The NEW ENGLAND JOURNAL of MEDICINE

DRAZEN'S DOZEN: ARTICLES THAT CHANGED PRACTICE SINCE 2000

NEJM GROUP

The NEW ENGLAND JOURNAL of MEDICINE

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Dear Reader,

It's been nearly 19 years since I edited my first issue of the *New England Journal of Medicine*. Since then, both medical science and medical publishing have undergone many changes.

But one constant for me has been the privilege each week of evaluating and, through the review and editing process, publishing some of the best, most creative, and most important biomedical research of our time. This has been the most rewarding part of my job.

Since 2000, our editors have evaluated over 80,000 submissions of original research and published nearly 4,000 of these studies. The vast majority of the published articles have strong implications for patient care or understanding disease biology.

In the coming months, I will retire from my role as editor-in-chief of the *Journal*. As I reflect on nearly two decades of research and advances that we have published, the articles that stand out the most are those that we physicians can act upon immediately to improve, and in some cases save, the lives of patients.

Here, we present Drazen's Dozen: My curated choice of practice-changing and lifesaving papers from the past 19 years. All present actionable information that you can use right now with your patients to address some of the most common diseases. A few highlights:

- One thing we can all do that will save lives is to encourage colonoscopic screening with polypectomy. Colonoscopy was common practice, with a long-suspected survival benefit, for years. But not until the study published in 2012 did we have direct evidence that colonoscopy combined with polypectomy could prevent cancer deaths. After a mean period of nearly 16 years, mortality from colorectal cancer in study subjects was 53% lower among those who had undergone colonoscopy and had adenomas removed than in a reference group.
- In 2015 we learned that for patients with acute ischemic stroke and proximal occlusion in the anterior circulation, intraarterial treatment (delivery of a thrombolytic agent, mechanical thrombectomy, or both) administered within 6 hours after stroke onset is safe, effective and can improve functional independence in daily life. In effect, we could *reverse the pathology* of an acute cerebrovascular event. Today, many people are leading high-functioning lives (myself included) in whom a stroke a decade or two earlier would have resulted in more dire outcomes.
- In just a few years, Hepatitis C has transformed from a disease with challenging, minimally successful treatments to one with a simple, safe, and curative treatment. A study published in December 2015 showed that once-daily use of a drug combination for 12 weeks provided high rates of sustained virologic response among patients infected with five HCV genotypes. This could profoundly reduce the risk of liver cancer and death, but affordability and access to care remain a challenge.

In 2000, I could not have predicted some of these changes. Nor would they have come about without diligent investigators and the patients who put themselves at risk for the sake of research.

We don't know exactly what lies ahead in the evolution of biomedical science and patient care. But you can be sure I will be following, alongside you, the most significant advances and new studies as they appear in the *New England Journal of Medicine*.

I hope our efforts have made it possible for you to serve your patients more effectively. It has been an honor to share your time and attention.

Sincerely,
Jeffrey M. Drazen, M.D.
Editor-in-Chief, The New England Journal of Medicine

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The NEW ENGLAND JOURNAL of MEDICINE

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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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EDITORIAL

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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1. Sicherer SH, Muñoz-Furlong A, Godbold JH, Sampson HA. US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow-up. J Allergy Clin Immunol 2010;125:1322-6.
2. Bunyavanich S, Rifas-Shiman SL, Platts-Mills TA, et al. Peanut allergy prevalence among school-age children in a US cohort not selected for any disease. J Allergy Clin Immunol 2014;134:753-5.
3. Sampson HA. Peanut allergy. N Engl J Med 2002;346:1294-9.
4. American Academy of Pediatrics, Committee on Nutrition. Hypoallergenic infant formulas. Pediatrics 2000;106:346-9.
5. Greer FR, Sicherer SH, Burks AW. Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. Pediatrics 2008;121:183-91.
6. Du Toit G, Katz Y, Sasieni P, et al. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. J Allergy Clin Immunol 2008;122:984-91.
7. Koplin JJ, Osborne NJ, Wake M, et al. Can early introduction of egg prevent egg allergy in infants? A population-based study. J Allergy Clin Immunol 2010;126:807-13.
8. Katz Y, Rajuan N, Goldberg MR, et al. Early exposure to cow's milk protein is protective against IgE-mediated cow's milk protein allergy. J Allergy Clin Immunol 2010;126:77-82.
9. Du Toit G, Roberts G, Sayre PH, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med 2015;372:803-13.

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Apixaban versus Warfarin in Patients with Atrial Fibrillation

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ABSTRACT

BACKGROUND

Vitamin K antagonists are highly effective in preventing stroke in patients with atrial fibrillation but have several limitations. Apixaban is a novel oral direct factor Xa inhibitor that has been shown to reduce the risk of stroke in a similar population in comparison with aspirin.

METHODS

In this randomized, double-blind trial, we compared apixaban (at a dose of 5 mg twice daily) with warfarin (target international normalized ratio, 2.0 to 3.0) in 18,201 patients with atrial fibrillation and at least one additional risk factor for stroke. The primary outcome was ischemic or hemorrhagic stroke or systemic embolism. The trial was designed to test for noninferiority, with key secondary objectives of testing for superiority with respect to the primary outcome and to the rates of major bleeding and death from any cause.

RESULTS

The median duration of follow-up was 1.8 years. The rate of the primary outcome was 1.27% per year in the apixaban group, as compared with 1.60% per year in the warfarin group (hazard ratio with apixaban, 0.79; 95% confidence interval [CI], 0.66 to 0.95; P<0.001 for noninferiority; P=0.01 for superiority). The rate of major bleeding was 2.13% per year in the apixaban group, as compared with 3.09% per year in the warfarin group (hazard ratio, 0.69; 95% CI, 0.60 to 0.80; P<0.001), and the rates of death from any cause were 3.52% and 3.94%, respectively (hazard ratio, 0.89; 95% CI, 0.80 to 0.99; P=0.047). The rate of hemorrhagic stroke was 0.24% per year in the apixaban group, as compared with 0.47% per year in the warfarin group (hazard ratio, 0.51; 95% CI, 0.35 to 0.75; P<0.001), and the rate of ischemic or uncertain type of stroke was 0.97% per year in the apixaban group and 1.05% per year in the warfarin group (hazard ratio, 0.92; 95% CI, 0.74 to 1.13; P=0.42).

CONCLUSIONS

In patients with atrial fibrillation, apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality. (Funded by Bristol-Myers Squibb and Pfizer; ARISTOTLE ClinicalTrials.gov number, NCT00412984.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Granger at the Duke Clinical Research Institute, Duke University Medical Center, DUMC Box 3850, Durham, NC 27715, or at christopher.granger@duke.edu.

*The members of the steering committee, as well as other committee members and investigators in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) study, are listed in the Supplementary Appendix, available at NEJM.org.

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EDITORIAL

A New Era for Anticoagulation in Atrial Fibrillation

Jessica L. Mega, M.D., M.P.H.

For more than 50 years, warfarin has been the primary medication used to reduce the risk of thromboembolic events in patients with atrial fibrillation. Despite its clinical efficacy, warfarin has multiple, well-known limitations, including numerous interactions with other drugs and the need for regular blood monitoring and dose adjustments. Thus, clinicians and patients have been eager to embrace alternative oral anticoagulants that are equally efficacious but easier to administer.

In this issue of the *Journal*, Granger and colleagues report the impressive primary results of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial (ARISTOTLE; ClinicalTrials.gov number, NCT00412984).[1] A total of 18,201 subjects with atrial fibrillation and at least one additional risk factor for stroke were enrolled in the trial and were randomly assigned to receive the direct factor Xa inhibitor apixaban (at a dose of 5 mg twice daily) or warfarin (target international normalized ratio [INR], 2.0 to 3.0). The trial was designed to test whether apixaban was noninferior to warfarin with respect to efficacy. The investigators found that apixaban was not only noninferior to warfarin, but actually superior, reducing the risk of stroke or systemic embolism by 21% and the risk of major bleeding by 31%. In predefined hierarchical testing, apixaban, as compared with warfarin, also reduced the risk of death from any cause by 11%.

These results come on the heels of two other, large, phase 3 trials in which novel anticoagulants were compared with warfarin in patients with atrial fibrillation: the Randomized Evaluation of Long-Term Anticoagulation Therapy trial (RE-LY, NCT00262600)[2] and Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF, NCT00403767).[3] The RE-LY trial evaluated the direct thrombin inhibitor dabigatran in two different doses, 110 mg and 150 mg, both administered twice daily. ROCKET AF evaluated the direct factor Xa inhibitor rivaroxaban at a dose of 20 mg once daily.

The trials have a number of similar conclusions. Apixaban, dabigatran, and rivaroxaban, as compared with warfarin, all significantly reduce the risk of hemorrhagic stroke. In fact, in all the studies, the reductions in the primary efficacy end point — which included hemorrhagic as well as ischemic stroke — were greatly influenced by this dramatic reduction in the risk of hemorrhagic stroke. Of the three drugs, only dabigatran at a dose of 150 mg holds the distinction of also having significantly reduced the risk of ischemic stroke as compared with warfarin; nonetheless, even in this case, there was a greater influence on hemorrhagic stroke than on ischemic cerebrovascular events. Similarly, the risk of particularly serious bleeding was reduced with each of the three drugs, as compared with warfarin, and apixaban therapy also resulted in lower rates of all major bleeding. Thus, the newer anticoagulants boast favorable bleeding profiles as compared with warfarin in patients with atrial fibrillation.

There is also a shared theme with respect to mortality. Apixaban is the first of the newer anticoagulants to show a significant reduction in the risk of death from any cause as compared with warfarin (hazard ratio, 0.89; 95% confidence interval [CI], 0.80 to 0.99; P=0.047). Although the current findings are notable, both dabigatran and rivaroxaban, as compared with warfarin, showed similar directional trends. In the RE-LY trial, there was a borderline reduction in the risk of death from any cause with dabigatran at a dose of 150 mg, as compared with warfarin (hazard ratio, 0.88; 95% CI, 0.77 to 1.00; P=0.051). Similar trends in the risk of death from any cause were observed with rivaroxaban in the intention-to-treat analysis in ROCKET AF (hazard ratio, 0.92; 95% CI, 0.82 to 1.03; P=0.15). Thus, there is approximately a 10% reduction in the risk of death from any cause across these three trials in which the newer anticoagulants were compared

with warfarin in patients with atrial fibrillation.

Despite these similarities, there are important differences in the design of the studies and in the administration of the drugs. In the RE-LY trial, the assignments to dabigatran or warfarin were not concealed. In contrast, the ROCKET AF and ARISTOTLE trials successfully achieved a double-blind design. In the RE-LY and ARISTOTLE trials, dabigatran and apixaban were administered twice daily; in ROCKET AF, rivaroxaban was administered once daily. Subjects in the RE-LY and ARISTOTLE trials could have only one additional risk factor for stroke, whereas ROCKET AF enrolled a higher-risk population. The mean percentage of time in which the INR was in the therapeutic range of 2.0 to 3.0 — a metric that assesses the quality of warfarin dosing — was 64% in the RE-LY trial, 55% in the ROCKET AF trial, and 62% in the ARISTOTLE trial. There were additional differences among the studies with respect to their statistical analysis plans and power. These factors highlight the challenges with cross-trial comparisons. Head-to-head studies, which are not currently available, would allow for direct assessments among these novel compounds.

Will these newer anticoagulants be better than warfarin for the treatment of all patients with atrial fibrillation? The direct thrombin and factor Xa inhibitors overcome the need for routine blood monitoring, and the trial results have been encouraging overall and across important subgroups. For example, in the ARISTOTLE trial, the efficacy of apixaban was consistent in subgroups according to baseline stroke risk and according to whether patients had or had not been taking warfarin before entering the study. However, switching to a newer agent may not be necessary for the individual patient in whom the INR has been well controlled with warfarin for years. In addition, although the newer anticoagulants have a more rapid onset and termination of anticoagulant action than does warfarin, agents to reverse the effect of the drugs are still under development and are not routinely available.

In addition, generic warfarin is expected to be markedly less expensive than the newer agents even after the costs associated with regular INR monitoring are considered. One analysis has suggested that dabigatran, as compared with warfarin, could be cost-effective in patients with atrial fibrillation.[4] Additional data on cost-effectiveness are likely to further influence clinical decision making. Thus, although the oral direct thrombin and factor Xa inhibitors are attractive alternatives, it is likely that warfarin will continue to be used worldwide in many patients with atrial fibrillation.

The original mission to replace warfarin began with a search for drugs that were simply noninferior to warfarin. The ARISTOTLE trial, in conjunction with the RE-LY and ROCKET AF trials, suggests that apixaban, dabigatran, and rivaroxaban have gone even further. Across three large studies with different populations of patients with atrial fibrillation, the direct thrombin and factor Xa inhibitors have been shown to have a more favorable bleeding profile than warfarin and are at least as efficacious. Information about another direct factor Xa inhibitor, edoxaban, in patients with atrial fibrillation, will be available at the conclusion of the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction Study 48 (ENGAGE AF-TIMI 48, NCT00781391).[5] After all this time, a new era of anticoagulation appears to be emerging for patients with atrial fibrillation.

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

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1. Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981-92.
2. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361:1139-51. [Erratum, N Engl J Med 2010;363:1877.]
3. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011; 365:883-91.
4. Freeman JV, Zhu RP, Owens DK, et al. Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in atrial fibrillation. Ann Intern Med 2011;154:1-11.
5. Ruff CT, Giugliano RP, Antman EM, et al. Evaluation of the novel factor Xa inhibitor edoxaban compared with warfarin in patients with atrial fibrillation: design and rationale for the Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation-Thrombolysis In Myocardial Infarction study 48 (ENGAGE AF-TIMI 48). Am Heart J 2010;160:635-41.

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REDUCTION IN THE INCIDENCE OF TYPE 2 DIABETES WITH LIFESTYLE INTERVENTION OR METFORMIN

DIABETES PREVENTION PROGRAM RESEARCH GROUP*

ABSTRACT

Background Type 2 diabetes affects approximately 8 percent of adults in the United States. Some risk factors — elevated plasma glucose concentrations in the fasting state and after an oral glucose load, overweight, and a sedentary lifestyle — are potentially reversible. We hypothesized that modifying these factors with a lifestyle-intervention program or the administration of metformin would prevent or delay the development of diabetes.

Methods We randomly assigned 3234 nondiabetic persons with elevated fasting and post-load plasma glucose concentrations to placebo, metformin (850 mg twice daily), or a lifestyle-modification program with the goals of at least a 7 percent weight loss and at least 150 minutes of physical activity per week. The mean age of the participants was 51 years, and the mean body-mass index (the weight in kilograms divided by the square of the height in meters) was 34.0; 68 percent were women, and 45 percent were members of minority groups.

Results The average follow-up was 2.8 years. The incidence of diabetes was 11.0, 7.8, and 4.8 cases per 100 person-years in the placebo, metformin, and lifestyle groups, respectively. The lifestyle intervention reduced the incidence by 58 percent (95 percent confidence interval, 48 to 66 percent) and metformin by 31 percent (95 percent confidence interval, 17 to 43 percent), as compared with placebo; the lifestyle intervention was significantly more effective than metformin. To prevent one case of diabetes during a period of three years, 6.9 persons would have to participate in the lifestyle-intervention program, and 13.9 would have to receive metformin.

Conclusions Lifestyle changes and treatment with metformin both reduced the incidence of diabetes in persons at high risk. The lifestyle intervention was more effective than metformin. (N Engl J Med 2002; 346:393-403.)

TYPE 2 diabetes mellitus, formerly called non-insulin-dependent diabetes mellitus, is a serious, costly disease affecting approximately 8 percent of adults in the United States.[1] Treatment prevents some of its devastating complications[2,3] but does not usually restore normoglycemia or eliminate all the adverse consequences. The diagnosis is often delayed until complications are present.[4] Since current methods of treating diabetes remain inadequate, prevention is preferable. The hypothesis that type 2 diabetes is preventable[5,6] is supported by observational studies and two clinical trials of diet, exercise, or both in persons at high risk for the disease[7,8] but not by studies of drugs used to treat diabetes.[5]

The validity of generalizing the results of previous prevention studies is uncertain.[9] Interventions that work in some societies may not work in others, because social, economic, and cultural forces influence diet and exercise. This is a special concern in the United States, where there is great regional and ethnic diversity in lifestyle patterns and where diabetes is especially frequent in certain racial and ethnic groups, including American Indians, Hispanics, African Americans, Asians, and Pacific Islanders.[10]

The Diabetes Prevention Program Research Group conducted a large, randomized clinical trial involving adults in the United States who were at high risk for the development of type 2 diabetes. The study was designed to answer the following primary questions: Does a lifestyle intervention or treatment with

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The NEW ENGLAND JOURNAL of MEDICINE

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Colonoscopic Polypectomy and Long-Term Prevention of Colorectal-Cancer Deaths

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ABSTRACT

BACKGROUND

In the National Polyp Study (NPS), colorectal cancer was prevented by colonoscopic removal of adenomatous polyps. We evaluated the long-term effect of colonoscopic polypectomy in a study on mortality from colorectal cancer.

METHODS

We included in this analysis all patients prospectively referred for initial colonoscopy (between 1980 and 1990) at NPS clinical centers who had polyps (adenomas and nonadenomas). The National Death Index was used to identify deaths and to determine the cause of death; follow-up time was as long as 23 years. Mortality from colorectal cancer among patients with adenomas removed was compared with the expected incidence-based mortality from colorectal cancer in the general population, as estimated from the Surveillance Epidemiology and End Results (SEER) Program, and with the observed mortality from colorectal cancer among patients with nonadenomatous polyps (internal control group).

RESULTS

Among 2602 patients who had adenomas removed during participation in the study, after a median of 15.8 years, 1246 patients had died from any cause and 12 had died from colorectal cancer. Given an estimated 25.4 expected deaths from colorectal cancer in the general population, the standardized incidence-based mortality ratio was 0.47 (95% confidence interval [CI], 0.26 to 0.80) with colonoscopic polypectomy, suggesting a 53% reduction in mortality. Mortality from colorectal cancer was similar among patients with adenomas and those with nonadenomatous polyps during the first 10 years after polypectomy (relative risk, 1.2; 95% CI, 0.1 to 10.6).

CONCLUSIONS

These findings support the hypothesis that colonoscopic removal of adenomatous polyps prevents death from colorectal cancer. (Funded by the National Cancer Institute and others.)

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N Engl J Med 2012;366:687-96.

EDITORIAL

Colonoscopy as a Triage Screening Test

Michael Bretthauer, M.D., Ph.D., and Mette Kalager, M.D.

Colorectal cancer is the third most common cancer worldwide. The lifetime risk of colorectal cancer in the United States is approximately 5%. Clinical symptoms develop late in the course of the disease, and precursor lesions (adenomas) can be easily detected and removed. The disease is a candidate for early detection and prevention by screening. This issue of the *Journal* features two important studies that shed light on a number of interesting features in screening for colorectal cancer.[1,2]

Zauber and colleagues present long-term follow-up data on mortality from colorectal cancer from the National Polyp Study.[1] After a mean period of 15.8 years, mortality from colorectal cancer was 53% lower among patients who had undergone colonoscopy and had adenomas removed than in a reference group from the Surveillance, Epidemiology, and End Results (SEER) Program (absolute risk, 0.8% vs. 1.5%). Interestingly, the risk of death from colorectal cancer was similarly low in the adenoma cohort and a concurrent nonadenoma cohort during the first 10 years of follow-up, when a strict surveillance strategy was applied for patients with adenomas, but the risk increased for patients with adenomas thereafter, when surveillance was not organized by the investigators. This highlights the importance of long-term surveillance for patients after the initial removal of adenomas.

The observed 50% reduction in mortality from colorectal cancer seems reasonable,[3] although it has to be recognized that the National Polyp Study is not a screening study and that the SEER comparison group had higher mortality from all causes, which may bias the results. Also, the study mimics a situation in which 100% of the population complies with screening, which is not a real-life scenario. Randomized, population-based trials are needed to obtain valid estimates of the effectiveness of screening on a population level. The article by Quintero and colleagues reports preliminary results of such a study.[2]

The primary aim of this large, randomized trial in Spain is to compare mortality from colorectal cancer after either once-only screening with colonoscopy or biennial screening with fecal immunochemical testing (FIT) for a period of 10 years. The article reports results after the once-only screening in the colonoscopy group and the first round of screening in the FIT group. The take-home messages are as follows. First, compliance with screening was low in both groups (24.6% in the colonoscopy group and 34.2% in the FIT group). Of note, compliance data for the FIT group are only for the first round, and compliance with fecal screening has been shown to decrease over time.[4] Second, as compared with colonoscopy, screening with FIT yielded a similar percentage of colorectal cancers per invited person, but colonoscopy detected more cancers per screened person. Third, the yield for adenomas in the FIT group was low, which indicates that FIT is not a good test for detecting adenomas. Finally, fewer complications were observed in the FIT group, but this finding is likely to change with more rounds of testing.

The diagnostic yield was low in both groups because the majority of invited persons did not participate in screening. Poor compliance may be overcome by reducing the barriers to participation. These barriers may be grounded in false assumptions about the real burden of the offered test and may thus be susceptible to education. A recent screening study showed that participants expected that colonoscopy would be more uncomfortable than computed tomographic (CT) colonography, but those who underwent procedures rated CT colonography as more burdensome than colonoscopy.[5]

The studies by Zauber et al. and Quintero et al. suggest that colonoscopy is an effective screening test, when compliance is adequate. Its estimated effect on mortality from colorectal cancer is expected to be large (50% in the study

by Zauber and colleagues), and there is no need for frequent screening. Perhaps the most attractive feature is the high yield for adenomas, which has an effect not only on mortality from cancer but also on its incidence.

There are few well-established risk factors for colorectal cancer. Adenoma status at baseline screening, however, is a strong predictor of the risk of colorectal cancer, and the study by Zauber and colleagues confirms that this risk can be reduced by strict surveillance after the removal of adenomas. Therefore, colonoscopy can be used to stratify patients according to their risk of colorectal cancer. An appealing concept would be to use colonoscopy as a triage screening test, offering it once for everybody at 60 years of age and using the results to classify persons as having a low risk of colorectal cancer (no adenomas detected) or a high risk (adenomas detected, particularly advanced ones), with strict surveillance for the latter group but no further screening for the former.

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

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1. Zauber AG, Winawer SJ, O'Brien MJ, et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. N Engl J Med 2012;366:687-96.
2. Quintero E, Castells A, Bujanda L, et al. Colonoscopy versus fecal immunochemical testing in colorectal-cancer screening. N Engl J Med 2012;366:697-706.
3. Ransohoff DF. How much does colonoscopy reduce colon cancer mortality? Ann Intern Med 2009;150:50-2.
4. Mandel JS, Bond JH, Church TR, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. N Engl J Med 1993;328:1365-71. [Erratum, N Engl J Med 1993;329:672.]
5. de Wijkerslooth TR, de Haan MC, Stoop EM, et al. Burden of colonoscopy compared to non-cathartic CT-colonography in a colorectal cancer screening programme: randomised controlled trial. Gut 2011 December 23 (Epub ahead of print).

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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.

Drs. Feld and Zeuzem contributed equally to this article.

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EDITORIAL

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

John W. Ward, M.D., and Jonathan H. Mermin, M.D., M.P.H.

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 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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1. Feld JJ, Jacobson IM, Hézode C, et al. Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection. N Engl J Med 2015;373:2599-607.
2. Foster GR, Afdhal N, Roberts SK, et al. Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection. N Engl J Med 2015;373:2608-17.
3. Curry MP, O'Leary JG, Bzowej N, et al. Sofosbuvir and velpatasvir for HCV in patients with decompensated cirrhosis. N Engl J Med 2015;373:2618-28.
4. Zeuzem S, Dusheiko GM, Salupere R, et al. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. N Engl J Med 2014;370:1993-2001.
5. World Health Organization. Hepatitis fact sheet no. 164. April 2014 (http://www.who.int/mediacentre/factsheets/fs164).
6. Centers for Disease Control and Prevention. Viral hepatitis (http://www.cdc.gov/hepatitis/).
7. Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945-1965. MMWR Recomm Rep 2012;61(RR-4):1-32.
8. Martin NK, Vickerman P, Grebely J, et al. Hepatitis C virus treatment for prevention among people who inject drugs: modeling treatment scale-up in the age of direct-acting antivirals. Hepatology 2013;58:1598-609.
9. Rein DB, Wittenborn JS, Smith BD, Liffmann DK, Ward JW. The cost-effectiveness, health benefits, and financial costs of new antiviral treatments for hepatitis C virus. Clin Infect Dis 2015;61:157-68.
10. American Association for the Study of Liver Diseases, Infectious Diseases Society of America. Recommendations for testing, managing, and treating hepatitis C (http://www.hcvguidelines.org).
11. Canary LA, Klevens RM, Holmberg SD. Limited access to new hepatitis C virus treatment under state Medicaid programs. Ann Intern Med 2015;163:226-8.
12. World Health Organization. Patent situation of key products for treatment of hepatitis C. August 2014 (http://www.who.int/phi/implementation/ip_trade/sofosbuvir_report_2014_09-02.pdf).
13. Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. J Hepatol 2014;61:Suppl:S45-S57.
14. Holmberg SD, Spradling PR, Moorman AC, Denniston MM. Hepatitis C in the United States. N Engl J Med 2013;368:1859-61.

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HEMATOLOGIC AND CYTOGENETIC RESPONSES TO IMATINIB MESYLATE IN CHRONIC MYELOGENOUS LEUKEMIA

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ABSTRACT

Background Chronic myelogenous leukemia (CML) is caused by the BCR-ABL tyrosine kinase, the product of the Philadelphia chromosome. Imatinib mesylate, formerly STI571, is a selective inhibitor of this kinase.

Methods A total of 532 patients with late–chronic-phase CML in whom previous therapy with interferon alfa had failed were treated with 400 mg of oral imatinib daily. Patients were evaluated for cytogenetic and hematologic responses. Time to progression, survival, and toxic effects were also evaluated.

Results Imatinib induced major cytogenetic responses in 60 percent of the 454 patients with confirmed chronic-phase CML and complete hematologic responses in 95 percent. After a median follow-up of 18 months, CML had not progressed to the accelerated or blast phases in an estimated 89 percent of patients, and 95 percent of the patients were alive. Grade 3 or 4 nonhematologic toxic effects were infrequent, and hematologic toxic effects were manageable. Only 2 percent of patients discontinued treatment because of drug-related adverse events, and no treatment-related deaths occurred.

Conclusions Imatinib induced high rates of cytogenetic and hematologic responses in patients with chronic-phase CML in whom previous interferon therapy had failed. (N Engl J Med 2002;346:645-52.)

CHRONIC myelogenous leukemia (CML) accounts for about 20 percent of newly diagnosed cases of leukemia in adults.[1,2] The course of the disease is characteristically triphasic: a chronic phase lasting three to six years is followed by transformation to accelerated and then blast phases of short duration.[1-6] The cause of CML is the translocation of regions of the *BCR* and *ABL* genes to form a *BCR-ABL* fusion gene.[1,7-12] In at least 90 percent of cases, this event is a reciprocal translocation termed t(9;22), which forms the Philadelphia (Ph) chromosome.[7,8] The product of the *BCR-ABL* gene, the BCR-ABL protein, is a constitutively active protein tyrosine kinase with an important role in the regulation of cell growth.[1,7]

CML is potentially curable with allogeneic stem-cell transplantation, but fewer than 30 percent of patients have suitably matched donors.[1,3,7,13] Treatment with interferon alfa can induce a complete cytogenetic response in 5 to 20 percent of patients and result in longer survival than that achievable with chemotherapy, but it is associated with serious toxic effects.[1,3,13-15] Patients in whom interferon therapy fails are usually treated with hydroxyurea, busulfan, or investigational agents. The rate of hematologic response with these second-line agents is approximately 50 percent, but cytogenetic responses are uncommon. Furthermore, the rate of response decreases rapidly as the time from the initial diagnosis to the initiation of second-line therapy increases, particularly when such therapy is started in the late chronic phase, defined as more than 12 months after the initial diagnosis.

Imatinib mesylate (Gleevec, Novartis, Basel, Swit-

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A Novel Coronavirus Associated with Severe Acute Respiratory Syndrome

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ABSTRACT

BACKGROUND

A worldwide outbreak of severe acute respiratory syndrome (SARS) has been associated with exposures originating from a single ill health care worker from Guangdong Province, China. We conducted studies to identify the etiologic agent of this outbreak.

METHODS

We received clinical specimens from patients in seven countries and tested them, using virus-isolation techniques, electron-microscopical and histologic studies, and molecular and serologic assays, in an attempt to identify a wide range of potential pathogens.

RESULTS

None of the previously described respiratory pathogens were consistently identified. However, a novel coronavirus was isolated from patients who met the case definition of SARS. Cytopathological features were noted in Vero E6 cells inoculated with a throat-swab specimen. Electron-microscopical examination revealed ultrastructural features characteristic of coronaviruses. Immunohistochemical and immunofluorescence staining revealed reactivity with group I coronavirus polyclonal antibodies. Consensus coronavirus primers designed to amplify a fragment of the polymerase gene by reverse transcription–polymerase chain reaction (RT-PCR) were used to obtain a sequence that clearly identified the isolate as a unique coronavirus only distantly related to previously sequenced coronaviruses. With specific diagnostic RT-PCR primers we identified several identical nucleotide sequences in 12 patients from several locations, a finding consistent with a point-source outbreak. Indirect fluorescence antibody tests and enzyme-linked immunosorbent assays made with the new isolate have been used to demonstrate a virus-specific serologic response. This virus may never before have circulated in the U.S. population.

CONCLUSIONS

A novel coronavirus is associated with this outbreak, and the evidence indicates that this virus has an etiologic role in SARS. Because of the death of Dr. Carlo Urbani, we propose that our first isolate be named the Urbani strain of SARS-associated coronavirus.

From the Special Pathogens Branch (T.G.K., J.A.C., P.E.R.), Respiratory and Enteric Virus Branch (D.E., T.P., S.E., S.T., P.R., W.J.B., L.J.A.), Infectious Disease Pathology Activity (C.S.G., S.R.Z., C.D.H., W.-J.S., J.G., C.D.P.), Influenza Branch (N.C.), Division of Bacterial and Mycotic Diseases (B.F.), and Office of the Director, Division of Viral and Rickettsial Diseases (J.W.L.), and Office of the Director, National Center for Infectious Diseases (J.M.H.), National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta; the World Health Organization, Hanoi, Vietnam (C.U.); the Government Virus Unit, Queen Mary Hospital, Hong Kong, China (W.L.); the International Emerging Infectious Diseases Program, Bangkok, Thailand (S.F.D.); the Department of Pathology, Singapore General Hospital (A.-E.L.); the University of California, San Francisco (J.D.); and the Center for Disease Control, Department of Health, Taipei, Taiwan (J.-Y. Y.).

*Deceased.

†Members of the SARS (Severe Acute Respiratory Syndrome) Working Group are listed in the Appendix.

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Quadrivalent Vaccine against Human Papillomavirus to Prevent High-Grade Cervical Lesions

The FUTURE II Study Group*

ABSTRACT

BACKGROUND

Human papillomavirus types 16 (HPV-16) and 18 (HPV-18) cause approximately 70% of cervical cancers worldwide. A phase 3 trial was conducted to evaluate a quadrivalent vaccine against HPV types 6, 11, 16, and 18 (HPV-6/11/16/18) for the prevention of high-grade cervical lesions associated with HPV-16 and HPV-18.

METHODS

In this randomized, double-blind trial, we assigned 12,167 women between the ages of 15 and 26 years to receive three doses of either HPV-6/11/16/18 vaccine or placebo, administered at day 1, month 2, and month 6. The primary analysis was performed for a per-protocol susceptible population that included 5305 women in the vaccine group and 5260 in the placebo group who had no virologic evidence of infection with HPV-16 or HPV-18 through 1 month after the third dose (month 7). The primary composite end point was cervical intraepithelial neoplasia grade 2 or 3, adenocarcinoma in situ, or cervical cancer related to HPV-16 or HPV-18.

RESULTS

Subjects were followed for an average of 3 years after receiving the first dose of vaccine or placebo. Vaccine efficacy for the prevention of the primary composite end point was 98% (95.89% confidence interval [CI], 86 to 100) in the per-protocol susceptible population and 44% (95% CI, 26 to 58) in an intention-to-treat population of all women who had undergone randomization (those with or without previous infection). The estimated vaccine efficacy against all high-grade cervical lesions, regardless of causal HPV type, in this intention-to-treat population was 17% (95% CI, 1 to 31).

CONCLUSIONS

In young women who had not been previously infected with HPV-16 or HPV-18, those in the vaccine group had a significantly lower occurrence of high-grade cervical intraepithelial neoplasia related to HPV-16 or HPV-18 than did those in the placebo group. (ClinicalTrials.gov number, NCT00092534.)

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*Members of the Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) II Study Group, who vouch for the completeness and accuracy of the data, are listed in the Appendix, along with other study participants.

N Engl J Med 2007;356:1915-27.

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EDITORIALS

Human Papillomavirus Vaccine — Opportunity and Challenge

Lindsey R. Baden, M.D., Gregory D. Curfman, M.D., Stephen Morrissey, Ph.D., and Jeffrey M. Drazen, M.D.

In this issue of the *Journal*, we publish three Original Articles,[1-3] two Perspective articles,[4,5] two editorials,[6,7] a letter to the editor,[8] and an audio interview[9] on the subject of human papillomavirus (HPV). We bring together this unique body of information in response to the enormity of the health problems that stem from HPV and the broad interest that has been kindled by the possibility of preventing HPV-related cervical cancer and other anogenital conditions through vaccination.

The HPV vaccine is the first vaccine explicitly designed to prevent cancer induced by a virus. (The hepatitis B vaccine was not primarily designed to prevent cancer.) As noted in the Perspective article by Agosti and Goldie,[5] the consequences of HPV infection are a global health concern that disproportionately affects those in developing countries. The potential ability to reduce the burden of HPV-related disease by vaccination against certain disease-inducing strains of the virus has created a volatile intersection between the community's interest in limiting the transmission of infectious diseases and promoting health on the one hand and social mores on the other, as discussed by Charo in her Perspective article[4] and related audio interview (podcast available at www.nejm.org).[9] However, this volatility should not keep us from recognizing the enormous potential for medical progress and from addressing the numerous unanswered questions that remain.

The finding that infection with HPV is a critical factor in the majority of cases of cervical cancer allowed the development of strategies to prevent this form of oncogenesis. It is important to note that several other cancers are also associated with HPV infection, including head and neck cancers, as demonstrated by D'Souza and colleagues.[3] Although there are many HPV serotypes, two of them — 16 and 18 — account for the lion's share of the oncogenesis. The data that are presented in reports on the vaccine efficacy trials in this issue of the *Journal*[1,2] confirm the success in reducing the incidence of precancerous cervical lesions with vaccine directed against the HPV-16 and HPV-18 serotypes.

Although this is a remarkable achievement, the efficacy of the vaccine is limited by at least these two factors. First, not all cervical cancer is caused by HPV-16 or HPV-18, and second, it appears necessary to vaccinate young women before they are infected with these two serotypes. Also, whether this approach will extend the paradigm of vaccination to the prevention of death and disability from cervical cancer is an unanswered question.

It is difficult to show that an intervention prevents cancer, given the relatively long induction phase between exposure to an inducing agent and development of disease. Thus, key surrogate markers, in this case cervical intraepithelial neoplasia grades 2 and 3, were used so that data could be gathered in a timely fashion. However, correlation with the ultimate outcome — cancer prevention — will require the long-term observation of a large number of treated women. We must also carefully monitor for unintended adverse consequences of vaccination. For example, when selective immunologic pressure is applied with vaccination, the potential exists for nonvaccine-related strains to emerge as important oncogenic serotypes. These critical points are clarified in the editorial by Sawaya and Smith-McCune.[6]

Many other questions are raised by these remarkable data. Should young men be vaccinated? What is the durability of immune protection? Could fewer than three vaccinations provide adequate protection? Will future HPV vaccines extend protection to cover additional pathogenic serotypes? Will the economics allow this therapy to reach all who may benefit, such as those in the developing world? Might HPV vaccination be beneficial in preventing other, noncervical HPV-induced cancers (such as HPV-related oropharyngeal cancer[3])?

There is no doubt that the findings reported

in this issue of the *Journal* open a new field at the interface of basic science, clinical medicine, public health, and public policy. It is important to keep in mind that these new treatments raise many scientific, medical, economic, and sociological questions. We have begun an exciting journey; we need to continue in the right direction.

1. The FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med 2007;356:1915-27.
2. Garland SM, Hernandez-Avila M, Wheeler CM, et al. Quadrivalent vaccine against the human papillovmavirus to prevent anogenital diseases. N Engl J Med 2007;356:1928-43.
3. D'Souza G, Kreimer AR, Viscidi R, et al. Case–control study of human papillomavirus and oropharyngeal cancer. N Engl J Med 2007;356:1944-56.
4. Charo RA. Politics, parents, and prophylaxis — mandating HPV vaccination in the United States. N Engl J Med 2007;356:1905-8.
5. Agosti JM, Goldie SJ. Introducing HPV vaccine in developing countries — key challenges and issues. N Engl J Med 2007;356:1908-10.
6. Sawaya GF, Smith-McCune K. HPV vaccination — more answers, more questions. N Engl J Med 2007;356:1991-3.
7. Syrjanen S. Human papillovmaviruses in head and neck carcinomas. N Engl J Med 2007;356:1993-5.
8. Stewart S. Mandating HPV vaccination — private rights, public good. N Engl J Med 2007;356:1998-9.
9. Interview with R. Alta Charo. (Available at www.nejm.org.)

HPV Vaccination — More Answers, More Questions

George F. Sawaya, M.D., and Karen Smith-McCune, M.D., Ph.D.

The availability of a "cancer vaccine" has elicited enormous enthusiasm from the medical community and the public, culminating in advocacy for mandatory vaccination against human papillomavirus (HPV) and a recommendation from the Centers for Disease Control and Prevention (CDC) that 30 million girls and women between the ages of 11 and 26 years in the United States be vaccinated.[1] Previous reports[2,3] showed a remarkable 100% efficacy of a quadrivalent vaccine targeting HPV types 6, 11, 16, and 18 on outcomes related to vaccine HPV types in women with no evidence of previous exposure to those types. Since HPV types 16 and 18 are implicated in 70% of cervical cancers,[4] these types are ideal targets for a new vaccine.

In this issue of the *Journal*, reports on two large, ongoing, randomized, placebo-controlled trials show the effect of this vaccine on important clinical outcomes, including rates of adenocarcinoma in situ and cervical intraepithelial neoplasia after an average of 3 years of follow-up.[5,6] Investigators in these trials have hit their mark soundly: the vaccine showed significant efficacy against anogenital and cervical lesions related to vaccine type in women with no evidence of previous exposure to vaccine-specific types; the vaccine also appeared to be safe. In addition, the studies report outcomes in all subjects regardless of HPV status at baseline and regardless of whether outcomes were related to HPV types targeted by the vaccine. Policymakers now have more evidence to assess the benefits and risks of widespread vaccination.

Given the rarity of incident cervical cancer, preinvasive cervical lesions with high invasive potential are used in contemporary studies as surrogate outcomes for cervical cancer. Adenocarcinoma in situ is a rare lesion widely considered to be a precursor of cancer. Cervical intraepithelial neoplasia is graded from 1 to 3 on the basis of histopathological criteria. Grade 1 cervical intraepithelial neoplasia indicates the presence of active HPV infection and is not considered to be precancerous; current guidelines discourage treatment of this condition.[7,8] Grade 2 cervical intraepithelial neoplasia is treated in most women but is not an irrefutable cancer surrogate, since up to 40% of such lesions regress spontaneously[9]; current guidelines suggest that some young women with such lesions do not need to be treated.[7,8] Grade 3 cervical intraepithelial neoplasia, on the other hand, has the lowest likelihood of regression and the strongest potential to be invasive. The Food and Drug Administration (FDA) considers grade 2 and 3 cervical intraepithelial neoplasia and adenocarcinoma in situ to be acceptable surrogate outcomes for cervical cancer; other observers consider grade 3 cervical intraepithelial neoplasia and adenocarcinoma in situ to be more appropriate surrogates.[9]

In these trials, called Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) I and II, what is the efficacy of vac-

cination among all subjects, regardless of causal HPV types? In the FUTURE I trial,[5] rates of grades 1 to 3 cervical intraepithelial neoplasia or adenocarcinoma in situ per 100 person-years were 4.7 in vaccinated women and 5.9 in unvaccinated women, an efficacy of 20%. Analyses by lesion type indicate that this reduction was largely attributable to a lower rate of grade 1 cervical intraepithelial neoplasia in vaccinated women; no efficacy was demonstrable for higher-grade disease, but the trial may have lacked adequate power to detect a difference. Vaccinated women also had lower rates of external anogenital and vaginal lesions (1.3 vs. 2.1). In the larger FUTURE II trial,[6] rates of grade 2 or 3 cervical intraepithelial neoplasia or adenocarcinoma in situ were 1.3 in vaccinated women and 1.5 in unvaccinated women, an efficacy of 17%. In analyses by lesion type, the efficacy appears to be significant only for grade 2 cervical intraepithelial neoplasia; no efficacy was demonstrable for grade 3 cervical intraepithelial neoplasia or adenocarcinoma in situ.

What can be inferred from these data about the potential effect of vaccination on populations that include sexually active women? In the FUTURE II trial, 93% of subjects were nonvirgins. With grade 2 or 3 cervical intraepithelial neoplasia or adenocarcinoma in situ as the outcome, the difference in risk so far appears to be modest: 219 of 6087 vaccinated women (3.6%) received this diagnosis over an average of 3 years, as compared with 266 of 6080 unvaccinated women (4.4%). The absolute risk difference of 0.8% indicates that 129 women would need to be vaccinated in order to prevent one case of grade 2 or 3 cervical intraepithelial neoplasia or adenocarcinoma in situ occurring during this period. If grade 3 cervical intraepithelial neoplasia or adenocarcinoma in situ were the most relevant outcome, evidence was insufficient to infer the effectiveness of vaccination.

Why is vaccine efficacy modest in the entire cohort? One factor is the apparent lack of efficacy among subjects with evidence of previous exposure to HPV types included in the vaccine. The FUTURE II trial showed no effect of vaccination up to month 12, perhaps owing either to preinvasive lesions or to vaccine-type HPV infections that were present at enrollment. Therefore, vaccination before the onset of sexual activity seems to be preferable. In contrast to the CDC's guidelines, the American Cancer Society does not recommend universal vaccination among women between 18 and 26 years of age, citing probable diminished vaccine efficacy as the number of lifetime sexual partners increases.[10] Trial outcomes stratified by risk factors that are strong surrogates for HPV exposure and are readily obtained clinically (e.g., the number of lifetime sexual partners) may prove to be useful in the future development of guidelines.

Another factor explaining the modest efficacy of the vaccine is the role of oncogenic HPV types not included in the vaccine. At least 15 oncogenic HPV types have been identified,[4] so targeting only 2 types may not have had a great effect on overall rates of preinvasive lesions. Findings from the FUTURE II trial showed that the contribution of nonvaccine HPV types to overall grade 2 or 3 cervical intraepithelial neoplasia or adenocarcinoma in situ was sizable. In contrast to a plateau in the incidence of disease related to HPV types 16 and 18 among vaccinated women, the overall disease incidence regardless of HPV type continued to increase, raising the possibility that other oncogenic HPV types eventually filled the biologic niche left behind after the elimination of HPV types 16 and 18. An interim analysis of vaccine trial data submitted to the FDA[11] showed a disproportionate, but not statistically significant, number of cases of grade 2 or 3 cervical intraepithelial neoplasia related to nonvaccine HPV types among vaccinated women. Updated analyses of data from these ongoing trials will be important to determine the effect of vaccination on rates of preinvasive lesions caused by nonvaccine HPV types.

What can be inferred from these data about the potential effect of vaccination among girls 11 and 12 years of age? The FUTURE trials did not enroll subjects in this age group. Within both trials, subgroups of subjects with no evidence of previous exposure to relevant vaccine HPV types were evaluated separately for vaccine efficacy. In these subgroups, efficacy of nearly 100% against all grades of cervical intraepithelial neoplasia and adenocarcinoma in situ related to vaccine HPV types was reported in both trials. However, it would be important to know the overall rates of grade 2 or 3 cervical intraepithelial neoplasia or adenocarcinoma in situ regardless of HPV types. Without these data, it is difficult to infer both

the effectiveness of vaccination and the role of nonvaccine HPV types in overall rates of preinvasive lesions.

What do these results mean for cervical-cancer screening? Screening should continue in all vaccinated women, given the cumulative lifetime risk of exposure to other oncogenic HPV types and the unknown duration of anti-HPV immunity. The effect of vaccination on cervical cytologic findings was not reported in either trial, but if vaccination reduces the rates of abnormal findings, this benefit would be important. Of note, a trial of a monovalent HPV-16 vaccine reported no effect on cytologic abnormalities.[12]

Policymakers, clinicians, and parents have a keen sense of urgency about HPV vaccination. On one hand, the vaccine has high efficacy against certain HPV types that cause life-threatening disease, and it appears to be safe; delaying vaccination may mean that many women will miss an opportunity for long-lasting protection. On the other hand, a cautious approach may be warranted in light of important unanswered questions about overall vaccine effectiveness, duration of protection, and adverse effects that may emerge over time. HPV vaccination has the potential for profound public health benefit if the most optimistic scenario of effectiveness is realized.

No potential conflict of interest relevant to this article was reported.

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1. Markowitz LE, Dunne EF, Saraiya M, Lawson HW, Chesson H, Unger ER. Quadrivalent human papillomavirus vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2007;56(RR-2):1-24.
2. Villa LL, Costa RL, Petta CA, et al. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. Lancet Oncol 2005;6:271-8.
3. Villa LL, Costa RL, Petta CA, et al. High sustained efficacy of a prophylactic quadrivalent human papillomavirus types 6/11/16/18 L1 virus-like particle vaccine through 5 years of follow-up. Br J Cancer 2006;95:1459-66.
4. Munoz N, Bosch FX, de Sanjose S, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med 2003;348:518-27.
5. Garland SM, Hernandez-Avila M, Wheeler CM, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. N Engl J Med 2007;356:1928-43.
6. The FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med 2007;356:1915-27.
7. Wright TC Jr, Cox JT, Massad LS, Twiggs LB, Wilkinson EJ. 2001 Consensus Guidelines for the management of women with cervical cytological abnormalities. JAMA 2002;287:2120-9.
8. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin number 66, September 2005: management of abnormal cervical cytology and histology. Obstet Gynecol 2005;106:645-64.
9. ASCUS-LSIL Triage Study (ALTS) Group. Results of a randomized trial on the management of cytology interpretations of atypical squamous cells of undetermined significance. Am J Obstet Gynecol 2003;188:1383-92.
10. Saslow D, Castle PE, Cox JT, et al. American Cancer Society guideline for human papillomavirus (HPV) vaccine use to prevent cervical cancer and its precursors. CA Cancer J Clin 2007;57:7-28.
11. Miller NB. FDA review of the Gardasil license application. (Accessed April 19, 2007, at http://www.fda.gov/OHRMS/DOCKETS/ac/06/slides/2006-4222S-2_files/frame.htm.)
12. Mao C, Koutsky LA, Ault KA, et al. Efficacy of human papillomavirus-16 vaccine to prevent cervical intraepithelial neoplasia: a randomized controlled trial. Obstet Gynecol 2006;107:18-27. [Erratum, Obstet Gynecol 2006;107:1425.]

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A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke

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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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EDITORIAL

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, 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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1. Emberson J, Lees KR, Lyden P, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. Lancet 2014 August 5 (Epub ahead of print).
2. Riedel CH, Zimmermann P, Jensen-Kondering U, Stingele R, Deuschl G, Jansen O. The importance of size: successful recanalization by intravenous thrombolysis in acute anterior stroke depends on thrombus length. Stroke 2011;42:1775-7.
3. Broderick JP, Palesch YY, Demchuk AM, et al. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. N Engl J Med 2013;368:893-903. [Erratum, N Engl J Med 2013;368:1265.]
4. Ciccone A, Valvassori L, Nichelatti M, et al. Endovascular treatment for acute ischemic stroke. N Engl J Med 2013;368:904-13.
5. Kidwell CS, Jahan R, Gornbein J, et al. A trial of imaging selection and endovascular treatment for ischemic stroke. N Engl J Med 2013;368:914-23.
6. Saver JL, Jahan R, Levy EI, et al. Solitaire flow restoration device versus the Merci Retriever in patients with acute ischaemic stroke (SWIFT): a randomised, parallel-group, non-inferiority trial. Lancet 2012;380:1241-9.
7. Khatri P, Yeatts SD, Mazighi M, et al. Time to angiographic reperfusion and clinical outcome after acute ischaemic stroke: an analysis of data from the Interventional Management of Stroke (IMS III) phase 3 trial. Lancet Neurol 2014;13:567-74.
8. Mazighi M, Chaudhry SA, Ribo M, et al. Impact of onset-to-reperfusion time on stroke mortality: a collaborative pooled analysis. Circulation 2013;127:1980-5.
9. Hacke W, Furlan AJ. (Here comes that) razors edge — endovascular stroke therapy: the end, or only the beginning? Int J Stroke 2013;8:331-3.
10. Berkhemer OA, Fransen PSS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med 2015;372:11-20.

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A RANDOMIZED TRIAL COMPARING RADICAL PROSTATECTOMY WITH WATCHFUL WAITING IN EARLY PROSTATE CANCER

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ABSTRACT

Background Radical prostatectomy is widely used in the treatment of early prostate cancer. The possible survival benefit of this treatment, however, is unclear. We conducted a randomized trial to address this question.

Methods From October 1989 through February 1999, 695 men with newly diagnosed prostate cancer in International Union against Cancer clinical stage T1b, T1c, or T2 were randomly assigned to watchful waiting or radical prostatectomy. We achieved complete follow-up through the year 2000 with blinded evaluation of causes of death. The primary end point was death due to prostate cancer, and the secondary end points were overall mortality, metastasis-free survival, and local progression.

Results During a median of 6.2 years of follow-up, 62 men in the watchful-waiting group and 53 in the radical-prostatectomy group died (P=0.31). Death due to prostate cancer occurred in 31 of 348 of those assigned to watchful waiting (8.9 percent) and in 16 of 347 of those assigned to radical prostatectomy (4.6 percent) (relative hazard, 0.50; 95 percent confidence interval, 0.27 to 0.91; P=0.02). Death due to other causes occurred in 31 of 348 men in the watchful-waiting group (8.9 percent) and in 37 of 347 men in the radical-prostatectomy group (10.6 percent). The men assigned to surgery had a lower relative risk of distant metastases than the men assigned to watchful waiting (relative hazard, 0.63; 95 percent confidence interval, 0.41 to 0.96).

Conclusions In this randomized trial, radical prostatectomy significantly reduced disease-specific mortality, but there was no significant difference between surgery and watchful waiting in terms of overall survival. (N Engl J Med 2002;347:781-9.)

THE management of early prostate cancer is controversial. Radical prostatectomy has become widely used, but its possible benefit has not been adequately documented in a randomized trial. Early studies indicated a lower rate of progression after surgery than after external radiotherapy,[1] but no gain in overall survival after more than 20 years of follow-up, as compared with primary expectant management (watchful waiting).[2,3] Systematic overviews of observational studies reveal a lack of reliable data to support any specific recommendation for the treatment of early prostate cancer.[4-7]

We conducted a randomized trial in 695 men with early prostate cancer, who were assigned to either watchful waiting or radical prostatectomy. The median follow-up was 6.2 years. Our presentation follows the revised CONSORT recommendations.[8]

METHODS

The protocol (available at http://www.roc.se) was defined in 1988. Our main purpose was to determine whether mortality from

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Editorials

Surgery and the Reduction of Mortality from Prostate Cancer

MORE than ever, it is important to establish definitively whether aggressive management of localized prostate cancer reduces the rate of death due to prostate cancer, because this tumor is now the second leading cause of cancer-related death among men in the United States.[1] The treatment of early prostate cancer, which has been the subject of great controversy for years, was well summarized by a question raised by Whitmore: "Is cure necessary in those in whom it may be possible, and is cure possible in those in whom it is necessary?"[2] In this issue of the *Journal*, a landmark study conducted by Holmberg et al. of the Scandinavian Prostatic Cancer Group[3] provides the first concrete evidence we need to answer Whitmore's question. The Scandinavian group conducted a randomized trial in which radical prostatectomy was compared with watchful waiting for localized prostate cancer. After eight years of follow-up, surgery had reduced cancer-specific mortality and the frequency of development of distant metastases by about 50 percent. For the first time, and after a surprisingly short follow-up period, we have clear evidence that surgical treatment of localized disease reduces the risk of death from prostate cancer.

Holmberg et al. found no difference between the two groups of patients in overall mortality, and the absolute reduction in cancer-specific mortality at eight years was only about 7 percent. However, an excess risk of death from prostate cancer persists for 20 to 25 years after diagnosis, and in a study from Sweden, 63 percent of conservatively treated men who lived longer than 10 years after receiving the diagnosis eventually died of prostate cancer.[4] In the trial by Holmberg et al., there was a 14 percent absolute reduction in the rate of development of distant metastases in the surgery group as compared with the watchful-waiting group after eight years of follow-up. Given that the median survival of men with distant metastases is only two to three years, I anticipate that with longer follow-up, the difference in mortality found by Holmberg et al. will increase.

During the past 20 years, the number of radical prostatectomies performed in the United States has risen dramatically, peaking at 104,000 in 1992 to 1993.[5] The estimated number of deaths from prostate cancer has declined from 40,400 in 1995 to 30,200 in 2002. It is difficult to know whether these two phenomena are related, but between 1983 and 1991, the proportion of men 60 to 79 years of age with prostate cancer who were treated surgically increased rapidly.[5,6] Men in this age group also had the greatest decline in mortality due to prostate cancer, which was lower in 1997 than it had been in any year since 1950.[7]

Quality of life in men who enrolled in the Scandinavian trial was evaluated approximately four years after randomization, reported in this issue of the *Journal* by Steineck et al.[8] Although base-line data were not collected prospectively, men in the surgery group had higher rates of erectile dysfunction and urinary leakage but a lower rate of urinary obstruction than men in the watchful-waiting group. Before 1980, radical prostatectomy was associated with severe complications: excessive life-threatening bleeding was common, and after the operation, all men were impotent and 10 to 25 percent had severe incontinence. However, anatomical discoveries made during the past 20 years have led to considerable refinements in surgical technique. Among men who are ideal candidates for radical prostatectomy (who are less than 65 years of age, with localized disease and no coexisting conditions), experienced academic urologists report potency rates of 62 to 86 percent and continence rates of 92 to 95 percent.[9] Other centers and surveys of individual surgeons, however, report potency rates of 10 to 30 percent and continence rates as low as 50 percent.[10]

In the Scandinavian trial, nerve-sparing surgery was not routinely performed. Furthermore, many patients in this trial were older than 65 years of age and thus more likely to have incontinence and impotence; 28 percent received hormonal therapy during follow-up. These factors — lack of standardized nerve-sparing surgery, older age, and the use of antiandrogen therapy — may explain why the frequency of complications of radical prostatectomy in this trial was higher than one might have expected if the procedure had been performed uniformly at a high-volume center.[11] Steineck et al. also found that patients in the watchful-waiting group had more erectile dysfunction and urinary leakage than would be expected in a control population, suggesting that local tumor progression, which occurred in 60 percent of the patients in the watchful-waiting group, or the treatment of progressive disease can also have side effects. As the authors of the study point out, a man evaluating treatment strategies for localized prostate cancer must recognize that all options can jeopardize his quality of life.

It is important to note that in this study, the diagnosis of prostate cancer was made clinically; 75 percent of the patients had palpable disease, and only 10 percent of the cases were diagnosed because of an elevated prostate-specific antigen level. These men are therefore not representative of most patients seen to-

day in the United States, where 75 percent of men who receive a diagnosis of prostate cancer have nonpalpable disease and undergo a biopsy because of an elevated prostate-specific antigen level. Consequently, the lead time in diagnosis (probably five years or more) must be taken into account before the findings from this study can be applied to contemporary patients.[12] Fortunately, several relatively advanced studies evaluating the efficacy of screening are under way in the United States and Europe, and they may have the statistical power to show definitive results by 2005 to 2008.[13] Furthermore, the Department of Veterans Affairs has just closed enrollment for a trial in which 731 patients were randomly assigned to radical prostatectomy or watchful waiting. In this trial, 50 percent of the participants have nonpalpable disease.[14]

How should the results of the Scandinavian study influence the advice we give to patients? Specifically, should no one be followed with watchful waiting? Should all patients undergo radical prostatectomy? The answer to both these questions is a categorical "no." There have always been, and always will be, many men who are best served by watchful waiting. They are the patients who are too old or too ill to survive longer than 10 years. If their cancer progresses to the point where it causes symptoms, there are many ways to palliate the disease. Furthermore, in the era of prostate-specific antigen screening, 10 to 20 percent of men with nonpalpable disease have small tumors and may also be candidates for watchful waiting. Criteria have been established to help identify such men.[15] For patients with larger tumors, definitive treatment with surgery, external-beam radiotherapy, or interstitial radiotherapy should be considered. In a young man with localized prostate cancer who is otherwise healthy, total surgical removal is an excellent option, and if it is performed by an experienced surgeon, the patient's subsequent quality of life should be more satisfactory. In an older patient or one with clinically significant coexisting conditions, however, radiation therapy is the best option and has the fewest side effects.

In between these two groups, there are many men who are candidates for either surgery or radiation therapy. During the past decade, substantial advances have been made in the technique of radiation therapy, making it possible to deliver high doses of radiation specifically to the prostate. As a result of these advances, patients with localized prostate cancer now clearly have two good options for treatment: surgery and radiotherapy. The Scandinavian Prostatic Cancer Group trial showed that surgery can reduce the rate of death from prostate cancer, but no similar trial of radiation therapy has been conducted. However, both randomized and cohort studies are being developed to compare radical prostatectomy with external-beam or interstitial radiotherapy. Until those trials have been completed, physicians must fully inform men with prostate cancer about their options and help them select the best specialist for the treatment they choose.

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REFERENCES

1. Jemal A, Thomas A, Murray T, Thun M. Cancer statistics, 2002. CA Cancer J Clin 2002;52:23-47. [Errata, CA Cancer J Clin 2002;52:119, 181-2.]
2. Whitmore WF Jr. Natural history of low-stage prostatic cancer and the impact of early detection. Urol Clin North Am 1990;17:689-97.
3. Holmberg L, Bill-Axelson A, Helgesen F, et al. A randomized trial comparing radical prostatectomy with watchful waiting in early prostate cancer. N Engl J Med 2002;347:781-9.
4. Aus G, Hugosson J, Norlen L. Long-term survival and mortality in prostate cancer treated with noncurative intent. J Urol 1995;154:460-5.
5. Wingo PA, Guest JL, McGinnis L, et al. Patterns of inpatient surgeries for the top four cancers in the United States, National Hospital Discharge Survey, 1988-95. Cancer Causes Control 2000;11:497-512.
6. Merrill RM. Changes in the use of radical prostatectomy for treating prostate cancer in the USA. Lancet 1996;348:963-4.
7. Tarone RE, Chu KC, Brawley OW. Implications of stage-specific survival rates in assessing recent declines in prostate cancer mortality rates. Epidemiology 2000;11:167-70.
8. Steineck G, Helgesen F, Adolfsson J, et al. Quality of life after radical prostatectomy or watchful waiting. N Engl J Med 2002;347:790-6.
9. Walsh PC, Marschke P, Ricker D, Burnett Al. Patient-reported urinary continence and sexual function after anatomic radical prostatectomy. Urology 2000;55:58-61.
10. Talcott JA, Reiker P, Propert KJ, et al. Patient-reported impotence and incontinence after nerve-sparing radical retropubic prostatectomy. J Natl Cancer Inst 1997;89:1117-23.
11. Begg CB, Riedel ER, Bach PB, et al. Variations in morbidity after radical prostatectomy. N Engl J Med 2002;346:1138-44.
12. Gann PH, Hennekens CH, Stampfer MJ. A prospective evaluation of plasma prostate-specific antigen for detection of prostate cancer. JAMA 1995;273:289-94.
13. de Koning HJ, Auvinen A, Berenguer Sanchez A, et al. Large-scale randomized prostate cancer screening trials: program performances in the European Randomized Screening for Prostate Cancer trial and the Prostate, Lung, Colorectal and Ovary Cancer trial. Int J Cancer 2002;97:237-44.
14. Wilt TJ, Brawer MK. The Prostate Cancer Intervention Versus Observation Trial (PIVOT). Oncology (Huntingt) 1997;11:1133-9.
15. Carter HB, Walsh PC, Landis P, Epstein JI. Expectant management of non-palpable prostate cancer with curative intent: preliminary results. J Urol 2002;167:1231-4.

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TWENTY-YEAR FOLLOW-UP OF A RANDOMIZED STUDY COMPARING BREAST-CONSERVING SURGERY WITH RADICAL MASTECTOMY FOR EARLY BREAST CANCER

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ABSTRACT

Background We conducted 20 years of follow-up of women enrolled in a randomized trial to compare the efficacy of radical (Halsted) mastectomy with that of breast-conserving surgery.

Methods From 1973 to 1980, 701 women with breast cancers measuring no more than 2 cm in diameter were randomly assigned to undergo radical mastectomy (349 patients) or breast-conserving surgery (quadrantectomy) followed by radiotherapy to the ipsilateral mammary tissue (352 patients). After 1976, patients in both groups who had positive axillary nodes also received adjuvant chemotherapy with cyclophosphamide, methotrexate, and fluorouracil.

Results Thirty women in the group that underwent breast-conserving therapy had a recurrence of tumor in the same breast, whereas eight women in the radical-mastectomy group had local recurrences ($P<0.001$). The crude cumulative incidence of these events was 8.8 percent and 2.3 percent, respectively, after 20 years. In contrast, there was no significant difference between the two groups in the rates of contralateral-breast carcinomas, distant metastases, or second primary cancers. After a median follow-up of 20 years, the rate of death from all causes was 41.7 percent in the group that underwent breast-conserving surgery and 41.2 percent in the radical-mastectomy group ($P=1.0$). The respective rates of death from breast cancer were 26.1 percent and 24.3 percent ($P=0.8$).

Conclusions The long-term survival rate among women who undergo breast-conserving surgery is the same as that among women who undergo radical mastectomy. Breast-conserving surgery is therefore the treatment of choice for women with relatively small breast cancers. (N Engl J Med 2002;347:1227-32.)

THE radical mastectomy introduced by Halsted[1] was the treatment of choice for breast cancer of any size or type, regardless of the patient's age, for 80 years. Apart from a few modifications, such as enlarging the extent of the dissection to include the internal mammary nodes or reducing it to spare the pectoralis muscles, the Halsted mastectomy was performed as originally described throughout this period. The possibility of attempting a surgical procedure that would conserve the breast was not widely considered during those years.[2,3]

In 1969, a randomized study to compare radical mastectomy with breast-conserving surgery, which was termed "quadrantectomy," was approved by the World Health Organization Committee of Investigators for Evaluation of Methods of Diagnosis and Treatment of Breast Cancer.[4] The recruitment of patients began at the Milan Cancer Institute in 1973, after the new procedure was standardized, and preliminary data showing that survival rates were equal after radical and breast-conserving surgery were published in 1977[5] and 1981.[6]

The main criticism of the data was that they were too preliminary; patients with small breast cancers must be followed for a very long time, even decades, to ensure that the evaluation of the efficacy of any new treatment is accurate. We carefully monitored the 701 women in the trial for up to 29 years, and we now report the results.

METHODS

Study Design

Enrollment in the trial began in 1973 and ended in May 1980 after the recruitment of 701 patients who had breast cancers with

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Editorials

Rational Local Therapy for Breast Cancer

In a 1976 lecture to the Society of Surgical Oncology, the late Jerome Urban lamented the loss of a rational approach to the treatment of breast cancer, which he thought had been replaced "by an emotional appeal to the patient's vanity. A great cry has been raised in the public media to save the breast, despite the long-term consequences."[1] In this issue of the *Journal*, Fisher and colleagues[2] and Veronesi and colleagues[3] describe the long-term outcomes of two pivotal randomized trials comparing breast-conserving surgery and mastectomy. These studies document how far our understanding of breast cancer has evolved since Urban's lecture. Breast cancer has a long natural history, and conclusions drawn from short-term follow-up studies may give an inaccurate picture of the ultimate outcome. The failure to observe a survival advantage of mastectomy after 20 years should convince even the most determined skeptics that mastectomy is not superior to breast conservation for the treatment of breast cancer.

In addition to the belief that a more extensive operation for cancer must be a better operation for cancer, the potential for local failure in the preserved breast has been a cause for concern. These two reports provide reassurance that at 20 years the incidence of recurrence in the ipsilateral breast is low: 8.8 percent in the study by Veronesi et al.[3] and 14.3 percent in the trial by Fisher et al.[2] In both studies, the incidence of recurrences in the node-positive women who received adjuvant chemotherapy was approximately half the incidence in their node-negative counterparts who did not receive systemic therapy. Today, the widespread use of adjuvant systemic therapy for both node-negative and node-positive breast cancer, coupled with improvements in the mammographic and pathological evaluation of patients undergoing breast-conserving surgery, has resulted in a decreased incidence of local failure, and 10-year actuarial rates of recurrence that are less than 5 percent[4,5] are not uncommon.

Despite these low rates of local failure in women who were selected for breast-conserving surgery on the basis of physical examination and mammography, it has been suggested that both ultrasonographic studies of the whole breast[6] and magnetic resonance imaging[7] should be part of the preoperative evaluation. These recommendations are based on the identification of unsuspected foci of carcinoma in 16 percent to 37 percent of women[6,7] who undergo these studies. The possibility that small foci of carcinoma can be present in apparently normal breast tissue has been recognized since the 1970s. Pathological studies of breast-tissue specimens from women with localized tumors have shown occult carcinoma in similar proportions of women.[8] In fact, these pathological studies formed the cornerstone of the argument that breast-conserving therapy was inappropriate. The B-06 trial conducted by Fisher et al.[2] demonstrates that these foci of tumor are clinically significant. Among patients treated with lumpectomy alone, the incidence of a recurrence in the ipsilateral breast was 39.2 percent, whereas it was 14.3 percent when the treatment was lumpectomy plus irradiation of the breast. Subjecting women to mastectomy because we now have an imaging technique that is sensitive enough to detect microscopical foci of tumor is not a step forward. Instead, we may be able to use such techniques to identify women who require radiation therapy only in the quadrant in which the primary tumor is located or those who do not require radiation therapy at all.

The risk of local failure in the preserved breast will never be entirely eliminated. Some local failures reflect biologically aggressive disease and are similar to recurrences in the chest wall that occur after mastectomy. Local failures that occur many years after the initial diagnosis are often new primary tumors, indicating that irradiation of the whole breast does not provide long-term protection against cancer. This phenomenon is apparent in the study by Veronesi et al.[3]: the rate of new ipsilateral tumors at a distance from the site of the original primary tumor was similar to the rate of new contralateral tumors (0.42 and 0.66 per 100 woman-years of observation, respectively). Twenty years of experience have shown us that local recurrences due to inappropriate selection of patients or inadequate therapy can be largely eliminated with the use of high-quality diagnostic mammography, excision with negative margins, and postoperative irradiation.

The focus on local recurrence has distracted us from a more serious problem with breast-conserving therapy. Despite a large body of mature scientific data from randomized trials, which is unequaled in the literature on the local treatment of cancer, many women today are not offered the option of breast-conserving therapy. My colleagues and I[9] found that in a national sample of 16,643 women with stage I or II breast cancer who were treated in 1994, only 42.6 percent were treated with a breast-conserving approach. There was a significant correlation between treatment with mastectomy and factors associated with a poor prognosis, such as the size of the tumor, nodal status, and histologic grade. The preferential use of mastectomy for women who have a poor prognosis strongly suggests that 20 years later breast-conserving therapy

is still not accepted as equivalent to mastectomy, but is instead viewed as a less aggressive therapy appropriate only for women with a good prognosis.

What proportion of women with breast cancer should receive breast-conserving therapy? The answer depends on the particular population of women, but a reasonable goal is that every woman should be informed of the availability of breast-conserving therapy and of the suitability of the procedure in her particular case. In a study of 231 women with breast cancer who were seen for a second opinion between 1996 and 1999, Clauson et al.[10] reported that 29 percent of the women had been offered only the option of a mastectomy during the initial consultation. The women in this study were from a metropolitan area, 70 percent had more than a high-school education, 62 percent reported an annual family income of more than $30,000, and more than 90 percent had health insurance. If a substantial proportion of educated and insured women do not receive complete information about options for treatment, the problem may be even more serious in disadvantaged populations.

Efforts to expand eligibility for breast-conserving therapy and to reduce the associated morbidity are well under way. Preoperative chemotherapy and endocrine therapy have been shown to be safe and effective ways to shrink tumors that are too large for a lumpectomy with a good cosmetic result. Accelerated fractionation schedules and brachytherapy are being studied as alternatives to six weeks of external-beam irradiation. However, if we do not apply what we have learned from the pioneering work of Fisher and Veronesi and their colleagues to the treatment of the women with breast cancer we see today, we will have made little or no progress over the past 20 years in the search for a rational approach to the local treatment of breast cancer. It is time to declare the case against breast-conserving therapy closed and focus our efforts on new strategies for the prevention and cure of breast cancer.

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REFERENCES

1. Urban JA. Changing patterns of breast cancer: Lucy Wortham James lecture (clinical). Cancer 1976;37:111-7.
2. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 2002; 347:1233-41.
3. Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med 2002;347:1227-32.
4. Smitt MC, Nowles KW, Zdeblich MJ, et al. The importance of the lumpectomy surgical margin status in long-term results of breast conservation. Cancer 1995;76:259-67.
5. Peterson ME, Schultz DJ, Reynolds C, Solin LJ. Outcomes in breast cancer patients relative to margin status after treatment with breast-conserving surgery and radiation therapy: the University of Pennsylvania experience. Int J Radiat Oncol Biol Phys 1999;43:1029-35.
6. Moon WK, Noh DY, Im GJ. Multifocal, multicentric, and contralateral breast cancers: bilateral whole-breast US in the preoperative evaluation of patients. Radiology 2002;224:569-76.
7. Orel SG, Schnall MD, Powell CM, et al. Staging of suspected breast cancer: effect of MR imaging and MR-guided biopsy. Radiology 1995; 196:115-22.
8. Rosen PP, Fracchia AA, Urban JA, Schottenfeld D, Robbins GF. "Residual" mammary carcinoma following simulated partial mastectomy. Cancer 1975;35:739-47.
9. Morrow M, White J, Moughan J, et al. Factors predicting the use of breast-conserving therapy in stage I and II breast carcinoma. J Clin Oncol 2001;19:2254-62.
10. Clauson J, Hsieh YC, Acharya S, Rademaker AW, Morrow M. Results of the Lynn Sage Second-Opinion Program for local therapy in patients with breast carcinoma: changes in management and determinants of where care is delivered. Cancer 2002;94:889-94.

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Labor Induction versus Expectant Management in Low-Risk Nulliparous Women

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ABSTRACT

BACKGROUND

The perinatal and maternal consequences of induction of labor at 39 weeks among low-risk nulliparous women are uncertain.

METHODS

In this multicenter trial, we randomly assigned low-risk nulliparous women who were at 38 weeks 0 days to 38 weeks 6 days of gestation to labor induction at 39 weeks 0 days to 39 weeks 4 days or to expectant management. The primary outcome was a composite of perinatal death or severe neonatal complications; the principal secondary outcome was cesarean delivery.

RESULTS

A total of 3062 women were assigned to labor induction, and 3044 were assigned to expectant management. The primary outcome occurred in 4.3% of neonates in the induction group and in 5.4% in the expectant-management group (relative risk, 0.80; 95% confidence interval [CI], 0.64 to 1.00). The frequency of cesarean delivery was significantly lower in the induction group than in the expectant-management group (18.6% vs. 22.2%; relative risk, 0.84; 95% CI, 0.76 to 0.93).

CONCLUSIONS

Induction of labor at 39 weeks in low-risk nulliparous women did not result in a significantly lower frequency of a composite adverse perinatal outcome, but it did result in a significantly lower frequency of cesarean delivery. (Funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development; ARRIVE ClinicalTrials.gov number, NCT01990612.)

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*A list of other members of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network is provided in the Supplementary Appendix, available at NEJM.org.

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EDITORIAL

Choices in Managing Full-Term Pregnancy

Michael F. Greene, M.D.

The distribution of the length of gestation at delivery in the United States has changed dramatically over the past 25 years. The percentage of all deliveries during the 39th or 40th week of gestation has increased, while the dispersion around that peak has narrowed considerably; this change is even more dramatic for singleton pregnancies. In 2015, a total of 60.2% of all singletons were delivered during the 39th or 40th week, 7.1% were delivered at 41 weeks or later, and 0.4% were delivered at 42 weeks or later (a decline from 0.6% in 2007).[1] Yet perinatal mortality at 41 weeks of gestation or later has increased (from 3.5 per 1000 deliveries in 2007 to 5.9 per 1000 deliveries in 2015).

Recognition of the fact that, among full-term fetuses, mortality is at its minimum at 39 weeks and increases with progression beyond 41 weeks (Fig. 1)[2] has stimulated interest in elective induction of labor at 39 weeks of gestation. Enthusiasm for routine elective induction has been tempered by concerns that the practice might increase the rate of operative deliveries and because of deference to a perceived public preference for a less interventionist approach to the management of healthy pregnancies at full term. A recent Cochrane meta-analysis of 20 randomized trials suggested that a policy of routine induction of labor at 39 weeks would not increase the risk of operative deliveries and might reduce the perinatal mortality rate.[3] Among these studies was a randomized trial conducted in the United Kingdom that compared induction of labor at 39 weeks with expectant management among 619 women 35 years of age or older; the trial showed that induction did not result in a higher rate of operative deliveries and did not adversely affect women's perceived experience of childbirth.[4]

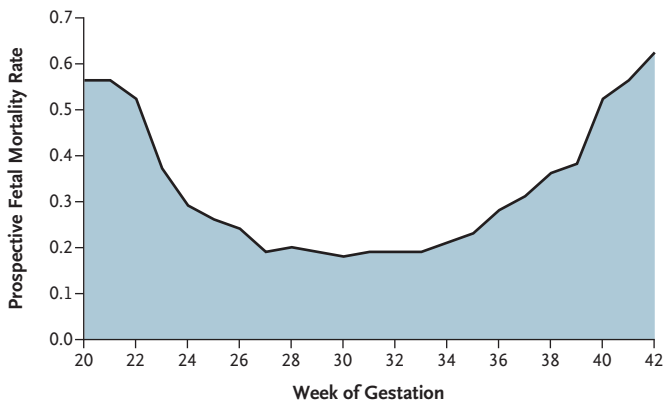

Figure 1. Prospective Fetal Mortality Rate According to Week of Gestation.
The prospective fetal mortality rate was calculated as the number of fetal deaths at a given gestational age per 1000 live births and fetal deaths at that gestational age or greater. Adapted from MacDorman and Gregory.[2]

In this issue of the *Journal*, Grobman et al. report the results of a randomized trial involving healthy women with singleton pregnancies and without indication for cesarean delivery at 41 obstetrical centers in the United States participating in the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network.[5] Women were randomly assigned in a 1:1 ratio to either routine induction of labor from 39 weeks 0 days to 39 weeks 4 days of gestation or to expectant management until 40 weeks 5 days, with delivery initiated no later than 42 weeks 2 days. The primary outcome was a composite of perinatal death or severe neonatal complications. The trial planned to enroll 6000 women to provide adequate power to detect a 40% lower rate of this outcome in the induction group than in the expectant-management group; the anticipated rate of the primary outcome was 3.5% in the expectant-management group.

More than 50,000 women were screened for

eligibility, more than 44,000 were excluded, and more than 16,000 declined to participate. Data from the National Center for Health Statistics suggest that the trial participants differed from the general population of women who delivered in the United States in 2016.[6] Participants in the trial were younger, with a median age of 23 to 24 (vs. a mean age of 28.7 years for all U.S. mothers), and 4.1% were 35 years of age or older (vs. 17% for all U.S. mothers). Participants in this trial were less likely to be white and more likely to be black or Hispanic than women who delivered in the United States in 2016.[6]

The rate of the primary outcome was 5.4% in the expectant-management group (greater than expected) and 4.3% in the induction group; this represented a 20% lower rate that was not significant at the prespecified $P<0.046$ level. The difference between the groups in the primary outcome was driven by a 29% lower rate in the requirement for respiratory support among neonates whose mothers were in the induction group than among those whose mothers were in the expectant-management group. In addition, there was a significantly lower rate of cesarean delivery, the principal secondary outcome, in the induction group than in the expectant-management group (18.6% vs. 22.2%) and 35% fewer diagnoses of hypertensive disorders of pregnancy. The overall length of mothers' hospital stay was shorter in the induction group (owing to the lower rate of cesarean delivery in this group), but this contrasted with a longer stay in the labor and delivery unit (a median of 20 hours, vs. 14 hours in the expectant-management group).

Readers can only speculate as to why so many women declined to participate in the trial and what implications the demographics of the participants may have for the generalizability of the trial results and the acceptability of elective induction of labor at 39 weeks among women in the United States more generally. If induction at 39 weeks becomes a widely popular option, busy obstetrical centers will need to find new ways to accommodate larger numbers of women with longer lengths of stay in the labor and delivery unit. These results across multiple obstetrical centers in the United States, however, should reassure women that elective induction of labor at 39 weeks is a reasonable choice that is very unlikely to result in poorer obstetrical outcomes.

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

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1. Ananth CV, Goldenberg RL, Friedman AM, Vintzileos AM. Association of temporal changes in gestational age with perinatal mortality in the United States, 2007-2015. JAMA Pediatr 2018;172:627-34.
2. MacDorman MF, Gregory EC. Fetal and perinatal mortality: United States, 2013. Natl Vital Stat Rep 2015;64:1-24.
3. Middleton P, Shepherd E, Crowther CA. Induction of labour for improving birth outcomes for women at or beyond term. Cochrane Database Syst Rev 2018;5:CD004945.
4. Walker KF, Bugg GJ, Macpherson M, et al. Randomized trial of labor induction in women 35 years of age or older. N Engl J Med 2016;374:813-22.
5. Grobman WA, Rice MM, Reddy UM, et al. Labor induction versus expectant management in low-risk nulliparous women. N Engl J Med 2018;379:513-23.
6. Martin JA, Hamilton BE, Osterman MJK, Driscoll AK, Drake P. Births: final data for 2016. Natl Vital Stat Rep 2018;67:1-55.

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