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ORIGINAL ARTICLE
Hemophilia with Factor VIII Inhibitors
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Table of Contents

ORIGINAL ARTICLE
Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy 1

ORIGINAL ARTICLE
Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation 2

IMAGES IN CLINICAL MEDICINE
Disseminated Cysticercosis 3

PERSPECTIVE
Hypertension Hot Potato — Anatomy of the Angiotensin-Receptor Blocker Recalls 4

ORIGINAL ARTICLE
Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes 5

ORIGINAL ARTICLE
Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients 6

ORIGINAL ARTICLE
A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy 7

ORIGINAL ARTICLE
Early or Delayed Cardioversion in Recent-Onset Atrial Fibrillation 8

REVIEW ARTICLE
Aspiration Pneumonia 9

ORIGINAL ARTICLE
Apixaban to Prevent Venous Thromboembolism in Patients with Cancer 10

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The NEW ENGLAND JOURNAL of MEDICINE

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Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

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ABSTRACT

BACKGROUND

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

METHODS

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

RESULTS

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

CONCLUSIONS

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

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

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

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Back to Table of Contents

ORIGINAL ARTICLE

Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation

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ABSTRACT

BACKGROUND

Appropriate antithrombotic regimens for patients with atrial fibrillation who have an acute coronary syndrome or have undergone percutaneous coronary intervention (PCI) are unclear.

METHODS

In an international trial with a two-by-two factorial design, we randomly assigned patients with atrial fibrillation who had an acute coronary syndrome or had undergone PCI and were planning to take a $P2Y_{12}$ inhibitor to receive apixaban or a vitamin K antagonist and to receive aspirin or matching placebo for 6 months. The primary outcome was major or clinically relevant nonmajor bleeding. Secondary outcomes included death or hospitalization and a composite of ischemic events.

RESULTS

Enrollment included 4614 patients from 33 countries. There were no significant interactions between the two randomization factors on the primary or secondary outcomes. Major or clinically relevant nonmajor bleeding was noted in 10.5% of the patients receiving apixaban, as compared with 14.7% of those receiving a vitamin K antagonist (hazard ratio, 0.69; 95% confidence interval [CI], 0.58 to 0.81; P<0.001 for both noninferiority and superiority), and in 16.1% of the patients receiving aspirin, as compared with 9.0% of those receiving placebo (hazard ratio, 1.89; 95% CI, 1.59 to 2.24; P<0.001). Patients in the apixaban group had a lower incidence of death or hospitalization than those in the vitamin K antagonist group (23.5% vs. 27.4%; hazard ratio, 0.83; 95% CI, 0.74 to 0.93; P=0.002) and a similar incidence of ischemic events. Patients in the aspirin group had an incidence of death or hospitalization and of ischemic events that was similar to that in the placebo group.

CONCLUSIONS

In patients with atrial fibrillation and a recent acute coronary syndrome or PCI treated with a $P2Y_{12}$ inhibitor, an antithrombotic regimen that included apixaban, without aspirin, resulted in less bleeding and fewer hospitalizations without significant differences in the incidence of ischemic events than regimens that included a vitamin K antagonist, aspirin, or both. (Funded by Bristol-Myers Squibb and Pfizer; AUGUSTUS ClinicalTrials.gov number, NCT02415400.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Lopes at the Duke Clinical Research Institute, 200 Morris St., Durham, NC 27701, or at renato.lopes@duke.edu.

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

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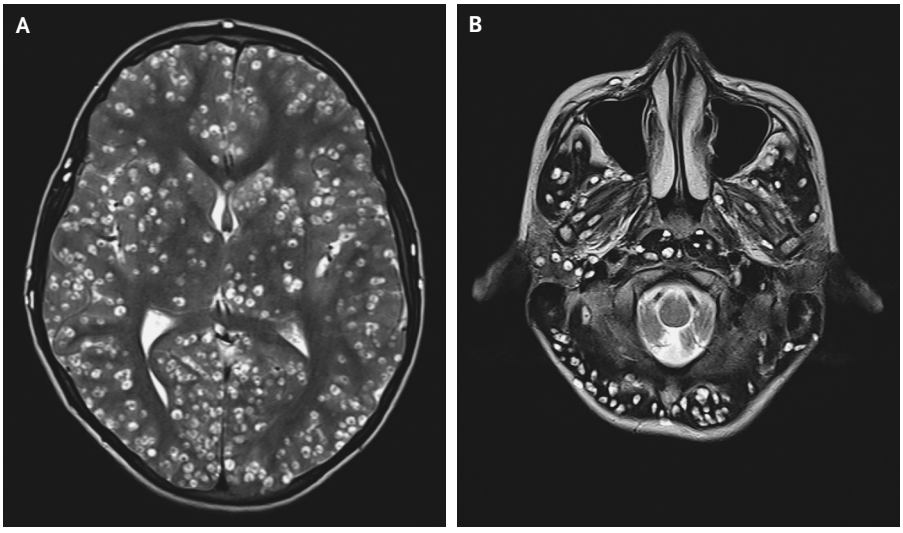
IMAGES IN CLINICAL MEDICINE

Chana A. Sacks, M.D., *Editor*

Disseminated Cysticercosis



An 18-year-old man presented to the emergency department with generalized tonic–clonic seizures. His parents reported that he had been having pain in the right groin for 1 week. On physical examination, the patient was confused. He had swelling over the right eye and tenderness in the right testis. Magnetic resonance imaging of the head showed numerous well-defined cystic lesions throughout the cerebral cortex (Panel A) and the brain stem and cerebellum (Panel B) that were consistent with neurocysticercosis. Well-defined cysts that contained echogenic nodules were seen on ultrasonography of the eye and the right testis. Western blot analysis and enzyme-linked immunosorbent assay showed positive results for serum cysticercosis IgG antibody. In the context of high cyst burden, treatment with antiparasitic medications can worsen inflammation and cerebral edema, and in the presence of ocular lesions, inflammation can lead to loss of vision. Therefore, antiparasitic medications were not administered in this case. Despite treatment with dexamethasone and antiepileptic medications, the patient died 2 weeks later.

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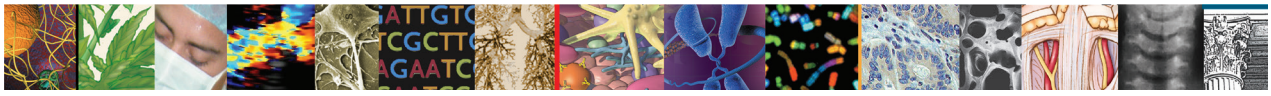
Back to Table of Contents



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Perspective

Hypertension Hot Potato — Anatomy of the Angiotensin-Receptor Blocker Recalls

J. Brian Byrd, M.D., M.S.C.I., Glenn M. Chertow, M.D., M.P.H., and Vivek Bhalla, M.D.

Angiotensin-receptor blockers (ARBs) are one of four drug classes recommended for the initial treatment of hypertension. These medications are commonly used not only for hypertension — a condition present in 45.6% of U.S. adults — but also for heart failure and chronic kidney disease.[1,2] On January 25, 2019, Food and Drug Administration (FDA) Commissioner Scott Gottlieb and Director of the FDA Center for Drug Evaluation and Research Janet Woodcock released a statement updating the public on large-scale voluntary recalls of various products containing ARBs. Two probable carcinogens had been identified in active pharmaceutical ingredients used by some manufacturers of valsartan, irbesartan, and losartan. The impurities arose during manufacture of the ingredients in two factories located in China and India. The same day, the *Wall Street Journal* reported that as many as 2 million patients had probably been exposed to the impurities, *N*-nitrosodimethylamine (NDMA) and *N*-nitroso-*N*-diethylamine (NDEA). Most recently, a third impurity, *N*-nitroso-*N*-methyl-4-aminobutyric acid (NMBA), has been identified in an ARB product, resulting in a new recall. These recalls are of growing concern to patients, clinicians, and organizations delivering primary care or complex, multidisciplinary health care, and they highlight several issues related to the readiness of our health systems to respond to drug recalls, trust between patients and providers, uncertain drug-dose equivalences, and the regulation of drug manufacturing in the global marketplace.

Although not all products containing valsartan, irbesartan, or losartan that are marketed in the United States have been recalled, the scope of the exposure, the scale of the 20 recalls, and their impact on patient care are substantial (see timeline). FDA officials believe that U.S. patients have been ingesting ARBs containing carcinogenic impurities for approximately 4 years; they estimate that for every 8000 patients taking the highest dose of an affected product for the full 4 years, one new cancer above the background incidence would be expected. More than 61 million prescriptions were written for valsartan, irbesartan, or losartan in the United States in 2016.[1]

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Back to Table of Contents

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

ABSTRACT

BACKGROUND

The effects of empagliflozin, an inhibitor of sodium–glucose cotransporter 2, in addition to standard care, on cardiovascular morbidity and mortality in patients with type 2 diabetes at high cardiovascular risk are not known.

METHODS

We randomly assigned patients to receive 10 mg or 25 mg of empagliflozin or placebo once daily. The primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, as analyzed in the pooled empagliflozin group versus the placebo group. The key secondary composite outcome was the primary outcome plus hospitalization for unstable angina.

RESULTS

A total of 7020 patients were treated (median observation time, 3.1 years). The primary outcome occurred in 490 of 4687 patients (10.5%) in the pooled empagliflozin group and in 282 of 2333 patients (12.1%) in the placebo group (hazard ratio in the empagliflozin group, 0.86; 95.02% confidence interval, 0.74 to 0.99; P=0.04 for superiority). There were no significant between-group differences in the rates of myocardial infarction or stroke, but in the empagliflozin group there were significantly lower rates of death from cardiovascular causes (3.7%, vs. 5.9% in the placebo group; 38% relative risk reduction), hospitalization for heart failure (2.7% and 4.1%, respectively; 35% relative risk reduction), and death from any cause (5.7% and 8.3%, respectively; 32% relative risk reduction). There was no significant between-group difference in the key secondary outcome (P=0.08 for superiority). Among patients receiving empagliflozin, there was an increased rate of genital infection but no increase in other adverse events.

CONCLUSIONS

Patients with type 2 diabetes at high risk for cardiovascular events who received empagliflozin, as compared with placebo, had a lower rate of the primary composite cardiovascular outcome and of death from any cause when the study drug was added to standard care. (Funded by Boehringer Ingelheim and Eli Lilly; EMPA-REG OUTCOME ClinicalTrials.gov number, NCT01131676.)

From the Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital (B.Z.) and the Divisions of Endocrinology (B.Z.) and Cardiology (D.F.), University of Toronto — all in Toronto; the Department of Medicine, Division of Nephrology, Würzburg University Clinic, Würzburg (C.W.), Boehringer Ingelheim Pharma, Biberach (E.B., S.H.), and Boehringer Ingelheim Pharma, Ingelheim (M.M., H.J.W., U.C.B.) — all in Germany; the Biostatistics Center, George Washington University, Rockville, MD (J.M.L.); Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT (T.D.); Boehringer Ingelheim Norway, Asker, Norway (O.E.J.); and the Section of Endocrinology, Yale University School of Medicine, New Haven, CT (S.E.I.). Address reprint requests to Dr. Zinman at Mount Sinai Hospital, 60 Murray St., Suite L5-024, Box 17, Toronto, ONT M5T 3L9, Canada, or at zinman@lunenfeld.ca.

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Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients

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ABSTRACT

BACKGROUND

Among patients with aortic stenosis who are at intermediate or high risk for death with surgery, major outcomes are similar with transcatheter aortic-valve replacement (TAVR) and surgical aortic-valve replacement. There is insufficient evidence regarding the comparison of the two procedures in patients who are at low risk.

METHODS

We randomly assigned patients with severe aortic stenosis and low surgical risk to undergo either TAVR with transfemoral placement of a balloon-expandable valve or surgery. The primary end point was a composite of death, stroke, or rehospitalization at 1 year. Both noninferiority testing (with a prespecified margin of 6 percentage points) and superiority testing were performed in the as-treated population.

RESULTS

At 71 centers, 1000 patients underwent randomization. The mean age of the patients was 73 years, and the mean Society of Thoracic Surgeons risk score was 1.9% (with scores ranging from 0 to 100% and higher scores indicating a greater risk of death within 30 days after the procedure). The Kaplan–Meier estimate of the rate of the primary composite end point at 1 year was significantly lower in the TAVR group than in the surgery group (8.5% vs. 15.1%; absolute difference, −6.6 percentage points; 95% confidence interval [CI], −10.8 to −2.5; P<0.001 for noninferiority; hazard ratio, 0.54; 95% CI, 0.37 to 0.79; P=0.001 for superiority). At 30 days, TAVR resulted in a lower rate of stroke than surgery (P=0.02) and in lower rates of death or stroke (P=0.01) and new-onset atrial fibrillation (P<0.001). TAVR also resulted in a shorter index hospitalization than surgery (P<0.001) and in a lower risk of a poor treatment outcome (death or a low Kansas City Cardiomyopathy Questionnaire score) at 30 days (P<0.001). There were no significant between-group differences in major vascular complications, new permanent pacemaker insertions, or moderate or severe paravalvular regurgitation.

CONCLUSIONS

Among patients with severe aortic stenosis who were at low surgical risk, the rate of the composite of death, stroke, or rehospitalization at 1 year was significantly lower with TAVR than with surgery. (Funded by Edwards Lifesciences; PARTNER 3 ClinicalTrials.gov number, NCT02675114.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Mack at Baylor Scott and White Health Heart Hospital–Plano, 1100 Allied Dr., Plano, TX 75093, or at michael.mack@bswhealth.org.

*A complete list of the PARTNER 3 Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Back to Table of Contents

ORIGINAL ARTICLE

A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy

Peter Hajek, Ph.D., Anna Phillips-Waller, B.Sc., Dunja Przulj, Ph.D., Francesca Pesola, Ph.D., Katie Myers Smith, D.Psych., Natalie Bisal, M.Sc., Jinshuo Li, M.Phil., Steve Parrott, M.Sc., Peter Sasieni, Ph.D., Lynne Dawkins, Ph.D., Louise Ross, Maciej Goniewicz, Ph.D., Pharm.D., Qi Wu, M.Sc., and Hayden J. McRobbie, Ph.D.

ABSTRACT

BACKGROUND

E-cigarettes are commonly used in attempts to stop smoking, but evidence is limited regarding their effectiveness as compared with that of nicotine products approved as smoking-cessation treatments.

METHODS

We randomly assigned adults attending U.K. National Health Service stop-smoking services to either nicotine-replacement products of their choice, including product combinations, provided for up to 3 months, or an e-cigarette starter pack (a second-generation refillable e-cigarette with one bottle of nicotine e-liquid [18 mg per milliliter]), with a recommendation to purchase further e-liquids of the flavor and strength of their choice. Treatment included weekly behavioral support for at least 4 weeks. The primary outcome was sustained abstinence for 1 year, which was validated biochemically at the final visit. Participants who were lost to follow-up or did not provide biochemical validation were considered to not be abstinent. Secondary outcomes included participant-reported treatment usage and respiratory symptoms.

RESULTS

A total of 886 participants underwent randomization. The 1-year abstinence rate was 18.0% in the e-cigarette group, as compared with 9.9% in the nicotine-replacement group (relative risk, 1.83; 95% confidence interval [CI], 1.30 to 2.58; P<0.001). Among participants with 1-year abstinence, those in the e-cigarette group were more likely than those in the nicotine-replacement group to use their assigned product at 52 weeks (80% [63 of 79 participants] vs. 9% [4 of 44 participants]). Overall, throat or mouth irritation was reported more frequently in the e-cigarette group (65.3%, vs. 51.2% in the nicotine-replacement group) and nausea more frequently in the nicotine-replacement group (37.9%, vs. 31.3% in the e-cigarette group). The e-cigarette group reported greater declines in the incidence of cough and phlegm production from baseline to 52 weeks than did the nicotine-replacement group (relative risk for cough, 0.8; 95% CI, 0.6 to 0.9; relative risk for phlegm, 0.7; 95% CI, 0.6 to 0.9). There were no significant between-group differences in the incidence of wheezing or shortness of breath.

CONCLUSIONS

E-cigarettes were more effective for smoking cessation than nicotine-replacement therapy, when both products were accompanied by behavioral support. (Funded by the National Institute for Health Research and Cancer Research UK; Current Controlled Trials number, ISRCTN60477608.)

From Queen Mary University of London (P.H., A.P.-W., D.P., K.M.S., N.B., H.J.M.), King's College London (F.P., P.S.), and London South Bank University (L.D.), London, the University of York, York (J.L., S.P., Q.W.), and Leicester City Council, Leicester (L.R.) — all in the United Kingdom; and Roswell Park Comprehensive Cancer Center, Buffalo, NY (M.G.). Address reprint requests to Dr. Przulj at Queen Mary University of London, Health and Lifestyle Research Unit, 2 Stayner's Rd., London E1 4AH, United Kingdom, or at d.przulj@qmul.ac.uk.

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Back to Table of Contents

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 18, 2019 VOL. 380 NO. 16

Early or Delayed Cardioversion in Recent-Onset Atrial Fibrillation

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

ABSTRACT

BACKGROUND

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

METHODS

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

RESULTS

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

CONCLUSIONS

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

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

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

Drs. Pluymaekers and Dudink contributed equally to this article.

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Back to Table of Contents

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Aspiration Pneumonia

Lionel A. Mandell, M.D., and Michael S. Niederman, M.D.

Aspiration pneumonia is best considered not as a distinct entity but as part of a continuum that also includes community- and hospital-acquired pneumonias. It is estimated that aspiration pneumonia accounts for 5 to 15% of cases of community-acquired pneumonia, but figures for hospital-acquired pneumonia are unavailable.[1] Robust diagnostic criteria for aspiration pneumonia are lacking, and as a result, studies of this disorder include heterogeneous patient populations.

Aspiration of small amounts of oropharyngeal secretions is normal in healthy persons during sleep, yet microaspiration is also the major pathogenetic mechanism of most pneumonias.[2] Large-volume aspiration (macroaspiration) of colonized oropharyngeal or upper gastrointestinal contents is the sine qua non of aspiration pneumonia. Variables affecting patient presentation and disease management include bacterial virulence, the risk of repeated events, and the site of acquisition (nursing home, hospital, or community). According to this spectrum, patients labeled as having aspiration pneumonia usually represent a clinical phenotype with risk factors for macroaspiration and involvement of characteristic anatomical pulmonary locations. Aspiration syndromes may involve the airways or pulmonary parenchyma, resulting in a variety of clinical presentations.[3]

This review focuses on aspiration involving the lung parenchyma, primarily aspiration pneumonia and chemical pneumonitis. Aspiration of noninfectious material such as blood or a foreign body is also important. Aspiration pneumonia is an infection caused by specific microorganisms, whereas chemical pneumonitis is an inflammatory reaction to irritative gastric contents. Our understanding of the interaction between bacteria and the lung has improved. We examine this improvement, along with changing concepts of the microbiology and pathogenesis of aspiration pneumonia. We also examine the clinical features, diagnosis, treatment, and prevention of both aspiration pneumonia and chemical pneumonitis, as well as the risk factors.

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Apixaban to Prevent Venous Thromboembolism in Patients with Cancer

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ABSTRACT

BACKGROUND

Patients with active cancer have an increased risk of venous thromboembolism, which results in substantial morbidity, mortality, and health care expenditures. The Khorana score (range, 0 to 6, with higher scores indicating a higher risk of venous thromboembolism) has been validated to identify patients with cancer at elevated risk for this complication and may help select those who could benefit from thromboprophylaxis.

METHODS

We conducted a randomized, placebo-controlled, double-blind clinical trial assessing the efficacy and safety of apixaban (2.5 mg twice daily) for thromboprophylaxis in ambulatory patients with cancer who were at intermediate-to-high risk for venous thromboembolism (Khorana score, ≥2) and were initiating chemotherapy. The primary efficacy outcome was objectively documented venous thromboembolism over a follow-up period of 180 days. The main safety outcome was a major bleeding episode.

RESULTS

Of the 574 patients who underwent randomization, 563 were included in the modified intention-to-treat analysis. Venous thromboembolism occurred in 12 of 288 patients (4.2%) in the apixaban group and in 28 of 275 patients (10.2%) in the placebo group (hazard ratio, 0.41; 95% confidence interval [CI], 0.26 to 0.65; P<0.001). In the modified intention-to-treat analysis, major bleeding occurred in 10 patients (3.5%) in the apixaban group and in 5 patients (1.8%) in the placebo group (hazard ratio, 2.00; 95% CI, 1.01 to 3.95; P=0.046). During the treatment period, major bleeding occurred in 6 patients (2.1%) in the apixaban group and in 3 patients (1.1%) in the placebo group (hazard ratio, 1.89; 95% CI, 0.39 to 9.24).

CONCLUSIONS

Apixaban therapy resulted in a significantly lower rate of venous thromboembolism than did placebo among intermediate-to-high-risk ambulatory patients with cancer who were starting chemotherapy. The rate of major bleeding episodes was higher with apixaban than with placebo. (Funded by the Canadian Institutes of Health Research and Bristol-Myers Squibb–Pfizer Alliance; AVERT ClinicalTrials.gov number, NCT02048865.)

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

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Back to Table of Contents

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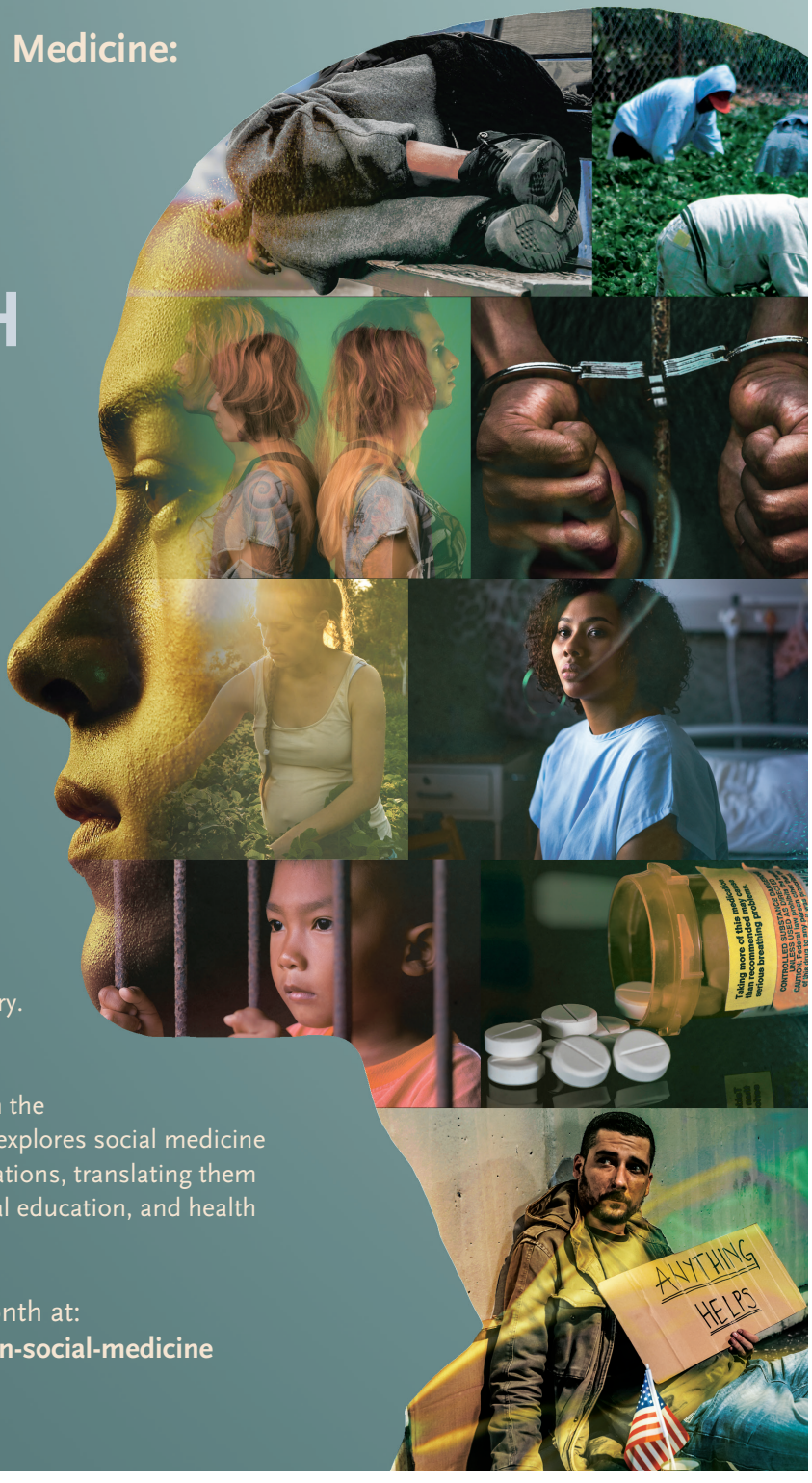

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