NOTABLE ARTICLES OF 2016

A collection of important studies from the past year as selected by NEJM editors
Dear Reader,

In 2016, the *Journal* published trials that sought to answer complicated questions. One such study looked at whether men with early prostate cancer should undergo prostatectomy, radiation, or “watchful waiting” to achieve the best outcome at 10 years. This study found that men with low-risk or intermediate-risk prostate cancer had low prostate-cancer–specific mortality after 10 years, irrespective of the treatment assigned. Importantly, these data helped with the conundrum of treating prostate cancer. Since this is a disease of older men, the study balanced the competing issues of aggressive treatment of a redolent disease with the reality that other factors may claim the life of the patient before he succumbs to prostate cancer. It provided solid landmarks for men wrestling with what to do when they were diagnosed with low-intermediate risk prostate cancer.

Another study examined whether inducing labor at 39 weeks in pregnant women 35 years of age or older, compared to expectant management, reduced stillbirth. While the study was underpowered to assess differences in perinatal outcomes, it found no effect between the two groups on the rate of caesarean section. This trial makes an important contribution to our current medical knowledge, and helps build the foundation for larger, forthcoming studies. And even without larger studies, the data presented helped pregnant women and their physicians visualize the risks and benefits of inducing labor.

As the medical information published in NEJM is regularly used in daily practice, we ensure each paper published meets exacting standards for editorial quality, clinical relevance, and impact on patient outcomes. Among all papers published in 2016, this “most notable” collection was selected by the editors as being the most meaningful in improving medical practice and patient care. We hope that you will take valuable insights from these articles as you continue along your path of lifelong learning.

Jeffrey M. Drazen, M.D.
Editor-In-Chief, The New England Journal of Medicine
Distinguished Parker B. Francis Professor of Medicine
Harvard Medical School
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BACKGROUND
The prevalence of dementia is expected to soar as the average life expectancy increases, but recent estimates suggest that the age-specific incidence of dementia is declining in high-income countries. Temporal trends are best derived through continuous monitoring of a population over a long period with the use of consistent diagnostic criteria. We describe temporal trends in the incidence of dementia over three decades among participants in the Framingham Heart Study.

METHODS
Participants in the Framingham Heart Study have been under surveillance for incident dementia since 1975. In this analysis, which included 5205 persons 60 years of age or older, we used Cox proportional-hazards models adjusted for age and sex to determine the 5-year incidence of dementia during each of four epochs. We also explored the interactions between epoch and age, sex, apolipoprotein E ε4 status, and educational level, and we examined the effects of these interactions, as well as the effects of vascular risk factors and cardiovascular disease, on temporal trends.

RESULTS
The 5-year age- and sex-adjusted cumulative hazard rates for dementia were 3.6 per 100 persons during the first epoch (late 1970s and early 1980s), 2.8 per 100 persons during the second epoch (late 1980s and early 1990s), 2.2 per 100 persons during the third epoch (late 1990s and early 2000s), and 2.0 per 100 persons during the fourth epoch (late 2000s and early 2010s). Relative to the incidence during the first epoch, the incidence declined by 22%, 38%, and 44% during the second, third, and fourth epochs, respectively. This risk reduction was observed only among persons who had at least a high school diploma (hazard ratio, 0.77; 95% confidence interval, 0.67 to 0.88). The prevalence of most vascular risk factors (except obesity and diabetes) and the risk of dementia associated with stroke, atrial fibrillation, or heart failure have decreased over time, but none of these trends completely explain the decrease in the incidence of dementia.

CONCLUSIONS
Among participants in the Framingham Heart Study, the incidence of dementia has declined over the course of three decades. The factors contributing to this decline have not been completely identified. (Funded by the National Institutes of Health.)
Is Dementia in Decline? Historical Trends and Future Trajectories

David S. Jones, M.D., Ph.D., and Jeremy A. Greene, M.D., Ph.D.

In 2005, researchers from the Duke Center for Demographic Studies reported a “surprising trend”; data from the National Long-Term Care Surveys showed that the prevalence of severe cognitive impairment in the Medicare population had decreased significantly between 1982 and 1999.¹ At a time when baby-boomer demographics led to predictions of a looming dementia crisis, this finding offered hope. Since that time, other reports have similarly shown that the incidence or prevalence of dementia is decreasing in various populations. Researchers have offered many possible explanations, including increased wealth, better education, control of vascular risk factors, and use of statins, antihypertensive agents, and nonsteroidal antiinflammatory drugs.²,³ However, even as researchers describe their “cautious optimism” about specific populations, they still project a quadrupling of global prevalence over the coming decades.³

In this issue of the Journal, Satizabal and colleagues report more “robust evidence” of dementia’s decline (pages 523–32). Using surveillance data collected from the Framingham Heart Study from 1975 to the present, they found a 20% decrease in dementia incidence each decade, even as average body-mass index, diabetes prevalence, and population age have increased. Can we now conclude that the tide has turned in the dementia epidemic? The potential decline of dementia, seen in light of the rise and fall of other major diseases, raises an even more tantalizing prospect: Can we control our burden of disease?

This is not the first time that the medical profession and the public health community have struggled to interpret reports of an unexpected reversal of a chronic-disease epidemic.⁴ In 1964, California health officials reported that rates of coronary artery disease (CAD) had begun to decrease. This finding, which defied the widespread belief that the CAD epidemic would only worsen as life expectancy grew, garnered scant attention. Even a decade later, most health officials assumed that CAD was still on the rise. It was only in 1974 that researchers began taking the prospect of decline seriously. By 1978, they had accepted that CAD’s national decline had begun in the mid-1960s. Similar decreases were soon reported in many other high-income countries, from Australia to Finland. This recognition triggered debate over the contribution of medical and public health interventions, in hopes that knowledge of the causes of decline would guide policies and resource allocation and ensure continuation of these health benefits.

The history of the debate on CAD decline carries important lessons for emerging reports of dementia’s decline. First, it can be extremely difficult to produce timely and convincing data about the trajectories of chronic diseases.⁴ When physicians began to debate CAD trends in 1974, they had to rely on government data that were 5 years out of date. It took 4 years of concerted effort to reach consensus about an inflection that had occurred more than a decade earlier. Even though better and timelier data are now available, dementia researchers must still be resourceful in seeking convincing data. As Satizabal et al. indicate, each existing report has limitations. Their new data, which overcome many of these limitations, demonstrate the value of investments in long-term, longitudinal epidemiologic research such as the Framingham Heart Study. But the data still reflect only one population sample. Whether they are accepted as conclusive evidence of a broad-based reduction in dementia incidence will become clear only over time.

Second, since trajectories of chronic-disease incidence reflect complex interactions of many causal factors, it will almost always be uncertain whether decreases will continue or reverse. Even as consensus about international CAD reduction consolidated between the 1970s and the 1990s, worrisome evidence about countervailing trends also appeared.⁴ Enthusiasm for anti-CAD public health campaigns has been fragile, even in countries like
Finland that demonstrated their promise so well. The widespread increases in obesity and diabetes could fuel CAD resurgences. Many researchers have warned that CAD’s decline could stall or even reverse — something that has happened among young adults and other subpopulations in Europe, Australia, and the United States. Other countries, such as China, continue to see increases in CAD with no evidence of plateau or reversal.

History offers reasons for hope. Evidence of dementia’s decline shows once again that our burden of disease is malleable.

All these countervailing trends could affect dementia as well. Rocca and colleagues have warned that increases in obesity, diabetes, and hypertension could undermine the gains achieved through improved education, wealth, and control of vascular risk factors. Even if a dementia decline has begun, it might not last: the outcome depends on the balance of diverging trends.2,3

Third, these ambiguities open up a battleground for conflicting interpretations by interested parties. Policymakers can use the same data to tell vastly different stories about public health. Forecasts of CAD’s future continue to swing between narratives of triumph and catastrophe.4 The good news is that more and more countries are reporting evidence of decline. The bad news is the evidence of the fragility of these gains.

Narratives of dementia remain similarly malleable. In the early 1980s, even after CAD’s decline had been accepted and despite knowledge that dementia shares many risk factors with CAD, physicians began to warn about an exploding dementia epidemic.5 The decrease in prevalence that surprised Manton and colleagues in 2005 could have been predicted decades earlier. But dementia will remain a problem despite these decreases. The prevalence of dementia can increase, even if the incidence falls, if global population live longer. The absolute number of people with dementia can increase, even if both incidence and prevalence fall, if the size of the elderly population grows. That explains why, 10 years into the era of reports of decreasing dementia in selected populations, Satizabal and colleagues still write that the “prevalence of dementia is expected to soar as our societies age.” Even researchers rigorously examining the evidence of decreases continue to worry about what the future will bring.

History offers reasons for hope. Evidence of dementia’s decline shows once again that our burden of disease is malleable. This lesson has been hard won. Mid-19th-century physicians saw cholera and tuberculosis as inevitable scourges of urban environments. But those epidemics yielded to sanitary reform, improved standards of living, and eventually medical care. As control of infectious disease led to dramatic gains in life expectancy, physicians in the early 20th century came to see CAD and cancer as the inevitable scourges of long lives. Over recent decades, that pessimism has largely given way as well: CAD and many forms of cancer are increasingly preventable and curable. The burden of disease of the 20th century, like that of the 19th, was not an inevitable fact of life, but a product of lives lived amid specific — and malleable — conditions.

What should we expect as cancer and heart disease come under control? Many people think that we can live even longer lives — but lives compromised by dementia, vision loss, and hearing loss. Whether that fate is inevitable or whether these, too, are malleable scourges remains to be seen. Such questions are better left to futurists and geriatricians than to historians. Yet Satizabal et al. believe there’s cause for “cautious hope.” Primary and secondary prevention might diminish the magnitude of the long-feared dementia epidemic. Something else might save our vision and hearing.

Faced with choices between equally defensible epidemiologic projections, physicians and researchers must think carefully about what stories they emphasize to patients and policymakers. The implications, especially for investment in long-term care facilities, are enormous. Our explanations of decline are equally important, since they guide investments in behavior change, medications, and other treatments.

With this latest contribution, optimism about dementia is more justified than ever before. Even if death and taxes remain inevita-
Is Dementia in Decline?

BLE, cancer, CAD, and dementia may not. But cautious optimism should not become complacency. If we can elucidate the changes that have contributed to these improvements, perhaps we can extend them. Today, the dramatic reductions in CAD-related mortality are under threat. The incipient improvements in dementia are presumably even more fragile. The burden of disease, ever malleable, can easily relapse.

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

From the Department of Global Health and Social Medicine, Harvard Medical School, Boston (D.S.); the Department of the History of Science, Harvard University, Cambridge, MA (D.S.); and the Division of General Internal Medicine and the Department of the History of Medicine, Johns Hopkins University School of Medicine, Baltimore (J.A.G.).


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Effects of Testosterone Treatment in Older Men

for the Testosterone Trials Investigators*

BACKGROUND
Serum testosterone concentrations decrease as men age, but benefits of raising testosterone levels in older men have not been established.

METHODS
We assigned 790 men 65 years of age or older with a serum testosterone concentration of less than 275 ng per deciliter and symptoms suggesting hypoandrogenism to receive either testosterone gel or placebo gel for 1 year. Each man participated in one or more of three trials — the Sexual Function Trial, the Physical Function Trial, and the Vitality Trial. The primary outcome of each of the individual trials was also evaluated in all participants.

RESULTS
Testosterone treatment increased serum testosterone levels to the mid-normal range for men 19 to 40 years of age. The increase in testosterone levels was associated with significantly increased sexual activity, as assessed by the Psychosexual Daily Questionnaire (P<0.001), as well as significantly increased sexual desire and erectile function. The percentage of men who had an increase of at least 50 m in the 6-minute walking distance did not differ significantly between the two study groups in the Physical Function Trial but did differ significantly when men in all three trials were included (20.5% of men who received testosterone vs. 12.6% of men who received placebo, P=0.003). Testosterone had no significant benefit with respect to vitality, as assessed by the Functional Assessment of Chronic Illness Therapy–Fatigue scale, but men who received testosterone reported slightly better mood and lower severity of depressive symptoms than those who received placebo. The rates of adverse events were similar in the two groups.

CONCLUSIONS
In symptomatic men 65 years of age or older, raising testosterone concentrations for 1 year from moderately low to the mid-normal range for men 19 to 40 years of age had a moderate benefit with respect to sexual function and some benefit with respect to mood and depressive symptoms but no benefit with respect to vitality or walking distance. The number of participants was too few to draw conclusions about the risks of testosterone treatment. ( Funded by the National Institutes of Health and others; ClinicaTrials.gov number, NCT00799617.)
Establishing a Framework — Does Testosterone Supplementation Help Older Men?

Eric S. Orwoll, M.D.

Aging is variably but inevitably accompanied by declines in health; concomitantly, in men, circulating sex-steroid levels fall with age. To what extent these two processes are causally linked and whether testosterone therapy can prevent or ameliorate important age-related problems have been major issues in men's health. In 2003, a committee assembled by the Institute of Medicine (IOM) found a paucity of randomized, placebo-controlled clinical trials involving older men and noted a lack of definite evidence that testosterone therapy conferred benefits. The committee recommended that clinical trials be initiated, first to evaluate the efficacy of testosterone supplementation in older men and then to assess long-term benefits and risks through large-scale trials.

Little has changed to alter the conclusions of that report; if anything, the issue of testosterone supplementation has become more controversial. However, in this issue of the Journal, Snyder et al. describe the long-awaited initial results of the National Institutes of Health–sponsored Testosterone Trials, which were designed to address the key issues identified by the IOM. Their report is important, not only because it deals with an essential public health issue but also because the investigators have succeeded in conducting the kind of generally well-conceived studies that are sorely needed in the field. The findings begin to provide a basis for more rational clinical decisions about testosterone use as well as for additional research.

The overall design of the Testosterone Trials is complex. It includes seven independent, double-blind, placebo-controlled trials intended to address specific outcomes that are postulated to be related to testosterone deficiency (sexual function, vitality, physical function, cognitive function, anemia, bone density, and cardiovascular status). The trials are knitted together by common methods and some shared measures, thus maximizing the power of the overall investigation. This inaugural report describes the findings of the three main studies (with primary outcomes related to sexual function, physical function, and vitality).

The results show that testosterone therapy did yield certain benefits, but at this point their clinical importance is uncertain. Therapy was not a panacea, and the findings alone might be insufficient to support a decision to initiate testosterone therapy in symptomatic older men. The study confirmed that testosterone supplementation can yield improvements in sexual function, but the benefits were modest, tended to wane in the latter months of the treatment period, and, as the authors note, were not as robust as those of phosphodiesterase type 5 inhibitors. There were only small gains in physical performance and in indexes of mood and depression; overall vitality was no better with testosterone therapy than with placebo. For each of the outcomes, some older men may have a more vigorous response to testosterone therapy and thus could be more attractive candidates for supplementation; however, it was not possible to confidently identify them by the testosterone levels achieved with therapy. As expected, estradiol levels also increased; those levels have been linked to key health variables in men (e.g., sexual function). It's not yet clear whether responses (or the lack thereof) in the Testosterone Trials may be due to changes in estradiol levels.

There is considerable controversy about possible adverse effects of testosterone therapy in older men, and these studies do not resolve this controversy. Although there were minor effects
on hemoglobin and prostate-specific antigen levels, and, reassuringly, no apparent major toxic effects, larger and more extended trials would be needed to determine whether therapy has negative effects on outcomes such as prostate or cardiovascular health.

Importantly, the study participants were recruited on the basis of stringent criteria (age ≥65 years, total testosterone levels below the normal range in men 19 to 40 years of age [≤275 ng per deciliter], symptoms related to predetermined outcomes, and no contraindications to participation). Only 1.5% of those screened (790 of 51,085 men) were eligible and enrolled. The average participant was 72 years of age; almost 90% of participants were white, most were obese, most had hypertension, more than one third had diabetes, and almost 20% had sleep apnea. The select nature of the participants reflects the scientific rigor of the trials (and the causes of low testosterone levels) but also clearly limits the generalizability of the conclusions. We should not assume that the benefits, lack of benefits, or adverse-event profile observed in these studies would be similar in younger men (most testosterone prescriptions are written for middle-aged men3), men with higher testosterone levels, or those with different demographic or clinical characteristics.

The report by Snyder et al. is likely to stimulate controversy and to engender additional research questions — as did the Women’s Health Initiative with respect to estrogen-replacement therapy. Nevertheless, it is a landmark study in the field of men’s health and no doubt a bellwether for additional important contributions from the Testosterone Trials.

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

From the Department of Medicine, Oregon Health and Science University, Portland.


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National Cluster-Randomized Trial of Duty-Hour Flexibility in Surgical Training


ABSTRACT

BACKGROUND
Concerns persist regarding the effect of current surgical resident duty-hour policies on patient outcomes, resident education, and resident well-being.

METHODS
We conducted a national, cluster-randomized, pragmatic, noninferiority trial involving 117 general surgery residency programs in the United States (2014–2015 academic year). Programs were randomly assigned to current Accreditation Council for Graduate Medical Education (ACGME) duty-hour policies (standard-policy group) or more flexible policies that waived rules on maximum shift lengths and time off between shifts (flexible-policy group). Outcomes included the 30-day rate of postoperative death or serious complications (primary outcome), other postoperative complications, and resident perceptions and satisfaction regarding their well-being, education, and patient care.

RESULTS
In an analysis of data from 138,691 patients, flexible, less-restrictive duty-hour policies were not associated with an increased rate of death or serious complications (9.1% in the flexible-policy group and 9.0% in the standard-policy group, P=0.92; unadjusted odds ratio for the flexible-policy group, 0.96; 92% confidence interval, 0.87 to 1.06; P=0.44; noninferiority criteria satisfied) or of any secondary postoperative outcomes studied. Among 4330 residents, those in programs assigned to flexible policies did not report significantly greater dissatisfaction with overall education quality (11.0% in the flexible-policy group and 10.7% in the standard-policy group, P=0.86) or well-being (14.9% and 12.0%, respectively; P=0.10). Residents under flexible policies were less likely than those under standard policies to perceive negative effects of duty-hour policies on multiple aspects of patient safety, continuity of care, professionalism, and resident education but were more likely to perceive negative effects on personal activities. There were no significant differences between study groups in resident-reported perception of the effect of fatigue on personal or patient safety. Residents in the flexible-policy group were less likely than those in the standard-policy group to report leaving during an operation (7.0% vs. 13.2%, P<0.001) or handing off active patient issues (32.0% vs. 46.3%, P<0.001).

CONCLUSIONS
As compared with standard duty-hour policies, flexible, less-restrictive duty-hour policies for surgical residents were associated with noninferior patient outcomes and no significant difference in residents’ satisfaction with overall well-being and education quality. (FIRST ClinicalTrials.gov number, NCT02050789.)
Surgical Resident Duty-Hour Rules — Weighing the New Evidence

John D. Birkmeyer, M.D.

Surgical training has always been hard on residents. During my own residency more than 20 years ago, 100-hour workweeks and in-house call every other night were routine. A resident’s life outside the hospital was simply not a priority. Residency may be even harder on patients. A large body of research has linked sleep deprivation in resident physicians to poor performance in neuropsychobehavioral testing and, more alarmingly, to higher rates of attention failure in patient care.1,2

Reacting to concerns about both resident well-being and patient safety, the Accreditation Council for Graduate Medical Education (ACGME) implemented duty-hour reforms in 2003 that constrained resident workweeks to 80 hours, among other changes. A 2011 update added new limits to the length of individual shifts (24 hours plus 4 hours for transition) and guaranteed a minimum amount of time off between 24-hour shifts (14 hours). Although they are not nearly as stringent as standards set in other occupations in which performance has implications for public safety (e.g., airline pilots), the ACGME rules were nonetheless criticized by many in the medical community. Surgeons in particular were concerned that the new duty-hour rules would paradoxically increase medical errors as a result of increased handoffs — residents signing out their sickest patients to providers who are not familiar with their cases.1,2

Extending the results of a previous national study based on Medicare claims data,3 a very ambitious, scientifically robust study by Bilimoria et al. now published in the Journal should help allay these concerns.4 By random assignment, 59 general-surgery training programs were required to adhere to the ACGME rules about maximum shift length and minimum time off between 24-hour shifts. Another 59 programs were granted “flexibility” and did not have to adhere to those rules. Both groups adhered to ACGME requirements for total workweek hours. Residents who were not required to adhere to the duty-hour rules were less likely to report dissatisfaction with continuity of care and hand-offs. After 1 year, however, the two groups of teaching hospitals had virtually indistinguishable rates of death, overall complications, and specific types of complications, on the basis of data on risk-adjusted clinical outcomes from the American College of Surgeons National Surgical Quality Improvement Program.

It is not surprising that outcomes did not vary according to whether programs adhered to ACGME requirements on maximum shift length and time off between shifts. The patients most likely to be affected by resident handoffs — those with acute or deteriorating clinical conditions — represent only a small percentage of surgical patients at teaching hospitals. More important, teaching hospitals have become far less reliant on surgical residents than they used to be. In earlier eras, surgical residents had considerable autonomy. During my own residency, surgical residents often operated independently, particularly at night and on weekends. Today, they operate almost exclusively in the presence of an attending surgeon. Intensive care units, which house the sickest surgical patients, are increasingly “closed” and staffed by board-certified intensivists. Postoperative care is delivered by multidisciplinary teams staffed with associate providers as well as residents.
The Flexibility in Duty Hour Requirements for Surgical Trainees (FIRST) Trial also assessed the effects of ACGME duty-hour restrictions on resident perceptions of educational quality and well-being, with the use of survey data collected annually by the American Board of Surgery. Residents in the two groups of teaching hospitals had similarly high rates of satisfaction with the quality of their training. Although residents in programs not required to adhere to the ACGME duty-hour rules were more likely to be dissatisfied with time for rest, there were no significant differences in overall resident well-being and morale between the two groups.

What do the results of the FIRST Trial mean for ACGME policy on resident duty hours? The authors conclude, as will many surgeons, that surgical training programs should be afforded more flexibility in applying work-hour rules. This interpretation implicitly places the burden of proof on the ACGME. Thus, because the FIRST Trial found no evidence that removing restrictions on resident shift length and time off between shifts was harmful to patients, programs should have more autonomy to train residents as they choose.

I reach a different conclusion. The FIRST Trial effectively debunks concerns that patients will suffer as a result of increased handoffs and breaks in the continuity of care. Rather than backtrack on the ACGME duty-hour rules, surgical leaders should focus on developing safe, resilient health systems that do not depend on overworked resident physicians. They should also recognize the changing expectations of post-millennial learners. To many current residents and medical students, 80-hour (or even 72-hour) workweeks and 24-hour shifts probably seem long enough. Although few surgical residents would ever acknowledge this publicly, I’m sure that many love to hear, “We can take care of this case without you. Go home, see your family, and come in fresh tomorrow.”

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

From the Dartmouth–Hitchcock Medical Center and the Dartmouth Institute for Health Policy and Clinical Practice — both in Lebanon, NH.

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In 2014, Facebook users were furious to discover that they’d unwittingly been experimented on. Researchers had randomly assigned users to news feeds with reduced “positive” content or reduced “negative” content and found that happy posts beget happy posts and that grim ones beget grim ones. Although that may now seem obvious, previous evidence had suggested that because we tend to compare ourselves to others, exposure to positive content compromises users’ well-being. There was thus no reason to believe that the status quo — news feeds curated by an algorithm tailored to users’ viewing habits — was any “safer” than the experimental interventions. And given Facebook’s reach, there were compelling reasons to find out. Nevertheless, the results triggered outrage that 700,000 users had been exposed to potential emotional damage without their consent.

Similar accusations have been leveled at investigators who are comparing the 2011 duty-hour restrictions imposed by the Accreditation Council for Graduate Medical Education (ACGME) with more flexible shift lengths for residents. The Flexibility in Duty Hour Requirements for Surgical Trainees (FIRST) trial, whose results are now reported by Bilimoria et al. in the Journal, compared 59 surgical training programs randomly assigned to an ACGME-compliant schedule with 58 grant-funded flexibility in designing shift lengths (still within an 80-hour workweek). The ongoing Individualized Comparative Effectiveness of Models Optimizing Safety and Resident Education (iCOMPARE) trial involves internal medicine programs. Both used cluster randomization at the residency-program level, and neither required consent of residents or patients. That consent waiver has drawn criticism from Public Citizen and the American Medical Student Association, which in open letters to the Office for Human Research Protections (OHRP) accuse the investigators of “egregious ethical and regulatory violations.”

The allegations, focused primarily on “serious health risks” to residents from long shifts, are dizzyingly tautological. The critics claim it’s unethical not to obtain residents’ consent; but because pressure on residents to conform makes seeking their consent akin to coercion, that’s unethical too. Thus, there’s no ethical way to study the duty-hour rules in a randomized fashion. But that’s fine, because we already know they’re beneficial; we know that because the ACGME made the rules in the first place. And if the trials found otherwise, their re-
sults challenging the status quo would be suspect because the investigators, who have publicly acknowledged the need for data to inform policy, are consequently too biased to generate those data.

To unpack these allegations, it’s important to understand that even if the trials are considered

**No drug would be approved solely on the basis of laboratory evidence. Yet we require neither consideration of complexity nor rigorous studies before implementing policies with broad implications. Why?**

human-subjects research, there are circumstances under which federal rules deem it ethical to waive consent. The key one here is that the incremental risk posed by the research should be, at most, minimal. For trials like these that evaluate a standard practice, the question becomes: Is there equipoise between the status quo and investigational groups in terms of possible risks? Though the letters to OHRP claim otherwise, the answer is unequivocally yes. The complaints ignore a considerable body of research suggesting, as Bilimoria et al. point out, that duty-hour reforms have not improved patient safety; some trials have even raised concerns that they’ve actually worsened quality of care and patient outcomes.

As for risks to residents, the letters cite data suggesting that fatigue causes harms such as increased motor vehicle accidents, needlesticks, and burnout. Yet there’s little evidence to suggest that shorter hours have reduced occupational hazards or burnout rates. Though I suspect that these findings partly reflect the emotional toll of “work compression” and the reality that many trainees don’t actually sleep more, they also speak to a fundamental challenge in improving care: the factors affecting physicians’ performance are so numerous and interdependent that no single variable, such as sleep, can be understood or targeted in isolation. Because of the unknown real-life consequences of such myriad interactions, no drug would be approved solely on the basis of laboratory evidence. Yet we require neither consideration of complexity nor rigorous studies before implementing policies with similarly broad implications. Why?

Bioethicist and legal scholar Michelle Meyer has described our “tendency to view a field experiment designed to study the effects of an existing or proposed practice as more morally suspicious than an immediate, universal implementation of an untested practice.” She argues that people in power often rely on intuition in creating and implementing wide-reaching policies. Indeed, neither residents nor patients consented to the ACGME rules, yet no one finds this omission ethically suspect. Moreover, intuition seems particularly salient to debates over duty hours, since everyone knows how it feels to be tired. Unfortunately, few people know how it feels to see a patient through illness, spend a fifth of your time engaged in hand-offs, leave halfway through an operation because your shift’s up, or perceive resentment in your supervisors who think you have it easier than they did. Given such trade-offs and uncertainties, it’s not just ethical but laudable to comparatively evaluate duty-hours policies. The question then becomes: Can the research be accomplished if consent is required?

The Facebook experiment’s results would have been invalid had consent been sought, since we couldn’t determine how much users adjusted their emotional content because they knew it was being monitored. Similarly, requiring residents’ consent in duty-hour trials would render the results uninterpretable, given the selection bias that would be introduced if those preferring longer hours were more likely to participate.

The challenges with regard to patients are more pragmatic. Consider, for instance, caring for a man with a myocardial infarction. After obtaining his consent for percutaneous coronary intervention, you’d have to add, “I also need your consent to be cared for by residents who are working longer hours.” If he said no, would you have to transfer him, as heart muscle continued to die, to a nonteaching hospital? Surely here the risk posed by seeking consent is greater than that from the research itself.

Moreover, as we examine the implications for efforts to develop “learning health systems,” a corollary of this hypothetical situation is worth considering. Imagine telling a patient, “I need your permission to care for you at a hospital where we’re using a new electronic health record, basing your doctor’s reimbursement...
on whether you stay healthy, and are under pressure to discharge you quickly and make sure you don’t come back. We don’t really know how all this will affect your health, but we believe it’s for the better. Can you sign here?”

The point is that our approach to human-subjects research perpetuates a misleading distinction between risks posed by research and those posed by practice, demanding greater scrutiny for investigative efforts while assuming that untested practice is safe. In describing this phenomenon, Meyer cites the moratorium that the OHRP imposed on a study assessing a checklist designed to reduce catheter-related bloodstream infections because researchers hadn’t obtained physicians’ or patients’ consent. The OHRP explained that its regulations don’t apply when institutions are merely “implementing” practices aiming to improve care, but if they’re “planning research activities examining the effectiveness of interventions to improve the quality of care, then the regulatory protections are important to protect the rights and welfare of human research subjects.” This double standard leaves us, paradoxically, with unregulated practices that may be ineffective and unsafe because we can’t surmount the regulatory hurdles to conducting research to improve them.

To address this problem, we must understand the values of the people we’re professing to protect. In one relevant study, Halpern and colleagues asked patients undergoing dialysis to imagine two hypothetical scenarios. In the “research scenario,” patients in a trial are randomly assigned to a prespecified dialysis duration of 4.5 hours or a duration at the physician’s discretion (both approaches are within the standard of care). In the “clinical care scenario,” patients receive dialysis for a duration determined by a protocol (also common practice). Participants were more willing in the research than the practice setting to give up their own decision-making autonomy, including written informed consent. They recognized the value of research and didn’t perceive the hypothetical study as posing higher risk than ordinary care. But they expressed deep reservations about compromising physicians’ autonomy to individualize treatment absent compelling reasons for doing so.

This last finding highlights the ultimate irony of both duty-hour restrictions and objections to studying them: we’ve created an educational system that compromises trainees’ freedom to judge for themselves when their patients need them. The value that physicians and patients place on such autonomy is not measurable in mortality rates or hours slept but should remain foremost in our discussions. An essential contribution of the duty-hour trials is that, in assessing flexibility itself, they remind us that autonomy is an ethical concept that matters to both doctors and patients — in research and in practice.

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

Dr. Rosenbaum is a national correspondent for the Journal.

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Randomized Trial of Labor Induction in Women 35 Years of Age or Older

Kate F. Walker, M.R.C.O.G., George J. Bugg, M.D., Marion Macpherson, M.D., Carol McCormick, M.Sc., Nicky Grace, M.A., Chris Wildsmith, B.A., Lucy Bradshaw, M.Sc., Gordon C.S. Smith, D.Sc., and James G. Thornton, M.D., for the 35/39 Trial Group*

ABSTRACT

BACKGROUND
The risk of antepartum stillbirth at term is higher among women 35 years of age or older than among younger women. Labor induction may reduce the risk of stillbirth, but it also may increase the risk of cesarean delivery, which already is common in this older age group.

METHODS
We conducted a randomized, controlled trial involving primigravida women who were 35 years of age or older. Women were randomly assigned to labor induction between 39 weeks 0 days and 39 weeks 6 days of gestation or to expectant management (i.e., waiting until the spontaneous onset of labor or until the development of a medical problem that mandated induction). The primary outcome was cesarean delivery. The trial was not designed or powered to assess the effects of labor induction on stillbirth.

RESULTS
A total of 619 women underwent randomization. In an intention-to-treat analysis, there were no significant between-group differences in the percentage of women who underwent a cesarean section (98 of 304 women in the induction group [32%] and 103 of 314 women in the expectant-management group [33%]; relative risk, 0.99; 95% confidence interval [CI], 0.87 to 1.14) or in the percentage of women who had a vaginal delivery with the use of forceps or vacuum (115 of 304 women [38%] and 104 of 314 women [33%], respectively; relative risk, 1.30; 95% CI, 0.96 to 1.77). There were no maternal or infant deaths and no significant between-group differences in the women’s experience of childbirth or in the frequency of adverse maternal or neonatal outcomes.

CONCLUSIONS
Among women of advanced maternal age, induction of labor at 39 weeks of gestation, as compared with expectant management, had no significant effect on the rate of cesarean section and no adverse short-term effects on maternal or neonatal outcomes. (Funded by the Research for Patient Benefit Programme of the National Institute for Health Research; Current Controlled Trials number, ISRCTN11517275.)
Induction of Labor and Cesarean Delivery

William A. Grobman, M.D.

At the heart of obstetrical care is a seemingly simple calculus: when are the benefits of delivery greater than the benefits of continued pregnancy? However, making this determination is anything but straightforward, given the potentially conflicting needs of the mother and the needs of her offspring, which must both be taken into account to maximize maternal and perinatal health.

In the absence of maternal or fetal complications, current consensus favors the consideration of delivery between 41 weeks 0 days and 42 weeks 0 days of gestation. In addition, for these women, delivery is recommended after 42 weeks 0 days and no later than 42 weeks 6 days of gestation, given the increase in perinatal morbidity and mortality at these gestational ages. Thus, induction before 41 weeks 0 days of gestation in the absence of complications is considered not to be medically indicated.

One consideration that traditionally has tipped the balance toward continuing pregnancy is the concern that labor induction may increase the risk of cesarean delivery, particularly among nulliparous women. This belief is based on the findings of multiple observational studies in which outcomes in women who underwent induction were compared with those of women who had spontaneous labor. However, spontaneous labor is not a clinical “strategy,” and thus it is not the appropriate comparison.

Observational studies in which outcomes in women who underwent induction were compared with those in women who received expectant management generally have not shown an increased risk of cesarean delivery among women who underwent induction. However, trials that have explored whether, in the absence of complications, labor induction before 41 weeks 0 days of gestation is associated with adverse maternal or perinatal outcomes have been too small to guide clinical practice.

In this issue of the Journal, Walker et al. have attempted to rectify this gap in evidence. They report the results of a trial in which more than 600 women who were at least 35 years of age were randomly assigned to labor induction between 39 weeks 0 days and 39 weeks 6 days of gestation or to expectant management. This study was powered to detect at least a 36% relative difference between the two groups in the frequency of cesarean delivery. A total of 32% of the women assigned to the induction group, as compared with 33% of the women assigned to the expectant-management group, underwent a cesarean delivery (relative risk, 0.99; 95% confidence interval, 0.87 to 1.14). There were no significant differences between the groups in other adverse maternal or perinatal outcomes, but such outcomes were uncommon.

On the basis of the results of this trial, it would be premature to alter recommendations regarding the timing of delivery in uncomplicated pregnancies. Although the study did not show evidence of harm from induction at 39 weeks of gestation, it also did not show evidence of benefit, and one could argue that medical interventions in general, and intervention in the natural progress of gestation specifically, should be performed only when benefit has been shown.

Because this trial was not designed or adequately powered to assess differences in perinatal outcomes, whether labor induction at 39 weeks of gestation affects these outcomes remains unknown. We do not know whether the findings of this trial are generalizable to women younger than 35 years of age or whether the results would differ according to whether or not women require cervical ripening. Finally, women in this trial received care in the United Kingdom, which
has a health delivery system that differs from that of the United States in ways that could affect the relationship between labor induction and cesarean delivery; these differences include a higher rate of operative vaginal delivery in the United Kingdom.9

The authors note the need for “a larger trial to test the effects of induction on stillbirth and uncommon adverse neonatal outcomes.” I am the principal investigator of such a trial (Clinical-Trials.gov number, NCT01990612), which is currently under way within the Maternal–Fetal Medicine Units Network of the Eunice Kennedy Shriver National Institute of Child Health and Human Development. This trial, which has a targeted enrollment of 6000 women, is designed to identify differences in perinatal outcomes among nulliparous women with uncomplicated singleton pregnancies who are randomly assigned to induction between 39 weeks 0 days and 39 weeks 4 days of gestation or to expectant management. The trial is more than halfway complete.

Although the trial by Walker et al. was not designed to assess the effect of labor induction on stillbirth and adverse neonatal outcomes, it makes an important contribution to medical knowledge. It is the largest trial of its type to be completed, and it suggests that a belief that guides decisions about the timing of delivery — namely, that induction of labor at term increases the risk of cesarean delivery — may not be true after all.

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

From the Northwestern University Feinberg School of Medicine, Chicago.


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Randomized Trial of Stent versus Surgery for Asymptomatic Carotid Stenosis

Kenneth Rosenfield, M.D., M.H.C.D.S., Jon S. Matsumura, M.D., Seemant Chaturvedi, M.D., Tom Riles, M.D., Gary M. Ansel, M.D., D. Chris Metzger, M.D., Lawrence Wechsler, M.D., Michael R. Jaff, D.O., and William Gray, M.D., for the ACT I Investigators*

BACKGROUND

Previous clinical trials have suggested that carotid-artery stenting with a device to capture and remove emboli (“embolic protection”) is an effective alternative to carotid endarterectomy in patients at average or high risk for surgical complications.

METHODS

In this trial, we compared carotid-artery stenting with embolic protection and carotid endarterectomy in patients 79 years of age or younger who had severe carotid stenosis and were asymptomatic (i.e., had not had a stroke, transient ischemic attack, or amaurosis fugax in the 180 days before enrollment) and were not considered to be at high risk for surgical complications. The trial was designed to enroll 1658 patients but was halted early, after 1453 patients underwent randomization, because of slow enrollment. Patients were followed for up to 5 years. The primary composite end point of death, stroke, or myocardial infarction within 30 days after the procedure or ipsilateral stroke within 1 year was tested at a noninferiority margin of 3 percentage points.

RESULTS

Stenting was noninferior to endarterectomy with regard to the primary composite end point (event rate, 3.8% and 3.4%, respectively; P=0.01 for noninferiority). The rate of stroke or death within 30 days was 2.9% in the stenting group and 1.7% in the endarterectomy group (P=0.33). From 30 days to 5 years after the procedure, the rate of freedom from ipsilateral stroke was 97.8% in the stenting group and 97.3% in the endarterectomy group (P=0.51), and the overall survival rates were 87.1% and 89.4%, respectively (P=0.21). The cumulative 5-year rate of stroke-free survival was 93.1% in the stenting group and 94.7% in the endarterectomy group (P=0.44).

CONCLUSIONS

In this trial involving asymptomatic patients with severe carotid stenosis who were not at high risk for surgical complications, stenting was noninferior to endarterectomy with regard to the rate of the primary composite end point at 1 year. In analyses that included up to 5 years of follow-up, there were no significant differences between the study groups in the rates of non-procedure-related stroke, all stroke, and survival. (Funded by Abbott Vascular; ACT I ClinicalTrials.gov number, NCT00106938.)
Long-Term Results of Stenting versus Endarterectomy for Carotid-Artery Stenosis

Thomas G. Brott, M.D., George Howard, Dr.P.H., Gary S. Roubin, M.D., Ph.D., James F. Meschia, M.D., Ariane Mackey, M.D., William Brooks, M.D., Wesley S. Moore, M.D., Michael D. Hill, M.D., Vito A. Mantese, M.D., Wayne M. Clark, M.D., Carlos H. Timaran, M.D., Donald Heck, M.D., Pierre P. Leimgruber, M.D., Alice J. Sheffet, Ph.D., Virginia J. Howard, Ph.D., Seemant Chaturvedi, M.D., Brajesh K. Lal, M.D., Jenifer H. Voeks, Ph.D., and Robert W. Hobson II, M.D.,* for the CREST Investigators†

BACKGROUND

In the Carotid Revascularization Endarterectomy versus Stenting Trial, we found no significant difference between the stenting group and the endarterectomy group with respect to the primary composite end point of stroke, myocardial infarction, or death during the periprocedural period or any subsequent ipsilateral stroke during 4 years of follow-up. We now extend the results to 10 years.

METHODS

Among patients with carotid-artery stenosis who had been randomly assigned to stenting or endarterectomy, we evaluated outcomes every 6 months for up to 10 years at 117 centers. In addition to assessing the primary composite end point, we assessed the primary end point for the long-term extension study, which was ipsilateral stroke after the periprocedural period.

RESULTS

Among 2502 patients, there was no significant difference in the rate of the primary composite end point between the stenting group (11.8%; 95% confidence interval [CI], 9.1 to 14.8) and the endarterectomy group (9.9%; 95% CI, 7.9 to 12.2) over 10 years of follow-up (hazard ratio, 1.10; 95% CI, 0.83 to 1.44). With respect to the primary long-term end point, postprocedural ipsilateral stroke over the 10-year follow-up occurred in 6.9% (95% CI, 4.4 to 9.7) of the patients in the stenting group and in 5.6% (95% CI, 3.7 to 7.6) of those in the endarterectomy group; the rates did not differ significantly between the groups (hazard ratio, 0.99; 95% CI, 0.64 to 1.52). No significant between-group differences with respect to either end point were detected when symptomatic patients and asymptomatic patients were analyzed separately.

CONCLUSIONS

Over 10 years of follow-up, we did not find a significant difference between patients who underwent stenting and those who underwent endarterectomy with respect to the risk of periprocedural stroke, myocardial infarction, or death and subsequent ipsilateral stroke. The rate of postprocedural ipsilateral stroke also did not differ between groups. (Funded by the National Institutes of Health and Abbott Vascular Solutions; CREST ClinicalTrials.gov number, NCT00004732.)

From the Mayo Clinic, Jacksonville, FL (T.G.B., J.F.M.); the University of Alabama at Birmingham (G.H., V.J.H.) and Cardiovascular Associates of the Southeast (G.S.R.) — both in Birmingham; Centre Hospitalier Universitaire de Québec–Université Laval, Quebec, QC (A.M.); and the University of Calgary, Calgary, AB (M.D.H.) — both in Canada; Baptist Health Lexington, KY (W.B.); the University of California, Los Angeles, Los Angeles (W.S.M.); Mercy Hospital St. Louis, St. Louis (V.A.M.); Oregon Health and Science University, Portland (W.M.C.); the University of Texas Southwestern Medical Center, Dallas (C.H.T); Novant Health Clinical Research, Winston-Salem, NC (D.H.); the Providence Sacred Heart Medical Center and Children’s Hospital, Spokane, WA (P.P.L.); Rutgers New Jersey Medical School, Newark (A.J.S., R.W.H.); the University of Miami Miller School of Medicine, Miami (S.C.); the University of Maryland Medical Center, Baltimore (B.K.L.); and the Medical University of South Carolina, Charleston (J.H.V.). Address reprint requests to Dr. Brott at the Mayo Clinic, Griffin Bldg. 1st Fl., Rm. 170, 4500 San Pablo Rd. S, Jacksonville, FL 32224, or at brott.thomas@mayo.edu.

*Deceased.
†A complete list of investigators in the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) is provided in the Supplementary Appendix, available at NEJM.org.

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Endarterectomy, Stenting, or Neither for Asymptomatic Carotid-Artery Stenosis

J. David Spence, M.D., and A. Ross Naylor, M.D.

Important data from two large, randomized trials comparing early and late outcomes after carotid endarterectomy and carotid-artery stenting have now been published in the Journal.\textsuperscript{1,2} In common with every other large, multicenter, randomized trial to date, the Asymptomatic Carotid Trial (ACT I) and the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) showed that after the perioperative period, there was no difference in the rate of late ipsilateral stroke after endarterectomy or stenting. In ACT I, which included asymptomatic patients who were deemed to be at average risk, the 5-year rate of ipsilateral stroke (excluding the perioperative period) was 2.2% after stenting (i.e., 0.4% per year) and 2.7% after endarterectomy (0.5% per year).\textsuperscript{1} In CREST, which included symptomatic and asymptomatic patients who were deemed to be at average risk, the estimated 10-year rate of ipsilateral stroke (excluding the perioperative period) was 6.9% after stenting (i.e., 0.7% per year) and 5.6% (0.6% per year) after endarterectomy.\textsuperscript{2}

The fact that there is near-unanimous consensus within randomized trials that after the perioperative period the rates of late ipsilateral stroke after stenting do not differ significantly from those after endarterectomy should dispel any lingering concerns about the durability of stenting. That issue has now surely been resolved. What has not been resolved, however, is the issue of the generalizability of randomized-trial findings into routine clinical practice, and, more importantly, the vexed question of how best to treat the asymptomatic patient. No one should harbor any illusions that ACT I and CREST have resolved the latter issue.

CREST and ACT I both used credentialing to ensure that only the best interventionists and surgeons performed stenting or endarterectomy within the trials. The commendably low rates of death and stroke during the procedure in ACT I and CREST attest to this. It therefore remains to be seen whether these findings can be translated into routine clinical practice, if guidelines are changed to further liberalize indications for stenting, especially in asymptomatic patients. This is an important point, because a recent systematic review showed that 9 of 21 large administrative data-set registries (43%) reported rates of death and stroke in excess of the 3% risk threshold that is recommended by the American Heart Association in asymptomatic patients undergoing stenting, as compared with 1 of 21 registries (5%) after endarterectomy.\textsuperscript{3} Furthermore, the 3% risk threshold is clearly too high, given the reduction of risk with intensive medical therapy. Discrepancies between randomized-trial data (i.e., from ACT I and CREST) and real-world practice are nothing new and, in this case, are probably attributable to the fact that many real-world practitioners in the United States are performing two or fewer procedures annually in asymptomatic patients, with poorer outcomes than their more experienced colleagues.\textsuperscript{4}

The magnitude of the initial procedural risk will ultimately determine whether endarterectomy or stenting is preferable in recently symptomatic patients, and this will be determined by recency of symptoms, age of the patient, and coexisting conditions. However, there is a major concern that the data from these two trials will be uncritically interpreted to mean that stenting is equivalent to endarterectomy and so further exacerbate the situation in the United States, where more than 90% of carotid-artery interventions are performed in asymptomatic patients, even though evidence suggests that up to 90% of them will undergo an ultimately unnecessary and potentially harmful procedure.\textsuperscript{5,6} By contrast, the percentage of interventions that are performed for asymptomatic stenoses is approximately 60% in Germany and Italy, 15% in Canada...
and Australia, and 0% in Denmark. Such discrepancies call into question the appropriateness of advocating routine interventions for asymptomatic carotid-artery stenosis.

The ACT I authors conceded that in hindsight it would have been preferable to have included a medical group in their trial. However, the debate about how improvements in modern medical therapy may have lowered the annual risk of stroke had not reached its zenith when ACT I was conceived. It is certainly a highly topical and controversial issue in the current era, because data from both randomized trials and nonrandomized studies suggest that the annual rate of stroke among medically treated asymptomatic patients has declined over the past two decades, regardless of the severity of stenosis at baseline. Evidence now suggests that the annual rate of ipsilateral stroke may be as low as 0.5 to 1% — a rate that is very similar to that observed in ACT I and CREST after successful stenting or endarterectomy.

Accordingly, contemporary guidelines, which recommend that interventions may be appropriate if they can be performed with a risk of less than 3%, are based on historical data from randomized trials that were completed decades ago and that should now be considered obsolete. Outside clinical trials, endarterectomy and stenting should be reserved for patients with symptomatic severe stenosis or for asymptomatic patients who are shown to be at higher risk for stroke with medical therapy than with intervention. Such patients (approximately 10 to 15% of patients with asymptomatic stenosis of 70 to 99%) may be identified by an algorithm that incorporates information about microemboli detected by means of transcranial Doppler, and in the future by imaging strategies that identify the vulnerable plaque.

It is hoped that the Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial (CREST-2; ClinicalTrials.gov number, NCT02089217), which includes a medical group, will help settle this issue. Unfortunately, the Stent-Protected Angioplasty in Asymptomatic Carotid Artery Stenosis vs. Endarterectomy (SPACE-2; Current Controlled Trials number, ISRCTN78592017) trial (which also had a third group receiving medical therapy) has now been abandoned because of poor recruitment. Pending the completion of CREST-2, we think that it would be desirable for interventionists and surgeons to forgo stenting and endarterectomy in low-risk asymptomatic patients outside that trial. This restraint would not only spare patients from procedures that may be unnecessary, but it should also facilitate early completion of the trial (and so avoid the fate of SPACE-2), so that it may be possible to identify which patients will benefit from an intervention rather than medical therapy alone in an evidence-based rather than an eminence-based manner.

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

From the Stroke Prevention and Atherosclerosis Research Centre, Robarts Research Institute, Western University, London, ON, Canada (J.D.S.); and the Vascular Surgery Group, Division of Cardiovascular Sciences, Leicester Royal Infirmary, Leicester, United Kingdom (A.R.N.).

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Blood-Pressure Lowering in Intermediate-Risk Persons without Cardiovascular Disease

Eva M. Lonn, M.D., Jackie Bosch, Ph.D., Patricio López-Jaramillo, M.D., Ph.D., Jun Zhu, M.D., Lisheng Liu, M.D., Prem Pais, M.D., Rafael Diaz, M.D., Denis Xavier, M.D., Karen Sliwa, M.D., Ph.D., Antonio Dans, M.D., Alvaro Avezu, M.D., Ph.D., Leopoldo S. Piega, M.D., Ph.D., Katalin Keltai, M.D., Ph.D., Matyas Keltai, M.D., Ph.D., Irina Chazova, M.D., Ph.D., Ron J.G. Peters, M.D., Ph.D., Claes Held, M.D., Ph.D., Khalid Yusoff, M.D., Basil S. Lewis, M.D., Petr Jansky, M.D., Alexander Parkhomenko, M.D., Ph.D., Kamlesh Khunti, M.D., Ph.D., William D. Toff, M.D., Christopher M. Reid, Ph.D., John Varigos, B.Sc., Lawrence A. Leiter, M.D., Dora I. Molina, M.D., Robert McKelvie, M.D., Ph.D., Janice Pogue, Ph.D.,‡ Joanne Wilkinson, B.A., Hyejung Jung, M.Sc., Gilles Dagenais, M.D., and Salim Yusuf, M.B., B.S., D.Phil., for the HOPE-3 Investigators†

ABSTRACT

BACKGROUND
Antihypertensive therapy reduces the risk of cardiovascular events among high-risk persons and among those with a systolic blood pressure of 160 mm Hg or higher, but its role in persons at intermediate risk and with lower blood pressure is unclear.

METHODS
In one comparison from a 2-by-2 factorial trial, we randomly assigned 12,705 participants at intermediate risk who did not have cardiovascular disease to receive either candesartan at a dose of 16 mg per day plus hydrochlorothiazide at a dose of 12.5 mg per day or placebo. The first coprimary outcome was the composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke; the second coprimary outcome additionally included resuscitated cardiac arrest, heart failure, and revascularization. The median follow-up was 5.6 years.

RESULTS
The mean blood pressure of the participants at baseline was 138.1/81.9 mm Hg; the decrease in blood pressure was 6.0/3.0 mm Hg greater in the active-treatment group than in the placebo group. The first coprimary outcome occurred in 260 participants (4.1%) in the active-treatment group and in 279 (4.4%) in the placebo group (hazard ratio, 0.93; 95% confidence interval [CI], 0.79 to 1.10; P = 0.40); the second coprimary outcome occurred in 312 participants (4.9%) and 328 participants (5.2%), respectively (hazard ratio, 0.95; 95% CI, 0.81 to 1.11; P = 0.51). In one of the three prespecified hypothesis-based subgroups, participants in the subgroup for the upper third of systolic blood pressure (>143.5 mm Hg) who were in the active-treatment group had significantly lower rates of the first and second coprimary outcomes than those in the placebo group; effects were neutral in the middle and lower thirds (P = 0.02 and P = 0.009, respectively, for trend in the two outcomes).

CONCLUSIONS
Therapy with candesartan at a dose of 16 mg per day plus hydrochlorothiazide at a dose of 12.5 mg per day was not associated with a lower rate of major cardiovascular events than placebo among persons at intermediate risk who did not have cardiovascular disease. (Funded by the Canadian Institutes of Health Research and AstraZeneca; ClinicalTrials.gov number, NCT00468923.)
Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease


BACKGROUND
Previous trials have shown that the use of statins to lower cholesterol reduces the risk of cardiovascular events among persons without cardiovascular disease. Those trials have involved persons with elevated lipid levels or inflammatory markers and involved mainly white persons. It is unclear whether the benefits of statins can be extended to an intermediate-risk, ethnically diverse population without cardiovascular disease.

METHODS
In one comparison from a 2-by-2 factorial trial, we randomly assigned 12,705 participants in 21 countries who did not have cardiovascular disease and were at intermediate risk to receive rosuvastatin at a dose of 10 mg per day or placebo. The first coprimary outcome was the composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, and the second coprimary outcome additionally included revascularization, heart failure, and resuscitated cardiac arrest. The median follow-up was 5.6 years.

RESULTS
The overall mean low-density lipoprotein cholesterol level was 26.5% lower in the rosuvastatin group than in the placebo group. The first coprimary outcome occurred in 235 participants (3.7%) in the rosuvastatin group and in 304 participants (4.8%) in the placebo group (hazard ratio, 0.76; 95% confidence interval [CI], 0.64 to 0.91; P = 0.002). The results for the second coprimary outcome were consistent with the results for the first (occurring in 277 participants [4.4%] in the rosuvastatin group and in 363 participants [5.7%] in the placebo group; hazard ratio, 0.75; 95% CI, 0.64 to 0.88; P<0.001). The results were also consistent in subgroups defined according to cardiovascular risk at baseline, lipid level, C-reactive protein level, blood pressure, and race or ethnic group. In the rosuvastatin group, there was no excess of diabetes or cancers, but there was an excess of cataract surgery (in 3.8% of the participants, vs. 3.1% in the placebo group; P = 0.02) and muscle symptoms (in 5.8% of the participants, vs. 4.7% in the placebo group; P = 0.005).

CONCLUSIONS
Treatment with rosuvastatin at a dose of 10 mg per day resulted in a significantly lower risk of cardiovascular events than placebo in an intermediate-risk, ethnically diverse population without cardiovascular disease. (Funded by the Canadian Institutes of Health Research and AstraZeneca; HOPE-3 ClinicalTrials.gov number, NCT00468923.)
ORIGINAL ARTICLE

Blood-Pressure and Cholesterol Lowering in Persons without Cardiovascular Disease

Salim Yusuf, M.B., B.S., D.Phil., Eva Lonn, M.D., Prem Pais, M.D., Jackie Bosch, Ph.D., Patricio López-Jaramillo, M.D., Ph.D., Jun Zhu, M.D., Denis Xavier, M.D., Alvaro Avezum, M.D., Ph.D., Lawrence A. Leiter, M.D., Leopoldo S. Piegas, M.D., Ph.D., Alexander Parkhomenko, M.D., Ph.D., Matyas Keltai, M.D., Ph.D., Katalin Keltai, M.D., Ph.D., Karen Sliwa, M.D., Ph.D., Irina Chazova, M.D., Ph.D., Ron J.G. Peters, M.D., Ph.D., Claes Held, M.D., Ph.D., Khalid Yusoff, M.D., Basil S. Lewis, M.D., Petr Jansky, M.D., Kamlesh Khunti, M.D., Ph.D., William D. Toff, M.D., Christopher M. Reid, Ph.D., John Varigos, B.S.c., Jose L. Accini, M.D., Robert McKelvie, M.D., Ph.D., Janice Pogue, Ph.D.,* Hyejung Jung, M.Sc., Lisheng Liu, M.D., Rafael Diaz, M.D., Antonio Dans, M.D., and Gilles Dagenais, M.D., for the HOPE-3 Investigators†

BACKGROUND
Elevated blood pressure and elevated low-density lipoprotein (LDL) cholesterol increase the risk of cardiovascular disease. Lowering both should reduce the risk of cardiovascular events substantially.

METHODS
In a trial with 2-by-2 factorial design, we randomly assigned 12,705 participants at intermediate risk who did not have cardiovascular disease to rosvastatin (10 mg per day) or placebo and to candesartan (16 mg per day) plus hydrochlorothiazide (12.5 mg per day) or placebo. In the analyses reported here, we compared the 3180 participants assigned to combined therapy (with rosvastatin and the two antihypertensive agents) with the 3168 participants assigned to dual placebo. The first coprimary outcome was the composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, and the second coprimary outcome additionally included heart failure, cardiac arrest, or revascularization. The median follow-up was 5.6 years.

RESULTS
The decrease in the LDL cholesterol level was 33.7 mg per deciliter (0.87 mmol per liter) greater in the combined-therapy group than in the dual-placebo group, and the decrease in systolic blood pressure was 6.2 mm Hg greater with combined therapy than with dual placebo. The first coprimary outcome occurred in 113 participants (3.6%) in the combined-therapy group and in 157 (5.0%) in the dual-placebo group (hazard ratio, 0.71; 95% confidence interval [CI], 0.56 to 0.90; P = 0.005). The second coprimary outcome occurred in 136 participants (4.3%) and 187 participants (5.9%), respectively (hazard ratio, 0.72; 95% CI, 0.57 to 0.89; P = 0.003). Muscle weakness and dizziness were more common in the combined-therapy group than in the dual-placebo group, but the overall rate of discontinuation of the trial regimen was similar in the two groups.

CONCLUSIONS
The combination of rosvastatin (10 mg per day), candesartan (16 mg per day), and hydrochlorothiazide (12.5 mg per day) was associated with a significantly lower rate of cardiovascular events than dual placebo among persons at intermediate risk who did not have cardiovascular disease. (Funded by the Canadian Institutes of Health Research and AstraZeneca; ClinicalTrials.gov number, NCT00468923.)
More HOPE for Prevention with Statins

William C. Cushman, M.D., and David C. Goff, Jr., M.D., Ph.D.

In view of the worldwide burden of cardiovascular disease and the high cost of and poor adherence to medication regimens for the prevention of cardiovascular disease, the concept of a “polypill” — a single pill that combines several medications — is an attractive public health approach. However, evidence that each component of a polypill would independently reduce the risk of cardiovascular events and that the combination of agents would be safe is lacking. The primary results of the Heart Outcomes Prevention Evaluation (HOPE)–3 trial are now reported in three articles in the Journal.1-3 HOPE-3 was a double-blind, randomized, placebo-controlled trial with a 2-by-2 factorial design, in which 12,705 intermediate-risk men (≥55 years of age) and women (≥60 years of age) who did not have cardiovascular disease were randomly assigned to receive cholesterol-lowering treatment with rosuvastatin at a dose of 10 mg per day or placebo and were also randomly assigned to receive blood-pressure-lowering treatment with candesartan at a dose of 16 mg per day plus hydrochlorothiazide at a dose of 12.5 mg per day or placebo for a median of 5.6 years. Treatment with rosuvastatin resulted in a 24% lower risk of cardiovascular events than that with placebo (absolute difference, 1.1 percentage points), but the antihypertensive therapy did not result in a significantly lower risk of cardiovascular events. The HOPE-3 trial provides evidence to reinforce some current guideline recommendations and to influence future guidelines.

The cholesterol-lowering component of the trial1 produced results consistent with a meta-analysis of randomized trials of statin therapy, which showed that a reduction of 1 mmol per liter in the low-density lipoprotein (LDL) cholesterol level was associated with a 25% lower risk of cardiovascular events in a primary-prevention population.4 Furthermore, the rate of cardiovascular events that was observed in the placebo group (4.8% over a period of 5.6 years) was within the range of the rates that were observed among the lowest-risk groups shown to have a benefit from statin therapy in the meta-analysis. The trial participants who had high-sensitivity C-reactive protein (CRP) levels higher than 2 mg per deciliter and those who had levels lower than 2 mg per deciliter had similar rates of cardiovascular events and a similar benefit from rosuvastatin. Hence, these results support a risk-based approach to statin use, which has been recommended in recent guidelines,5 rather than an approach that is based primarily on LDL cholesterol levels, and the results add to the evidence supporting statin use for primary prevention.

The blood-pressure-lowering component of the trial2 showed no significant benefit of antihypertensive therapy in reducing the risk of cardiovascular events. The observed difference between the active-treatment group and the placebo group in the decrease in blood pressure over the course of the trial (6.0/3.0 mm Hg) was small, and the 95% confidence interval for the estimated hazard ratio did not exclude the benefit one might expect (on the basis of the results from the meta-analysis) from this degree of blood-pressure lowering.6 Neither of the drugs for blood-pressure lowering that were used in the trial have been shown to reduce the risk of cardiovascular events at such low doses. If higher doses had been used, the risk of cardiovascular events might have been significantly reduced, whether from greater blood-pressure lowering, additional effects of the antihypertensive drugs, or both. Hydrochlorothiazide, even at a dose of 25 mg per day, has been less effective in reducing the risk of cardiovascular events than has a full dose of amlodipine,7 whereas chlorthalidone
at a dose of 25 mg per day has been effective in reducing the risk of cardiovascular events in a placebo-controlled trial and has been at least as effective as amlodipine. These observations suggest that the use of chlorthalidone could have been more effective than the use of hydrochlorothiazide in HOPE-3.

The trial population was at a lower cardiovascular risk than the populations in previous hypertension trials. The observed rate of cardiovascular events in the dual-placebo group was 5.0% over a period of 5.6 years. Since most previous trials of blood-pressure lowering have used inclusion criteria that are designed to increase the level of cardiovascular risk in order to increase trial efficiency, those trials have included few low-risk adults. Meta-analyses of such trials provide evidence of cardiovascular benefit from the use of blood-pressure–lowering medications in adults with an average systolic blood pressure higher than 130 mm Hg and either clinical cardiovascular disease or a high cardiovascular risk (defined as a 5-year risk of cardiovascular events of ≥6.5%). In addition, the Systolic Blood Pressure Intervention Trial (SPRINT) provides support for the use of blood-pressure–lowering medications in patients who do not have cardiovascular disease but who have a systolic blood pressure higher than 130 mm Hg; in SPRINT, the risks of cardiovascular events and death from any cause were significantly reduced with the use of regimens for blood-pressure lowering that were more intensive than the regimen used in this trial. However, the SPRINT participants who did not have clinical cardiovascular disease at baseline were required to have subclinical cardiovascular disease or a 10-year cardiovascular risk (on the basis of the Framingham risk score) that was higher than 15%. The difference in systolic blood pressure between the active-treatment and control groups that was seen in SPRINT was twice the difference seen in HOPE-3 because the treatment regimen was more intensive.

The overall null results of the blood-pressure–lowering component of HOPE-3 could be due to insufficient dosing of antihypertensive medications, treatment of a relatively low-risk group, or chance. Setting aside the play of chance, we may take from these results new insight regarding the initiation threshold and treatment targets for blood-pressure–lowering medications. Although no benefit of blood-pressure lowering was observed overall, a prespecified subgroup analysis showed a 27% lower risk of cardiovascular events with blood-pressure–lowering therapy in the subgroup of participants who were in the upper third of systolic blood pressure levels (>143.5 mm Hg). Among the patients in that subgroup who received placebo, the rate of cardiovascular events was 6.5% over a period of 5.6 years. This rate is within the range of rates reported in the previously mentioned meta-analysis. However, the rates of cardiovascular events in the subgroups of participants in the lower and middle thirds of systolic blood pressure levels who received placebo were lower than the rates among the lowest-risk groups shown to have benefit from blood-pressure lowering in previous trials. Blood-pressure–lowering treatment with low doses of the two drugs used in HOPE-3 may not be effective over the period studied in this trial among patients with low levels of systolic blood pressure and low levels of cardiovascular risk. These results may help to define the combined threshold of systolic blood pressure (<140 mm Hg) and cardiovascular risk (<5.0%) below which the use of blood-pressure–lowering medications may not be useful in the short term. However, these results do not rule out the possibility of a benefit with longer-term treatment in a portion of this relatively low-risk population.

The results of the comparison of the effects of the combined intervention (rosuvastatin and candesartan plus hydrochlorothiazide) with placebo generally agreed with the results for the separate interventions. There was no evidence of harm or synergy between the two interventions. Although the addition of blood-pressure lowering to rosuvastatin therapy appeared to provide more benefit than that observed with rosuvastatin alone in the subgroup of participants who were in the upper third of systolic blood pressure levels, the P value for interaction was not significant.

The results of the HOPE-3 trial suggest that rosuvastatin at a dose of 10 mg per day is more effective in preventing cardiovascular events than is candesartan at a dose of 16 mg per day plus hydrochlorothiazide at a dose of 12.5 mg per day in this relatively low-risk population. Although these results do not exclude the possibility that more effective therapy for blood-pressure lowering might be beneficial in a relatively low-risk,
older population, they provide support for the use of statins as a safe and effective intervention to prevent cardiovascular events in such patients.

The opinions expressed in this article do not necessarily represent the official views of the Department of Veterans Affairs or the U.S. government.

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

From the Preventive Medicine Section, Veterans Affairs Medical Center, Memphis, TN (W.C.C.); and the Colorado School of Public Health, University of Colorado Anschutz Medical Campus, Aurora (D.C.G.).

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Efficacy of the Herpes Zoster Subunit Vaccine in Adults 70 Years of Age or Older


BACKGROUND
A trial involving adults 50 years of age or older (ZOE-50) showed that the herpes zoster subunit vaccine (HZ/su) containing recombinant varicella–zoster virus glycoprotein E and the AS01B adjuvant system was associated with a risk of herpes zoster that was 97.2% lower than that associated with placebo. A second trial was performed concurrently at the same sites and examined the safety and efficacy of HZ/su in adults 70 years of age or older (ZOE-70).

METHODS
This randomized, placebo-controlled, phase 3 trial was conducted in 18 countries and involved adults 70 years of age or older. Participants received two doses of HZ/su or placebo (assigned in a 1:1 ratio) administered intramuscularly 2 months apart. Vaccine efficacy against herpes zoster and postherpetic neuralgia was assessed in participants from ZOE-70 and in participants pooled from ZOE-70 and ZOE-50.

RESULTS
In ZOE-70, 13,900 participants who could be evaluated (mean age, 75.6 years) received either HZ/su (6950 participants) or placebo (6950 participants). During a mean follow-up period of 3.7 years, herpes zoster occurred in 23 HZ/su recipients and in 223 placebo recipients (0.9 vs. 9.2 per 1000 person-years). Vaccine efficacy against herpes zoster was 89.8% (95% confidence interval [CI], 84.2 to 93.7; P<0.001) and was similar in participants 70 to 79 years of age (90.0%) and participants 80 years of age or older (89.1%). In pooled analyses of data from participants 70 years of age or older in ZOE-50 and ZOE-70 (16,596 participants), vaccine efficacy against herpes zoster was 91.3% (95% CI, 86.8 to 94.5; P<0.001), and vaccine efficacy against postherpetic neuralgia was 88.8% (95% CI, 68.7 to 97.1; P<0.001). Solicited reports of injection-site and systemic reactions within 7 days after injection were more frequent among HZ/su recipients than among placebo recipients (79.0% vs. 29.5%). Serious adverse events, potential immune-mediated diseases, and deaths occurred with similar frequencies in the two study groups.

CONCLUSIONS
In our trial, HZ/su was found to reduce the risks of herpes zoster and postherpetic neuralgia among adults 70 years of age or older. (Funded by GlaxoSmithKline Biologicals; ZOE-50 and ZOE-70 ClinicalTrials.gov numbers, NCT01165177 and NCT01165229.)
Preventing Shingles and Its Complications in Older Persons

Kathleen M. Neuzil, M.D., M.P.H., and Marie R. Griffin, M.D., M.P.H.

In the United States each year, herpes zoster, or shingles, develops in half a million people 60 years of age or older. Although the symptoms are often mild in younger persons, the risk for serious complications of herpes zoster, including postherpetic neuralgia, ocular involvement, and central nervous system disease, increases with advancing age. The rising age-specific incidence of shingles and the aging population in the United States are likely to contribute to additional shingles-associated morbidity in coming years. The prevention of herpes zoster and its complications in older persons will improve quality of life and should be a public health priority.

Since 2008, the U.S. Advisory Committee on Immunization Practices has recommended that all immunocompetent persons 60 years of age or older receive a single dose of a live attenuated herpes zoster vaccine (Zostavax). In a large, placebo-controlled trial, the efficacy of this vaccine against herpes zoster was 51.3%, and the efficacy against postherpetic neuralgia was 66.5%. Further follow-up of participants and postmarketing studies have confirmed the effectiveness of the vaccine over time. Among 176,078 members of Kaiser Permanente who were 60 years of age or older and matched controls, the effectiveness of the live attenuated vaccine against herpes zoster decreased from 68.7% (95% confidence interval [CI], 66.3 to 70.9) in the first year after vaccination to 4.2% (95% CI, −24.0 to 25.9) in the eighth year. These data, coupled with information on the immunogenicity of booster doses of the vaccine, will inform recommendations regarding the need for a subsequent dose or doses.

In this issue of the Journal, Cunningham et al. report on the efficacy of two doses of an investigational, adjuvanted herpes zoster subunit vaccine (HZ/su) in immunocompetent persons 70 years of age or older. This trial, involving 13,900 persons, was conducted concurrently with a previously reported trial involving persons 50 years or age or older in which the same vaccine and schedule were used. The vaccine contains a recombinant varicella–zoster virus (VZV) glycoprotein E with a novel adjuvant (AS01b) designed to improve CD4+ T-cell–mediated immune responses, which are thought to be important in preventing the reactivation of latent VZV. A lower dose of this adjuvant is used in a malaria vaccine that was approved in 2015 by the European Medicines Agency for children living in areas in which malaria is endemic.

In 2015, the efficacy of HZ/su against herpes zoster was reported as 97.2% (95% CI, 93.7 to 99.0) among participants 50 years of age or older and as 97.9% (95% CI, 87.9 to 100.0) among participants 70 years of age or older during a mean follow-up period of 3.2 years. In the current trial, during a mean follow-up period of 3.7 years, the efficacy against herpes zoster was 89.8% (95% CI, 84.2 to 93.7) in persons 70 years of age or older. Efficacy was similar among participants who were 70 to 79 years of age and those who were 80 years of age or older, and it was maintained for the duration of the trial. For the outcome of postherpetic neuralgia, the investigators included the participants who were 70 years of age or older from both trials, and they report an efficacy of 88.8% (95% CI, 68.7 to 97.1).

Given the limited efficacy and duration of Zostavax, newer vaccine formulations with improved efficacy are welcome. Although the higher point estimates of efficacy with the HZ/su vaccine are encouraging, the direct comparison of results from different trials is problematic. For example, in the pivotal trial evaluating Zostavax, the incidence of postherpetic neuralgia in the control group was higher than that in the control group in the HZ/su trial, which may indicate that the
Zostavax efficacy trial included a more frail population, more active surveillance, or the use of a more sensitive case definition. A major benefit of the HZ/su vaccine as compared with Zostavax appears to be retention of high efficacy against herpes zoster and postherpetic neuralgia in the oldest age groups and over time. Continued follow-up of the vaccinated cohorts is warranted.

Although the safety profile regarding serious adverse events reported in the trials of HZ/su was reassuring, a full understanding of less common serious side effects will be known only as larger and more diverse populations are vaccinated. This is particularly pertinent given the new adjuvant included in this vaccine. It is worth noting that the short-term reactogenicity with this adjuvanted vaccine is higher than with other adult vaccines. In the first 7 days after vaccination, 79.0% of vaccine recipients, versus 29.5% of placebo recipients, reported local or systemic reactions, and 11.9% of vaccine recipients, versus 2.0% of placebo recipients, reported that their reactions were severe enough to prevent normal activity. It is remarkable that few participants declined the second injection, but whether adherence would be similar in a different population, especially one that included more frail older adults, is unknown.

Policy deliberations regarding the HZ/su vaccine will need to include consideration of how these trial data will translate into routine conditions of use. The HZ/su trials reported data on participants who received two doses of vaccine — therefore, the efficacy of a single dose, or of two doses given on a different schedule, is not known. Persons with a history of herpes zoster or of herpes zoster vaccination were excluded from these trials, so the benefit of the vaccine in those populations is uncertain. Ultimately, HZ/su may provide an option for immunocompromised persons who are at high risk for herpes zoster and its complications and are unable to receive the live attenuated vaccine. This would be a major advance in efforts to prevent herpes zoster.

Despite the 2008 recommendations for the zoster vaccine, by 2014 only 27.9% of adults 60 years of age or older reported being vaccinated. In the early years after vaccine approval, supply constraints limited uptake. In more recent years, the supply has been sufficient, and the reasons for the continued poor uptake include provider challenges (e.g., cost, storage of the frozen formulation, and complex Medicare reimbursement), limited public awareness of the disease and vaccine, a lack of requirements for adult vaccination, and the focus on acute medical care over prevention among practitioners caring for adult patients. Although HZ/su may address some of these issues, such as easier storage requirements for a nonreplicating product, it will have its own challenges, including the two-dose schedule and the higher reactogenicity. Thus, the full public health value of herpes zoster vaccines will not be realized unless we identify and address barriers to delivery and uptake.

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

From the Center for Vaccine Development, University of Maryland School of Medicine, Baltimore (K.M.N.); and the Departments of Health Policy and Medicine, Vanderbilt University Medical Center, Nashville (M.R.G.).

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10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer


ABSTRACT

BACKGROUND
The comparative effectiveness of treatments for prostate cancer that is detected by prostate-specific antigen (PSA) testing remains uncertain.

METHODS
We compared active monitoring, radical prostatectomy, and external-beam radiotherapy for the treatment of clinically localized prostate cancer. Between 1999 and 2009, a total of 82,429 men 50 to 69 years of age received a PSA test; 2664 received a diagnosis of localized prostate cancer, and 1643 agreed to undergo randomization to active monitoring (545 men), surgery (553), or radiotherapy (545). The primary outcome was prostate-cancer mortality at a median of 10 years of follow-up. Secondary outcomes included the rates of disease progression, metastases, and all-cause deaths.

RESULTS
There were 17 prostate-cancer–specific deaths overall: 8 in the active-monitoring group (1.5 deaths per 1000 person-years; 95% confidence interval [CI], 0.7 to 3.0), 5 in the surgery group (0.9 per 1000 person-years; 95% CI, 0.4 to 2.2), and 4 in the radiotherapy group (0.7 per 1000 person-years; 95% CI, 0.3 to 2.0); the difference among the groups was not significant (P = 0.48 for the overall comparison). In addition, no significant difference was seen among the groups in the number of deaths from any cause (169 deaths overall; P = 0.87 for the comparison among the three groups). Metastases developed in more men in the active-monitoring group (33 men; 6.3 events per 1000 person-years; 95% CI, 4.5 to 8.8) than in the surgery group (13 men; 2.4 per 1000 person-years; 95% CI, 1.4 to 4.2) or the radiotherapy group (16 men; 3.0 per 1000 person-years; 95% CI, 1.9 to 4.9) (P = 0.004 for the overall comparison). Higher rates of disease progression were seen in the active-monitoring group (112 men; 22.9 events per 1000 person-years; 95% CI, 19.0 to 27.5) than in the surgery group (46 men; 8.9 events per 1000 person-years; 95% CI, 6.7 to 11.9) or the radiotherapy group (46 men; 9.0 events per 1000 person-years; 95% CI, 6.7 to 12.0) (P<0.001 for the overall comparison).

CONCLUSIONS
At a median of 10 years, prostate-cancer–specific mortality was low irrespective of the treatment assigned, with no significant difference among treatments. Surgery and radiotherapy were associated with lower incidences of disease progression and metastases than was active monitoring. (Funded by the National Institute for Health Research; ProtecT Current Controlled Trials number, ISRCTN20141297; ClinicalTrials.gov number, NCT02044172.)
Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer


ABSTRACT

BACKGROUND
Robust data on patient-reported outcome measures comparing treatments for clinically localized prostate cancer are lacking. We investigated the effects of active monitoring, radical prostatectomy, and radical radiotherapy with hormones on patient-reported outcomes.

METHODS
We compared patient-reported outcomes among 1643 men in the Prostate Testing for Cancer and Treatment (ProtecT) trial who completed questionnaires before diagnosis, at 6 and 12 months after randomization, and annually thereafter. Patients completed validated measures that assessed urinary, bowel, and sexual function and specific effects on quality of life, anxiety and depression, and general health. Cancer-related quality of life was assessed at 5 years. Complete 6-year data were analyzed according to the intention-to-treat principle.

RESULTS
The rate of questionnaire completion during follow-up was higher than 85% for most measures. Of the three treatments, prostatectomy had the greatest negative effect on sexual function and urinary continence, and although there was some recovery, these outcomes remained worse in the prostatectomy group than in the other groups throughout the trial. The negative effect of radiotherapy on sexual function was greatest at 6 months, but sexual function then recovered somewhat and was stable thereafter; radiotherapy had little effect on urinary continence. Sexual and urinary function declined gradually in the active-monitoring group. Bowel function was worse in the radiotherapy group at 6 months than in the other groups but then recovered somewhat, except for the increasing frequency of bloody stools; bowel function was unchanged in the other groups. Urinary voiding and nocturia were worse in the radiotherapy group at 6 months but then mostly recovered and were similar to the other groups after 12 months. Effects on quality of life mirrored the reported changes in function. No significant differences were observed among the groups in measures of anxiety, depression, or general health-related or cancer-related quality of life.

CONCLUSIONS
In this analysis of patient-reported outcomes after treatment for localized prostate cancer, patterns of severity, recovery, and decline in urinary, bowel, and sexual function and associated quality of life differed among the three groups. (Funded by the U.K. National Institute for Health Research Health Technology Assessment Program; ProtecT Current Controlled Trials number, ISRCTN20141297; ClinicalTrials.gov number, NCT02044172.)
Treatment or Monitoring for Early Prostate Cancer

Anthony V. D’Amico, M.D., Ph.D.

The “best” initial approach to early (low-risk or intermediate-risk) prostate cancer remains unknown. Specifically, does active monitoring with the use of prostate-specific antigen (PSA) testing as opposed to treatment lead to increased metastasis and death from prostate cancer? If yes, then which treatment, radical prostatectomy or radiation with or without short-term (3 to 6 months) androgen-suppression therapy, minimizes metastasis and death from prostate cancer? Hamdy and colleagues now report in the Journal the results of a randomized comparison of three of these four approaches after a median follow-up of 10 years, and Donovan and colleagues present data on patient-reported health-related quality of life at 6 years of follow-up. Men were screened with PSA testing and presented at a median age of 62 years with favorable clinical characteristics: 76% had stage T1c (PSA-detected) disease, 77% and 21% had tumors with Gleason scores of 6 and 7, respectively (on a scale from 6 to 10, with higher scores indicating a worse prognosis), and the median PSA level was 4.6 ng per milliliter. Although a median follow-up of 10 years was too short to evaluate the primary outcome of prostate-cancer mortality in this favorable cohort (death from prostate cancer occurred in 8 of the 545 men assigned to active monitoring, 5 of the 553 men assigned to surgery, and 4 of the 545 men assigned to radiotherapy), it was adequate to evaluate the secondary outcome of the incidence of metastatic disease, defined as bony, visceral, or lymph-node metastasis on imaging or a PSA level above 100 ng per milliliter.

Several important observations were made. First, men assigned to active monitoring were significantly more likely to have metastatic disease than those assigned to treatment (P=0.004 for the overall comparison), with an incidence that was more than twice as high (6.3 per 1000 person-years vs. 2.4 to 3.0 per 1000 person-years). There was also a trend toward decreased death from prostate cancer among men assigned to surgery (hazard ratio, 0.63; 95% confidence interval [CI], 0.21 to 1.93) or radiation and androgen-deprivation therapy (hazard ratio, 0.51; 95% CI, 0.15 to 1.69) versus active monitoring. Although further follow-up will determine whether these trends become significant, causality between an increase in metastatic disease and the use of active monitoring versus treatment was established. The clinical significance of this finding is that with the use of active monitoring, more men will have metastasis and the side effects of salvage treatment (meaning at least lifelong intermittent androgen-deprivation therapy), which are not inconsequential.

Second, within the prerandomization stratum of age, a near-significant interaction (P=0.09 for interaction) was observed given that men 65 years of age or older were more likely to die from prostate cancer if assigned to active monitoring than if assigned to treatment. This finding probably reflects the fact that advancing age is associated with higher-grade disease than disease identified at an initial biopsy owing to sampling error, resulting in undergrading, the risk of which rises with the increasing prostate-gland volume that occurs with advancing age. Should the interaction between age and death from prostate cancer among men assigned to treatment versus monitoring become significant, it would support recommending treatment as opposed to monitoring to otherwise healthy men 65 years of age or older with early prostate cancer who today are increasingly being placed on active surveillance, given that the reduction in death from prostate cancer (hazard ratio, 0.63; 95% CI, 0.36 to 1.09) in the Prostate Cancer Intervention versus Observation Trial (PIVOT) only trended toward significance (P=0.09). However, the increasing use of surveillance is already of potential concern, considering that men enrolled in PIVOT had a shorter life expectancy owing to coexisting disease than men of similar age entered into...
Finally, a trend favoring radiation and short-course androgen-deprivation therapy over surgery was observed. Specifically, the point estimate for the hazard ratio for death from prostate cancer when comparing these two treatments was 0.80 (95% CI, 0.22 to 2.99). If this trend becomes significant, then one may consider radiation and androgen-deprivation therapy as a preferred option for otherwise healthy men 65 years of age or older with early prostate cancer for whom treatment as compared with monitoring may be more effective (P=0.09 for interaction) in reducing death from prostate cancer.

For today, we can conclude on the basis of level 1 evidence that PSA monitoring, as compared with treatment of early prostate cancer, leads to increased metastasis. Therefore, if a man wishes to avoid metastatic prostate cancer and the side effects of its treatment, monitoring should be considered only if he has life-shortening coexisting disease such that his life expectancy is less than the 10-year median follow-up of the current study. In addition, given no significant difference in death due to prostate cancer with surgery versus radiation and short-course androgen-deprivation therapy, men with low-risk or intermediate-risk prostate cancer should feel free to select a treatment approach using the data on health-related quality of life and without fear of possibly selecting a less effective cancer therapy.

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

From the Department of Radiation Oncology, Brigham and Women’s Hospital and Dana–Farber Cancer Institute, Boston.

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Guillain–Barré Syndrome Associated with Zika Virus Infection in Colombia

Beatriz Parra, Ph.D., Jairo Lizarrazo, M.D., Jorge A. Jiménez-Arangó, M.D., Andrés F. Zea-Vera, M.D., Ph.D., Guillermo González-Manrique, M.D., José Vargas, M.D., Jorge A. Angarita, M.D., Gonzalo Zuñiga, M.D., Reydar Lopez-Gonzalez, M.D., Cindy L. Beltran, M.D., Karen H. Rizcza, M.D., Maria T. Morales, M.D., Oscar Pacheco, M.D., Martha L. Ospina, M.D., Anupama Kumar, M.B., B.S., David R. Cornblath, M.D., Laura S. Muñoz, M.D., Lyda Osorio, M.D., Ph.D., Paula Barreras, M.D., and Carlos A. Pardo, M.D.

BACKGROUND
Zika virus (ZIKV) infection has been linked to the Guillain–Barré syndrome. From November 2015 through March 2016, clusters of cases of the Guillain–Barré syndrome were observed during the outbreak of ZIKV infection in Colombia. We characterized the clinical features of cases of Guillain–Barré syndrome in the context of this ZIKV infection outbreak and investigated their relationship with ZIKV infection.

METHODS
A total of 68 patients with the Guillain–Barré syndrome at six Colombian hospitals were evaluated clinically, and virologic studies were completed for 42 of the patients. We performed reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assays for ZIKV in blood, cerebrospinal fluid, and urine, as well as antiflavivirus antibody assays.

RESULTS
A total of 66 patients (97%) had symptoms compatible with ZIKV infection before the onset of the Guillain–Barré syndrome. The median period between the onset of symptoms of ZIKV infection and symptoms of the Guillain–Barré syndrome was 7 days (interquartile range, 3 to 10). Among the 68 patients with the Guillain–Barré syndrome, 50% were found to have bilateral facial paralysis on examination. Among 46 patients in whom nerve-conduction studies and electromyography were performed, the results in 36 patients (78%) were consistent with the acute inflammatory demyelinating polyneuropathy subtype of the Guillain–Barré syndrome. Among the 42 patients who had samples tested for ZIKV by RT-PCR, the results were positive in 17 patients (40%). Most of the positive RT-PCR results were in urine samples (in 16 of the 17 patients with positive RT-PCR results), although 3 samples of cerebrospinal fluid were also positive. In 18 of 42 patients (43%) with the Guillain–Barré syndrome who underwent laboratory testing, the presence of ZIKV infection was supported by clinical and immunologic findings. In 20 of these 42 patients (48%), the Guillain–Barré syndrome had a parainfectious onset. All patients tested were negative for dengue virus infection as assessed by RT-PCR.

CONCLUSIONS
The evidence of ZIKV infection documented by RT-PCR among patients with the Guillain–Barré syndrome during the outbreak of ZIKV infection in Colombia lends support to the role of the infection in the development of the Guillain–Barré syndrome. (Funded by the Bart McLean Fund for Neuroimmunology Research and others.)
Parra and colleagues report in the Journal the results of a prospective study of 68 Colombian patients who had a syndrome consistent with the Guillain–Barré syndrome, 66 of whom had previously had symptoms of Zika virus (ZIKV) infection. Major strengths of this study include the documentation of a temporal relationship between the Guillain–Barré syndrome and ZIKV infection (marked by a substantial increase in the incidence of the Guillain–Barré syndrome after the introduction of ZIKV, from 20 to 90 cases per month throughout Colombia), the criteria applied for the diagnosis of the Guillain–Barré syndrome, and the molecular and serologic flavivirus data from analyses of serum, cerebrospinal fluid (CSF), and urine.

However, the difficulties related to diagnosing ZIKV infection are multifold. First, the symptoms associated with ZIKV infection are similar to those caused by dengue virus (DENV) and chikungunya virus, both of which are endemic in Colombia. Second, the serologic cross-reactivity among flaviviruses (including yellow fever virus, West Nile virus, DENV, and Japanese encephalitis virus) have been well described. Although the Centers for Disease Control and Prevention (CDC) recommends neutralizing antibody testing with a plaque-reduction neutralization test to distinguish among flaviviruses, this testing is expensive, requires cell culture, and is also susceptible to cross-reactivity. Polymerase-chain-reaction (PCR) testing can definitively identify ZIKV, but molecular studies of serum are usually sensitive only during the first week after infection. Because the Guillain–Barré syndrome has been linked to microbial pathogens through a molecular mimicry mechanism, it is typically diagnosed 1 week or longer after an infection.

Indeed, Parra et al. observed that the median time to onset of the Guillain–Barré syndrome was 7 days after ZIKV infection.

The authors deal with these diagnostic dilemmas by showing that ZIKV PCR testing of other body fluids (particularly urine) may remain sensitive for a longer duration than does testing of serum. Indeed, in 13 patients, ZIKV PCR results were positive only in urine, whereas serum, CSF, or both were PCR-negative when tested in a similar time frame. IgM antibody testing of CSF for both ZIKV and DENV may be another diagnostic strategy, since the IgM pentamer is too large to cross the blood–brain barrier. Therefore, CSF that is positive for ZIKV IgM and negative for DENV IgM would be suggestive of a primary central nervous system ZIKV infection. Of the patients who tested positive for ZIKV by PCR and underwent CSF IgM testing, 8 were PCR-positive but ZIKV IgM–negative in CSF, which suggested that ZIKV PCR testing of urine may be more sensitive than serologic testing of CSF.

The difficulties in diagnosing ZIKV infection are borne out in this study, as only 17 patients had definitive laboratory evidence of recent ZIKV infection. On the basis of Table S5 in the Parra et al. Supplementary Appendix, of these 17 patients, only 14 had electrophysiological data consistent with the Guillain–Barré syndrome and therefore could have met Brighton level 1 diagnostic criteria for the syndrome, although the actual number of patients meeting level 1 criteria may have been smaller because we do not know the corresponding results of CSF testing for these patients. Because of these limitations in diagnostic certainty for both ZIKV infection and the Guillain–Barré syndrome, a strong association was identified in approximately 20% of pa-
tients in this cohort (14 of 68). Among the 25 ZIKV PCR–negative patients, DENV IgG antibodies were present in the CSF of 12 patients and in the serum of 10 patients, and serum DENV IgM test results were positive in 1. These data raise the possibility of primary DENV infection and false positive ZIKV serologic test results due to cross-reactivity. In addition, data on yellow fever vaccination or infection were not provided; yellow fever is also endemic in much of Colombia and may complicate the interpretation of the ZIKV serologic results.

As is true with most clinical studies, proving a causal relationship between ZIKV infection and the Guillain–Barré syndrome is challenging. In keeping with Hill criteria for causality, the authors show a consistent, specific, temporal relationship, which is analogous to relationships between ZIKV infection and the Guillain–Barré syndrome observed in other countries. What is more difficult to demonstrate is pathophysiological plausibility. The authors point out that 20 patients had neurologic symptoms immediately after the viral syndrome (only 9 of 20 had definite laboratory-proven ZIKV) and speculate that other mechanisms, including a hyperacute immune response or direct viral neuropathic mechanisms, may be in effect, rather than postinfectious molecular mimicry. Although studies using human neural progenitor cells have shown that ZIKV infection increases cell death and dysregulates cell-cycle progression, evidence of direct neuropotropism in adult neuronal cells is still lacking. A recent study showed that there is a high peptide overlap between the ZIKV polyprotein and human proteins related to myelin and axons, which suggests that an immune-mediated mechanism may be more likely. Although protein epitopes and antibodies that are normally involved in the genesis of the Guillain–Barré syndrome seem not to be highly involved in one cohort with ZIKV-associated acute motor axonal neuropathy, it is possible that differences in subtypes of the Guillain–Barré syndrome and host genetic factors may lead to varying immune-mediated mechanisms in different populations.

Overall, the study by Parra and colleagues supports the association between ZIKV and the Guillain–Barré syndrome, although confirmation in another cohort would strengthen this assertion. Although high rates of seropositivity may prove protective against further waves of ZIKV-related Guillain–Barré syndrome in Central and South America, the ZIKV pandemic is just beginning in North America and Africa, and an increase in the incidence of the Guillain–Barré syndrome may follow.

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

From the Cerebrovascular Center of the Neurological Institute, Cleveland Clinic, Cleveland (J.A.F.); and the Neurology Department, Universidade Federal Fluminense, Niterói (I.R.F.S.) — both in Brazil.

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A Randomized Trial of Long-Term Oxygen for COPD with Moderate Desaturation

The Long-Term Oxygen Treatment Trial Research Group*

ABSTRACT

BACKGROUND
Long-term treatment with supplemental oxygen has unknown efficacy in patients with stable chronic obstructive pulmonary disease (COPD) and resting or exercise-induced moderate desaturation.

METHODS
We originally designed the trial to test whether long-term treatment with supplemental oxygen would result in a longer time to death than no use of supplemental oxygen among patients who had stable COPD with moderate resting desaturation (oxyhemoglobin saturation as measured by pulse oximetry [SpO₂], 89 to 93%). After 7 months and the randomization of 34 patients, the trial was redesigned to also include patients who had stable COPD with moderate exercise-induced desaturation (during the 6-minute walk test, SpO₂ ≥80% for ≥5 minutes and <90% for ≥10 seconds) and to incorporate the time to the first hospitalization for any cause into the new composite primary outcome. Patients were randomly assigned, in a 1:1 ratio, to receive long-term supplemental oxygen (supplemental-oxygen group) or no long-term supplemental oxygen (no-supplemental-oxygen group). In the supplemental-oxygen group, patients with resting desaturation were prescribed 24-hour oxygen, and those with desaturation only during exercise were prescribed oxygen during exercise and sleep. The trial-group assignment was not masked.

RESULTS
A total of 738 patients at 42 centers were followed for 1 to 6 years. In a time-to-event analysis, we found no significant difference between the supplemental-oxygen group and the no-supplemental-oxygen group in the time to death or first hospitalization (hazard ratio, 0.94; 95% confidence interval [CI], 0.79 to 1.12; P=0.52), nor in the rates of all hospitalizations (rate ratio, 1.01; 95% CI, 0.91 to 1.13), COPD exacerbations (rate ratio, 1.08; 95% CI, 0.98 to 1.19), and COPD-related hospitalizations (rate ratio, 0.99; 95% CI, 0.83 to 1.17). We found no consistent between-group differences in measures of quality of life, lung function, and the distance walked in 6 minutes.

CONCLUSIONS
In patients with stable COPD and resting or exercise-induced moderate desaturation, the prescription of long-term supplemental oxygen did not result in a longer time to death or first hospitalization than no long-term supplemental oxygen, nor did it provide sustained benefit with regard to any of the other measured outcomes. (Funded by the National Heart, Lung, and Blood Institute and the Centers for Medicare and Medicaid Services; LOTT ClinicalTrials.gov number, NCT00692198.)

*The members of the writing committee (Richard K. Albert, M.D., David H. Au, M.D., Amanda L. Blackford, Sc.M., Richard Casaburi, M.D., Ph.D., J. Allen Cooper, Jr., M.D., Gerard J. Criner, M.D., Philip Diaz, M.D., Anne L. Fuhlbrigge, M.D., Steven E. Gay, M.D., Richard E. Kanner, M.D., Neil MacIntyre, M.D., Fernando J. Martinez, M.D., Ralph J. Panos, M.D., Steven Piantadosi, M.D., Ph.D., Frank Sciruba, M.D., David Shade, J.D., Thomas Stibolt, M.D., James K. Stoller, M.D., Robert Wise, M.D., Roger D. Yusen, M.D., James Tonascia, Ph.D., Alice L. Sternberg, Sc.M., and William Bailey, M.D.) assume responsibility for this article. The affiliations of the members of the writing committee are listed in the Appendix. Address reprint requests to Dr. Wise at the Johns Hopkins Asthma and Allergy Center, 48.72, Division of Pulmonary and Critical Care, 5501 Hopkins Bayview Circle, Baltimore, MD 21224, or at rwise@jhmi.edu.

A complete list of investigators in the Long-Term Oxygen Treatment Trial (LOTT) Research Group is provided in the Supplementary Appendix, available at NEJM.org.

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The fact that we all need oxygen to survive might make the benefit of supplemental oxygen in hypoxemia seem obvious. It is not. Long-term oxygen therapy was the first treatment to improve prognosis in patients with chronic obstructive pulmonary disease (COPD) and chronic severe hypoxemia.\(^1,2\) However, the question of whether long-term oxygen therapy is beneficial in moderate hypoxemia has been floating in the air.

The literature on the efficacy of long-term oxygen therapy requires no librarian. The current indications for its use are based on two unblinded, randomized trials that were conducted in the 1970s and involved a total of 290 patients.\(^1,2\) Long-term oxygen therapy given for 15 hours or more per day prolonged survival, as compared with only nocturnal use or no such therapy.\(^1,2\) Participants had COPD and chronic severe hypoxemia (a partial pressure of arterial oxygen [\(\text{Pa}_\text{O}_2\)] of \(\leq 55\) mm Hg or an oxyhemoglobin saturation level as measured by pulse oximetry [\(\text{Sp}_\text{O}_2\)] of approximately 88%) or moderate hypoxemia (\(\text{Pa}_\text{O}_2\) of 56 to 59 mm Hg or \(\text{Sp}_\text{O}_2\) between 88% and 90%) with signs of heart failure on the right side or polycythemia.\(^1,2\) These characteristics have since been the clinical eligibility criteria for long-term oxygen therapy.\(^3\) Of note, patients in the trials were younger and had fewer coexisting conditions than patients starting long-term oxygen therapy in current practice.\(^4\) A survival benefit was not seen in two smaller trials in the 1990s of nocturnal oxygen (in 76 patients)\(^5\) or long-term oxygen therapy (in 135)\(^6\) among patients with mild-to-moderate hypoxemia.

But does long-term oxygen therapy reduce breathlessness or improve quality of life? With regard to patients who have COPD with mild-to-moderate hypoxemia, some data suggest that supplemental oxygen decreases breathlessness during exercise testing or structured training,\(^7\) but evidence of efficacy with regard to symptoms and quality of life in the home setting is lacking.\(^3,8,9\) In patients with severe hypoxemia, the effect of long-term oxygen therapy on patient-reported outcomes has not been studied.\(^9\)

Thus, despite frequent prescription, relatively high costs, and the potential burden on patients of long-term oxygen therapy, quality evidence regarding its clinical usefulness in patients with COPD and moderate hypoxemia has been lacking.\(^3\) Until now.

As published in this issue of the Journal, the Long-Term Oxygen Treatment Trial (LOTT)\(^10\) randomly assigned 738 participants with COPD (73% of whom were men) and mild-to-moderate hypoxemia at rest or during a 6-minute walk test to receive either long-term supplemental oxygen or no long-term supplemental oxygen. The supplemental oxygen was prescribed as 2 liters of oxygen per minute continuously in participants with resting hypoxemia (57% of the participants) and as an adjusted oxygen dose during exercise and 2 liters of oxygen per minute during sleep in participants with exertional hypoxemia only (43%). During a median follow-up of 18.4 months, there was no significant between-group difference in the rate of death or first hospitalization in the time-to-event analysis (primary outcome) or in mortality and the rate of hospitalizations separately, COPD exacerbations, quality of life, anxiety, depression, or functional status.

This landmark study is the largest to date with regard to long-term oxygen therapy. It evaluated clinically relevant patient outcomes in daily life. Owing to slow recruitment, there were early changes in the trial; from two separate trials, one involving patients with resting desaturation and one involving patients with exercise desatu-
ration, the investigators created a composite trial that included both types of patients. Although this change added complexity, the trial met its target sample size and included clinically relevant subgroups of patients and treatment strategies for which evidence is needed. Similar to previous trials, \(^1,^2,^5,^6\) the LOTT was unblinded, which may have confounded the effect of long-term oxygen therapy to seem more beneficial (e.g., because of a placebo effect or more clinical contacts in the supplemental-oxygen group, especially for patient-reported outcomes) or less beneficial (e.g., a lower threshold for seeking or providing care in people in the no-supplemental-oxygen group). The validity of the findings is supported by the consistent lack of effect across outcomes, which was not modified by type of oxygen prescription, desaturation profile, oxygen use, sex, smoking status, and lung function.

I believe that on the basis of all available current data, long-term oxygen therapy should be prescribed to prolong survival among patients with COPD who have chronic (>3 weeks) severe resting hypoxemia (\(\text{PaO}_2\) of ≤55 mm Hg or \(\text{SpO}_2\) of <88%) while they are breathing ambient air. Since a lack of evidence of effect is not evidence of a lack of any clinical effectiveness, a trial of oxygen use might still be appropriate in selected patients with moderate exertional hypoxemia and intractable breathlessness despite appropriate evidence-based treatment. I think that the oxygen treatment should be evaluated by means of blinded exercise tests while the patient is breathing ambient air or oxygen and discontinued if the patient perceives no benefit during the test or within a day or two after it.\(^8\) If there is benefit, these selected patients should be prescribed oxygen, and I think that this treatment should be covered by insurance payers. However, long-term oxygen therapy should not be routinely prescribed in patients with mild or moderate hypoxemia at rest or during exercise.

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

From the Department of Clinical Sciences, Division of Respiratory Medicine and Allergology, Lund University, Lund, and the Department of Medicine, Blekinge Hospital, Karlskrona — both in Sweden.


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The explosive pandemic of Zika virus infection occurring throughout South America, Central America, and the Caribbean (see map) and potentially threatening the United States is the most recent of four unexpected arrivals of important arthropod-borne viral diseases in the Western Hemisphere over the past 20 years. It follows dengue, which entered this hemisphere stealthily over decades and then more aggressively in the 1990s; West Nile virus, which emerged in 1999; and chikungunya, which emerged in 2013. Are the successive migrations of these viruses unrelated, or do they reflect important new patterns of disease emergence? Furthermore, are there secondary health consequences of this arbovirus pandemic that set it apart from others?

“Arbovirus” is a descriptive term applied to hundreds of predominantly RNA viruses that are transmitted by arthropods, notably mosquitoes and ticks. Arboviruses are often maintained in complex cycles involving vertebrates such as mammals or birds and blood-feeding vectors. Until recently, only a few arboviruses had caused clinically significant human diseases, including mosquito-borne alphaviruses such as chikungunya and flaviviruses such as dengue and West Nile. The most historically important of these is yellow fever virus, the first recognized viral cause of deadly epidemic hemorrhagic fever.

Zika, which was discovered incidentally in Uganda in 1947 in the course of mosquito and primate surveillance, had until now remained an obscure virus confined to a narrow equatorial belt running across Africa and into Asia. The virus circulated predominantly in wild primates and arboreal mosquitoes such as Aedes africanus and rarely caused recognized “spillover” infections in humans, even in highly enzootic areas. Its current explosive pandemic reemergence is therefore truly remarkable. Decades ago, African researchers noted that aedes-transmitted Zika epizootics inexplicably tended to follow aedes-transmitted chikungunya epizootics and epidemics. An analogous pattern began in 2013, when chikungunya spread pandemically from west to east, and Zika later followed. Zika has now circled the globe, arriving not only in the Americas but also, in September, in the country of Cape Verde in West Africa, near its presumed ancient ancestral home.

With the exception of West Nile virus, which is predominantly spread by culex-species mosquitoes, the arboviruses that recently reached the Western Hemisphere...
have been transmitted by aedes mosquitoes, especially the yellow fever vector mosquito *A. aegypti*. These viruses started to emerge millennia ago, when North African villagers began to store water in their dwellings. Arboreal *A. aegypti* then adapted to deposit their eggs in domestic water-containing vessels and to feed on humans, which led to adaptation of arboreal viruses to infect humans. The yellow fever, dengue, and chikungunya viruses evolved entirely new maintenance cycles of human–*A. aegypti*–human transmission. Now, 5000 years later, the worst effects of this evolutionary cascade are being seen in the repeated emergence of arboviruses into new ecosystems involving humans. Moreover, arboviruses transmitted by different mosquitoes have, in parallel, adapted to humans’ domestic animals, such as horses in the case of Venezuelan equine encephalitis and pigs in the case of Japanese encephalitis virus, or to vertebrate hosts and non-aedes mosquitoes found in areas of human habitation, as West Nile virus did. The possibility that Zika may yet adapt to transmission by *A. albopictus*, a much more widely distributed mosquito found in at least 32 states in the United States, is cause for concern.

Through early epidemiologic surveillance and human challenge studies, Zika was characterized as a mild or inapparent dengue-like disease with fever, muscle aches, eye pain, prostration, and maculopapular rash. In more than 60 years of observation, Zika has not been noted to cause hemorrhagic fever or death. There is in vitro evidence that Zika virus mediates antibody-dependent enhancement of infection, a phenomenon observed in dengue hemorrhagic fever; however, the clinical significance of that finding is uncertain.

The ongoing pandemic confirms that Zika is predominantly a mild or asymptomatic dengue-like disease. However, data from French Polynesia documented a concomitant epidemic of 73 cases of Guillain–Barré syndrome and other neurologic conditions in a population of approximately 270,000, which may represent complications of Zika. Of greater concern is the explosive Brazilian epidemic of microcephaly, manifested by an apparent 20-fold increase in incidence from 2014 to 2015, which some public health officials believe is caused by Zika virus infections in pregnant women. Although no other flavivirus is known to have teratogenic effects, the microcephaly epidemic has not yet been linked to any other cause, such as increased diagnosis or reporting, increased ultrasound examinations of pregnant women, or other infectious or environmental agents. Despite the lack of definitive proof of any causal relationship, some health authorities in afflicted regions are recommending that pregnant women take meticulous precautions to avoid mosquito bites and even to delay pregnancy. It is critically impor-
The mainstays of management are bed rest and supportive care. When multiple arboviruses are co-circulating, specific viral diagnosis, if available, can be important in anticipating, preventing, and managing complications. For example, in dengue, aspirin use should be avoided and patients should be monitored for a rising hematocrit predictive of impending hemorrhagic fever, so that potentially lifesaving treatment can be instituted promptly. Patients with chikungunya virus infection should be monitored and treated for acute arthralgias and postinfectious chronic arthritis.

There are no Zika vaccines in advanced development, although a number of existing flavivirus vaccine platforms could presumably be adapted, including flavivirus chimera or glycoprotein subunit technologies. Zika vaccines would, however, face the same problem as vaccines for chikungunya, West Nile, St. Louis encephalitis, and other arboviruses: since epidemics appear sporadically and unpredictably, preemptively vaccinating large populations in anticipation of outbreaks may be prohibitively expensive and not cost-effective, yet vaccine stockpiling followed by rapid deployment may be too slow to counter sudden explosive epidemics. Although yellow fever has historically been prevented entirely by aggressive mosquito control, in the modern era vector control has been problematic because of expense, logistics, public resistance, and problems posed by inner-city crowding and poor sanitation. Among the best preventive measures against Zika virus are house screens, air-conditioning, and removal of yard and household debris and containers that provide mosquito-breeding sites, luxuries often unavailable to impoverished residents of crowded urban locales where such epidemics hit hardest.

With its recent appearance in Puerto Rico, Zika virus forces us to confront a potential new disease-emergence phenomenon: pandemic expansion of multiple, heretofore relatively unimportant arboviruses previously restricted to remote ecologic niches. To respond, we urgently need research on these viruses and the ecologic, entomologic, and host determinants of viral maintenance and emergence. Also needed are better public health strategies to control arboviral spread, including vaccine platforms for flaviviruses, alphaviruses, and other arbovirus groups that can be quickly modified to express immunogenic antigens of newly emerging viruses. With respect to treatment, the arbovirus pandemics suggest that the one-bug–one-drug approach is inadequate; broad-spectrum antiviral drugs effective against whole classes of viruses are urgently needed.

As was realized more than 50 years ago, when enzootic Zika virus spread was linked to human activity, arboviruses continually evolve and adapt within ecologic niches that are increasingly being perturbed by humans. Zika is still a pandemic in progress, and many important questions about it, such as that of teratogenicity, remain to be answered. Yet it has already reinforced one important lesson: in our human-dominated world, urban crowding, constant international travel, and other human behaviors combined with human-caused micro-perturbations in ecologic balance can cause innumerable slumbering infectious agents to emerge unexpectedly. In response, we clearly need to up our game with broad and integrated research that expands understanding of the complex ecosystems in which agents of future pandemics are aggressively evolving.

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From the National Institute of Allergy and Infectious Diseases, Bethesda, MD.

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3. Marcondes CB, Ximenes MF. Zika virus in Brazil and the danger of infestation by Aedes (Stegomyia) mosquitoes. Rev Soc Bras
Deaths from prescription-opioid overdose have increased dramatically in the United States, quadrupling in the past 15 years. Efforts to improve pain management resulted in quadrupled rates of opioid prescribing, which propelled a tightly correlated epidemic of addiction, overdose, and death from prescription opioids that is now further evolving to include increasing use and overdoses of heroin and illicitly produced fentanyl.

The pendulum of opioid use in pain management has swung back and forth several times over the past 100 years. Beginning in the 1990s, efforts to improve treatment of pain failed to adequately take into account opioids’ addictiveness, low therapeutic ratio, and lack of documented effectiveness in the treatment of chronic pain. Increased prescribing was also fueled by aggressive and sometimes misleading marketing of long-acting opioids to physicians. It has become increasingly clear that opioids carry substantial risks and uncertain benefits, especially as compared with other treatments for chronic pain.

On March 15, 2016, the Centers for Disease Control and Prevention (CDC) released a “Guideline for Prescribing Opioids for Chronic Pain” to chart a safer, more effective course. The guideline is designed to support clinicians caring for patients outside the context of active cancer treatment or palliative or end-of-life care. More research is needed to fill in critical evidence gaps regarding the effectiveness, safety, and economic efficiency of long-term opioid therapy. However, given what we know about the risks associated with long-term opioid therapy and the availability of effective nonpharmacologic and nonopioid pharmacologic treatment options, the guideline uses the best available scientific data to provide information and recommendations to support patients and clinicians in balancing the risks of addiction and overdose with the limited evidence of benefits of opioids for the treatment of chronic pain.

Most placebo-controlled, randomized trials of opioids have lasted 6 weeks or less, and we are aware of no study that has compared opioid therapy with other treatments in terms of long-term (more than 1 year) outcomes related to pain, function, or quality of life. The few randomized trials to evaluate opioid efficacy for longer than 6 weeks had consistently poor results. In fact, several studies have showed that use of

Reducing the Risks of Relief — The CDC Opioid-Prescribing Guideline

Thomas R. Frieden, M.D., M.P.H., and Debra Houry, M.D., M.P.H.
<table>
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<th>The CDC Opioid-Prescribing Guideline.</th>
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<tr>
<td>1. Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate.</td>
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<td>2. Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and should consider how therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety.</td>
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<td>3. Before starting and periodically during opioid therapy, clinicians should discuss with patients known risks and realistic benefits of opioid therapy and patient and provider responsibilities for managing therapy.</td>
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<td>4. When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids.</td>
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<td>5. When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when increasing dosing to ≥50 morphine milligram equivalents (MME) per day, and should avoid increasing dosage to ≥90 MME per day or carefully justify a decision to titrate dosage to ≥90 MME per day.</td>
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<td>6. Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than 7 days will rarely be needed.</td>
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<td>7. Clinicians should evaluate benefits and harms with patients within 1–4 weeks of starting opioid therapy for chronic pain or of dose escalation. Clinicians should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently. If benefits do not outweigh harms of continued opioid therapy, clinicians should optimize other therapies and work with patients to taper opioids to lower dosages or to taper and discontinue opioids.</td>
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<td>8. Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages (≥50 MME/day), or concurrent benzodiazepine use are present.</td>
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<td>9. Clinicians should review the patient’s history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months.</td>
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<td>10. When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs.</td>
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<td>11. Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible.</td>
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<td>12. Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid-use disorder.</td>
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Opioids for chronic pain may actually worsen pain and functioning, possibly by potentiating pain perception. A 3-year prospective observational study of more than 69,000 postmenopausal women with recurrent pain conditions showed that patients who had received opioid therapy were less likely to have improvement in pain (odds ratio, 0.42; 95% confidence interval [CI], 0.36 to 0.49) and had worsened function (odds ratio, 1.25; 95% CI, 1.04 to 1.51). An observational case-control study of patients undergoing orthopedic surgery showed that those receiving long-term opioid therapy had significantly higher levels of preoperative hyperalgesia. After surgery, patients who had received long-term opioid therapy reported higher pain intensity (a rating of 7.6 vs. 5.5 out of 10) in the recovery room than patients who had not been taking opioids.

Whereas the benefits of opioids for chronic pain remain uncertain, the risks of addiction and overdose are clear. Although partial agonists such as buprenorphine may carry a lower risk of dependence, prescription opioids that are full mu-opioid-receptor agonists — nearly all the products on the market — are no less addictive than heroin. Although abuse-deterrent formulations may reduce the likelihood that patients will inject melted pills, these formulations are no less addictive and do not prevent opioid abuse or fatal overdose through oral intake.

The prevalence of opioid dependence may be as high as 26% among patients in primary care receiving opioids for chronic non–cancer-related pain. Risk-stratification tools do not allow clinicians to predict accurately whether a patient will become addicted to opioids, although persons with a history of mental illness or addiction are at higher risk. Overdose risk increases in a dose–response manner, at least doubling at 50 to 99 morphine milli-
gram equivalents (MME) per day and increasing by a factor of up to 9 at 100 or more MME per day, as compared with doses of less than 20 MME per day.\textsuperscript{2} Overall, 1 of every 350 patients started on opioid therapy died of opioid-related causes a median of 2.6 years after the first opioid prescription; the proportion was as high as 1 in 32 among patients receiving doses of 200 MME or higher.\textsuperscript{3} We know of no other medication routinely used for a nonfatal condition that kills patients so frequently.

The new CDC guideline emphasizes both patient care and safety. We developed the guideline using a rigorous process that included a systematic review of the scientific evidence and input from hundreds of leading experts and practitioners, other federal agencies, more than 150 professional and advocacy organizations, a wide range of key patient and provider groups, a federal advisory committee, peer reviewers, and more than 4000 public comments.

Three key principles underlie the guideline’s 12 recommendations (see box). First, nonopioid therapy is preferred for chronic pain outside the context of active cancer, palliative, or end-of-life care. Opioids should be added to other treatments for chronic pain only when their expected benefits for both pain and function are likely to outweigh the substantial risks inherent in this class of medication.

Nonpharmacologic therapies can ameliorate chronic pain while posing substantially less risk to patients. In some instances, other therapies result in better outcomes than opioids. These therapies include exercise therapy, weight loss, psychological therapies such as cognitive behavioral therapy, interventions to improve sleep, and certain procedures. The evidence review conducted in developing the guideline revealed that exercise therapy helped improve, and sustain improvements in, pain and function in patients with osteoarthritis. It did not find evidence that nonopioids were more effective for pain reduction than nonopioid treatments such as nonsteroidal anti-inflammatory drugs for low back pain or antidepressants for neuropathic pain, but it did find that nonopioid treatments could be better tolerated and superior for improving physical function while conferring little or no risk of addiction and substantially lower risks of overdose and death.\textsuperscript{2}

Second, when opioids are used, the lowest possible effective dose should be prescribed to reduce the risks of opioid use disorder and overdose. Clinicians should carefully reassess individual benefits and risks when increasing a dose to 50 MME or more per day. Doses of 90 MME or more should be avoided, or the decision to titrate above this level should be carefully considered and justified. When prescribing opioids, the rule of thumb is to “start low and go slow.”

Third, clinicians should exercise caution when prescribing opioids and should monitor all patients closely. Prescribers should mitigate risk by, for example, avoiding concurrent use of benzodiazepines if possible, reviewing data from a prescription-drug monitoring program when deciding whether to start or continue opioid therapy, offering naloxone at least to patients who are at greater risk for overdose, having a clear “off-ramp” plan to taper and discontinue therapy, reevaluating the dosage and necessity of opioid treatment regularly, and obtaining urine toxicology screening at the initiation of treatment and, for some patients, periodically thereafter. For patients who become addicted to opioids, treatment with methadone, buprenorphine, or naltrexone improves outcomes.

Initiation of treatment with opioids is a momentous decision and should be undertaken only with full understanding by both the physician and the patient of the substantial risks involved. Clinicians need to recognize the risk associated with any treatment with opioids and should prescribe only the shortest course needed. Although the guideline addresses chronic pain, many patients become addicted to opioids after being treated for acute pain. Three days of treatment or less will often be sufficient; more than 7 days will rarely be required. Some trauma and surgery may require longer courses; treatment of postsurgical pain is beyond the scope of this guideline. Furthermore, it is important to discuss storage of opioids in a secure location to prevent diversion, as well as to counsel patients regarding the overdose risk posed to household members and other persons.

Management of chronic pain is an art and a science. The science of opioids for chronic pain is clear: for the vast majority of patients, the known, serious, and too-often-fatal risks far outweigh the unproven and transient benefits.
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From the Centers for Disease Control and Prevention, Atlanta.

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The adult population of the United States will soon have a different primary care experience than we’ve been used to. In the primary care practice of the future, the physician’s role will increasingly be played by nurse practitioners (NPs). In addition, the 150 million adults with one or more chronic conditions will receive some of their care from registered nurses (RNs) functioning as care managers.

Workforce experts agree on the growing gap between the population’s demand for primary care and the number of primary care physicians available to meet that demand. About 8000 primary care physicians (including doctors of osteopathy and international medical graduates) entered the workforce in 2015, up only slightly from 7500 in 2005. And in fact, the number of yearly entrants is expected to plateau at around 8000. But the number of primary care physicians who retire each year is projected to reach 8500 in 2020 — in other words, the number of retirees may exceed that of new entrants. And the size of the primary care physician workforce will be declining even as the U.S. population grows, ages, and becomes more adequately insured.\(^1\)

In contrast, the number of NPs entering the workforce each year has mushroomed from 6600 in 2003 to 18,000 in 2014. The number of primary care NPs is projected to increase by 84% between 2010 and 2025. The number of physician assistants (PAs) entering the workforce is also growing, though not as rapidly. If these trends continue, the proportion of primary care practitioners who are physicians will drop from 71% in 2010 to 60% in 2025 and will continue to decline thereafter. The proportion of practitioners who are NPs will jump from 19% to 29% during those years and will continue to rise.\(^2\) In rural communities, this trend is even more pronounced, since NPs are considerably more likely than physicians to settle in rural America.

Clearly, more and more patients will see an NP or a PA as their primary care practitioner. Physicians will probably focus on diagnostic conundrums and lead teams caring for patients with complex health care needs. A large and growing body of research demonstrates that care delivered by NPs is at least as high quality as that delivered by physicians. In addition, patient-satisfaction scores are similar for NPs and physicians.\(^3\) Moreover, care may cost less when it’s provided by NPs rather than physicians: Medicare beneficiaries assigned to an NP had primary care costs that were 29% lower and office-visit and inpatient costs that were 11 to 18% lower than those of beneficiaries assigned to a primary care physician.

Even with the increased numbers of NP and PA graduates, the ratio of primary care practitioners to population will decline, because...
only 50% of NPs and 32% of PAs choose primary care careers. Thus, other professionals will be needed to care for the growing number of U.S. adults with chronic conditions and geriatric syndromes. Enter the enhanced role of the RN.

While the NP role begins to approximate that of the physician, RNs are assuming three important emerging primary care functions: managing the care of patients with chronic disease by helping them with behavior change and adjusting their medications (e.g., for hypertension and diabetes) according to physician-written protocols; leading complex care management teams to help improve care and reduce the cost of care for patients with multiple diagnoses who are high users of health care services; and coordinating care between the primary care home and providers of other health care services — in particular, assisting with transitions among hospital, primary care settings, and home.4

RNs are well on their way to filling the gap. In 2015, a total of 43% of U.S. physicians worked with nurse care managers for patients with chronic conditions. The 3.1 million RNs in the United States represent the country's largest health profession, and its numbers are projected to grow by an astonishing 33% between 2012 and 2025. Government data show that the number of RN graduates per year has increased from 69,000 in 2001 to 155,000 in 2013 (see graph); a separate analysis put the number of RN graduates at 200,000 in 2014. Thus, primary care practices are likely to benefit from a pool of RNs who could be hired to serve as chronic care managers.

Several studies indicate that RNs are qualified to perform these enhanced roles. For example, in a randomized, controlled trial, patients with diabetes and elevated blood pressure who received care from RN care managers (including initiation of medications and titration of doses) were more likely to reach their blood-pressure goals than patients whose care was managed by physicians alone.5 Some state boards of registered nursing have created a mechanism by which RNs can change medication doses using standardized procedures authorized by their physician leadership.4 Using these procedures, RNs who've been trained as health coaches could provide most of the care for patients with uncomplicated diabetes, hypertension, and hyperlipidemia, thereby adding considerable primary care capacity. And RN coordination of transitions from hospital to home has resulted in improved patient self-management and reduced hospital readmissions.

Although NPs and RNs are increasingly central to primary care, there are still obstacles to their performing these roles that need to be overcome. Physicians report that new NP graduates are not initially comfortable taking responsibility for a panel of patients. To address this problem, intensive 1-year primary care NP residencies are springing up. Thus far, 37 such programs exist. Doctor of Nursing Practice degree programs were designed to supplant master's level NP programs, but they are growing more slowly than expected.

As for an enhanced role for RNs, one barrier is that public and private insurers rarely pay for RN services, but that barrier is beginning to crumble. Even under the fee-for-service payment model, practices can receive payment for Medicare wellness visits and chronic care management encounters, both of which can be conducted entirely by RNs. As alternative payment models gradually expand, primary care payment will become less visit-based, which will allow practices to reallocate more and more responsibilities to RNs and other team members.

The inadequacy of primary care training in nursing schools presents another obstacle to RNs' becoming chronic care managers.

The focus of nursing education on inpatient care skills has left...
some primary care RNs unprepared for the care manager role. The American Academy of Ambulatory Care Nursing and nursing leaders are addressing this problem with new curricula and training programs.

Finally, although RNs may be attracted to primary care’s regular work hours, its focus on prevention, and long-term relationships with patients, the fact that salaries are lower in primary care than in hospitals could also be a barrier.

Despite these challenges, the shortage of primary care physicians and the increasing prevalence of chronic diseases are powerful forces pushing primary care toward stronger NP and RN participation. It’s fortunate that the growth in the supply of NPs and RNs enables us to rethink who does what in primary care.

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From the Center for Excellence in Primary Care (T.B.) and the School of Nursing (L.B.), University of California, San Francisco.


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