California with varying exposures to the pollutants of concern (ozone, nitrogen dioxide, and particulate matter). Repeated lung-function measurements were taken for these children for 8 years, the period of life during which the greatest growth of lung function occurs.

In this first cohort, children living in more polluted communities had lower cumulative lung growth during the follow-up period.[2] These results were important clinically because even modest reductions in attained lung function at maturity are predictive of respiratory disease, coronary heart disease, and reduced life expectancy.[3]

Of course, such an association does not prove causality. However, the case for a causal relationship can be strengthened by consistent evidence from repeated studies. To that end, Gauderman and his colleagues enrolled two additional cohorts of children from the Children's Health Study and found consistent associations between community air pollution and lung-function growth in the children recruited in 1993,[2] 1997,[4] and 2003.[5]

The consistency of findings in the three separate cohorts is compelling. Moreover, the investigators sought to minimize the potential for confounding by controlling for known individual and community predictors of lung-function growth. Nevertheless, unmeasured or imperfectly measured characteristics of these communities, such as differences in ethnic background or socioeconomic status, may have confounded these analyses and produced a false positive association.

Although lung-function growth and potential confounders were measured for each child, air-pollution exposures were based on community means. Such studies have been described as "semi-individual"[6] with respect to the exposure variables. Thus, these analyses could also have been influenced by differences in community characteristics not captured in the individual data. A community is more than the aggregate of individual characteristics.[7]

In this issue of the *Journal*, Gauderman et al.[8] examine the association between improvements in air quality and changes in lung-function growth from 11 to 15 years of age across these three cohorts of children. They show that 4-year growth in forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) improved as levels of air pollution (nitrogen dioxide and particulate matter with an aerodynamic diameter of <2.5 μm [$PM_{2.5}$] and <10 μm [PM_{10}]) declined in five of these communities.

This study provides corroborating information because the analyses are based on comparisons within communities and thus are not con-

founded by differences between communities. The potential confounders of these temporal comparisons are characteristics of the communities that changed during the period of study. Recall that, to be a confounder, a variable must be associated with both air-pollution levels and lung-function growth. The advantage of these complementary approaches is that characteristics of the communities are less likely to confound both spatial and temporal comparisons.

In the original Children's Health Study cohort design, communities were selected to represent extremes of exposure to particulate matter, nitrogen dioxide, and ozone air pollution. For example, in 1994 mean concentrations of $PM_{2.5}$ ranged from 31.5 μg per cubic meter (in Mira Loma) to 6.7 μg per cubic meter (in Santa Maria), and the nitrogen dioxide level ranged from 36.4 ppb (in Long Beach) to 2.7 ppb (in Lompoc).[9] Between 1994 and 2010, the period analyzed by Gauderman et al., changes in $PM_{2.5}$ and nitrogen dioxide levels within the five study communities approached the between-community differences in 1994. For example, the mean $PM_{2.5}$ level improved from 31.5 μg per cubic meter (1994–1997) to 17.8 μg per cubic meter (2007–2010) in Mira Loma, and the nitrogen dioxide level improved from 34.4 ppb (1994–1997) to 20.3 ppb (2007–2010) in Long Beach. Temporal changes in ozone, however, were modest.

These results suggest that the children born after air-pollution levels had declined in these communities had greater lung-function growth. These investigators had previously shown, in a relatively small number of children, that participants who moved out of the study area to cleaner communities had improved lung-function growth, whereas those who moved to more polluted communities had reduced growth.[10] This raises the possibility that some of the loss of lung function associated with exposure to air pollution is reversible.

In recent years, much of the research on the effects of community air pollution has focused on premature death and on clinical events such as myocardial infarctions or hospital admissions. Because these events occur primarily among older adults, there has been less interest in intermediate physiological (subclinical) measures. Nevertheless, there is growing awareness of the effects of early life events on the risk of adult-onset chronic diseases. Reduced lung function is a powerful predictor not only of chronic respiratory disease in adults but also of chronic cardiovascular disease. The reported net deficits in lung function in children living in the more polluted communities may provide a partial explanation for the associations between air-pollution levels and mortality rates observed both in southern California[11] and nationally.[12]

Some have argued that the substantial improvements in air quality over the past 40 years are sufficient to protect public health and that there is little evidence to support more stringent standards. However, the current report and other studies suggest that further improvement in air quality may have beneficial public health effects.

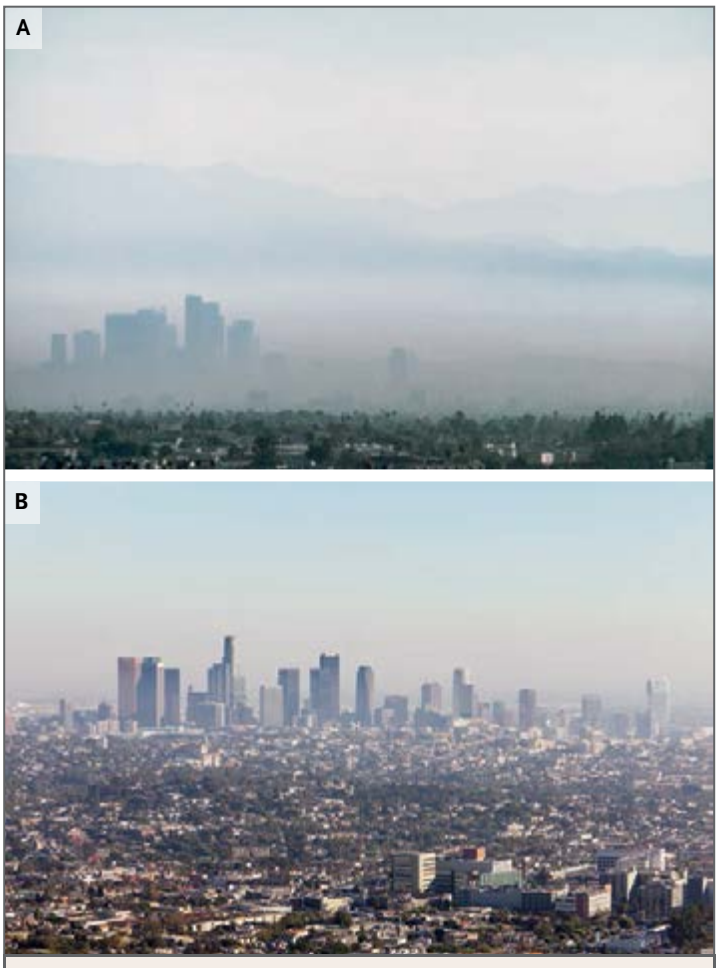

Figure 1. Pollution in Los Angeles.
Los Angeles is shown in the late 1980s (Panel A) and in 2014 (Panel B).

Ted Spiegel/Corbis (Panel A), Ted Soqui/Corbis (Panel B)

Four decades ago, most Americans were exposed to much higher levels of air pollution than those observed today. At that time, it was difficult to find communities with little or no exposure, which limited the ability of investigators to determine a "no-effect level." With the improvements in air quality, observational studies can now assess the benefits of reductions in air-pollution exposure into the range below those historical levels. These new observational studies often show that there are health benefits associated with improvements in air quality even when the pollution levels are within a range previously thought to be safe.

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ORIGINAL ARTICLE

Community-Acquired Pneumonia Requiring Hospitalization among U.S. Adults

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ABSTRACT

BACKGROUND

Community-acquired pneumonia is a leading infectious cause of hospitalization and death among U.S. adults. Incidence estimates of pneumonia confirmed radiographically and with the use of current laboratory diagnostic tests are needed.

METHODS

We conducted active population-based surveillance for community-acquired pneumonia requiring hospitalization among adults 18 years of age or older in five hospitals in Chicago and Nashville. Patients with recent hospitalization or severe immunosuppression were excluded. Blood, urine, and respiratory specimens were systematically collected for culture, serologic testing, antigen detection, and molecular diagnostic testing. Study radiologists independently reviewed chest radiographs. We calculated population-based incidence rates of community-acquired pneumonia requiring hospitalization according to age and pathogen.

RESULTS

From January 2010 through June 2012, we enrolled 2488 of 3634 eligible adults (68%). Among 2320 adults with radiographic evidence of pneumonia (93%), the median age of the patients was 57 years (interquartile range, 46 to 71); 498 patients (21%) required intensive care, and 52 (2%) died. Among 2259 patients who had radiographic evidence of pneumonia and specimens available for both bacterial and viral testing, a pathogen was detected in 853 (38%): one or more viruses in 530 (23%), bacteria in 247 (11%), bacterial and viral pathogens in 59 (3%), and a fungal or mycobacterial pathogen in 17 (1%). The most common pathogens were human rhinovirus (in 9% of patients), influenza virus (in 6%), and *Streptococcus pneumoniae* (in 5%). The annual incidence of pneumonia was 24.8 cases (95% confidence interval, 23.5 to 26.1) per 10,000 adults, with the highest rates among adults 65 to 79 years of age (63.0 cases per 10,000 adults) and those 80 years of age or older (164.3 cases per 10,000 adults). For each pathogen, the incidence increased with age.

CONCLUSIONS

The incidence of community-acquired pneumonia requiring hospitalization was highest among the oldest adults. Despite current diagnostic tests, no pathogen was detected in the majority of patients. Respiratory viruses were detected more frequently than bacteria. (Funded by the Influenza Division of the National Center for Immunizations and Respiratory Diseases.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Jain at the Centers for Disease Control and Prevention, 1600 Clifton Rd. NE, MS A-32, Atlanta, GA 30333, or at bwc8@cdc.gov.

*A complete list of members of the Centers for Disease Control and Prevention (CDC) Etiology of Pneumonia in the Community (EPIC) Study Team is provided in the Supplementary Appendix, available at NEJM.org.

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ORIGINAL ARTICLE

Idarucizumab for Dabigatran Reversal

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ABSTRACT

BACKGROUND

Specific reversal agents for non–vitamin K antagonist oral anticoagulants are lacking. Idarucizumab, an antibody fragment, was developed to reverse the anticoagulant effects of dabigatran.

METHODS

We undertook this prospective cohort study to determine the safety of 5 g of intravenous idarucizumab and its capacity to reverse the anticoagulant effects of dabigatran in patients who had serious bleeding (group A) or required an urgent procedure (group B). The primary end point was the maximum percentage reversal of the anticoagulant effect of dabigatran within 4 hours after the administration of idarucizumab, on the basis of the determination at a central laboratory of the dilute thrombin time or ecarin clotting time. A key secondary end point was the restoration of hemostasis.

RESULTS

This interim analysis included 90 patients who received idarucizumab (51 patients in group A and 39 in group B). Among 68 patients with an elevated dilute thrombin time and 81 with an elevated ecarin clotting time at baseline, the median maximum percentage reversal was 100% (95% confidence interval, 100 to 100). Idarucizumab normalized the test results in 88 to 98% of the patients, an effect that was evident within minutes. Concentrations of unbound dabigatran remained below 20 ng per milliliter at 24 hours in 79% of the patients. Among 35 patients in group A who could be assessed, hemostasis, as determined by local investigators, was restored at a median of 11.4 hours. Among 36 patients in group B who underwent a procedure, normal intraoperative hemostasis was reported in 33, and mildly or moderately abnormal hemostasis was reported in 2 patients and 1 patient, respectively. One thrombotic event occurred within 72 hours after idarucizumab administration in a patient in whom anticoagulants had not been reinitiated.

CONCLUSIONS

Idarucizumab completely reversed the anticoagulant effect of dabigatran within minutes. (Funded by Boehringer Ingelheim; RE-VERSE AD ClinicalTrials.gov number, NCT02104947.)

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EDITORIALS

Targeted Anti-Anticoagulants

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Four direct oral anticoagulants have been approved for use in many countries. These drugs are valuable alternatives to vitamin K antagonists, such as warfarin, for many patients requiring anticoagulation to prevent stroke due to nonvalvular atrial fibrillation and to treat and prevent venous thromboembolism. The mechanism of these agents is to selectively inhibit either thrombin or factor Xa, which are critical enzymes in the common pathway of blood coagulation. Dabigatran etexilate inhibits thrombin, whereas apixaban, edoxaban, and rivaroxaban inhibit factor Xa.

Direct oral anticoagulants have several pharmacologic advantages over vitamin K antagonists, including a wider therapeutic window, a rapid onset of action, and shorter half-lives that range between 7 hours and 14 hours in healthy persons. Direct oral anticoagulants are administered at fixed doses to adults without laboratory monitoring, which is more convenient than warfarin with its requirement for monitoring of the international normalized ratio and periodic dose adjustments. In randomized trials with good anticoagulation management (i.e., with international normalized ratios generally in the desired therapeutic range of 2 to 3 for >60% of the time), direct oral anticoagulants were noninferior, and in some cases superior, to dose-adjusted warfarin for the prevention and treatment of thrombosis. As compared with warfarin, direct oral anticoagulants reduced the rate of major bleeding by 28% and the rates of intracranial and fatal hemorrhage by 50%.[1]

Despite the better bleeding profile of direct oral anticoagulants, as compared with warfarin, some physicians and patients have been unwilling to consider these drugs in the absence of an established way to reverse their anticoagulant activity. Although the anticoagulant activity of warfarin can be reversed with vitamin K, fresh-frozen plasma, and prothrombin complex concentrates, major bleeding events that occur in patients taking this drug often lead to poor outcomes; approximately 10% of patients who are hospitalized with warfarin-related bleeding die within 90 days,[2,3] and the mortality among patients with intracranial hemorrhage can be as high as 50%.[4,5] The high mortality is attributable in part to coexisting conditions in this patient population. Experimental data suggest that nonspecific reversal agents such as prothrombin complex concentrates, activated prothrombin complex concentrates, or recombinant factor VIIa can reduce the anticoagulant effect of direct oral anticoagulants in vitro, in animal models, and in human volunteers.[6] However, these agents are of unproven benefit in improving hemostasis in patients with bleeding related to direct oral anticoagulant use, and they carry a risk of thrombosis; thus, they are currently reserved for patients with severe bleeding who cannot be treated with supportive measures.

With the growing use of direct oral anticoagulants, it would be advantageous to have reversal agents that can rapidly and completely neutralize the anticoagulant activity of the drug and restore normal hemostasis. Specific reversal agents in clinical development include andexanet alfa, a recombinant factor Xa variant that specifically binds all the oral factor Xa inhibitors but lacks coagulant activity.[7] There is also a nonspecific reversal agent in clinical development, PER977, which binds to several of the direct oral anticoagulants by means of electrostatic interactions.[8] Given that there are no

established reversal strategies for the direct oral anticoagulants, it is appropriate to undertake clinical trials of these agents without a control group.

Idarucizumab is a humanized monoclonal antibody fragment with high affinity for the oral direct thrombin inhibitor dabigatran that selectively and immediately neutralizes its anticoagulant activity.[9] Pollack et al.[10] now report in the *Journal* the results of an interim analysis of data from 90 patients who were taking dabigatran and who presented with either serious bleeding or the need for urgent surgery or intervention and received intravenous idarucizumab. This multicenter observational study evaluated the effect of a single 5-g dose of antibody in eligible patients who were judged by the treating clinician to require a reversal agent. The major end points of the study were pharmacodynamic assessments of the ability of idarucizumab to neutralize the anticoagulant activity of dabigatran. The data are convincing that the antidote effectively and immediately neutralized the activity of dabigatran with a satisfactory safety profile. Normal hemostasis was reported in more than 90% of the patients who underwent procedures after the administration of idarucizumab.

Without a control group, it is difficult to assess the clinical benefit that is conferred by the administration of idarucizumab in patients with dabigatran-related bleeding. The mortality in the study population was high at 20%; half the deaths occurred more than 96 hours after the administration of the antidote and were attributable to coexisting illness. Given that the half-life of dabigatran is 12 to 14 hours if renal function is normal, how important is it to be able to neutralize the anticoagulant activity of dabigatran rapidly in addition to providing supportive care measures? Major bleeding events in patients taking anticoagulants originate from anatomical lesions, and anticoagulation can lead to a rapid loss of blood from these sites. Thus, the location and size of the lesion along with the coexisting conditions of the patient may have a greater effect on prognosis than the ability to rapidly neutralize an anticoagulant that the patient is taking.

Laboratory measurements of the concentration of dabigatran were performed centrally in this study and were not used to guide therapy. The results of one of these tests, the dilute thrombin time, were normal on study entry in nearly one quarter of the study population. This group of patients had little or no circulating anticoagulant in their blood and would not be expected to benefit from the administration of idarucizumab. Thus, it will be useful to have activity measurements available for the various direct oral anticoagulants in real time to help guide the treatment of such patients and to prevent overutilization of what will surely be a costly medication.

The development of antidotes that are able to neutralize the activity of the various direct oral anticoagulants rapidly and completely is an important advance. When they become available, guidelines and clinical pathways will need to be developed to care effectively for patients with, or at risk for, major bleeding related to direct oral anticoagulant use. Additional studies, however, will be required to determine in which situations the antidotes improve clinical outcomes.

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ORIGINAL ARTICLE

Screening for Occult Cancer in Unprovoked Venous Thromboembolism

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ABSTRACT

BACKGROUND

Venous thromboembolism may be the earliest sign of cancer. Currently, there is a great diversity in practices regarding screening for occult cancer in a person who has an unprovoked venous thromboembolism. We sought to assess the efficacy of a screening strategy for occult cancer that included comprehensive computed tomography (CT) of the abdomen and pelvis in patients who had a first unprovoked venous thromboembolism.

METHODS

We conducted a multicenter, open-label, randomized, controlled trial in Canada. Patients were randomly assigned to undergo limited occult-cancer screening (basic blood testing, chest radiography, and screening for breast, cervical, and prostate cancer) or limited occult-cancer screening in combination with CT. The primary outcome measure was confirmed cancer that was missed by the screening strategy and detected by the end of the 1-year follow-up period.

RESULTS

Of the 854 patients who underwent randomization, 33 (3.9%) had a new diagnosis of occult cancer between randomization and the 1-year follow-up: 14 of the 431 patients (3.2%) in the limited-screening group and 19 of the 423 patients (4.5%) in the limited-screening-plus-CT group (P=0.28). In the primary outcome analysis, 4 occult cancers (29%) were missed by the limited screening strategy, whereas 5 (26%) were missed by the strategy of limited screening plus CT (P=1.0). There was no significant difference between the two study groups in the mean time to a cancer diagnosis (4.2 months in the limited-screening group and 4.0 months in the limited-screening-plus-CT group, P=0.88) or in cancer-related mortality (1.4% and 0.9%, P=0.75).

CONCLUSIONS

The prevalence of occult cancer was low among patients with a first unprovoked venous thromboembolism. Routine screening with CT of the abdomen and pelvis did not provide a clinically significant benefit. (Funded by the Heart and Stroke Foundation of Canada; SOME ClinicalTrials.gov number, NCT00773448.)

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EDITORIAL

Cancer Workup after Unprovoked Clot — Less Is More

Alok A. Khorana, M.D.

Consider this not unfamiliar scenario: a 56-year-old educator presents with sudden onset of swelling and pain in the right thigh. She has no coexisting conditions except for well-controlled hypertension and has no family history of thrombophilia. She is admitted to the hospital after compression ultrasonography reveals the presence of a femoral-vein thrombosis. There are no provoking factors such as recent surgery or hospitalization. The phrase "possible cancer" is brought up on rounds, despite the patient's recent normal results on colonoscopy and mammography. The patient is anxious about undiagnosed cancer and asks whether extensive imaging to rule out cancer is needed.

This important clinical question is at the heart of a well-conducted randomized trial now reported in the *Journal*.[1] Unprovoked cases represent more than 40% of all venous thromboembolisms.[2] Epidemiologic studies have consistently shown that a portion of unprovoked events are associated with undiagnosed cancer; an analysis of more than 500,000 Californians showed a standardized incidence ratio of 1.3 unprovoked venous events (95% confidence interval, 1.2 to 1.5) 1 year before cancer diagnosis.[3] A systematic review showed that the period prevalence of previously undiagnosed cancer in this context was 6.1% at baseline and 10.0% from baseline to 12 months.[4]

Subjecting patients to an extensive diagnostic workup could alter their clinical course: an earlier cancer diagnosis might lead to earlier and more effective treatment and would also affect anticoagulant choice. Prior studies have investigated the effect of extensive testing for cancer in this context but with suboptimal study design and sample sizes.[5,6] Indeed, a 2015 Cochrane systematic review was able to identify only two randomized or quasi-randomized studies involving a total of 396 patients.[7] It concluded that there was insufficient evidence regarding the effectiveness of testing for undiagnosed cancer in reducing cancer-related and venous-thromboembolism–related morbidity and mortality and that the results could be consistent with either harm or benefit.

In this context, the current report substantially fills existing knowledge gaps. Carrier et al. randomly assigned patients across nine Canadian centers to either a limited screening strategy involving standard age- and sex-specific screening or to an extensive strategy that added computed tomography (CT) of the abdomen and pelvis. It should be noted that the latter test was an enhanced version of the standard clinical scan and included a virtual colonoscopy and gastroscopy as well as parenchymal pancreatography. Among 854 patients, 3.2% of the patients in the limited-screening group and 4.5% of the patients in the extensive-screening group had a new diagnosis of cancer between randomization and the 1-year follow-up — rates that were lower than anticipated. The primary outcome of the study was the number of cancers "missed" at the initial screening but diagnosed by the end of the 1-year follow-up period. Here, too, the numbers were encouraging: only 4 patients (0.93%) in the limited-screening group and 5 (1.18%) in the extensive-screening group had a cancer detected after the completion of the initial screening. In other words, the risk of subsequent cancer was also quite low, and "doing more" did not lead to earlier cancer detection. Furthermore, secondary outcome analyses found no significant between-group differences in the time to

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cancer diagnosis, overall mortality, or cancer-related mortality.

One limitation of this study is generalizability: the mean age of the study population was 54 years, whereas in the California study cited earlier, the mean age at cancer diagnosis was 66 years.[3] An older study population would have had a greater prevalence of cancer. A second concern relates to whether the extensive screening was extensive enough. CT of the chest was not mandated; however, roughly 25% of patients had undergone such testing for diagnostic workup of pulmonary embolism, and no subsequent lung-cancer cases were diagnosed. Finally, the limited screening may have been too limited. Surprisingly, only 6.7% of the patients 50 years of age or older in the limited-screening group underwent colorectal-cancer screening, and no cancers were found; in contrast, the extensive screening strategy (which mandated virtual colonoscopy) identified three colorectal cancers. This limitation, however, supports the null hypothesis and if valid would only strengthen the conclusions of the study.

Thus, despite these concerns, the study results should do much to reassure our patient described above who has already had appropriate screening that the risk of the subsequent discovery of cancer is roughly only 1% during the next year. Additional testing would be unlikely to provide benefit and may cause harm by exposing the patient to unnecessary radiation. For decades, we have led ourselves to believe that doing more is doing better for our patients. In this context and many others, clinicians would do well to recall Robert Browning's admonishment, channeling the voice of the eponymous failed painter in his poem *Andrea del Sarto*: "Yet do much less, so much less, . . . — so much less! Well, less is more."

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ORIGINAL ARTICLE

A Randomized, Controlled Trial of Total Knee Replacement

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ABSTRACT

BACKGROUND

More than 670,000 total knee replacements are performed annually in the United States; however, high-quality evidence to support the effectiveness of the procedure, as compared with nonsurgical interventions, is lacking.

METHODS

In this randomized, controlled trial, we enrolled 100 patients with moderate-to-severe knee osteoarthritis who were eligible for unilateral total knee replacement. Patients were randomly assigned to undergo total knee replacement followed by 12 weeks of nonsurgical treatment (total-knee-replacement group) or to receive only the 12 weeks of nonsurgical treatment (nonsurgical-treatment group), which was delivered by physiotherapists and dietitians and consisted of exercise, education, dietary advice, use of insoles, and pain medication. The primary outcome was the change from baseline to 12 months in the mean score on four Knee Injury and Osteoarthritis Outcome Score subscales, covering pain, symptoms, activities of daily living, and quality of life ($KOOS_4$); scores range from 0 (worst) to 100 (best).

RESULTS

A total of 95 patients completed the 12-month follow-up assessment. In the nonsurgical-treatment group, 13 patients (26%) underwent total knee replacement before the 12-month follow-up; in the total-knee-replacement group, 1 patient (2%) received only nonsurgical treatment. In the intention-to-treat analysis, the total-knee-replacement group had greater improvement in the $KOOS_4$ score than did the nonsurgical-treatment group (32.5 vs. 16.0; adjusted mean difference, 15.8 [95% confidence interval, 10.0 to 21.5]). The total-knee-replacement group had a higher number of serious adverse events than did the nonsurgical-treatment group (24 vs. 6, P=0.005).

CONCLUSIONS

In patients with knee osteoarthritis who were eligible for unilateral total knee replacement, treatment with total knee replacement followed by nonsurgical treatment resulted in greater pain relief and functional improvement after 12 months than did nonsurgical treatment alone. However, total knee replacement was associated with a higher number of serious adverse events than was nonsurgical treatment, and most patients who were assigned to receive nonsurgical treatment alone did not undergo total knee replacement before the 12-month follow-up. (Funded by the Obel Family Foundation and others; MEDIC ClinicalTrials.gov number, NCT01410409.)

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EDITORIALS

Parachutes and Preferences — A Trial of Knee Replacement

Jeffrey N. Katz, M.D.

The term parachute trial entered the medical lexicon to depict studies of treatments everyone already assumes to be effective. (In other words, do we need a trial to show that parachutes save the lives of persons who jump from airplanes?[1]) The parachute trial has been invoked to decry randomized trials of total joint replacement as senseless. After all, joint replacements are among the most significant advances of the 20th century; don't we already know they are successful?

Nearly 1 million elective total knee and hip replacements are performed annually in the United States; rates of total knee replacement tripled in the past 20 years and are projected to increase further.[2,3] More than 90% of total knee replacements are performed for knee osteoarthritis, which affects approximately 14% of adults in the United States in their lifetimes.[4] Prior to the introduction of total knee replacement in the 1970s, patients with advanced knee osteoarthritis frequently became housebound; now such patients can remain mobile. By all accounts, total knee replacement is a game changer. So why subject it to a randomized, controlled trial?

First, total knee replacement poses risks. About 0.5 to 1% of patients die during the 90-day postoperative period. The risks of deep venous thrombosis, pulmonary embolus, deep prosthetic infection, and periprosthetic fracture range from 0.1 to 1.0%,[5-7] with higher risks among older persons and those with a higher number of coexisting conditions.[5,7] Second, the procedure is not universally successful; approximately 20% of patients who undergo total knee replacement have residual pain 6 or more months after the procedure.[8] Third, there are alternatives. Clinical trials have shown that physical therapy (including exercises and manual therapies) can diminish pain and improve functional status in patients with advanced knee osteoarthritis.[9-11] Until now, we have lacked rigorously controlled comparisons between total knee replacement and its alternatives.

Finally, an ideal treatment for one patient may not be right for the next. Patients with knee osteoarthritis differ in the importance they attach to pain relief, functional improvement, and risk of complications. Therefore, treatment decisions should be shared between patients and their clinicians and anchored by the probabilities of pain relief and complications and the importance patients attach to these outcomes.

These considerations set the stage for the carefully designed and executed trial by Skou et al., whose results are reported in this issue of the *Journal*.[12] In this randomized, controlled trial, involving 100 patients with symptomatic knee osteoarthritis, patients were assigned to undergo total knee replacement followed by a rigorous 12-week nonsurgical-treatment regimen (total-knee-replacement group) or to receive only the nonsurgical treatment (nonsurgical-treatment group), which consisted of supervised exercise, education, dietary advice, use of insoles, and pain medication. Total knee replacement proved markedly superior to nonsurgical treatment alone in terms of pain relief and functional improvement. The percentage of patients who had an improvement of at least 15% (a clinically important difference) in the score for pain after 1 year was 85% in the total-knee-replacement group and 68% in the nonsurgical-treatment group. In

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fact, 26% of patients in the nonsurgical-treatment group elected to undergo total knee replacement before the 12-month follow-up, and more patients are likely to cross over as follow-up extends further.

However, it is noteworthy that more than two thirds of the patients in the nonsurgical-treatment group had clinically meaningful improvements in the pain score and that this group had a lower risk of complications. In the total-knee-replacement group, several severe adverse events occurred, including three episodes of deep venous thrombosis, one deep infection, one supracondylar fracture, and three episodes of stiffness requiring manipulation of the knee while the patient was anesthetized. The nonsurgical-treatment group had one episode of stiffness requiring manipulation of the knee while the patient was anesthetized and none of the other complications. In short, although total knee replacement was clearly superior in terms of pain relief, these findings suggest that the decision for treatment with total knee replacement is no parachute at all. Patients face choices that are associated with different levels of symptomatic improvement and risk: as compared with nonsurgical treatment, total knee replacement is associated with a higher level of improvement and a higher risk of adverse events. Each patient must weigh these considerations and make the decision that best suits his or her values.

As with all good studies, this randomized, controlled trial answers some questions and raises others. Sham-controlled trials have suggested that both surgical therapy and physical therapy can have a potent placebo effect.[13,14] In the absence of an untreated control group, some of the improvement that was seen in both groups may be attributable to placebo effects. Also, we do not know whether the benefit of nonsurgical treatment will be sustained over time. Finally, the study by Skou et al. was too small to examine the efficacy of total knee replacement in relevant subgroups, such as patients with mild baseline pain and dysfunction.

The trial by Skou et al. provides the first rigorously controlled data to inform discussions between patients and their physicians about whether to undergo total knee replacement or rigorous nonsurgical therapy. For most patients, the dramatic pain relief associated with total knee replacement provides a compelling rationale to choose surgery. Other patients, particularly those who are more risk-averse, may prefer nonsurgical care. Since patients vary considerably in their preferences, physicians should present the relevant data to their patients and then listen carefully.

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ORIGINAL ARTICLE

Prospective Validation of a 21-Gene Expression Assay in Breast Cancer

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ABSTRACT

BACKGROUND

Prior studies with the use of a prospective–retrospective design including archival tumor samples have shown that gene-expression assays provide clinically useful prognostic information. However, a prospectively conducted study in a uniformly treated population provides the highest level of evidence supporting the clinical validity and usefulness of a biomarker.

METHODS

We performed a prospective trial involving women with hormone-receptor–positive, human epidermal growth factor receptor type 2 (HER2)–negative, axillary node–negative breast cancer with tumors of 1.1 to 5.0 cm in the greatest dimension (or 0.6 to 1.0 cm in the greatest dimension and intermediate or high tumor grade) who met established guidelines for the consideration of adjuvant chemotherapy on the basis of clinicopathologic features. A reverse-transcriptase–polymerase-chain-reaction assay of 21 genes was performed on the paraffin-embedded tumor tissue, and the results were used to calculate a score indicating the risk of breast-cancer recurrence; patients were assigned to receive endocrine therapy without chemotherapy if they had a recurrence score of 0 to 10, indicating a very low risk of recurrence (on a scale of 0 to 100, with higher scores indicating a greater risk of recurrence).

RESULTS

Of the 10,253 eligible women enrolled, 1626 women (15.9%) who had a recurrence score of 0 to 10 were assigned to receive endocrine therapy alone without chemotherapy. At 5 years, in this patient population, the rate of invasive disease–free survival was 93.8% (95% confidence interval [CI], 92.4 to 94.9), the rate of freedom from recurrence of breast cancer at a distant site was 99.3% (95% CI, 98.7 to 99.6), the rate of freedom from recurrence of breast cancer at a distant or local–regional site was 98.7% (95% CI, 97.9 to 99.2), and the rate of overall survival was 98.0% (95% CI, 97.1 to 98.6).

CONCLUSIONS

Among patients with hormone-receptor–positive, HER2-negative, axillary node–negative breast cancer who met established guidelines for the recommendation of adjuvant chemotherapy on the basis of clinicopathologic features, those with tumors that had a favorable gene-expression profile had very low rates of recurrence at 5 years with endocrine therapy alone. (Funded by the National Cancer Institute and others; ClinicalTrials.gov number, NCT00310180.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Sparano at the Department of Oncology, Montefiore Medical Center, 1695 Eastchester Rd., Bronx, NY 10461, or at jsparano@montefiore.org.

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EDITORIALS

Biology before Anatomy in Early Breast Cancer — Precisely the Point

Clifford A. Hudis, M.D.

Building on a foundation of clinical and laboratory observations, translational research, broad collaborations, and global education, adjuvant therapy for early-stage breast cancer has been an effective public health intervention. Standardization and even a one-size-fits-all philosophy were supported by individual trials and the worldwide overviews that showed proportional reductions in risk with chemotherapy in particular. Because higher risk, identified anatomically on the basis of tumor size or the presence of ipsilateral axillary nodal metastases, was associated with greater absolute therapeutic benefit, many clinical groups set risk thresholds, defined as a tumor size of 1 cm in the greatest dimension or any involved nodes, to guide chemotherapy use.[1]

However, we also began to recognize that we could take a different approach with both older (endocrine) and newer (anti–human epidermal growth factor receptor type 2 [HER2]) targeted treatments. Here we could be more biologically selective by using markers — which can be favorable or unfavorable prognostic factors — primarily for their predictive usefulness.[2] Predictive biomarkers can identify tumors that are more likely to respond to specific targeted treatments, and they allow us to avoid ineffective options. The inability to select similarly for or against chemotherapy use, coupled with the toxic effects, costs, and inconvenience of chemotherapy, has been a growing source of concern.

The initial publication in the *Journal* regarding the 21-gene assay (Oncotype Dx, Genomic Health) described its prognostic performance but did not establish clinical usefulness.[3] The world did not (and still does not) need yet another prognostic factor. Clinical usefulness was suggested later when this test was shown to be possibly predictive for chemotherapy benefit. The evidence came from two retrospective subgroup analyses of two different prospective, randomized clinical trials that tested combination chemotherapy added to standard endocrine treatment.[4,5] One study enrolled patients with node-negative disease, and the other enrolled patients with node-positive disease. All the patients received tamoxifen, and in both trials the patients with higher-score tumors (score of ≥31, on a scale from 0 to 100, with higher scores indicating a greater risk of recurrence) benefited from the addition of chemotherapy, whereas those with a score of less than 18 did not.

The limited validation provided by these retrospective subgroup analyses across traditional risk strata (including node-negative and node-positive disease) distinguished this prognostic and would-be predictive test from many others in development that might be equally or even more useful. Prospective trials were then launched to refine our understanding of the clinical usefulness of the assay. The first results from any of these trials, limited to a key subgroup, are now reported in the *Journal*.[6] These results cannot come soon enough, given the already widespread adoption of the test as a key component of guidelines and routine clinical decision making.[7-9]

As described by Sparano et al., an arbitrary and purposefully conservative decision was made in the first of these trials to limit any potential harms of omitting chemotherapy. This goal was accomplished by setting new, lower thresholds for risk-group assignment. Thus, we are con-

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fronted by a newly defined low-risk group of patients with a score of 10 or less (instead of <18). As reported, the study included 1626 endocrine-treated patients with hormone-receptor–positive, HER2-negative, node-negative tumors that measured a median of 1.5 cm in the greatest dimension. A very low event rate was seen, with a rate of freedom from recurrence of breast cancer at a distant site of 99.3% at 5 years. This result is numerically good enough to exclude any potentially meaningful benefit for additional chemotherapy.

For those seeking confirmation that this assay can identify a cohort of patients who should be spared chemotherapy, this result is both reassuring and frustrating. For patients in this new "lower risk" group, it is clearly helpful, if broadly anticipated. However, for the many physicians already using the test, the gap between this cutoff point of 10 and the higher "standard" cutoff point of 18 may be a concern. Some others will wonder whether chemotherapy is beneficial or indicated even in patients with scores up to 25. If chemotherapy is effective in this newly defined intermediate-risk group (score, 11 to 25), then examination of the subgroup of patients with scores of 11 to 17 will be critical, since there will be two conflicting guides to their treatment that need to be reconciled: the cutoff point used in this trial and the previously available cutoff point that is associated with the commercial test.

This multigene assay is unlikely to be the only test that can provide a prediction of chemotherapy benefit. A less expensive and broadly distributed test would be valuable globally. For now, however, this assay is the most rigorously tested option and provides proof of the principle that we can develop reproducible predictive tests to select patients who should not receive chemotherapy. In that regard, it is one more step toward precision. There are more steps ahead.

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ORIGINAL ARTICLE

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group*

ABSTRACT

BACKGROUND

The most appropriate targets for systolic blood pressure to reduce cardiovascular morbidity and mortality among persons without diabetes remain uncertain.

METHODS

We randomly assigned 9361 persons with a systolic blood pressure of 130 mm Hg or higher and an increased cardiovascular risk, but without diabetes, to a systolic blood-pressure target of less than 120 mm Hg (intensive treatment) or a target of less than 140 mm Hg (standard treatment). The primary composite outcome was myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes.

RESULTS

At 1 year, the mean systolic blood pressure was 121.4 mm Hg in the intensive-treatment group and 136.2 mm Hg in the standard-treatment group. The intervention was stopped early after a median follow-up of 3.26 years owing to a significantly lower rate of the primary composite outcome in the intensive-treatment group than in the standard-treatment group (1.65% per year vs. 2.19% per year; hazard ratio with intensive treatment, 0.75; 95% confidence interval [CI], 0.64 to 0.89; P<0.001). All-cause mortality was also significantly lower in the intensive-treatment group (hazard ratio, 0.73; 95% CI, 0.60 to 0.90; P=0.003). Rates of serious adverse events of hypotension, syncope, electrolyte abnormalities, and acute kidney injury or failure, but not of injurious falls, were higher in the intensive-treatment group than in the standard-treatment group.

CONCLUSIONS

Among patients at high risk for cardiovascular events but without diabetes, targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, resulted in lower rates of fatal and nonfatal major cardiovascular events and death from any cause, although significantly higher rates of some adverse events were observed in the intensive-treatment group. (Funded by the National Institutes of Health; ClinicalTrials.gov number, NCT01206062.)

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EDITORIALS

A SPRINT to the Finish

Jeffrey M. Drazen, M.D., Stephen Morrissey, Ph.D., Edward W. Campion, M.D., and John A. Jarcho, M.D.

When investigators enroll patients in a clinical study, they make an implicit contract with each participant. Through the data and safety monitoring board (DSMB) mechanism, they fulfill the first part of the contract — protecting the participant from avoidable harm that might result from participation in the trial. They fulfill the second part of the contract — the commitment to honor the time at risk that the participant spent in the trial — by deriving the clearest and most clinically directive information possible from the data gathered during the trial. This task takes tremendous time and energy.

The SPRINT (Systolic Blood Pressure Intervention Trial) investigators now report in the *Journal* the results of a National Institutes of Health (NIH)–sponsored trial studying the impact on major cardiovascular events of a lower systolic blood-pressure target in adults with hypertension.[1] To the surprise of many, the trial was stopped on September 11, 2015, years earlier than planned. The leadership of the National Heart, Lung, and Blood Institute (NHLBI) stopped the trial on the recommendation of the DSMB, which had identified a survival benefit in patients assigned to the lower blood-pressure target.

When the study was stopped, the NIH immediately notified the participants that those in the low-target group had done better than those in the usual-care control group; the public was also notified, although a full report of the study was not yet available. The investigators, who were also taken by surprise, then hunkered down to the serious business of understanding the available data, knowing that the data set they had would change, since close-out visits are still ongoing.

Although unraveling the clinical messages buried in a data set may sound like a simple task, it is not. Rarely does a trial's clinically important message jump out fully formed. Instead, the process requires detailed analyses that weigh the risks and benefits of the study intervention as translated into a clinical care setting.

The trial investigators are uniquely qualified to analyze the data, and their only agenda is a meticulous, fair, and informative reporting of the study results. Not only are they the ones who delineated the end points, crafted the inclusion and exclusion criteria, and collected the data, they are also the ones who best understand the adverse events. The process requires a deep knowledge of the study design and, most of all, time for scrupulous analysis and thoughtful reflection. Even in this rapid-fire information age, there is no substitute for serious thought, and that takes time.

We were therefore surprised by the call from Topol and Krumholz for immediately "placing the data on the NIH website."[2] We believe that it is critical to give the investigators, on behalf of the study participants, who invested years of their lives in the study, the opportunity to see what led the sponsor to stop the trial and then the opportunity to distill a clinical message from it. There are cogent reasons to follow this approach rather than put trial data in the public domain before those who gathered the data have had a chance to analyze it.

Although no one denies the importance of treating hypertension, the clinical message from

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SPRINT is a matter of public health urgency and not an emergency. The subtleties of the clinical message need to be teased from the data. To put the issue in perspective, the investigators took about 8 weeks to prepare their study for publication; they had previously spent over 250 weeks conducting the trial and perhaps another 50 to 100 weeks getting the trial ready to enroll patients at all. Through their perseverance and hard work, the data were accrued and an important clinical question has been addressed. The investigators have spent the past 5 years thinking about and working on the study question, and they are the ones best qualified to undertake the first interpretation of the data. Once their interpretation is in the public domain, scientific discourse on the strengths and weaknesses of the trial design, the gathered data, and the clinical directions should follow.

The manuscript reporting on SPRINT arrived in our office 4 weeks after the trial was stopped. That manuscript was reviewed rapidly by multiple outside peer reviewers, a statistical consultant, and several editors. Their critiques and queries led to two rounds of substantial revision. After expedited editing of the manuscript and preparation of the figures, the report has been published to coincide with the investigators' presentation at the meeting of the American Heart Association. Together with this important report, *Journal* readers have a pair of expert commentaries in an editorial and a Perspective article. There is also a short Quick Take video summary of the article and a Clinical Decisions article in which readers can participate in a poll and comment on the key questions and clinical concerns raised by SPRINT.

This clinical trial will change practice, and we are proud to publish it and to defend the importance of the expedited peer-review and publication process that it has undergone. The report is now in the public domain, and the investigators' data interpretation, analysis, and clinical discussion are open to examination and comment. We understand that in the months ahead the underlying data from this taxpayer-funded trial will be put in the public domain by the NHLBI. We agree with the importance of making those data open and available to others. But with the article now published, physicians and the public have a detailed, critical, peer-reviewed report from the investigators who conducted the study and know it best.

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EDITORIALS

Redefining Blood-Pressure Targets — SPRINT Starts the Marathon

Vlado Perkovic, M.B., B.S., Ph.D., and Anthony Rodgers, M.B., Ch.B., Ph.D.

Blood pressure is a potent determinant of cardiovascular risk, but the most appropriate targets for blood-pressure lowering have long been debated. Observational studies with a low risk of confounding have shown a linear relationship between blood pressure and cardiovascular risk down to 115/75 mm Hg,[1] but some observational studies with a greater potential for confounding, involving persons at increased risk, have suggested a J-shaped curve — that is, below a given blood pressure, risk would increase. When trials of blood-pressure–lowering drugs have shown benefits in patients without hypertension, these effects have often been ascribed to alternative mechanisms. The widespread uncertainty about blood-pressure targets was increased when the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial showed no significant overall difference in cardiovascular events between patients with type 2 diabetes assigned to a systolic blood-pressure target of less than 120 mm Hg and those assigned to a target of less than 140 mm Hg.[2]

The eagerly awaited results of the Systolic Blood Pressure Intervention Trial (SPRINT), now reported in the *Journal*,[3] are certain to have far-reaching implications. SPRINT randomly assigned 9361 persons with a systolic blood pressure of 130 mm Hg or higher and an increased cardiovascular risk to a target of less than 120 mm Hg (intensive treatment) or a target of less than 140 mm Hg (standard treatment). People with difficult-to-control blood pressure were excluded and will require separate study. The mean blood pressure at baseline was 139.7/78.2 mm Hg in the intensive-treatment group and 139.7/78.0 mm Hg in the standard-treatment group, and the mean pressure at 1 year was 121.4/68.7 mm Hg and 136.2/76.3 mm Hg in the respective groups. During follow-up, the average difference in systolic pressure was 13.1 mm Hg, and the mean number of blood-pressure medications was 2.8 in the intensive-treatment group and 1.8 in the standard-treatment group.

The trial was stopped early, after a median follow-up of 3.26 years. Overall, participants assigned to the intensive-treatment group, as compared with those assigned to the standard-treatment group, had a 25% lower relative risk of major cardiovascular events (95% confidence interval [CI], 11 to 36), with consistent results across subgroups defined according to age, sex, race, medical history, and baseline blood pressure. In addition, the intensive-treatment group had a 27% lower relative risk of death from any cause (95% CI, 10 to 40). Rates of some serious adverse events, including hypotension and acute kidney injury or failure, were higher in the intensive-treatment group than in the standard-treatment group, but these higher rates appear unlikely to outweigh the benefits overall.

Are the results reliable? Small trials can overestimate benefits when stopped early,[4] but this is unlikely for SPRINT, which had more than 500 primary outcome events. Lack of blinding is inevitable in trials involving blood-pressure targets,

but this was mitigated by structured assessment of outcomes and adverse events. Some findings require further elucidation and follow-up, particularly the renal outcomes. The lack of effect on injurious falls will surprise many but is consistent with the finding of the largest trial involving the elderly.[5]

Are the results of SPRINT different from those of the ACCORD trial? As shown in Fig. 1, the effects on individual outcomes in SPRINT and the ACCORD trial are generally consistent. The main differences were that the ACCORD trial had less statistical power than SPRINT, and its primary outcome included a higher proportion of events that are less sensitive to blood-pressure reduction. Previous trials have also shown similar-sized benefits in persons with diabetes and those without diabetes.[6] More broadly, labeling trials as "positive" or "negative" is seductive but ultimately counterproductive; it is more helpful to look at the totality of available data. Several previous large trials of blood-pressure lowering[7,8] included participants at high cardiovascular risk, about half of whom had a baseline systolic blood pressure below 140 mm Hg. These trials also showed benefits for people with a pressure of at least 140 mm Hg and those with a pressure below 140 mm Hg. The benefits seen in SPRINT are also consistent with those seen in previous trials of more intensive versus less intensive blood-pressure control[9] and, more broadly, in previous trials in which differences in blood pressure were achieved between groups.[1]

SPRINT provides another cautionary reminder about using data from nonrandomized trials or biologic plausibility to assess efficacy and safety. We are reminded that real-world data, such as J-curve associations, can be really wrong. Randomized trials are required to reliably assess treatment effects. SPRINT also brings into focus approaches to synthesizing trial evidence for guidelines. The Eighth Joint National Committee took a targeted approach to consideration of previous trials and concluded that systolic blood-pressure targets should be below 140 mm Hg, or below 150 mm Hg in those 60 years of age or older. More inclusive trial reviews have indicated benefits of blood-pressure lowering in persons at high cardiovascular risk without hypertension.[1] Current guidelines and guideline processes require revision.

Clearly, our current concept of hypertension is insufficient to determine who benefits from blood-pressure lowering or how far to lower blood pressure.[10] SPRINT strongly supports pharmacotherapy decisions based on absolute risk levels, in a similar way to current recommendations for lipid lowering. For people at high cardiovascular risk, a systolic goal of less than 120 mm Hg is appropriate. Substantial effort and resources are required: initial combination therapy was the norm in SPRINT, with monthly visits until blood pressure was at the target level. Even with intensive lifestyle modification and medical therapy, blood pressure will remain above target in many patients, which suggests the need for population-level initiatives (e.g., reduced sodium content in food), new therapies, and multifactorial intervention. In SPRINT, less than half the patients were taking statins, 13% were still smoking, and most were overweight or obese.

SPRINT redefines blood-pressure target goals and challenges us to improve blood-pressure management. Success will require a marathon effort.

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ORIGINAL ARTICLE

Trial of Continuous or Interrupted Chest Compressions during CPR

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ABSTRACT

BACKGROUND

During cardiopulmonary resuscitation (CPR) in patients with out-of-hospital cardiac arrest, the interruption of manual chest compressions for rescue breathing reduces blood flow and possibly survival. We assessed whether outcomes after continuous compressions with positive-pressure ventilation differed from those after compressions that were interrupted for ventilations at a ratio of 30 compressions to two ventilations.

METHODS

This cluster-randomized trial with crossover included 114 emergency medical service (EMS) agencies. Adults with non–trauma-related cardiac arrest who were treated by EMS providers received continuous chest compressions (intervention group) or interrupted chest compressions (control group). The primary outcome was the rate of survival to hospital discharge. Secondary outcomes included the modified Rankin scale score (on a scale from 0 to 6, with a score of ≤3 indicating favorable neurologic function). CPR process was measured to assess compliance.

RESULTS

Of 23,711 patients included in the primary analysis, 12,653 were assigned to the intervention group and 11,058 to the control group. A total of 1129 of 12,613 patients with available data (9.0%) in the intervention group and 1072 of 11,035 with available data (9.7%) in the control group survived until discharge (difference, −0.7 percentage points; 95% confidence interval [CI], −1.5 to 0.1; P=0.07); 7.0% of the patients in the intervention group and 7.7% of those in the control group survived with favorable neurologic function at discharge (difference, −0.6 percentage points; 95% CI, −1.4 to 0.1, P=0.09). Hospital-free survival was significantly shorter in the intervention group than in the control group (mean difference, −0.2 days; 95% CI, −0.3 to −0.1; P=0.004).

CONCLUSIONS

In patients with out-of-hospital cardiac arrest, continuous chest compressions during CPR performed by EMS providers did not result in significantly higher rates of survival or favorable neurologic function than did interrupted chest compressions. (Funded by the National Heart, Lung, and Blood Institute and others; ROC CCC ClinicalTrials.gov number, NCT01372748.)

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*A complete list of the Resuscitation Outcomes Consortium (ROC) Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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EDITORIALS

Continuous or Interrupted Chest Compressions for Cardiac Arrest

Rudolph W. Koster, M.D., Ph.D.

High-quality cardiopulmonary resuscitation (CPR) is identified as a critical but often poorly performed component of the rescue efforts for patients in cardiac arrest. Chest compressions have often been too shallow, and compression rates too low or too high. Prolonged interruptions of chest compressions have been observed during resuscitation both in the hospital and outside the hospital.[1,2] All prolonged pauses (not only those for defibrillation) are associated with worse survival.[3] Interruptions of chest compressions cause a rapid decline in coronary perfusion pressure, reducing myocardial blood flow, which has previously been shown with shorter interruptions for rescue breathing.[4] Experiments in animals have suggested that the rate of survival may increase if CPR is performed with continuous chest compressions, not interrupted for ventilations. Retrospective cohort studies have seemed to confirm this concept. A prospective statewide observational study in Arizona showed that training the population in continuous chest compressions until the arrival of emergency medical services (EMS) increased the rate of bystander-initiated CPR and increased the rate of survival to discharge from the hospital.[5]

Randomized studies involving patients with cardiac arrest are difficult and require considerable resources that are often not available. In the EMS setting, the concept of continuous chest compressions has been introduced and its potential benefit has been studied in observational studies with historical controls. In the largest of these studies, several measures were introduced simultaneously as a "bundle of care." In addition to three periods of 200 chest compressions each, which were interrupted only for rhythm analysis and defibrillation, this bundle of care included a single-shock scenario (three stacked shocks were allowed previously), no delay of chest compressions for rhythm or pulse checks, deferred insertion of an advanced-airway device, and passive oxygen insufflation replacing positive-pressure ventilation until 6 minutes had passed during which the three periods of 200 chest compressions were delivered. The introduction of this bundle of care resulted in a significant increase in the rate of survival to discharge, from 1.8% to 5.4%; among patients with witnessed arrest and ventricular fibrillation, the rate increased from 4.7% to 17.6%.[6] On the basis of this study and similar studies, the 2015 American Heart Association (AHA) guidelines for resuscitation included a new class IIb recommendation that it may be reasonable for EMS to initiate resuscitation with three initial periods of 200 continuous chest compressions with passive oxygen insufflation.[7] This recommendation was not made in the concurrent 2015 guidelines for resuscitation from the European Resuscitation Council (ERC).[8]

Bundles of care are a pragmatic way to introduce and study new treatments. But if studies show higher rates of survival with the new techniques, it is not clear which components of the bundle contributed to the improved survival. The results of a new randomized clinical trial from the Resuscitation Outcomes Consortium (ROC) have now been published in the *Journal*.[9] This trial was designed as a cluster-randomized study of non–trauma-related cardiac arrest treated by

EMS providers. Patients received either continuous chest compressions or the standard approach of chest compressions that were interrupted for positive-pressure ventilation in a ratio of 30 compressions to two ventilations (termed "interrupted chest compressions"). In the group that received continuous chest compressions, asynchronous positive-pressure ventilations were given with a recommended rate of 10 ventilations per minute. The primary outcome of the study was the rate of survival to hospital discharge.

A total of 12,653 patients were included in the group that received continuous chest compressions (intervention group) and 11,058 in the group that received interrupted chest compressions (control group). The overall rate of survival to hospital discharge was 9.0% in the intervention group and 9.7% in the control group — a nonsignificant difference. Survival with favorable neurologic function at discharge, defined as a score of 3 or less on the modified Rankin scale (on which scores range from 0, indicating no symptoms, to 6, indicating death), did not differ significantly between the two groups. A prespecified per-protocol analysis that was based on strict adherence to the treatment algorithm showed significantly lower rates of survival among patients in the intervention group than among those in the control group (7.6% vs. 9.6%).

Why did this new large, randomized study show no benefit from continuous chest compressions, whereas previous observational studies showed a clear survival benefit among patients treated with this approach? First, in the bundle-of-care studies, measures other than the continuous chest compressions could be the changes that improved the rate of survival. Second, in this study, the mean chest-compression fraction (the proportion of each minute during which compressions were given), which is an important marker of interruptions of chest compressions, was already high (0.77) in the control group and was not much lower than the mean chest-compression fraction of 0.83 in the intervention group. Both values were much higher than the target for chest-compression fraction of more than 0.60 that is recommended in the new AHA and ERC resuscitation guidelines.[7,8] Third, pauses for ventilation may be less critical, and less detrimental for survival, than is currently believed.[10] And of course, the randomized trial is the best tool to investigate causality.

The new 2015 AHA resuscitation guidelines were published only recently.[7] If the results of the current ROC study had been available, the guidelines committee might have decided to retain the previous recommendation to give chest compressions interrupted for ventilations and perhaps even to upgrade that recommendation to a class IIa recommendation for EMS providers. Should the AHA reconsider their recommendation?

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ORIGINAL ARTICLE

Sofosbuvir and Velpatasvir for HCV Genotype 1, 2, 4, 5, and 6 Infection

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ABSTRACT

BACKGROUND

A simple treatment regimen that is effective in a broad range of patients who are chronically infected with the hepatitis C virus (HCV) remains an unmet medical need.

METHODS

We conducted a phase 3, double-blind, placebo-controlled study involving untreated and previously treated patients with chronic HCV genotype 1, 2, 4, 5, or 6 infection, including those with compensated cirrhosis. Patients with HCV genotype 1, 2, 4, or 6 were randomly assigned in a 5:1 ratio to receive the nucleotide polymerase inhibitor sofosbuvir and the NS5A inhibitor velpatasvir in a once-daily, fixed-dose combination tablet or matching placebo for 12 weeks. Because of the low prevalence of genotype 5 in the study regions, patients with genotype 5 did not undergo randomization but were assigned to the sofosbuvir–velpatasvir group. The primary end point was a sustained virologic response at 12 weeks after the end of therapy.

RESULTS

Of the 624 patients who received treatment with sofosbuvir–velpatasvir, 34% had HCV genotype 1a, 19% genotype 1b, 17% genotype 2, 19% genotype 4, 6% genotype 5, and 7% genotype 6. A total of 8% of patients were black, 19% had cirrhosis, and 32% had been previously treated for HCV. The rate of sustained virologic response among patients receiving sofosbuvir–velpatasvir was 99% (95% confidence interval, 98 to >99). Two patients receiving sofosbuvir–velpatasvir, both with HCV genotype 1, had a virologic relapse. None of the 116 patients receiving placebo had a sustained virologic response. Serious adverse events were reported in 15 patients (2%) in the sofosbuvir–velpatasvir group and none in the placebo group.

CONCLUSIONS

Once-daily sofosbuvir–velpatasvir for 12 weeks provided high rates of sustained virologic response among both previously treated and untreated patients infected with HCV genotype 1, 2, 4, 5, or 6, including those with compensated cirrhosis. (Funded by Gilead Sciences; ClinicalTrials.gov number, NCT02201940.)

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

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EDITORIALS

Simple, Effective, but Out of Reach? Public Health Implications of HCV Drugs

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The results of four clinical trials showing the excellent safety and efficacy of a 12-week course of sofosbuvir (an NS5B inhibitor licensed in the United States in 2013) and velpatasvir (a new NS5A inhibitor) in treating patients with hepatitis C infection (HCV) are reported now in the *Journal*.[1-3] In two of these studies, ASTRAL-1 and ASTRAL-2, 97 to 100% of patients with HCV genotype 1a, 1b, 2, 4, 5, or 6 had a sustained virologic response at 12 weeks after the end of therapy, a marker that is indicative of virologic cure. Similar efficacy was observed among patients in whom previous treatment had failed and those with compensated cirrhosis, factors that have been associated with a reduced response to the treatment of HCV infection.[4]

In the ASTRAL-3 study, sofosbuvir–velpatasvir was 95% efficacious in achieving a sustained virologic response among patients with genotype 3 (the viral strain associated with a reduced treatment response).[4] Efficacy was 89 to 91% for patients with cirrhosis or previous treatment failure.

In these three studies, sofosbuvir–velpatasvir was associated with few serious adverse events, high study-completion rates, and rates of sustained virologic response that were superior to those with selected study comparators. In addition, the data suggest that the pretreatment presence of NS5A resistance-associated variants was not a major factor in treatment outcomes but that more study is needed, particularly in patients with genotype 3.

For HCV-infected patients with decompensated cirrhosis, ASTRAL-4 showed 94% efficacy with the addition of ribavirin, as compared with a sustained virologic response of 83% for the 12-week regimen of sofosbuvir–velpatasvir alone. The proportions of patients with serious adverse events were similar across treatment regimens (16 to 19%). Indicators of liver function improved in nearly half the patients. Together, these studies indicate that this drug regimen can achieve high rates of HCV cure regardless of genotype.

The public health implications of simple, safe, and curative HCV therapies could be profound. HCV chronically infects 2.7 million to 3.5 million persons in the United States and 130 million to 150 million persons globally,[5,6] causing more than 700,000 deaths from cirrhosis or primary liver cancer worldwide every year.[6] In the United States, the rate of new HCV infection has risen by more than 150% in recent years, fueled by increases in injection-drug use.[6] HCV treatment could dramatically reverse these trends. A cure of HCV infection reduces the risk of liver cancer by 76% and of death from any cause by 50%. Theoretically, such a cure could reduce the force of infection and HCV transmission within a population.[7,8] Given the benefits of safe, simple, and curative therapy, why are we still concerned about the public's health with respect to HCV treatment?

Patients do not benefit from a drug they cannot afford. Although studies by the Centers for Disease Control and Prevention have shown that treating all HCV-infected persons is cost-effective from a societal perspective,[9] the price of current medications is a formidable barrier for many. Despite U.S. recommendations that all HCV-infected persons should receive treatment,[10] health plans and payers have responded to the cost of HCV medications ($83,000 to $153,000

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per course of treatment) by instituting restrictive reimbursement policies. In 33 state Medicaid programs, only patients in whom the infection has progressed to severe liver disease qualify for HCV treatment.[11] Drug expenditures for the treatment of HCV infection have declined as a result of mandated 23% rebates for Medicaid and privately negotiated prices by health plans, but inequities in patient access to such therapies persist.

In response, on November 5, 2015, the Centers for Medicare and Medicaid Services (CMS) notified state programs that limitations on drug coverage should not deny access to clinically appropriate antiviral therapy for beneficiaries with chronic HCV infection. CMS also requested that manufacturers disclose value-based pricing agreements so that states can participate in such arrangements.[6] Globally, a generic version of sofosbuvir has been licensed for use in 91 low-resource countries.[12] Access to these drugs is also a challenge in middle-income countries, in which more than 60% of HCV-infected persons reside.[13] Licensure of sofosbuvir–velpatasvir and other HCV regimens that are now being studied creates opportunities for innovative pricing strategies that increase affordability of new HCV medications and of those already on the market.

Benefits of curative therapy can be realized only for persons who have been tested and know they are infected with HCV. In the United States, HCV infection remains undiagnosed in at least half of all persons with the disease,[7] and the proportions are even higher in other countries.[14] A combination of testing strategies is recommended to identify persons with ongoing transmission risks (e.g., those who inject drugs) and those who were infected in the distant past who are at highest risk for dying from HCV infection. In the United States, even a modest increase in the capacity to implement HCV testing for all persons who were born from 1945 through 1965 could avert more than 320,000 deaths[9] but only when testing is linked to care and curative treatment.

The progressive steps in HCV care from viral detection to HCV cure are poor in the United States and in many other countries.[11,14] Education for providers and creation of models for care improve quality.[6,7] Although currently licensed therapies require that HCV-infected persons undergo genotyping and disease staging before the initiation of treatment, most HCV-infected persons do not receive this level of care. The sofosbuvir–velpatasvir regimen could simplify HCV management by reducing the need for these steps, paving the way for simple "test and cure" strategies appropriate for primary care and other settings, such as addiction-treatment programs.

The availability of simple, safe, and curative regimens creates opportunities for improving the health of the millions of patients living with HCV infection. At a population level, the effect of HCV medications will be determined by affordability and equitable access to HCV testing, care, and treatment. Only through these improvements can our focus be directed to what matters most: reducing the morbidity and mortality associated with HCV infection, stopping HCV transmission, and ultimately eliminating HCV as a public health threat in the United States and worldwide.

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

From the Centers for Disease Control and Prevention, Atlanta.

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