The NEW ENGLAND JOURNAL of MEDICINE

Notable Articles of 2017

A collection of articles selected by NEJM editors

NEJM GROUP

The NEW ENGLAND JOURNAL of MEDICINE

December 2017

Dear Reader,

2017 was the year of big data. One study took data from 61 million Americans and looked at the association between air pollution and mortality. The trial found that for every increase of 10 μg per cubic meter in fine particulate matter ($PM_{2.5}$), there was an associated 7.3% increase in all-cause mortality. These findings stress the need for tighter regulation of air-pollutant levels, and make the point that we still have time to make a difference.

Another study analyzed data from 68.5 million people from 195 countries to find the trends in the prevalence of overweight and obesity among children and adults between 1980 and 2015. This study found that the global obesity epidemic is worsening in most parts of the world, but — as with the air pollution study — our future is not immutable.

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 2017, 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.

Sincerely,

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

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ORIGINAL ARTICLE

Radiation with or without Antiandrogen Therapy in Recurrent Prostate Cancer

W.U. Shipley, W. Seiferheld, H.R. Lukka, P.P. Major, N.M. Heney, D.J. Grignon, O. Sartor, M.P. Patel, J.-P. Bahary, A.L. Zietman, T.M. Pisansky, K.L. Zeitzer, C.A.F. Lawton, F.Y. Feng, R.D. Lovett, A.G. Balogh, L. Souhami, S.A. Rosenthal, K.J. Kerlin, J.J. Dignam, S.L. Pugh, and H.M. Sandler, for the NRG Oncology RTOG*

ABSTRACT

BACKGROUND

Salvage radiation therapy is often necessary in men who have undergone radical prostatectomy and have evidence of prostate-cancer recurrence signaled by a persistently or recurrently elevated prostate-specific antigen (PSA) level. Whether antiandrogen therapy with radiation therapy will further improve cancer control and prolong overall survival is unknown.

METHODS

In a double-blind, placebo-controlled trial conducted from 1998 through 2003, we assigned 760 eligible patients who had undergone prostatectomy with a lymphadenectomy and had disease, as assessed on pathological testing, with a tumor stage of T2 (confined to the prostate but with a positive surgical margin) or T3 (with histologic extension beyond the prostatic capsule), no nodal involvement, and a detectable PSA level of 0.2 to 4.0 ng per milliliter to undergo radiation therapy and receive either antiandrogen therapy (24 months of bicalutamide at a dose of 150 mg daily) or daily placebo tablets during and after radiation therapy. The primary end point was the rate of overall survival.

RESULTS

The median follow-up among the surviving patients was 13 years. The actuarial rate of overall survival at 12 years was 76.3% in the bicalutamide group, as compared with 71.3% in the placebo group (hazard ratio for death, 0.77; 95% confidence interval, 0.59 to 0.99; P=0.04). The 12-year incidence of death from prostate cancer, as assessed by means of central review, was 5.8% in the bicalutamide group, as compared with 13.4% in the placebo group (P<0.001). The cumulative incidence of metastatic prostate cancer at 12 years was 14.5% in the bicalutamide group, as compared with 23.0% in the placebo group (P=0.005). The incidence of late adverse events associated with radiation therapy was similar in the two groups. Gynecomastia was recorded in 69.7% of the patients in the bicalutamide group, as compared with 10.9% of those in the placebo group (P<0.001).

CONCLUSIONS

The addition of 24 months of antiandrogen therapy with daily bicalutamide to salvage radiation therapy resulted in significantly higher rates of long-term overall survival and lower incidences of metastatic prostate cancer and death from prostate cancer than radiation therapy plus placebo. (Funded by the National Cancer Institute and AstraZeneca; RTOG 9601 ClinicalTrials.gov number, NCT00002874.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Shipley at the Department of Radiation Oncology, Massachusetts General Hospital, 55 Fruit St., Cox 3, Boston, MA 02114, or at wshipley@partners.org.

*A complete list of the investigators in the NRG Oncology Radiation Therapy Oncology Group (RTOG) is provided in the Supplementary Appendix, available at NEJM.org.

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EDITORIAL

Improved Therapy for PSA Recurrence after Prostatectomy

Ian M. Thompson, Jr., M.D.

In developed countries around the world, prostate cancer is the most common solid neoplastic disease. In the United States, approximately half the men with localized prostate cancer undergo radical prostatectomy.[1] Prostate-specific antigen (PSA) levels should be undetectable after surgery; a detectable PSA level usually indicates disease recurrence. Almost uniformly, patients who have progression to metastatic disease and subsequently die from prostate cancer present with a detectable PSA level as the first evidence of cancer recurrence.

In many patients, residual or recurrent disease is limited to the prostatic bed or pelvis, a phenomenon that has been confirmed by observations that adjuvant radiation therapy (in patients with high-risk cancer) or salvage radiation therapy (at the time of PSA recurrence) can result in long-term survival without evidence of disease. The prognosis for patients with PSA recurrence is related to the initial tumor characteristics — grade, volume, and local stage. Despite randomized trials showing benefits of radiation after prostatectomy, the disease may recur and patients may ultimately die from prostate cancer.

Shipley and colleagues report in this issue of the *Journal* the long-term outcomes of a randomized trial comparing pelvic radiation therapy plus 2 years of antiandrogen therapy with pelvic radiation therapy plus placebo in high-risk patients who have PSA recurrence after surgery.[2] Using a moderate dose of radiation and high-dose (150 mg) bicalutamide as the androgen-deprivation therapy, the investigators found a 23% higher rate of overall survival and a 51% lower rate of death from prostate cancer in the bicalutamide group than in the placebo group. The number needed to treat with the nonsteroidal antiandrogen drug bicalutamide to prevent one death from prostate cancer was 20. By comparison, the number needed to treat (surgery or radiation therapy) to prevent one death from prostate cancer has been estimated to be 27, which shows the magnitude of the benefit of antiandrogen therapy.[3] As expected, the primary side effect of bicalutamide was gynecomastia, which was seen in 70% of the men treated. This side effect can be distressing but can be mitigated by prophylactic radiation of the breast or by the administration of tamoxifen.[4]

Androgen-deprivation therapy with high-dose bicalutamide may be used in place of luteinizing hormone–releasing hormone–based (LHRH) therapy to reduce sexual and bone side effects. More commonly, contemporary trials of adjuvant therapy have used LHRH-based agents; most data suggest that LHRH-based agents have a similar effect as bicalutamide.[5] Higher contemporaneous doses of radiation, delivered with intensity-modulated radiation therapy or other techniques, may have greater efficacy than the dose prescribed in the trial conducted by Shipley et al. Given the magnitude of benefit that was seen with bicalutamide in this trial, it is unlikely that higher doses of radiation would reduce this benefit, but the treatment outcomes would probably be even better.

Despite evidence supporting and guidelines calling for the use of salvage radiation therapy at the time that PSA becomes detectable, in clinical practice, radiation therapy is often not administered or treatment may be delayed until the PSA level continues to rise.[6] The benefit of the conclusions of this trial can be accrued only if salvage radiation therapy is administered appropriately; this is clearly an opportunity for national quality-improvement initiatives.

Androgen-deprivation therapy in combination with radiation therapy is worth serious consider-

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ation in high-risk patients with PSA recurrence. Nonetheless, in the era of precision medicine, it is our ultimate goal to administer this therapy to patients who are likely to benefit. The RADICALS (Radiation Therapy and Androgen Deprivation Therapy in Treating Patients Who Have Undergone Surgery for Prostate Cancer) trial (ongoing in Europe and Canada; ClinicalTrials.gov number, NCT00541047) will help to address this issue by investigating two critical questions. With evidence that adjuvant radiation therapy significantly reduces the risk of disease recurrence and, in the National Cancer Institute clinical trial,[7] reduced the risk of metastases and prolonged survival, the RADICALS trial is comparing adjuvant radiation therapy (in high-risk patients after surgery) with salvage radiation therapy (at the time of PSA recurrence). The other question that is addressed is the duration of androgen-deprivation therapy: none, 6 months, or 24 months. A recent secondary analysis of a randomized trial of androgen-deprivation therapy showed that the benefit of 6 months of androgen-deprivation therapy added to radiation therapy was seen only in men with no or minimal coexisting conditions.[8] Given the range of side effects of androgen deprivation in older men with coexisting conditions, especially in those with early cognitive decline or with the metabolic syndrome, the use of antiandrogen therapy in lieu of LHRH-based therapies or the omission of hormonal therapy entirely may be considered.[9]

This remarkable contribution by the National Clinical Trials Network of the National Cancer Institute shows the importance of randomized clinical trials with very long follow-up. Studies that incorporate interventions without proprietary intellectual property (e.g., surgery or radiation therapy) or pharmaceutical agents whose patents often expire before the study is completed can be achieved only with the use of this invaluable national resource.

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

From the Christus Santa Rosa Health System and Christus Oncology Research Council, San Antonio, TX.

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ORIGINAL ARTICLE

Survival and Neurodevelopmental Outcomes among Periviable Infants

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ABSTRACT

BACKGROUND

Data reported during the past 5 years indicate that rates of survival have increased among infants born at the borderline of viability, but less is known about how increased rates of survival among these infants relate to early childhood neurodevelopmental outcomes.

METHODS

We compared survival and neurodevelopmental outcomes among infants born at 22 to 24 weeks of gestation, as assessed at 18 to 22 months of corrected age, across three consecutive birth-year epochs (2000–2003 [epoch 1], 2004–2007 [epoch 2], and 2008–2011 [epoch 3]). The infants were born at 11 centers that participated in the National Institute of Child Health and Human Development Neonatal Research Network. The primary outcome measure was a three-level outcome — survival without neurodevelopmental impairment, survival with neurodevelopmental impairment, or death. After accounting for differences in infant characteristics, including birth center, we used multinomial generalized logit models to compare the relative risk of survival without neurodevelopmental impairment, survival with neurodevelopmental impairment, and death.

RESULTS

Data on the primary outcome were available for 4274 of 4458 infants (96%) born at the 11 centers. The percentage of infants who survived increased from 30% (424 of 1391 infants) in epoch 1 to 36% (487 of 1348 infants) in epoch 3 (P<0.001). The percentage of infants who survived without neurodevelopmental impairment increased from 16% (217 of 1391) in epoch 1 to 20% (276 of 1348) in epoch 3 (P=0.001), whereas the percentage of infants who survived with neurodevelopmental impairment did not change significantly (15% [207 of 1391] in epoch 1 and 16% [211 of 1348] in epoch 3, P=0.29). After adjustment for changes in the baseline characteristics of the infants over time, both the rate of survival with neurodevelopmental impairment (as compared with death) and the rate of survival without neurodevelopmental impairment (as compared with death) increased over time (adjusted relative risks, 1.27 [95% confidence interval {CI}, 1.01 to 1.59] and 1.59 [95% CI, 1.28 to 1.99], respectively).

CONCLUSIONS

The rate of survival without neurodevelopmental impairment increased between 2000 and 2011 in this large cohort of periviable infants. (Funded by the National Institutes of Health and others; ClinicalTrials.gov numbers, NCT00063063 and NCT00009633.)

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*A complete list of investigators and participating sites in the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network is provided in the Supplementary Appendix, available at NEJM.org.

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EDITORIAL

Neonatal Intensive Care — The Only Constant Is Change

Prakesh S. Shah, M.D.

The rate of survival of infants born extremely early — previously considered to be periviable (≤24 weeks) — has increased with advances in perinatal–neonatal care. However, concerns regarding higher rates of neurodevelopmental impairment among survivors have been raised. A precise interpretation of outcomes in periviable neonates requires an understanding of competing outcomes bias, differences in outcome reporting, denominators used in the calculation of rates, and health care philosophies at the personal, institutional, regional, and national level that influence care provision.

In this issue of the *Journal*, Younge et al.[1] report data on 4227 neonates born at 22 to 24 weeks of gestation from 11 neonatal centers in the United States. The data were compared across three consecutive birth-year epochs (2000–2003 [epoch 1], 2004–2007 [epoch 2], and 2008–2011 [epoch 3]). Survival free of neurodevelopmental impairment increased between epoch 1 and epoch 3 (adjusted relative risk, 1.59; 95% confidence interval, 1.28 to 1.99). When the data are analyzed according to gestational age, improvements in survival are still not seen for infants born at 22 weeks; epoch 2 was the turning point for infants born at 23 weeks, and random variations in outcomes characterized infants born at 24 weeks of gestation. There was a 4 percentage point increase in the rate of survival without clinically significant neurodevelopmental impairment from epoch 1 to epoch 3 ($P=0.001$) and a 1 percentage point increase in the rate of survival with clinically significant neurodevelopmental impairment from epoch 1 to epoch 3 ($P=0.29$). The study attempts to signal a progressive change in neonatal intensive care by reporting on the largest cohort of periviable neonates from the United States and, more importantly, shows variability across centers. However, limitations include the exclusion of neonates not born in the 11 centers, evaluation of outcomes by arbitrary segmental epochs rather than by process control charts, and lack of generalizability — the study population represents only 4 to 5% of periviable neonates born in the United States.

In addition to the study by Younge et al., other multicenter studies have reported on periviable neonates (Table 1). Reported rates of death or clinically significant neurodevelopmental impairment were greater than 94% for infants born at 22 weeks, between 80% and 90% for infants born at 23 weeks, and between 51% and 72% for infants born at 24 weeks of gestation, with the exception of Japan and Sweden (Table 1). There is wide variation in these rates, but the key to a correct interpretation lies in the denominator used, as well as the differing definitions of neurodevelopmental impairment in these reports. For example, in the study from Japan,[7] data were from selected neonatal units, whereas in the studies from Sweden,[4] France,[3] and the United Kingdom,[2] data included all births within a defined period. The classification of motor, cognitive, and sensory impairments that composed clinically significant neurodevelopmental impairment differed among studies. Therefore, it is difficult to counsel families on the basis of these different population bases and different outcomes. Studies from the United Kingdom and France have attempted to overcome such limitations and provided results using several denominators — all alive fetuses, all births, live births, neonates in whom active intervention was at-

Table 1. Multicenter Reports of Outcomes of Neonates Born between 22 and 24 Weeks of Gestation.*

Region or Country, Year (Base Population)	Exclusion Criteria	Outcomes	Definition of Clinically Significant NDI†	Denominator‡	Gestational Age		
					22 wk	23 wk	24 wk
					no./total no. (%)		
United Kingdom, 2006 (entire region)[2]	Not reported	Death or severe impairment at 3 yr	GMFCS level 3 to 5, DQ >3 SDs below the mean, blindness, sensorineural hearing loss not improved by aids	Alive at the onset of labor	270/272 (99)	370/416 (89)	354/494 (72)
				Live births	150/152 (99)	293/339 (86)	302/442 (68)
				Admission to neonatal ICU	17/19 (89)	171/217 (79)	241/381 (63)
France, 2011 (98% of entire population)[3]	None	Death before discharge	Not applicable	Live births	58/58 (100)	88/89 (99)	128/186 (69)
Sweden, 2004–2007 (all 7 regions in the country)[4]	Refusal to provide data	Death or clinically significant NDI at 2.5 yr	Nonambulatory cerebral palsy, Bayley-III score 3 SDs below the mean, blindness in both eyes, deafness in both ears	Live births (inborn and outborn)	48/51 (94)	59/96 (61)	60/135 (44)
Victoria, Australia, 2010–2011 (all hospitals in the state)[5]	Major congenital anomalies, termination of pregnancy	Death before discharge from neonatal ICU	Not applicable	Live births (inborn and outborn)	40/40 (100)	44/55 (80)	43/84 (51)
United States, 2006–2011 (24 hospitals)[6]	Congenital malformation	Death or clinically significant NDI at 18 to 22 mo	GMFCS level 4 to 5, Bayley-III score in any domain of <70, blindness in both eyes, severe hearing impairment in both ears	Live births (inborn)	345/357 (97)	624/755 (83)	665/1152 (58)
United States, 2000–2011 (11 neonatal units)[1]	Not enrolled in the registry	Death or severe NDI at 18 to 22 mo	GMFCS level 2 to 5, MDI score <70 (Bayley-II) or Cognitive Composite score <85 (Bayley-III), visual acuity <20/200 in both eyes, hearing amplification in both ears	Live births (inborn)	740/749 (99)	1287/1435 (90)	1504/2090 (72)
Japan, 2003–2005 (48 centers in network)[7]	Admission after 28 days of age	Death or profound NDI at 36 to 42 mo	GMFCS level 4 to 5, DQ <70, blindness in either eye, hearing deficit requiring aids	Admission to neonatal ICU in the first 28 days	55/75 (73)	136/245 (56)	99/332 (30)
Canada, 2009–2011 (26 of 30 units in the country)[8]	Death in delivery room, major congenital anomalies, not assessed, not linked§	Clinically significant NDI at 18 to 21 mo	GMFCS level 3 to 5, Bayley-III score <70 in any domain, hearing aid, visual impairment in both eyes	Survivors who were followed up	23/62 (37)¶	—¶	54/186 (29)

* Bayley-II and Bayley-III denotes Bayley Scales of Infant and Toddler Development (second edition and third edition, respectively), DQ developmental quotient, GMFCS Gross Motor Function Classification System, ICU intensive care unit, MDI Mental Developmental index, NDI neurodevelopmental impairment, and SDs standard deviations.

† A child was considered to have clinically significant NDI if any of the components of the disability were present. GMFCS levels range from 1 (mild impairment) to 5 (most severe impairment). Domains of the Bayley-II and Bayley-III have a mean ±SD score of 100±15, with lower scores indicating greater degree of impairment. DQ was calculated by dividing the developmental age by the chronological age and multiplying by 100. In the study from Japan,[7] a DQ of less than 70 was considered to represent clinically significant delayed performance.

‡ Inborn denotes neonates delivered in participating hospitals; and outborn, neonates delivered in other hospitals and then transferred to participating or tertiary hospital for expert care.

§ "Not linked" indicates infants who were seen in follow-up clinic but who could not be linked to the neonatal database and vice versa.

¶ Values for infants born at 22 and 23 weeks of gestation are combined.

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tempted, and neonates who were admitted to neonatal units. However, caution is needed when counting all births; the termination of pregnancies at 22 to 24 weeks of gestation because of major congenital malformations may artificially increase the calculated mortality rate.

As neonatal care advances, new reports of survival and outcomes at periviable gestational ages will emerge. A consistent reporting framework is needed to permit comparisons of results and to use them to create benchmarks and pursue quality improvement. Death and neurodevelopmental impairment are competing outcomes, and reports need to delineate them in combination and in isolation. Determination of what constitutes neurodevelopmental impairment and whose perspectives are considered (health care workers, parents, or children) remains debatable. Undoubtedly, our obligations to society will be unfulfilled if survivors are not followed longitudinally to better guide neonatal, postneonatal, infantile, and childhood care and to improve the quality of life for patients and families.

No discussion on neonatal outcomes is complete without consideration of the philosophy of care provision at these gestational ages. Of the national guidelines reviewed previously,[9] none have suggested active care for neonates born at 22 to 23 weeks of gestation. Differences in the initiation of resuscitation for such neonates have explained a significant proportion of variation in outcomes between centers.[6] "Gentler" approaches to provision of care have initiated a mini-revolution in neonatology. In providing care for periviable neonates, opportunities for testing several organ-protective strategies (e.g., less invasive respiratory support, tolerance in permitting levels of physiological measures that are outside the normal range, melatonin therapy, and administration of erythropoietin) in a rigorous manner should be a priority. Nonetheless, one must not forget the implementation of proven interventions, because outcomes can be greatly improved if we act on existing knowledge.[10] Reports of outcomes in periviable neonates, such as the study by Younge et al., remind us that the only constant thing in neonatal intensive care is change.

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

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ORIGINAL ARTICLE

Osimertinib or Platinum–Pemetrexed in *EGFR* T790M–Positive Lung Cancer

T.S. Mok, Y.-L. Wu, M.-J. Ahn, M.C. Garassino, H.R. Kim, S.S. Ramalingam, F.A. Shepherd, Y. He, H. Akamatsu, W.S.M.E. Theelen, C.K. Lee, M. Sebastian, A. Templeton, H. Mann, M. Marotti, S. Ghiorghiu, and V.A. Papadimitrakopoulou, for the AURA3 Investigators*

ABSTRACT

BACKGROUND

Osimertinib is an epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) that is selective for both EGFR-TKI sensitizing and T790M resistance mutations in patients with non–small-cell lung cancer. The efficacy of osimertinib as compared with platinum-based therapy plus pemetrexed in such patients is unknown.

METHODS

In this randomized, international, open-label, phase 3 trial, we assigned 419 patients with T790M-positive advanced non–small-cell lung cancer, who had disease progression after first-line EGFR-TKI therapy, in a 2:1 ratio to receive either oral osimertinib (at a dose of 80 mg once daily) or intravenous pemetrexed (500 mg per square meter of body-surface area) plus either carboplatin (target area under the curve, 5 [AUC5]) or cisplatin (75 mg per square meter) every 3 weeks for up to six cycles; maintenance pemetrexed was allowed. In all the patients, disease had progressed during receipt of first-line EGFR-TKI therapy. The primary end point was investigator-assessed progression-free survival.

RESULTS

The median duration of progression-free survival was significantly longer with osimertinib than with platinum therapy plus pemetrexed (10.1 months vs. 4.4 months; hazard ratio; 0.30; 95% confidence interval [CI], 0.23 to 0.41; P<0.001). The objective response rate was significantly better with osimertinib (71%; 95% CI, 65 to 76) than with platinum therapy plus pemetrexed (31%; 95% CI, 24 to 40) (odds ratio for objective response, 5.39; 95% CI, 3.47 to 8.48; P<0.001). Among 144 patients with metastases to the central nervous system (CNS), the median duration of progression-free survival was longer among patients receiving osimertinib than among those receiving platinum therapy plus pemetrexed (8.5 months vs. 4.2 months; hazard ratio, 0.32; 95% CI, 0.21 to 0.49). The proportion of patients with adverse events of grade 3 or higher was lower with osimertinib (23%) than with platinum therapy plus pemetrexed (47%).

CONCLUSIONS

Osimertinib had significantly greater efficacy than platinum therapy plus pemetrexed in patients with T790M-positive advanced non–small-cell lung cancer (including those with CNS metastases) in whom disease had progressed during first-line EGFR-TKI therapy. (Funded by AstraZeneca; AURA3 ClinicalTrials.gov number, NCT02151981.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Mok at the Department of Clinical Oncology, Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, China, or at tony@clo.cuhk.edu.hk.

*A complete list of the AURA3 Investigators is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Mok and Wu contributed equally to this article.

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ORIGINAL ARTICLE

Long-Term Outcomes of Imatinib Treatment for Chronic Myeloid Leukemia

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ABSTRACT

BACKGROUND

Imatinib, a selective BCR-ABL1 kinase inhibitor, improved the prognosis for patients with chronic myeloid leukemia (CML). We conducted efficacy and safety analyses on the basis of more than 10 years of follow-up in patients with CML who were treated with imatinib as initial therapy.

METHODS

In this open-label, multicenter trial with crossover design, we randomly assigned patients with newly diagnosed CML in the chronic phase to receive either imatinib or interferon alfa plus cytarabine. Long-term analyses included overall survival, response to treatment, and serious adverse events.

RESULTS

The median follow-up was 10.9 years. Given the high rate of crossover among patients who had been randomly assigned to receive interferon alfa plus cytarabine (65.6%) and the short duration of therapy before crossover in these patients (median, 0.8 years), the current analyses focused on patients who had been randomly assigned to receive imatinib. Among the patients in the imatinib group, the estimated overall survival rate at 10 years was 83.3%. Approximately half the patients (48.3%) who had been randomly assigned to imatinib completed study treatment with imatinib, and 82.8% had a complete cytogenetic response. Serious adverse events that were considered by the investigators to be related to imatinib were uncommon and most frequently occurred during the first year of treatment.

CONCLUSIONS

Almost 11 years of follow-up showed that the efficacy of imatinib persisted over time and that long-term administration of imatinib was not associated with unacceptable cumulative or late toxic effects. (Funded by Novartis Pharmaceuticals; IRIS ClinicalTrials.gov numbers, NCT00006343 and NCT00333840.)

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*A complete list of participating investigators in the International Randomized Study of Interferon and STI571 (IRIS) is provided in the Supplementary Appendix, available at NEJM.org.

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EDITORIAL

Imatinib Changed Everything

Dan L. Longo, M.D.

The initial successes of combination chemotherapy were stunning. Childhood acute leukemia, several forms of lymphoma, and testicular cancer all became largely curable malignant conditions. Adjuvant chemotherapy led to dramatically longer survival among persons with breast cancer. The fundamental principle of chemotherapy was to target dividing cells, because it was assumed that more rapid proliferation than "normal" was an underlying common defect in cancer. The effective agents generally attacked DNA or the mitotic spindle. Some tumors, such as breast cancer and prostate cancer, were susceptible to hormonal manipulation because of growth regulation of their normal-tissue counterparts.

Gradually data emerged that, except in the case of Burkitt's lymphoma, the fraction of tumor cells that were actively progressing through the cell cycle at any given time was quite small and generally no greater than in normal bone marrow, skin, or intestinal mucosa. Yet efforts to use chemotherapy in patients with other types of cancer continued with rare success and with well-known toxic effects.

Then along came Brian Druker. His focus on chronic myeloid leukemia (CML) was both clever and lucky. What we know now, which we didn't know then, is that CML is less complex genetically than most cancers. The introduction of the *bcr-abl* gene product into murine hematopoietic stem cells was sufficient for the reproduction of humanlike disease in these animals,[1-3] an unusual finding. These results led to the idea that interference with the function of this chimeric gene product might exert antitumor effects. This was a new idea.

Novartis (then called Ciba Geigy) had made a number of compounds that were capable of inhibiting protein tyrosine kinases, and one from the 2-phenylaminopyrimidine class (called CGP 57148 in some places and STI 571 in others and known today as imatinib) interfered with the viral oncogene v-abl and platelet-derived growth factor receptor activity in vitro and in mice.[4] It also inhibited the growth of BCR-ABL–positive cells.[5] Five years later, Druker and colleagues reported data from 54 patients with CML who had been treated with imatinib in a phase 1 study; complete hematologic responses were seen in 53 of the 54 patients, and in 7 patients, the Philadelphia chromosome was no longer detectable.[6] No other drug had achieved such results.

In this issue of the *Journal*, Hochhaus, Druker, and colleagues[7] report data from more than 10 years of follow-up in a randomized trial comparing interferon alfa and cytarabine with imatinib as initial therapy in patients with CML. The estimated survival rate at 10 years among patients in the imatinib group was 83%; in the course of the trial, 83% of the patients in the imatinib group had a complete cytogenetic response. Patients were mainly treated continuously, and no unexpected late toxic effects emerged. Approximately one patient in five had a stable deep molecular response for 1 year or longer, and some had the therapy discontinued, although this was not done on a consistent basis. Approximately 40% of the patients who stopped therapy remained in remission for 3 years or longer, with the rest having a relapse. Thus, imatinib is highly successful at controlling the disease in the long term, but few, if any, patients would be consid-

ered to be "cured" (in a stable remission and not taking any therapy). Yet the imatinib story suggested that the understanding of the pathogenesis of this tumor led to a less toxic and more effective treatment approach. Subsequent studies revealed other cancers in which imatinib was active through a different target,[8] identified the molecular mechanisms of imatinib resistance (and showed that they are often shared by other tyrosine kinase inhibitors),[9] and led to the design of new second- and third-generation agents.[10]

The development of imatinib fundamentally altered the field of oncology. Priorities shifted from agents that were active on dividing cells to understanding the biology of individual types of cancer. Once genetic analysis of tumors began, nearly all the cancer types had more complex genetic abnormalities than did CML, but the complexity gave rise to a revolution in cancer nosology. We now recognize that the grouping of tumors on the basis of the appearance of a hematoxylin and eosin–stained tissue fragment examined under a light microscope lumps together entities that are distinct both genetically and clinically. Lung cancer is now considered to be at least eight or nine entities, and the number of variants is continuing to expand. That is the good news. The bad news is that the inherent genetic instability of many cancers also facilitates the development of resistance to these interventions. In some instances, new genetic abnormalities create vulnerabilities that can be attacked by new agents.

The future of oncology is more hopeful now. The analysis of cancer at the genetic level and the development of (mainly) oral agents that can inhibit driver mutations constitute a conceptual departure from the medical oncology of the 1990s. An increasing number of agents hit an increasing number of targets. Tumor heterogeneity and mechanisms of resistance still limit our therapies, but the analysis of plasma for tumor DNA may help us to detect and anticipate the adaptation of the tumor to therapy and to select secondary treatments that target those changes. On top of the genetic guidance of therapeutic decisions is the remarkable recent progress in activating the immune system as a weapon in the battle. In this arena, too, much more needs to be learned.

We need to resist the temptation to be self-congratulatory. The prognosis for patients with common cancers is improving somewhat, but none of the new tools appears to cure a majority of patients. We still need to learn how to combine therapies that have different targets, to identify patients who are likely to have a response, and to define mechanisms of resistance. Although the journey to cancer cure has just begun, the use of imatinib to treat CML has pointed oncology in a new direction.

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

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ORIGINAL ARTICLE

Mepolizumab or Placebo for Eosinophilic Granulomatosis with Polyangiitis

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ABSTRACT

BACKGROUND

Eosinophilic granulomatosis with polyangiitis is an eosinophilic vasculitis. Mepolizumab, an anti–interleukin-5 monoclonal antibody, reduces blood eosinophil counts and may have value in the treatment of eosinophilic granulomatosis with polyangiitis.

METHODS

In this multicenter, double-blind, parallel-group, phase 3 trial, we randomly assigned participants with relapsing or refractory eosinophilic granulomatosis with polyangiitis who had received treatment for at least 4 weeks and were taking a stable prednisolone or prednisone dose to receive 300 mg of mepolizumab or placebo, administered subcutaneously every 4 weeks, plus standard care, for 52 weeks. The two primary end points were the accrued weeks of remission over a 52-week period, according to categorical quantification, and the proportion of participants in remission at both week 36 and week 48. Secondary end points included the time to first relapse and the average daily glucocorticoid dose (during weeks 48 through 52). The annualized relapse rate and safety were assessed.

RESULTS

A total of 136 participants underwent randomization, with 68 participants assigned to receive mepolizumab and 68 to receive placebo. Mepolizumab treatment led to significantly more accrued weeks of remission than placebo (28% vs. 3% of the participants had ≥24 weeks of accrued remission; odds ratio, 5.91; 95% confidence interval [CI], 2.68 to 13.03; P<0.001) and a higher percentage of participants in remission at both week 36 and week 48 (32% vs. 3%; odds ratio, 16.74; 95% CI, 3.61 to 77.56; P<0.001). Remission did not occur in 47% of the participants in the mepolizumab group versus 81% of those in the placebo group. The annualized relapse rate was 1.14 in the mepolizumab group, as compared with 2.27 in the placebo group (rate ratio, 0.50; 95% CI, 0.36 to 0.70; P<0.001). A total of 44% of the participants in the mepolizumab group, as compared with 7% of those in the placebo group, had an average daily dose of prednisolone or prednisone of 4.0 mg or less per day during weeks 48 through 52 (odds ratio, 0.20; 95% CI, 0.09 to 0.41; P<0.001). The safety profile of mepolizumab was similar to that observed in previous studies.

CONCLUSIONS

In participants with eosinophilic granulomatosis with polyangiitis, mepolizumab resulted in significantly more weeks in remission and a higher proportion of participants in remission than did placebo, thus allowing for reduced glucocorticoid use. Even so, only approximately half the participants treated with mepolizumab had protocol-defined remission. (Funded by GlaxoSmithKline and the National Institute of Allergy and Infectious Diseases; ClinicalTrials.gov number, NCT02020889.)

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*A complete list of the members of the EGPA Mepolizumab Study Team is provided in the Supplementary Appendix, available at NEJM.org.

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EDITORIAL

Targeting Eosinophils in Eosinophilic Granulomatosis with Polyangiitis

Ratko Djukanovic, M.D., and Paul M. O'Byrne, M.B.

Eosinophilic granulomatosis with polyangiitis, first described in the early 1950s by Dr. Jacob Churg and Dr. Lotte Strauss (hence the original name, the Churg–Strauss syndrome), is a rare condition that can affect many organ systems, most commonly the lung, with the majority of patients presenting with asthma symptoms, occasionally complicated by the fleeting presence of pulmonary infiltrates.[1] Many different treatments have been tried for eosinophilic granulomatosis with polyangiitis, with limited or no success, and systemic glucocorticoids are the standard treatment for both eosinophilic granulomatosis with polyangiitis[1] and severe refractory asthma.[2]

The predominance of eosinophils in the peripheral blood and tissues in patients with eosinophilic granulomatosis with polyangiitis has suggested a central role for eosinophils in the pathogenesis of this disease. Several small, open-label studies[3-5] have shown evidence that the blocking of interleukin-5, a cytokine known to be involved in the maturation, tissue accumulation, activation, and survival of eosinophils, with the monoclonal antibody mepolizumab provides clinical benefit in patients with eosinophilic granulomatosis with polyangiitis. Mepolizumab has already been shown to reduce the incidence of severe exacerbations among patients with severe refractory eosinophilic asthma.[6,7] In this issue of the *Journal*, Wechsler and colleagues[8] report the results of a placebo-controlled, double-blind trial of mepolizumab in participants who had relapsing eosinophilic granulomatosis with polyangiitis or who had eosinophilic granulomatosis with polyangiitis that was refractory to treatment with oral glucocorticoids, but the trial excluded participants with organ-threatening or life-threatening disease.

The trial showed a benefit of mepolizumab with regard to the two primary end points: the accrued weeks of disease remission and the proportion of participants who were in remission at weeks 36 and 48 of the trial. The annualized relapse rate was approximately 50% lower in the mepolizumab group than in the placebo group, a finding that is similar to that observed with mepolizumab with regard to exacerbation rates among patients with severe eosinophilic asthma.[7] Although the trial was powered to evaluate relapses on the basis of a worsening condition in any of three categories (asthma, vasculitis, and sinonasal disease alone or in combination), the benefit of treatment was slightly greater with regard to relapses defined according to exacerbating asthma-based or sinonasal-based symptoms. This finding suggests that the vasculitic component of eosinophilic granulomatosis with polyangiitis may respond less well to mepolizumab than do other components of the disease.

After remission, some participants in this trial had a relapse during treatment with mepolizumab. This situation raises questions about the mechanism of relapses of eosinophilic granulomatosis with polyangiitis (in particular, the role of eosinophils) and the dose of mepolizumab that was used in the trial. Eosinophils have been the focus of research for decades but gained mechanistic and biomarker prominence in the study of severe asthma after studies showed that the use of sputum or blood eosinophil counts as biomarkers to adjust the dose of inhaled glucocorticoids[9] or to enrich the population of patients with severe eosinophilic asthma for treatment with mepolizumab effectively reduced exacerbation frequency.[6,7] As has been the case with asthma, in the current trial, the blood eosinophil count was a risk factor for relapse, in that participants with a blood eosinophil count of 150 or more per cubic millimeter at enrollment benefited markedly from mepolizumab versus placebo (odds ratio, 26.10), whereas those with a blood eosinophil count of less than 150 per cubic millimeter did not (odds ratio, 0.95).[8] Also, the dose of mepolizumab that was used (300 mg monthly) was higher than the dose approved for severe eosinophilic asthma (100 mg monthly) but lower than that used in an initial study involving

patients with severe asthma (750 mg monthly).[6] It is uncertain whether a dose of 300 mg monthly is the most effective dose for treating patients with eosinophilic granulomatosis with polyangiitis, in whom blood eosinophil counts are often much higher than in patients with severe eosinophilic asthma. Unfortunately, blood eosinophil counts were not recorded during exacerbations, which is a missed opportunity to explore the pathobiologic features of exacerbations.

All the participants in this trial had relapsing or refractory eosinophilic granulomatosis with polyangiitis, despite taking at least 7.5 mg of prednisone per day. The reduction in the prednisone dose that occurred with mepolizumab shows an important benefit from treatment, with 18% of the participants being able to discontinue prednisone completely. The trial design allowed the reduction of the oral glucocorticoid dose as early as 4 weeks after trial onset, which leaves an open question as to whether the effect of mepolizumab on the prevention of relapse may have been better if the dose of glucocorticoids had remained constant throughout the trial.

After many years of research into eosinophilic diseases and failure of treatment with anti–interleukin-5 antibodies in all patients with severe asthma,[10] drug developers are increasingly using biomarkers to select patients who are most likely to have a response to a given treatment. After this proof-of-concept study, additional research is needed to identify biomarkers that inform success and failure of mepolizumab in patients with eosinophilic granulomatosis with polyangiitis and to elucidate the fate of tissue eosinophils, especially in vasculitic lesions. Further studies may discover previously unknown pro-eosinophilic mechanisms or identify eosinophil-independent mechanisms in eosinophilic granulomatosis with polyangiitis. Future trials will also need not only to establish the appropriate dosing of mepolizumab but also to include participants with life-threatening eosinophilic granulomatosis with polyangiitis who were not included in this trial and possibly to evaluate synergy with immunosuppressants such as azathioprine and cyclophosphamide.

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

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ORIGINAL ARTICLE

Air Pollution and Mortality in the Medicare Population

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ABSTRACT

BACKGROUND

Studies have shown that long-term exposure to air pollution increases mortality. However, evidence is limited for air-pollution levels below the most recent National Ambient Air Quality Standards. Previous studies involved predominantly urban populations and did not have the statistical power to estimate the health effects in underrepresented groups.

METHODS

We constructed an open cohort of all Medicare beneficiaries (60,925,443 persons) in the continental United States from the years 2000 through 2012, with 460,310,521 person-years of follow-up. Annual averages of fine particulate matter (particles with a mass median aerodynamic diameter of less than 2.5 μm [$PM_{2.5}$]) and ozone were estimated according to the ZIP Code of residence for each enrollee with the use of previously validated prediction models. We estimated the risk of death associated with exposure to increases of 10 μg per cubic meter for $PM_{2.5}$ and 10 parts per billion (ppb) for ozone using a two-pollutant Cox proportional-hazards model that controlled for demographic characteristics, Medicaid eligibility, and area-level covariates.

RESULTS

Increases of 10 μg per cubic meter in $PM_{2.5}$ and of 10 ppb in ozone were associated with increases in all-cause mortality of 7.3% (95% confidence interval [CI], 7.1 to 7.5) and 1.1% (95% CI, 1.0 to 1.2), respectively. When the analysis was restricted to person-years with exposure to $PM_{2.5}$ of less than 12 μg per cubic meter and ozone of less than 50 ppb, the same increases in $PM_{2.5}$ and ozone were associated with increases in the risk of death of 13.6% (95% CI, 13.1 to 14.1) and 1.0% (95% CI, 0.9 to 1.1), respectively. For $PM_{2.5}$, the risk of death among men, blacks, and people with Medicaid eligibility was higher than that in the rest of the population.

CONCLUSIONS

In the entire Medicare population, there was significant evidence of adverse effects related to exposure to $PM_{2.5}$ and ozone at concentrations below current national standards. This effect was most pronounced among self-identified racial minorities and people with low income. (Supported by the Health Effects Institute and others.)

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EDITORIAL

Air Pollution Still Kills

Rebecca E. Berger, M.D., Ramya Ramaswami, M.B., B.S., M.P.H., Caren G. Solomon, M.D., M.P.H., and Jeffrey M. Drazen, M.D.

In late October 1948, a dense smog descended over the town of Donora, Pennsylvania. The town was home to a zinc plant and a steel mill, both run by the United States Steel Corporation. Susan Gnora, a 62-year-old resident of Donora, started to gasp and cough as the smog descended.[1] She died the next day. Dr. William Rongaus, a physician and a member of the board of health, went door to door, treating patients for their respiratory symptoms and encouraging them to leave town if they could. Many thousands were ill, and at least 20 people died in one of the worst air-pollution disasters in U.S. history. The Donora tragedy transformed our perception of smog from a nuisance to a potential killer.

We started to improve air quality with the Clean Air Act of 1963. In 1970, Richard Nixon established the Environmental Protection Agency (EPA) by executive order, and the Clean Air Act was amended to institute National Ambient Air Quality Standards (NAAQS), which set exposure limits for six major air pollutants.[2] Among the pollutants regulated by the EPA is fine particulate matter — inhalable particles with an aerodynamic diameter of less than 2.5 μm ($PM_{2.5}$). Major contributors to $PM_{2.5}$ in the United States include various types of transportation and the coal-fired generation of electricity.[3,4] Since the 1970s, hundreds of articles have been written establishing an association between $PM_{2.5}$ and poor health outcomes, including asthma, ischemic heart disease, and all-cause mortality in urban populations.[5,6] In response to these findings, regulators have lowered NAAQS for the allowable amount of $PM_{2.5}$ in the air.[7] Current NAAQS, last updated in 2012, set an annual mean $PM_{2.5}$ level of 12 μg per cubic meter. This standard, which is to be reviewed every 5 years, aims to protect the population, especially those who are particularly sensitive to the adverse effects of air pollution, including children, elderly persons, and persons with cardiopulmonary disease.[2] As communities meet these stricter standards, fewer people will become sick and die as a result of air pollution. A 2011 report from the EPA projected that by 2020, amendments to the Clean Air Act would prevent more than 230,000 premature deaths, largely as a result of reductions in $PM_{2.5}$ levels.[8] But are current standards sufficient to protect public health?

Di et al. now report in the *Journal* the results of a large study, including more than 60 million Medicare beneficiaries from the years 2000 through 2012, that addresses the association between annual average levels of $PM_{2.5}$ and ozone,[9] as measured at the ZIP Code level, and mortality. For every increase of 10 μg per cubic meter in $PM_{2.5}$, there was an associated 7.3% increase in all-cause mortality (95% confidence interval [CI], 7.1 to 7.5), after adjustment for demographic characteristics, Medicaid eligibility, and area-level covariates. Below the current NAAQS for $PM_{2.5}$ of 12 μg per cubic meter, the data showed that each increase in $PM_{2.5}$ of 10 μg per cubic meter was associated with an even greater increase (13.6%) in mortality (95% CI, 13.1 to 14.1). There was no appreciable level below which the risk of death tapered off — and thus no "safe" level of $PM_{2.5}$. Owing to the large size of the cohort, Di et al. were able to perform robust sub-

group analyses and identified greater risks of death associated with air pollutants among blacks and Medicaid-eligible populations; moreover, these groups were more likely to be exposed to higher pollutant levels.

The findings of Di et al. stress the need for tighter regulation of air-pollutant levels, including the imposition of stricter limits on levels of $PM_{2.5}$. Despite compelling data, the Trump administration is moving headlong in the opposite direction. In March, Trump signed an executive order that lifted a moratorium on new leases for coal mined on public and tribal lands and began a process to dismantle guidelines intended to reduce emissions from coal-fired electricity plants.[10] Earlier this month, he announced his intention to withdraw the United States from the Paris climate agreement. Although these actions were primarily intended to undo efforts made by the Obama administration to address climate change, the potentially dire consequences also include increasing people's exposure to particulate matter. In addition, EPA Administrator Scott Pruitt has not ruled out the possibility of revoking a waiver included in the 1970 Clean Air Act that allows California to set limits on automotive tailpipe emissions that are more stringent than national standards[11]; 15 states have adopted California's standards. Revoking this waiver could have the effect of exposing more than 100 million Americans to higher levels of automobile emissions. Trump's proposed budget includes crippling cuts to the EPA, including cuts in funding for both federal and state enforcement of regulations. The increased air pollution that would result from loosening current restrictions would have devastating effects on public health.

In explaining his withdrawal from the Paris climate agreement, Trump stated, "I was elected to represent the citizens of Pittsburgh, not Paris." Ironically, Pittsburgh is less than 30 miles from the Donora Smog Museum, where a sign reads, "Clean Air Started Here." With the report by Di et al. adding to the large body of evidence indicating the risks of air pollution, even at current standards, we must redouble our commitment to clean air. If such protections lapse, Americans will suffer and we are doomed to repeat history. Do we really want to breathe air that kills us?

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

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ORIGINAL ARTICLE

Health Effects of Overweight and Obesity in 195 Countries over 25 Years

The GBD 2015 Obesity Collaborators*

ABSTRACT

BACKGROUND

Although the rising pandemic of obesity has received major attention in many countries, the effects of this attention on trends and the disease burden of obesity remain uncertain.

METHODS

We analyzed data from 68.5 million persons to assess the trends in the prevalence of overweight and obesity among children and adults between 1980 and 2015. Using the Global Burden of Disease study data and methods, we also quantified the burden of disease related to high body-mass index (BMI), according to age, sex, cause, and BMI in 195 countries between 1990 and 2015.

RESULTS

In 2015, a total of 107.7 million children and 603.7 million adults were obese. Since 1980, the prevalence of obesity has doubled in more than 70 countries and has continuously increased in most other countries. Although the prevalence of obesity among children has been lower than that among adults, the rate of increase in childhood obesity in many countries has been greater than the rate of increase in adult obesity. High BMI accounted for 4.0 million deaths globally, nearly 40% of which occurred in persons who were not obese. More than two thirds of deaths related to high BMI were due to cardiovascular disease. The disease burden related to high BMI has increased since 1990; however, the rate of this increase has been attenuated owing to decreases in underlying rates of death from cardiovascular disease.

CONCLUSIONS

The rapid increase in the prevalence and disease burden of elevated BMI highlights the need for continued focus on surveillance of BMI and identification, implementation, and evaluation of evidence-based interventions to address this problem. (Funded by the Bill and Melinda Gates Foundation.)

*The names, academic degrees, and affiliations of the authors, who are members of the Global Burden of Disease (GBD) 2015 Obesity Collaborators, are listed in the Appendix. The authors assume responsibility for the content and integrity of this article. Address reprint requests to Dr. Murray at the Institute for Health Metrics and Evaluation, University of Washington, 2301 5th Ave., Suite 600, Seattle, WA 98121, or at cjlm@uw.edu.

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EDITORIAL

Global Health Effects of Overweight and Obesity

Edward W. Gregg, Ph.D., and Jonathan E. Shaw, M.D.

The Global Burden of Disease (GBD) study that is now reported in the *Journal* offers a discouraging reminder that the global obesity epidemic is worsening in most parts of the world and that its implications regarding both physical health and economic health remain ominous.[1] The study, in which researchers assembled data from 195 countries to model trends in overweight and obesity and related morbidity and mortality, showed that the prevalence of obesity has more than doubled since 1980 and is now 5% in children and 12% in adults — findings that mirror similar global trends in type 2 diabetes. Apart from a possible recent plateau in the prevalence of obesity in high-income countries, the prevalence has increased in all other sociodemographic strata.

On the encouraging side, despite this increase in prevalence, the effect of high body-mass index (BMI) on population-level age-adjusted rates of death and disability has not grown, which suggests that obese persons are healthier and live longer now than in previous decades because of better care and risk-factor management. Unfortunately, even this success brings a new burden, since the mix of increased prevalence and decreased mortality leads to more years spent with obesity and more time for the damaging coexisting illnesses, such as type 2 diabetes and chronic kidney disease, to develop.

The most worrisome finding is the approximate tripling of obesity seen in youth and young adults of developing, middle-income countries such as China, Brazil, and Indonesia. An early onset of obesity is likely to translate into a high cumulative incidence of type 2 diabetes, hypertension, and chronic kidney disease. These findings come on the heels of reports from the United States that the incidence of type 2 diabetes in youth has increased substantially in minority populations, and when type 2 diabetes occurs in youth, it brings a much higher prevalence of complications than does type 1 diabetes.[2,3] Since reductions in diabetes complications have been dominated by improvements among older adults, an increased incidence of diabetes among children may shift a proportionately greater load of morbidity into middle age[4] and spread the burden of chronic disease more fully across the entire age distribution, even as populations continue to age.

The findings of the GBD investigators are an impressive and essential effort to provide policymakers with both global and country-specific estimates that most countries alone lack. However, some of the modeling assumptions in the current report might obscure important variation in both the threats and the successes underlying the obesity epidemic. First, the assumption that the risk of outcomes at any given level of obesity is uniform across populations could skew morbidity estimates. For example, at any given level of BMI, Asians have been shown to have a higher absolute risk of diabetes and hypertension and African Americans to have a lower risk of cardiovascular disease than other groups.[5] Once chronic conditions such as diabetes and cardiovascular disease develop, the associated relative risk of death may vary according to location — as was recently seen in Mexico, where the relative risk of death associated with diabetes far exceeds that in the United States and Europe.[6] Second, there may be important, missed variation in the high end of the BMI distribution, which disproportionately drives the development of type 2 diabetes and other coexisting illnesses.[7]

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In some regions, the high prevalence of severe obesity may persist even when levels of overweight and obesity appear to plateau. Finally, global findings only hint at some of the actual successes in prevention that may finally be under way. In the United States, the past decade has brought an apparent peak and plateau in the prevalence of obesity and diagnosed diabetes, decreases in the intake of overall calories and of sugared beverages, and increasing levels of physical activity.[8-10] Similarly, more communities in the United States now report reductions in the incidence of childhood obesity and adult type 2 diabetes.

Gaps in available data have forced the GBD researchers to make the best of a checkerboard of periodic and suboptimal data to provide a global picture. However, the magnitude of obesity-related morbidity and the demands for effective public health decision making point to the need for improvements in at least three types of data: efficient, continuous surveillance systems to assess risk factors, prevalence, care, and outcomes of chronic diseases; cohorts in more diverse populations to capture variation in progression to outcomes; and platforms for natural experimental studies to determine which of the interventions are working locally and why. Although obesity and diabetes have become a shared global burden requiring a strong response from governments, their determinants and effects — and particularly their solutions — also depend on the specific environment in which people live. Better data systems would permit policymakers in the hardest hit areas of the world to respond more quickly and to shorten the long learning period that is typically required to overcome chronic diseases.

The views expressed in this editorial are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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

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ORIGINAL ARTICLE

Trial of Tocilizumab in Giant-Cell Arteritis

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ABSTRACT

BACKGROUND

Giant-cell arteritis commonly relapses when glucocorticoids are tapered, and the prolonged use of glucocorticoids is associated with side effects. The effect of the interleukin-6 receptor alpha inhibitor tocilizumab on the rates of relapse during glucocorticoid tapering was studied in patients with giant-cell arteritis.

METHODS

In this 1-year trial, we randomly assigned 251 patients, in a 2:1:1:1 ratio, to receive subcutaneous tocilizumab (at a dose of 162 mg) weekly or every other week, combined with a 26-week prednisone taper, or placebo combined with a prednisone taper over a period of either 26 weeks or 52 weeks. The primary outcome was the rate of sustained glucocorticoid-free remission at week 52 in each tocilizumab group as compared with the rate in the placebo group that underwent the 26-week prednisone taper. The key secondary outcome was the rate of remission in each tocilizumab group as compared with the placebo group that underwent the 52-week prednisone taper. Dosing of prednisone and safety were also assessed.

RESULTS

Sustained remission at week 52 occurred in 56% of the patients treated with tocilizumab weekly and in 53% of those treated with tocilizumab every other week, as compared with 14% of those in the placebo group that underwent the 26-week prednisone taper and 18% of those in the placebo group that underwent the 52-week prednisone taper ($P<0.001$ for the comparisons of either active treatment with placebo). The cumulative median prednisone dose over the 52-week period was 1862 mg in each tocilizumab group, as compared with 3296 mg in the placebo group that underwent the 26-week taper ($P<0.001$ for both comparisons) and 3818 mg in the placebo group that underwent the 52-week taper ($P<0.001$ for both comparisons). Serious adverse events occurred in 15% of the patients in the group that received tocilizumab weekly, 14% of those in the group that received tocilizumab every other week, 22% of those in the placebo group that underwent the 26-week taper, and 25% of those in the placebo group that underwent the 52-week taper. Anterior ischemic optic neuropathy developed in one patient in the group that received tocilizumab every other week.

CONCLUSIONS

Tocilizumab, received weekly or every other week, combined with a 26-week prednisone taper was superior to either 26-week or 52-week prednisone tapering plus placebo with regard to sustained glucocorticoid-free remission in patients with giant-cell arteritis. Longer follow-up is necessary to determine the durability of remission and safety of tocilizumab. (Funded by F. Hoffmann–La Roche; ClinicalTrials.gov number, NCT01791153.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Stone at Massachusetts General Hospital, 55 Fruit St., Boston, MA 02114, or at jhstone@mgh.harvard.edu.

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EDITORIAL

Giant-Cell Arteritis — More Ecstasy, Less Agony

David B. Hellmann, M.D.

If Irving Stone had written a book about giant-cell arteritis rather than about Michelangelo, he might have chosen *The Ecstasy and the Agony* as the more appropriate title. As many physicians know, diagnosing giant-cell arteritis and witnessing the patient's dramatic initial response to treatment are much more fulfilling than managing a disease that lasts for months or years and that leads to the use of glucocorticoids in doses that result in a litany of side effects, including weight gain, hypertension, diabetes, and osteoporosis. This vexing challenge of treating giant-cell arteritis explains why doctors and patients will welcome the results of the trial conducted by Stone et al., now published in the *Journal*,[1] that suggest that there is an effective glucocorticoid-sparing treatment for giant-cell arteritis.

Giant-cell arteritis, the most common systemic vasculitis among North Americans, causes granulomatous inflammation chiefly of the aortic arch and the extracranial portion of the carotid artery.[2,3] The disease manifests after 50 years of age, most frequently with headache, polymyalgia rheumatica, jaw claudication, and visual loss. The laboratory hallmark of active disease is a markedly elevated erythrocyte sedimentation rate (or C-reactive protein [CRP] level). The most feared complication is blindness, which is usually irreversible. Early diagnosis and treatment with prednisone at a daily dose of 40 to 60 mg per day prevents blindness and dramatically ameliorates symptoms. The tapering of prednisone usually begins after the first 2 to 4 weeks of treatment. Although a minority of patients can taper off prednisone over a period of 3 to 6 months, the majority have repeated cycles of flares and remissions that result in a yo-yoing of prednisone therapy over a period of many months or years. Unfortunately, alternatives to glucocorticoids have not been reliably effective in randomized, controlled trials.

Although the cause of giant-cell arteritis is unknown, activated dendritic cells, T cells, macrophages, and the cytokines they secrete (including interferon-γ, interleukin-17, interleukin-1, and interleukin-6) play central roles in the pathogenesis of this disorder.[4,5] Might blocking one of these pathways treat giant-cell arteritis?[6,7] To answer this question, some investigators have tested tocilizumab, an inhibitor of interleukin-6 receptor alpha that has been previously approved for the treatment of rheumatoid arthritis. In 2016, a phase 2 trial showed that tocilizumab allowed prednisone tapering without a return of symptoms.[8] Stone et al. now report the results of a randomized, double-blind, placebo-controlled, phase 3 trial that convincingly shows that tocilizumab can result in sustained prednisone-free remissions in giant-cell arteritis over a period of 52 weeks.

In this trial, patients with active giant-cell arteritis were randomly assigned to one of two groups that received different doses of tocilizumab administered subcutaneously and combined with a 26-week prednisone taper or to one of two groups that received placebo and prednisone with the prednisone tapered over a period of either 26 weeks or 52 weeks. Sustained remission at week 52, the primary outcome, occurred in 53% and 56% of the patients treated with the two different doses of tocilizumab, as compared with 14% and 18% of those in the two placebo groups. Over the 52-week trial period, patients treated with tocilizumab also had higher quality-of-life scores and received approximately half the cumulative dose of prednisone as those in the placebo groups.

Adverse events occurred with similar frequency in the tocilizumab groups and the placebo groups, but serious adverse events developed less often in patients who received tocilizumab than in those who received placebo.

Despite these impressive results and the recent approval by the Food and Drug Administration for the use of subcutaneously administered tocilizumab in patients with giant-cell arteritis, additional studies are needed before tocilizumab can be recommended for all patients with active giant-cell arteritis. As Stone et al. emphasize, the long-term effect of tocilizumab cannot be determined in 1 year. Although tocilizumab was much more effective than prednisone alone, only approximately 50% of the patients treated with tocilizumab had prednisone-free remission. Perhaps blocking other cytokines or cells (such as T cells) or interrupting multiple pathways will be more effective.[9] The previous report of a patient with giant-cell arteritis who appeared to have remission with tocilizumab but had a myocardial infarction and was found to have active arteritis suggests that tocilizumab may suppress manifestations of giant-cell arteritis (especially the elevated CRP level) without eliminating the arteritis.[6]

Moreover, since other studies have shown that interleukin-6, in addition to causing inflammation, might also promote angiogenesis and protect against blindness in patients with giant-cell arteritis, it will be important to determine the long-term risk of visual loss or stroke.[10] Larger studies will be useful in determining whether ischemic events will be a risk with the long-term use of the drug. Although the current trial showed fewer serious side effects with tocilizumab than with placebo, the drug carries black-box warnings about the risk of opportunistic infection. Although I believe that the report by Stone et al. is likely to herald the coming of more ecstasy and less agony for patients with giant-cell arteritis, pending longer-term evaluations, I will reserve tocilizumab for patients who are at high risk for serious side effects from prednisone and for patients who have repeated flares that are not manageable with low doses of prednisone.

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

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ORIGINAL ARTICLE

Analysis of Plasma Epstein–Barr Virus DNA to Screen for Nasopharyngeal Cancer

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ABSTRACT

BACKGROUND

Circulating cell-free Epstein–Barr virus (EBV) DNA is a biomarker for nasopharyngeal carcinoma. We conducted a prospective study to investigate whether EBV DNA in plasma samples would be useful to screen for early nasopharyngeal carcinoma in asymptomatic persons.

METHODS

We analyzed EBV DNA in plasma specimens to screen participants who did not have symptoms of nasopharyngeal carcinoma. Participants with initially positive results were retested approximately 4 weeks later, and those with persistently positive EBV DNA in plasma underwent nasal endoscopic examination and magnetic resonance imaging (MRI).

RESULTS

A total of 20,174 participants underwent screening. EBV DNA was detectable in plasma samples obtained from 1112 participants (5.5%), and 309 (1.5% of all participants and 27.8% of those who initially tested positive) had persistently positive results on the repeated sample. Among these 309 participants, 300 underwent endoscopic examination, and 275 underwent both endoscopic examination and MRI; of these participants, 34 had nasopharyngeal carcinoma. A significantly higher proportion of participants with nasopharyngeal carcinoma that was identified by screening had stage I or II disease than in a historical cohort (71% vs. 20%, P<0.001 by the chi-square test) and had superior 3-year progression-free survival (97% vs. 70%; hazard ratio, 0.10; 95% confidence interval, 0.05 to 0.18). Nine participants declined to undergo further testing, and 1 of them presented with advanced nasopharyngeal carcinoma 32 months after enrollment. Nasopharyngeal carcinoma developed in only 1 participant with negative EBV DNA in plasma samples within 1 year after testing. The sensitivity and specificity of EBV DNA in plasma samples in screening for nasopharyngeal carcinoma were 97.1% and 98.6%, respectively.

CONCLUSIONS

Analysis of EBV DNA in plasma samples was useful in screening for early asymptomatic nasopharyngeal carcinoma. Nasopharyngeal carcinoma was detected significantly earlier and outcomes were better in participants who were identified by screening than in those in a historical cohort. (Funded by the Kadoorie Charitable Foundation and the Research Grants Council of the Hong Kong government; ClinicalTrials.gov number, NCT02063399.)

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EDITORIAL

Plasma Epstein–Barr Virus DNA for Screening

Richard F. Ambinder, M.D., Ph.D.

In this issue of the *Journal*, Chan et al.[1] report on the monitoring of Epstein–Barr virus (EBV) DNA in plasma samples to screen a population that was at high risk for nasopharyngeal carcinoma. Although interest in monitoring circulating cell-free tumor DNA has surged, the application of this method to early detection of tumors remains challenging.[2,3] Among the challenges are assay sensitivity and specificity. In healthy persons, circulating cell-free DNA is composed of DNA originating from normal cells. In early-stage cancer, only a small fraction of cell-free DNA is derived from tumor. Sensitive screening for cancer-associated mutations in turn yields false positive results, because with increasing age, people in whom cancer will never develop during their lifetimes nonetheless acquire cancer-associated mutations.

The targeted EBV DNA sequence described in the article by Chan and colleagues allowed high sensitivity. Each nasopharyngeal carcinoma cell carries approximately 50 copies of the EBV genome. The particular sequence target chosen for amplification is repeated approximately 10 times in tandem in the EBV genome. Thus, each tumor cell harbors approximately 500 target sequences for amplification, some of which are released into the circulation and can be detected by means of a polymerase-chain-reaction assay.

Specificity has been another problem. Although EBV is consistently associated with nasopharyngeal carcinoma (i.e., viral DNA and RNA proteins can be detected in tumor cells), the infection is ubiquitous, and one might justly be skeptical about screening for early nasopharyngeal cancers by testing to detect viral DNA. In the vast majority of adults, latent EBV is harbored in a fraction of resting memory B cells. EBV shedding in saliva can be intermittently detected in adults indefinitely after primary infection.

In devising a screening procedure, Chan et al. chose not to select a cutoff value for the detection of EBV in plasma so as not to compromise the sensitivity. Any amplification signal was considered to be a positive result. A previous study by some of the same researchers showed that patients with nasopharyngeal carcinoma tended to have persistently positive results, whereas those without nasopharyngeal carcinoma did not.[4] Thus, the investigators minimized false positives by conducting a second evaluation approximately 4 weeks after the first. Patients with persistently positive results were defined as "screen-positive." The positive predictive value of the screening protocol was 11%. Because early-stage nasopharyngeal carcinoma is usually cured with local radiation therapy and because almost half the participants with nasopharyngeal carcinoma in this study had stage I disease, the findings are clinically important and the data presented suggest that lives have been saved because of this screening.

Viral-load measurements have proved useful in the management of hepatitis B, hepatitis C, human immunodeficiency virus, and cytomegalovirus infections. As measurements of EBV DNA in plasma become more widely used, it will be important that measurement of the EBV DNA viral copy number not be misinterpreted as a measurement of virions. The target of measurement in plasma samples obtained from patients with nasopharyngeal carcinoma is predominantly

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viral sequences released from tumor cells into cell-free blood — a very important distinction.[5] Virion DNA is tightly packed inside a protein capsid, which is in turn inside a lipid envelope. Production of virion DNA involves a viral DNA polymerase that can be inhibited by nucleoside analogues such as acyclovir and ganciclovir. In contrast, viral DNA in latently infected cells persists as a nuclear plasmid or episome that is replicated by host-cell DNA polymerases in synchrony with the cell cycle such that after mitosis, daughter cells also carry viral DNA. In tumors, virus is predominantly latent and cellular proliferation results in the perpetuation of nuclear plasmids. Thus, the addition of antiviral agents that inhibit the EBV DNA polymerase and block the production of virions would not be expected to alter either measurements of EBV DNA in plasma or the natural history of an established tumor.

A further caution is that in a retrospective survey of unselected patients in whom EBV DNA was detected in plasma samples at Johns Hopkins Hospital, approximately 1% had nasopharyngeal carcinoma.[6] Thus, as Chan et al. warn, the positive predictive value of EBV DNA in plasma to screen for nasopharyngeal carcinoma is much lower outside of endemic areas, high-risk populations, or high-risk persons than it is in these areas and populations. However, the study by Chan et al. shows that in the right context, population screening of plasma DNA is a very promising approach to detect early-stage cancer. Like cervical cytologic testing or testing for human papillomavirus in the cervix for early detection of cervical cancer, plasma EBV DNA screening may profoundly change the natural history of nasopharyngeal carcinoma.

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

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ORIGINAL ARTICLE

Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke

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ABSTRACT

BACKGROUND

Trials of patent foramen ovale (PFO) closure to prevent recurrent stroke have been inconclusive. We investigated whether patients with cryptogenic stroke and echocardiographic features representing risk of stroke would benefit from PFO closure or anticoagulation, as compared with antiplatelet therapy.

METHODS

In a multicenter, randomized, open-label trial, we assigned, in a 1:1:1 ratio, patients 16 to 60 years of age who had had a recent stroke attributed to PFO, with an associated atrial septal aneurysm or large interatrial shunt, to transcatheter PFO closure plus long-term antiplatelet therapy (PFO closure group), antiplatelet therapy alone (antiplatelet-only group), or oral anticoagulation (anticoagulation group) (randomization group 1). Patients with contraindications to anticoagulants or to PFO closure were randomly assigned to the alternative noncontraindicated treatment or to antiplatelet therapy (randomization groups 2 and 3). The primary outcome was occurrence of stroke. The comparison of PFO closure plus antiplatelet therapy with antiplatelet therapy alone was performed with combined data from randomization groups 1 and 2, and the comparison of oral anticoagulation with antiplatelet therapy alone was performed with combined data from randomization groups 1 and 3.

RESULTS

A total of 663 patients underwent randomization and were followed for a mean (±SD) of 5.3±2.0 years. In the analysis of randomization groups 1 and 2, no stroke occurred among the 238 patients in the PFO closure group, whereas stroke occurred in 14 of the 235 patients in the antiplatelet-only group (hazard ratio, 0.03; 95% confidence interval, 0 to 0.26; P<0.001). Procedural complications from PFO closure occurred in 14 patients (5.9%). The rate of atrial fibrillation was higher in the PFO closure group than in the antiplatelet-only group (4.6% vs. 0.9%, P=0.02). The number of serious adverse events did not differ significantly between the treatment groups (P=0.56). In the analysis of randomization groups 1 and 3, stroke occurred in 3 of 187 patients assigned to oral anticoagulants and in 7 of 174 patients assigned to antiplatelet therapy alone.

CONCLUSIONS

Among patients who had had a recent cryptogenic stroke attributed to PFO with an associated atrial septal aneurysm or large interatrial shunt, the rate of stroke recurrence was lower among those assigned to PFO closure combined with antiplatelet therapy than among those assigned to antiplatelet therapy alone. PFO closure was associated with an increased risk of atrial fibrillation. (Funded by the French Ministry of Health; CLOSE ClinicalTrials.gov number, NCT00562289.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Mas at the Department of Neurology, Hôpital Sainte-Anne, 1 rue Cabanis, 75014 Paris, France, or at jl.mas@ch-sainte-anne.fr.

*A complete list of the Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence (CLOSE) investigators is provided in the Supplementary Appendix, available at NEJM.org.

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EDITORIAL

Tipping Point for Patent Foramen Ovale Closure

Allan H. Ropper, M.D.

On the basis of what I had read previously in the *Journal*, I recently explained to my 44-year-old patient that closing his patent foramen ovale (PFO) after his stroke was not advisable. How can we now have three trials showing that closure prevents recurrent stroke, given that in the past 5 years, the *Journal* published articles from three other trials that showed the opposite? It would be simple if the conversion from a negative to a positive outlook with respect to PFO closure could be explained by studying the various antiplatelet and anticoagulant treatments, or the various durations of follow-up among the trials, or the tyranny of a P value of 0.05, as discussed previously by other editorialists,[1] but I found it futile to discover the answer in these details.

I will review the history; a tabular summary is also provided as a scorecard to assist in following the trail of trials and their names (Table 1). It begins with the CLOSURE I trial in 2012[2]; the findings were flatly negative but, as pointed out by an editorialist,[8] the trial had entry criteria that allowed inclusion of patients who had had strokes such as lacunes that would not benefit from PFO closure. The extended follow-up of the RESPECT trial,[7] reported in this issue of the *Journal*, is the most provocative of the trials with positive results because it serves as its own control, in that the entry criteria and treatments were the same as those of the original trial; the main difference was that the median duration of follow-up was 2.1 years in the original trial[4] and 5.9 years in the extended follow-up. During that interval of follow-up, the number of patients who had a stroke increased from 9 to 18 in the PFO closure group and from 16 to 28 in the medical-therapy group (P=0.046 for the difference between the treatment groups at the extended follow-up time point); note that there was a higher percentage of patients in the medical-therapy group than in the PFO closure group who withdrew from the trial before completion of the extended follow-up period. However, the longer duration of follow-up alone is probably not the reason for a change from negative to positive results, as evidenced by the PC trial,[3] in which findings were again emphatically negative despite a mean duration of follow-up of 4 years.

A hint to explaining the discrepancies in results among the trials may be the stringent entry criteria in the CLOSE trial,[6] the results of which are also reported in this issue of the *Journal*, which required that patients have a large interatrial shunt at rest (more than 30 microbubbles in the left atrium within three cardiac cycles after opacification of the right atrium) or an atrial septal aneurysm (a septum primum excursion greater than 10 mm). Although the rates of stroke in the PFO closure groups of all six PFO trials were low (generally less than 5%), in the CLOSE trial, no patient in the PFO closure group had a stroke, whereas stroke occurred in 6% of the patients in the antiplatelet-only group. The Gore REDUCE trial,[5] a trial with positive results that are also reported in this issue of the *Journal*, represented a middle ground by including patients with a moderate-to-large interatrial shunt but not requiring that patients have an atrial septal aneurysm (approximately 20% of the patients in the PFO closure group were found to have one at the time of the procedure). Therefore, in patients who have had a stroke, are

Table 1. Six Trials of Patent Foramen Ovale Closure for Stroke with Results Published in the *Journal*.*

Trial Name (Year of Publication)	No. of Patients	Mean or Median No. of Years of Follow-up	Comparator	Primary Outcome	Hazard Ratio†	P Value†
Trials with negative findings						
CLOSURE I (2012)[2]	909	2	Antiplatelet therapy, warfarin, or both	Composite of stroke or transient ischemic attack at 2 years, death from any cause during the first 30 days, or death from neurologic causes between 31 days and 2 years after randomization	0.78	0.37
PC (2013)[3]	414	4.1 (PFO closure group), 4.0 (medical-therapy group)	Antiplatelet therapy or anticoagulation‡	Composite of death, stroke, transient ischemic attack, or peripheral embolism	0.63	0.34
RESPECT (2013)[4]	980	2.1	Antiplatelet therapy or warfarin	Composite of recurrent nonfatal ischemic stroke, fatal ischemic stroke, or early death after randomization	0.49	0.08
Trials with positive findings						
Gore REDUCE (2017)[5]	664	3.2	Antiplatelet therapy	Ischemic stroke and new brain infarction on imaging	0.23	0.002
CLOSE (2017)[6]	663	5.3	Antiplatelet therapy or anticoagulation‡	Stroke	0.03	<0.001
RESPECT extended follow-up (2017)[7]	980	5.9	Antiplatelet therapy or warfarin	Composite of recurrent nonfatal ischemic stroke, fatal ischemic stroke, or early death after randomization	0.55	0.046

* CLOSE denotes Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence, CLOSURE I Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale, Gore REDUCE Gore HELEX Septal Occluder and Antiplatelet Medical Management for Reduction of Recurrent Stroke or Imaging-Confirmed TIA in Patients with Patent Foramen Ovale (PFO), PC Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism, and RESPECT Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment.

† The hazard ratio and P value are for the expected probability of stroke or other primary outcome after closure of the PFO versus medical treatment in the intention-to-treat analysis.

‡ Anticoagulation refers to any form of anticoagulation.

younger than 60 years of age, and have a PFO with characteristics that are highly likely to allow paradoxical embolism to occur, the effect of closure becomes persuasive.

An adjoined problem is the ill-defined and ill-used term "cryptogenic stroke." In most trials, this term has been defined by the absence of an overt source of stroke. Hart and colleagues refined the definition by adding a category of strokes that they termed "embolic stroke of undetermined source" and described as " . . . a non-lacunar brain infarct without proximal arterial stenosis or cardioembolic sources . . . "[9] — a category that is also defined by what is *not* found in the workup of stroke. A useful scale has been developed to estimate the likelihood that PFO is the cause of cryptogenic stroke on the basis of age and the presence of a cortical stroke on brain imaging, and again, on the basis of the absence of risk factors for atherosclerosis and the absence of a history of stroke or transient ischemic attack.[10] Shunt or atrial septal aneurysms are not components of the score. All these schema are circumscribed by the aspects of stroke that are absent, rather than by characteristics that are present and that would lead to the conclusion that PFO is likely to be the mechanism of recurrent stroke.

The evidence for causation of embolic stroke in any given person is, of course, circumstantial (e.g., atrial fibrillation or carotid stenosis), and it seems reasonable that the presence of a PFO and a sizable interatrial shunt should similarly no longer result in the categorization of a stroke as cryptogenic. One conclusion from the six trials described above is that the potential benefit from closure is determined on the basis of the positive characteristics of the PFO rather than on the basis of exclusionary factors that make a stroke cryptogenic. Restricting PFO closure entirely to patients with high-risk characteristics of the PFO may perhaps be too conservative, but the boundaries of the features that support the procedure are becoming clearer.

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

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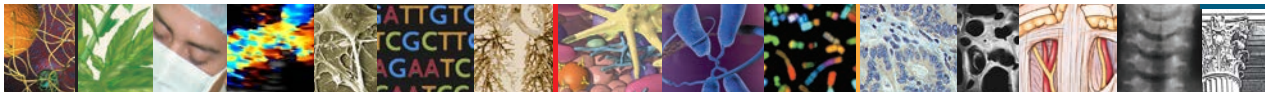

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

MAY 18, 2017

Letter to a Young Female Physician

Suzanne Koven, M.D.

This past June, I participated in an orientation session during which new interns were asked to write self-addressed letters expressing their hopes and anxieties. The sealed envelopes were collected and then returned 6 months later, when I'm sure the interns felt encouraged to see how far they'd come.

This exercise, in which the intern serves as both letter writer and recipient, both novice and veteran, offers a new twist on an old tradition. In 1855, James Jackson published *Letters to a Young Physician Just Entering Upon Practice.* More recent additions to this epistolary canon include Richard Selzer's *Letters to a Young Doctor*, which appeared in 1982, and *Treatment Kind and Fair: Letters to a Young Doctor*, which Perri Klass published in 2007 on the occasion of her son's entry into medical school.

When I started my internship 30 years ago, I wasn't invited to share my hopes and anxieties in a letter — or anywhere else, for that matter. In fact, I recall no orientation at all, other than lining up to receive a stack of ill-fitting white uniforms, a tuberculin skin test, and a hasty and not particularly reassuring review of CPR.

Perhaps the memory of my own abrupt initiation explains my response as I sat at the conference table watching the new interns hunched earnestly over their letters: I was filled with longing. I wanted so much to tell them, particularly the women — more than half the group, I was pleased to note — what I wished I'd known. Even more, I yearned to tell my younger self what I wished I'd known. As the interns wrote, I composed a letter of my own.

Dear Young Female Physician:

I know you are excited and also apprehensive. These feelings are not unwarranted. The hours you will work, the body of knowledge you must master, and the responsibility you will bear for people's lives and well-being are daunting. I'd be worried if you weren't at least a little worried.

As a woman, you face an additional set of challenges, but you know that already. On your urology rotation in medical school, you were informed that your presence was pointless since "no self-respecting man would go to a lady urologist."

There will be more sexism, some infuriating, some merely annoying. As a pregnant resident, I inquired about my hospital's maternity-leave policy for house officers and was told that it was a great idea and I should draft one. Decades into practice, when I call in a prescription, some pharmacists still ask for the name of the doctor I'm calling for.

And there will be more serious and damaging discrimination as well. It pains me to tell you that in 2017, as I'm nearing the end of my career, female physicians earn on average $20,000 less than our male counterparts (even allowing for factors such as numbers of publications and hours worked)[1]; are still underrepresented in lead-

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ership positions, even in specialties such as OB–GYN in which we are a majority[2]; and are subjected to sexual harassment ranging from unwelcome "bro" humor in operating rooms and on hospital rounds to abuse so severe it causes some women to leave medicine altogether.[3]

But there's also a more insidious obstacle that you'll have to contend with — one that resides in your own head. In fact, one of the greatest hurdles you confront may be one largely of your own making. At least that has been the case for me. You see, I've been haunted at every step of my career by the fear that I am a fraud.

This fear, sometimes called "imposter syndrome," is not unique to women. Your male colleagues also have many moments of insecurity, when they're convinced that they alone among their peers are incapable of understanding the coagulation pathway, tying the perfect surgical knot, or detecting a subtle heart murmur.

I believe that women's fear of fraudulence is similar to men's, but with an added feature: not only do we tend to perseverate over our inadequacies, we also often denigrate our strengths.

A 2016 study suggested that patients of female physicians have superior outcomes.[4] The publication of that finding prompted much speculation about why it might be so: perhaps women are more intuitive, more empathic, more attentive to detail, better listeners, or even kinder? I don't know whether any of those generalizations are true, but my personal experience and observations make me sure of this: when women do possess these positive traits, we tend to discount their significance and may even consider them liabilities. We assume that anyone can be a good listener, be empathic — that these abilities are nothing special and are the least of what we have to offer our patients.

I have wasted much time and energy in my career looking for

reassurance that I was not a fraud and, specifically, that I had more to offer my patients than the qualities they seemed to value most.

Early on, I believed that displaying medical knowledge — the more obscure the better — would make me worthy. That belief was a useful spur to learning, but ultimately provided only superficial comfort. During my second-year clinical skills course, an oncologist asked me to identify a rash. "Mycosis fungoides!" I blurted out, since it was one of the few rashes whose name I knew and the only one associated with cancer. My answer turned out to be correct, causing three jaws to drop at once — the oncologist's, the patient's, and my own — but the glow of validation lasted barely the rest of the day.

A little further on in training, I thought that competence meant knowing how to do things. I eagerly performed lumbar punctures and inserted central lines, and I applied for specialty training in gastroenterology — a field in which I had little interest — thinking that I could endoscope my way to self-confidence.

My first few years in practice, I was sure that being a good doctor meant curing people. I felt buoyed by every cleared chest x-ray, every normalized blood pressure. Unfortunately, the converse was also true: I took cancer recurrences personally. When the emergency department paged to alert me that one of my patients had arrived unexpectedly, I assumed that some error on my part must have precipitated the crisis.

Now, late in my clinical career, I understand that I've been neither so weak nor so powerful. Sometimes even after I studied my hardest and tried my best, people got sick and died anyway. How I wish I could spare you years of self-flagellation and transport you directly to this state of humility!

I now understand that I should have spent less time worrying about being a fraud and more time appreciating about myself some of the things my patients appreciate most about me: my large inventory of jokes, my knack for knowing when to butt in and when to shut up, my hugs. Every clinician has her or his own personal armamentarium, as therapeutic as any drug.

My dear young colleague, you are not a fraud. You are a flawed and unique human being, with excellent training and an admirable sense of purpose. Your training and sense of purpose will serve you well. Your humanity will serve your patients even better.

Sincerely,

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Disclosure forms provided by the author are available at NEJM.org.

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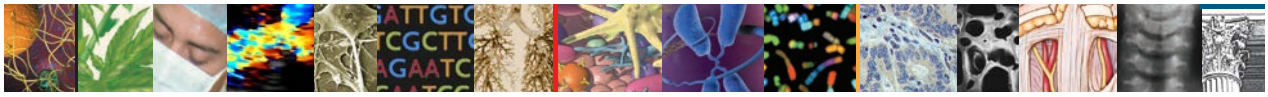

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

OCTOBER 5, 2017

Tragedy, Perseverance, and Chance — The Story of CAR-T Therapy

Lisa Rosenbaum, M.D.

In 2010, 5-year-old Emily Whitehead was diagnosed with acute lymphoblastic leukemia (ALL). Though her parents were told that if you had to have a kid with cancer, ALL was the best one to have, Emily's course was hardly typical. After two rounds of chemotherapy, necrotizing fasciitis developed in both legs and she barely avoided amputation. Sixteen months later, she had a relapse. Bone marrow transplantation was recommended, but the Whiteheads, concerned about toxic effects, sought a second opinion at Children's Hospital of Pennsylvania. There they learned about a new therapy, developed by University of Pennsylvania investigators and known as CART-19, which involved genetically engineering the patient's own T cells to kill tumor cells.

Unfortunately, a clinical trial had not yet been cleared by the Food and Drug Administration (FDA), and Emily's leukemic cells were doubling daily. So Emily returned to her local hospital and received another round of intensive chemotherapy, which bought her 3 weeks but no remission. Out of options, one oncologist recommended hospice. But "That just didn't make sense to us," says Tom Whitehead, Emily's father. When the Whiteheads said they wanted to return to Children's Hospital, the oncologist told them that hospice was preferable to entering Emily into an experimental study that wouldn't help her get better.

But her parents opted to enroll her in a study, and she became the first child to receive CART-19. As a result, not only is she now a thriving 12-year-old, but her survival helped reenergize a line of research that was nearing failure. In August 2017, the FDA approved the first chimeric antigen receptor T-cell (CAR-T) therapy, Novartis's tisagenlecleucel, which uses the Penn-developed technology, for patients up to 25 years of age with relapsed or refractory ALL. Though the indication is narrow, the results are striking in a patient population with otherwise limited options: 83% of the 63 evaluable children who received tisagenlecleucel in Novartis's phase 2 trial had complete elimination of malignant cells at 3 months.[1]

The approval is probably the first of many for CAR-T products. Gilead recently announced its $11.9 billion acquisition of

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Kite Pharma, whose CAR-T technology, initially developed at the National Institutes of Health (NIH), has shown efficacy in patients with chemorefractory, aggressive B-cell non-Hodgkin's lymphoma.[2] And some 40 other companies, many in partnership with academic institutions, are racing to develop CAR-T technologies for myriad indications. Though early data are most promising for other hematologic cancers, such as relapsed chronic lymphocytic leukemia (CLL),[3] similar therapies may eventually prove effective for solid tumors as well.

The emergence of CAR-T therapy, like most scientific advances, reflects the incremental insights of hundreds of scientists over decades. Indeed, the story of CAR-T therapy says as much about the methodical nature of scientific progress as it does about the passions that sustain it.

The emergence of CAR-T therapy, like most scientific advances, reflects the incremental insights of hundreds of scientists over decades — from surgeon William Coley's recognition of the immune system's potential for treating cancer when, in 1893, he injected streptococcus into inoperable osteosarcoma and observed the tumor shrink, to the making of the first CAR-T cells by the Israeli immunologist Zelig Eshhar in 1993.[4] Indeed, the story of CAR-T therapy says as much about the methodical nature of scientific progress as it does about the passions that sustain it.

As Carl June, the immunologist who led the development of Penn's CAR-T technology, recalled, "So many times, I almost had to quit." June spent his early career developing a technique to boost immune function in patients with HIV by modifying their T cells and inducing proliferation ex vivo. Though he and his colleague Bruce Levine would later build on this technique to engineer patients' T cells to attack leukemia, June might have continued focusing solely on the basic science. But in 1996, his 41-year-old wife was diagnosed with ovarian cancer. June tried unsuccessfully to get a pharmaceutical company to provide the tools he needed to attempt immunotherapy. When his wife died in 2001, June resolved to apply emerging immunologic insights to the development of cancer therapies, even though that meant creating a biotech infrastructure within academia.

The translational hurdles remained formidable. The field had been dogged by skepticism and setbacks, and the NIH wouldn't fund a clinical trial. Once again, tragedy propelled the research forward. In 2001, Barbara and Edward Netter, having watched their daughter-in-law die of breast cancer, started the Alliance for Cancer Gene Therapy (ACGT), hoping to develop alternative approaches. In 2008, ACGT granted June and his coinvestigator David Porter $1 million, enough to treat their first three patients with relapsed CLL with CART-19. Two of the three patients achieved complete remission, but the investigators ran out of funding. Knowing they couldn't prove efficacy statistically, they published their findings as case reports.[3,5] Soon, the National Cancer Institute offered June a grant, and Novartis licensed Penn's CAR-T technology. But June acknowledges the tenuous nature of anecdote: "Were we lucky? Were they representative? Would it be durable?"

Indeed, anecdote can easily break a field rather than make it: the death of Jesse Gelsinger in a trial at Penn had set the field of gene therapy back at least a decade. And as both June and Stephan Grupp, the Children's Hospital oncologist and principal investigator of the CART-19 trial in children, emphasized, had Emily died, the CAR-T field would probably have died with her. But though unexpected toxic effects in phase 1 studies can fell any new therapy, the unfortunate reality is that it often takes time, and human lives, to distinguish fatal toxic effects from those that can be managed. As Grupp explained, "There was no way to predict a great deal of what we learned. The toxicity issues can only be learned from human beings."

Emily Whitehead was a case in point. After receiving her third dose of CART-19, she developed high fevers, respiratory failure, and shock necessitating the use of three pressors. Though Emily

was experiencing what's now understood to be cytokine-release syndrome, which occurred in 78% of patients in Novartis's phase 2 trial, it wasn't clear at the time what was driving this response, much less how to treat it.

That she survived gives new meaning to the adage "Chance favors the prepared mind." Per protocol, participants' blood was sent for cytokine analysis, with about a 2-week turnaround time. But as Emily rapidly deteriorated, Grupp called the lab and begged them to run Emily's blood more quickly. Two hours later, in time for his 3 p.m. lab meeting, Grupp learned that Emily's level of interleukin-6 was elevated 1000-fold. He recalls the meeting, as everyone pored over the results. "No one thought we should be thinking about this thing, IL6," Grupp explained. "It isn't even made by T cells." That fact, however, made interleukin-6 acceptable for Emily's doctors to target, since any interference with T-cell function could interfere with the antileukemic activity, without which she would die. But how to quash interleukin-6? As Grupp and his lab members started Googling, June, giving a talk in Seattle, received the results and had an idea. His daughter, who has juvenile rheumatoid arthritis, had recently started taking tocilizumab, a monoclonal antibody that targets interleukin-6. As the investigators converged on a similar conclusion, one hurdle remained: how to get the drug in time for Emily?

Once again, they got lucky. Tocilizumab was on the hospital's formulary for rheumatologic indications, which meant that rather than having to wait for up to 2 days, by 8 p.m. that evening, Emily received a dose. Within hours, she began to improve, so dramatically that her doctors could barely wean the pressors fast enough. On her seventh birthday, Emily woke up. Eight days later, on the basis of a bone marrow biopsy, Grupp reported that the treatment had worked.

Though the remissions achieved with CAR-T therapy are impressive, much remains unknown. CAR-T products vary in ways that will have implications for both efficacy and toxicity. Some variation arises from the chimeric antigen receptors (CARs) themselves, which are programmed to recognize various antigens and contain various types and numbers of costimulatory domains to induce proliferation. In the case of CART-19, for instance, the engineered T cells bind to lymphocytes displaying the CD19 antigen, a hallmark of leukemic B cells and thus an attractive target because humans can tolerate B-cell aplasia. Identifying antigen targets in solid tumors while preventing destruction of healthy tissue remains challenging, however, especially since the tumor microenvironment can be immunologically hostile to introduction of a CAR. Moreover, toxicities remain formidable. Though tocilizumab is now often used to manage the cytokine-release syndrome, other toxic effects, such as cerebral edema, remain poorly understood and difficult to manage.

Meanwhile, the CAR-T discussion has become dominated by cost concerns. Critics argue that tisagenlecleucel's $475,000 price tag is unaffordable and unjustifiable given the taxpayer-supported basic research underpinning its development, while manufacturers point to the tremendous investment required to produce the drug and fund trials. With many patients unable to afford their medications and ongoing instances of unconscionable drug-company profiteering, these discussions are both essential and complex. Regardless of the finances, we all hope that these remissions are prolonged or, even better, turn out to be cures. There is no way to know whether they will without prolonged observation, but while we carefully observe each patient, it is important to remember that therapeutic advances are motivated by more than money — that it's the hope, vision, and perseverance of both patients and investigators that have made this critical conversation possible.

Disclosure forms provided by the author are available at NEJM.org.

Dr. Rosenbaum is a national correspondent for the *Journal*.

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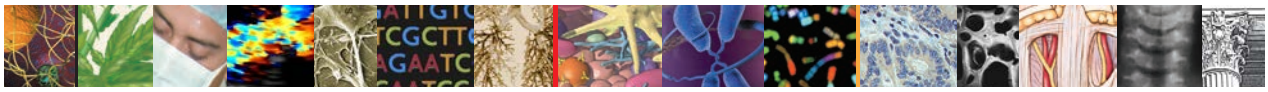

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

AUGUST 24, 2017

Stretching the Scope — Becoming Frontline Addiction-Medicine Providers

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On our infectious diseases (ID) consult service, we recently cared for Mr. C., a young man with *Staphylococcus aureus* tricuspid valve endocarditis, septic arthritis, and empyema that were consequences of his opioid use disorder (OUD). Several years earlier, he had started taking oxycodone at parties, and eventually, when the cost of pills became prohibitive, he'd progressed to injecting heroin. His days were consumed by the logistics of obtaining heroin to stave off the exhausting cycle of opioid withdrawal. Despite his deep desire to stop using, he was initially ambivalent when we offered to start treatment with buprenorphine, which is commonly coformulated with naloxone as Suboxone (Reckitt Benckiser). "Doc," he said, "you gotta understand that as an addict, the scariest thing right now is the idea of putting another opioid in my body, even if it's going to help me."

Although Mr. C. had done well on buprenorphine in the past, accumulating several months of recovery, he felt overwhelmed by the prospect of starting the process again. In the days after his clinical status stabilized and the ID service defined his antibiotic course, we kept visiting Mr. C. on the ward. We confronted the dual imperatives to treat his infection and his OUD to reduce his near-term chance of dying from an overdose or relapsed infection. During our visits, we discussed his resolving empyema, but also his cravings, withdrawal symptoms, and readiness to start buprenorphine treatment. On the day before his discharge, as he faced impending relapse, Mr. C. decided he was ready. That afternoon, we completed an observed buprenorphine induction and made an appointment to see him the following week in the ID clinic for ongoing buprenorphine and antibiotic treatment.

As the opioid use and overdose epidemic ravages the United States, bearing witness to the physical and psychosocial consequences of addiction has become part of many physicians' daily work. Despite our position on the epidemic's front lines, the remarkable reality is that we remain systematically undertrained and underengaged in addiction-treatment efforts.[1] Though we have taken steps toward recognizing our profession's complicity in the epidemic's roots, most physicians feel paralyzed when it comes to effecting change for individual patients.

The history of medicine is, in part, the history of physicians stretching the scope of their practice to answer the pressing needs

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of their times. In the face of OUD, a treatable illness with a striking capacity to rapidly and definitively alter the lives of our patients, their families, and the communities we serve, we have been late and ineffective in our response. In recent years, the number of hospitalizations for the medical consequences of OUD has escalated, and in 2015 alone, more than 33,000 people died in the United States from opioid-related overdose.[2] Yet rates of active physician engagement in addiction treatment remain embarrassingly low.

At some point, it became culturally acceptable to treat all conditions in a patient except addiction. It's a diagnosis still frequently and falsely regarded as untreatable — a convenient assumption driven by the stigma against people with this disease. ID specialists have historically been ardent advocates for social justice and public health, championing patients on the margins of society who have stigmatizing illnesses. In the age of the opioid epidemic, treatment of life-threatening infections arising from injection drug use accounts for an increasing proportion of our practice. Far too often, however, infections that we treat resolve while underlying substance use disorders are left to fester.

Under the federal Drug Addiction Treatment Act of 2000, physicians who register with the Drug Enforcement Administration, regardless of their subspecialty, can receive a waiver to prescribe buprenorphine for OUD treatment after undergoing 8 hours of training. According to the Substance Abuse and Mental Health Services Administration, the federal body that oversees the buprenorphine waiver program, there are currently 37,448 physicians with such waivers,[3] representing only approximately 4% of all professionally active U.S. physicians.[4] Nationally, the distribution of physicians with waivers is grossly uneven, and many suffering communities are left with little to no capacity for buprenorphine treatment. Obtaining a waiver is one concrete action that all physicians can take to help stem the tide of this epidemic. Physicians practicing in clinical contexts in which long-term prescribing is not possible can prescribe a short course of buprenorphine therapy as a bridge to long-term treatment managed by one of a growing number of primary care physicians and psychiatrists.

As a small group of ID fellows and faculty practicing at Beth Israel Deaconess Medical Center, a large tertiary care hospital in Boston, we have pursued this strategy. We offer buprenorphine in conjunction with antibiotics to patients who are hospitalized with infectious complications of injection drug use. We ask patients about injection practices, counsel them about harm reduction, and prescribe intranasal naloxone for overdose reversal, recognizing that OUD is marked by both recovery and relapse. We partner with colleagues in social work to build viable treatment plans to facilitate recovery and eventually transfer addiction care to long-term programs. As we have waited for institutional capacity to increase, we have also started to offer inpatient buprenorphine induction for patients without concurrent infection.

We anticipated some resistance on both the institutional and the provider levels, but in practice, we have largely encountered appreciation, and our work has served as one impetus for a larger hospital initiative to address the opioid crisis. This pilot program was born in our ID division, but we believe it is replicable by any physician group — for example, surgical teams discharging patients admitted with OUD-related complications or psychiatry teams discharging patients with both substance use disorder and mental illness. For all physicians, it is vital to recognize that medication treatment for OUD is a cornerstone of recovery for most patients, and when it's omitted, high rates of relapse are consistently observed.

We are wading into the turbulent waters of our patients' lives to see them through to a time when they are clear of their infection and on the continuum of recovery. Though our efforts are still relatively new, we have been changed by the experience. Some of our patients have had relapses or haven't returned for care. But we've also seen remarkable successes — patients who presented in the depths of addiction and illness who have subsequently reconnected with their families, have started to work again, and now use opioids less or not at all. By providing the bridge to long-term addiction treatment, we have observed patients remain in care at higher rates and start to mend their badly damaged sense of trust in a medical system that has long treated them with judgment and neglect.

We are providing this care outside the realm of traditional ID consultation because the crisis demands it. Today in the United States, another 91 people will die from an opioid overdose.[5] Under the watchful eyes of physicians, many people survive their acute illnesses only to die in public rest-

rooms, in private homes, or on the street. There are many inspiring examples of physicians and health care communities that have similarly stretched the scope of their practice, and lives have been saved as a result. We believe it's time for more of us to join the movement.

Two months after being discharged, Mr. C. continues to receive buprenorphine treatment. He gets his prescriptions through a program close to his home, where he attends weekly group meetings and individual counseling sessions. He wholly understands the gravity of his infection; his heart valve has been left severely damaged, and he still feels weak. But he has reconnected with friends and family and is making plans to return to work. He is in early recovery from his OUD and from the chaos, social isolation, and depression that come with it. As we see it, the medical community is also in early recovery — moving past implicit biases, stigma, and fear to connect with our patients and respond to a defining crisis of our time.

An audio interview with Dr. Rapoport is available at NEJM.org

Disclosure forms provided by the authors are available at NEJM.org.

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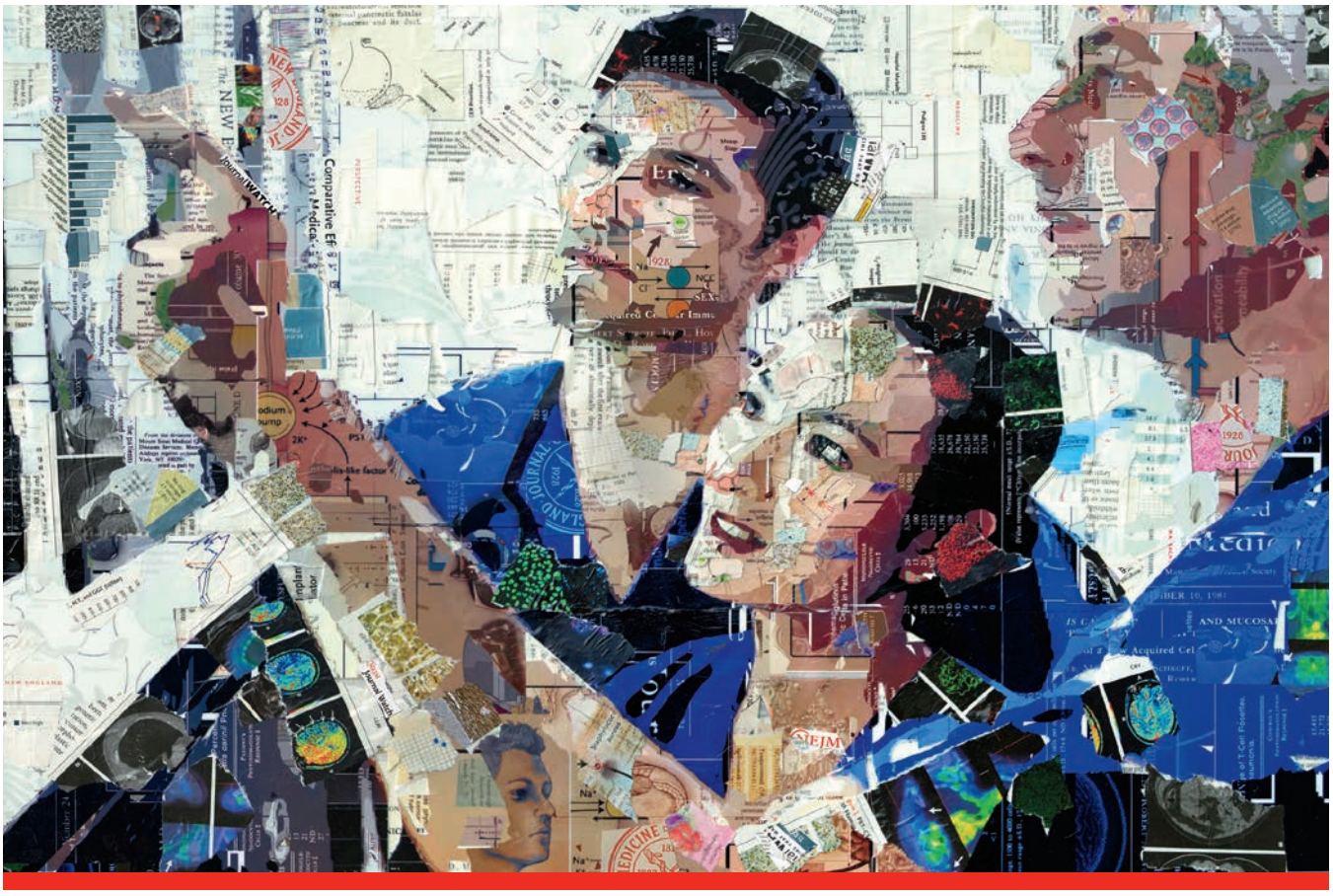

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