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ABSTRACT & COMMENTARY

An Update to the Management of Atrial Fibrillation

By Joshua Moss, MD

Associate Professor of Clinical Medicine, Cardiac Electrophysiology, Division of Cardiology, University of California, San Francisco

Dr. Moss reports he is a consultant for Abbott, Boston Scientific, and Medtronic.

SYNOPSIS: This focused update to the 2014 guidelines for the management of atrial fibrillation (AF) includes revisions to anticoagulation recommendations and the role of catheter ablation of AF in patients with heart failure.

SOURCE: January CT, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2019; Jan 21. pii: S0735-1097(19)30209-8. doi: 10.1016/j.jacc.2019.01.011. [Epub ahead of print].

Numerous landmark studies relevant to atrial fibrillation (AF) management have been published since the comprehensive 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines were released. The 2019 focused update reflects new data regarding oral anticoagulant choices, AF in patients with acute coronary syndrome and heart failure, ambulatory device detection of AF, and weight loss.

For the prevention of AF-related stroke, edoxaban is now included in the recommended list of non-vitamin K oral anticoagulants (NOACs). All NOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) are preferred to warfarin unless there is moderate-to-severe mitral stenosis or a mechanical heart valve (Class I, Level A). Also, apixaban is the recommended alternative to coumadin for those with chronic kidney disease (CrCl < 15mL/min) or on dialysis (Class IIb, Level B-NR).

The update also provides new guidance on the use of the NOAC reversal agents. If there is a life-threatening bleeding event or an urgent procedure, idarucizumab is recommended for reversal of dabigatran (Class I, Level B-NR) and andexanet alfa for the reversal of rivaroxaban and apixaban (Class IIa, Level B-NR). Finally, in

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those who are contraindicated to long-term anticoagulation, percutaneous left atrial appendage occlusion may be considered in AF patients with a higher risk of stroke (Class IIb, Level B-NR).

The use of oral anticoagulants for AF in the setting of acute coronary syndrome also has been revised. In those who have undergone percutaneous coronary intervention for ACS, double therapy with clopidogrel and low-dose rivaroxaban (15 mg daily) or dabigatran (150 mg twice daily) is reasonable to reduce the risk of bleeding compared with triple therapy (Class IIa, Level B-R). In patients with heart failure with reduced ejection fraction, catheter ablation of AF is reasonable, as it has been shown to lower the mortality rate and reduce heart failure hospitalizations (Class IIb, Level B-R).

Finally, there are new statements regarding ambulatory device detection of AF and weight loss. A loop recorder is reasonable for silent AF detection in patients with cryptogenic stroke and inconclusive ambulatory monitoring. In overweight and obese patients with AF, weight loss and modification of other key risk factors (including, but not limited to, sleep apnea, hypertension, alcohol, and smoking) are recommended (Class I, Level B-R).

■ COMMENTARY

These revisions arrive at an important time following numerous practice-changing publications. Obesity is associated with atrial remodeling and increasingly is recognized as both a risk factor for AF and a barrier to maintenance of sinus rhythm. Lifestyle modifications and weight loss, both via bariatric surgery and structured weight management programs, have been shown to reduce AF episodes and severity of AF-related symptoms convincingly.

The use of NOACs as first-line therapy for thromboembolic prophylaxis now carries a Class IA recommendation, although this has been the standard practice for most cardiologists and electrophysiologists for several years. That said, warfarin remains the first-line therapy for patients with moderate-to-severe mitral stenosis or a mechanical heart valve. Optimal therapy for patients with bioprosthetic heart valves is uncertain, although limited data suggest that apixaban and edoxaban are noninferior to warfarin in that population. Additional studies may be needed before routine recommendation of NOACs in the setting of AF and bioprosthetic valves. The recommendation for loop recorder implant for detection of "silent AF" is not surprising, considering both the ease of implant and the growing evidence to suggest sensitivity increases dramatically beyond several weeks of monitoring. However, the potential implications for use of consumer products, such as the Kardia monitor or the Apple Watch, will be interesting to follow. While there is no published consensus, "incidentally" detected AF is likely to be treated no differently by the cardiology community than more "traditionally" diagnosed AF. Thus, clinicians will need to consider and follow anticoagulation guidelines pending risk evaluation while taking care not to overtreat asymptomatic AF in patients without other sequelae such as cardiomyopathy.

The role of catheter ablation for AF continues to evolve rapidly. Multiple randomized trials published since 2014 have been taken into consideration with the new guidelines. In 2016, the results of the AATAC trial demonstrated that AF ablation was superior to amiodarone in maintaining sinus rhythm and reducing heart failure hospitalizations and mortality in patients with cardiomyopathy and heart failure. In 2017, CAMERA-MRI showed superiority of AF ablation over medical rate control in improving left ventricular ejection fraction (LVEF), six-minute walk test performance, and quality of life in patients with cardiomyopathy and persistent AF. In 2018, CASTLE-AF showed that heart failure patients who underwent catheter ablation for AF demonstrated reduced mortality, fewer hospitalizations for worsening heart failure, and better LVEF compared to the medical therapy group. That the focused update only assigns a Class IIb, Level B-R recommendation for catheter ablation in patients with AF and heart failure suggests that the task force believed some or all these studies provided only moderate-quality evidence. Indeed, there were important limitations to each study.

Nevertheless, referral of patients with reduced LVEF, heart failure symptoms, and paroxysmal or persistent AF for catheter ablation should be considered early — certainly prior to committing patients to long-term amiodarone or if a potentially recoverable cardiomyopathy AF is eliminated. ■

ABSTRACT & COMMENTARY

Rethinking the Prophylactic Use of Proton Pump Inhibitors in the ICU

By Betty Tran, MD, MSc

Assistant Professor of Medicine, Pulmonary and Critical Care Medicine, Rush University Medical Center, Chicago

Dr. Tran reports no financial relationships relevant to this field of study.

SYNOPSIS: The authors of this multicenter, blinded, randomized trial found that among critically ill adults at risk for gastrointestinal (GI) bleeding, fewer patients in the pantoprazole group exhibited clinically important GI bleeding compared to placebo, although mortality at 90 days was similar in both groups.

SOURCE: Krag M, et al. Pantoprazole in patients at risk for gastrointestinal bleeding in the ICU. *N Engl J Med* 2018;379:2199-2208.

Prophylactic use of proton pump inhibitors (PPIs) in critically ill patients at risk for gastrointestinal bleeding (GIB), such as those receiving mechanical ventilation, is standard protocol in the ICU. In fact, it is a component of the daily ICU checklist as an important reminder to ensure compliance. However, data supporting their use are limited in terms of quality, and there are concerns surrounding higher risks of pneumonia and *Clostridium difficile* that may limit any benefits.[1,2] The Stress Ulcer Prophylaxis in the Intensive Care Unit (SUP-ICU) trial was conducted in 33 ICUs in Denmark, Finland, the Netherlands, Norway, Switzerland, and the United Kingdom between 2016 and 2017. Investigators screened critically ill adults (age > 18 years) who were admitted to the ICU for an acute condition with at least one risk for GIB (shock; use of anticoagulants, nonsteroidal anti-inflammatory drugs, acetylsalicylic acid, and IV thrombolysis; acute renal replacement therapy; mechanical ventilation > 24 hours; chronic liver disease; and coagulopathy).

Ultimately, 3,298 patients were enrolled in the trial and were randomized either to IV pantoprazole 40 mg daily until ICU discharge or death (maximum 90 days) or placebo. If a patient was readmitted to the ICU within 90 days, the original assigned regimen was resumed. The primary outcome was death by 90 days after randomization. Secondary outcomes included clinically important GIB, new infection with either pneumonia or *C. difficile*, percentage of days alive without life support, serious adverse reactions (e.g., anaphylaxis, pancytopenia, acute hepatic failure), and a composite outcome of clinically important ICU events (GIB, pneumonia, *C. difficile* infection, or myocardial ischemia).

In addition to analyzing the per-protocol population, investigators assessed the primary outcome in predefined subgroups, including presence of liver disease, history of or ongoing coagulopathy, medical vs. surgical ICU, presence of shock, use of mechanical ventilation, and a Simplified Acute Physiology Score (SAPS) II above 53 at baseline (a score of 53 was chosen as predictive of a 50% mortality rate). At 90 days, similar mortality rates were seen in both the pantoprazole and placebo groups (31.1% vs. 30.4%, respectively; relative risk [RR], 1.02; 95% confidence interval [CI], 0.91-1.13; $P = 0.76$). There was no heterogeneity in the effect of pantoprazole on 90-day mortality in any predefined subgroup except for the group of patients with SAPS II scores > 53, where the mortality appeared higher in the pantoprazole group (RR, 1.13; 95% CI, 0.99-1.30; $P = 0.05$). In terms of secondary outcomes, the rate of clinically important ICU events was similar in both groups: 21.9% in the PPI group vs. 22.5% in the placebo group (RR, 0.96; 95% CI, 0.83-1.11). More patients in the placebo group demonstrated clinically important GIB compared to the PPI group (4.2% vs. 2.5%, respectively; RR, 0.58; 95% CI, 0.40-0.86). Rates of one or more new infections with pneumonia or *C. difficile*, serious adverse reactions, and days alive without life support were similar between the two groups. The authors did not provide any *P* values for the secondary outcomes, as no adjustments were made for multiple comparisons.

■ COMMENTARY

Although SUP-ICU was a large, multicenter, randomized, placebo-controlled, blinded trial, its results are unlikely to change current practice at this time. The trial did not reveal a significant difference in 90-day mortality between patients at risk for GIB who received a PPI vs. those who did not.

First, the trial was powered to detect an absolute between-group difference of 5%, which may be a large margin to detect. Second, there are no data regarding whether patients were receiving enteral nutrition at baseline, which can modify the effect of PPI prophylaxis on the development of stress ulcer-related GIB as well as risk of pneumonia.[3] Third, the finding of higher 90-day mortality among patients receiving a PPI with a SAPS II score > 53 is hypothesis-generating at best. The finding was of borderline significance, and the trial was not powered to address the primary outcome in this subgroup. Finally, although it is difficult to interpret the secondary outcomes in this trial given no adjustment

was made for multiple comparisons, the investigators did report an increase in the number of patients with clinically important GIB in the placebo group compared to those receiving a PPI without a difference in the rates of infection.

The composite secondary outcome that combined these measures (referred to as "clinically important events in the ICU") was similar in both groups, but inferences are difficult to draw from this finding as this composite endpoint combines outcomes that are affected by PPI prophylaxis in opposite directions (e.g., PPI prophylaxis theoretically increases the risk of infection but reduces the risk of GIB). Currently, the standard of care in the ICU is stress ulcer prophylaxis in patients at risk for GIB. Considering that there was an observed higher rate of GIB in patients receiving only placebo without clear evidence of increased risk of infection or mortality in patients receiving PPI prophylaxis in this trial, this standard practice will continue until further evidence emerges to dictate otherwise. ■

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ABSTRACT & COMMENTARY

IV to Oral Conversion of Antibiotic Therapy for Bacteremia Due to *Enterobacteriaceae*

By Stan Deresinski, MD, FIDSA, FACP

Clinical Professor of Medicine, Stanford University

Dr. Deresinski reports no financial relationships relevant to this field of study.

SYNOPSIS: Oral step-down antibiotic therapy (IV to oral conversion) is safe and effective in patients with bloodstream infection due to *Enterobacteriaceae*.

SOURCE: Tamma PD, et al; Antibacterial Resistance Leadership Group. Association of 30-day mortality with oral step-down vs continued intravenous therapy in patients hospitalized with *Enterobacteriaceae* bacteremia. *JAMA Intern Med* 2019; Jan 22. doi: 10.1001/jamainternmed.2018.6226. [Epub ahead of print].

Tamma et al examined the efficacy and safety of oral step-down therapy (IV to oral conversion) in patients with bacteremia due to commonly isolated *Enterobacteriaceae* in a multicenter retrospective study using propensity analysis. Only 2,161 of 4,967 bacteremic patients met entry criteria, 876 of whom underwent step-down of their therapy. Compared to those who received their entire course of therapy intravenously, the step-down group was less likely to be severely neutropenic, severely ill, or to have received combination antibiotic therapy for at least 48 hours. In the step-down group, the urinary tract was more likely to be the source of bacteremia. To overcome these differences in their analysis, the authors performed propensity analysis with matching, yielding 739 patients in each study arm. The most frequently isolated pathogens (in decreasing order of frequency) were *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter* spp., *Proteus mirabilis*, *Serratia marcescens*, and *Citrobacter* spp. Approximately two-fifths of infections arose from the urinary tract, one-fifth each from an intra-abdominal source and a venous catheter, one-seventh from the biliary tract, and the remainder from the lungs and skin or skin structure. Patients in the IV-only group received a median of 14 days of IV therapy, while the step-down cohort received only a median three days of therapy by that route. In comparisons of the oral step-down and IV groups, there were no significant differences in 30-day mortality (13.1% vs. 13.4%) or recurrent bacteremia (0.8% vs. 0.5%). The duration of hospitalization was two days shorter in the step-down group: five days vs. seven days. Antibiotics considered to have high oral bioavailability (fluoroquinolones and trimethoprim-sulfamethoxazole) were administered to 83.9% of patients receiving step-down therapy, with the remaining receiving oral beta-lactams, with all considered to have low bioavailability. No significant differences in outcomes were observed in a comparison of the two groups.

■ COMMENTARY

The number of patients in this study who received step-down therapy with low bioavailability drugs was small, making the finding that they appeared to do as well as those who received high bioavailability oral antibiotics

potentially suspect. However, the authors noted this finding is consistent with the results of other retrospective analyses. This is not terribly surprising, especially in view of a recent randomized trial that revealed that seven days of IV therapy was noninferior in a randomized trial in patients with gram-negative bacteremia.[1,2] It seems likely to me that the median of five days of IV therapy given to step-down patients by Tamma et al may have been sufficient to cure most cases of bacteremia, and the subsequent oral therapy may have been irrelevant. Clinicians have been using step-down commonly as early as day 3 of IV antibiotic therapy to complete a total of seven days of therapy in uncomplicated cases with good initial responses. ■

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2. Deresinski S. Treatment of Gram-negative bacteremia: How long is long enough? *Infect Dis Alert* 2019;38:49-50.

BRIEF REPORT

Dual Antiplatelet Therapy With Cilostazol for Secondary Stroke Prevention (LB3)

By Matthew E. Fink, MD

Feil Professor and Chairman, Department of Neurology, and Assistant Dean of Clinical Affairs, Weill Cornell Medical College; Neurologist-in-Chief, New York Presbyterian Hospital

Dr. Fink reports no financial relationships relevant to this field of study.

SOURCE: Toyoda K, et al. Dual antiplatelet therapy using cilostazol for high-risk ischemic stroke: The cilostazol stroke prevention study for antiplatelet combination. Available at: https://bit.ly/2CiTYEy. Accessed March 12, 2019.

In previous studies, dual antiplatelet therapy with aspirin and clopidogrel was shown to reduce early recurrence of ischemic stroke, with short-term benefit and a long-term risk of major bleeding. Cilostazol has been used to reduce the risk of recurrent stroke with a low bleeding risk and is safe for long-term use.

Toyoda et al reported on a multicenter, open-label trial in which high-risk patients with benign cardioembolic ischemic stroke identified on MRI were assigned to receive aspirin or clopidogrel alone, or a combination of cilostazol 100 mg twice daily with aspirin or clopidogrel for secondary stroke prevention. High-risk patients were defined as meeting one or more of the following criteria: > 50% stenosis of a major intracranial or extracranial artery and two or more vascular risk factors. The primary outcome was the first recurrence of an ischemic stroke. Safety outcomes included severe or life-threatening bleeding.

Following enrollment, 1,839 patients were available for analysis, with 756 taking aspirin and 1,083 taking clopidogrel. Ischemic stroke occurred in 29 of 913 patients with dual therapy including cilostazol and in 64 of 926 patients on monotherapy during a median follow-up of 17 months (P = 0.001). Severe bleeding occurred in 0.9% of patients on dual therapy and 1.4% of patients on monotherapy (P = 0.354). Investigators concluded that patients treated with dual antiplatelet therapy combining cilostazol with either aspirin or clopidogrel were at a lower risk of ischemic stroke recurrence and at a similar risk of significant bleeding compared to patients treated with aspirin or clopidogrel alone. ■

ABSTRACT & COMMENTARY

Ripples From Original WHI Study Results Continue: Is This Appropriate?

By Robert W. Rebar, MD

Professor and Chair, Department of Obstetrics and Gynecology, Western Michigan University Homer Stryker M.D. School of Medicine, Kalamazoo

Dr. Rebar reports no financial relationships relevant to this field of study.

SYNOPSIS: Recommendations for menopausal hormone therapy were widely publicized and adopted following the original publication of the results of the Women's Health Initiative, affecting both initiation and continuation of estrogen therapy through at least 2013.

SOURCE: Crawford SL, et al. Menopausal therapy trends before versus after 2002: Impact of the Women's Health Initiative study results. *Menopause* 2018; Dec. 21. doi: 10.1097/GME.0000000000001282. [Epub ahead of print].

To better appreciate how to educate patients and providers about menopausal hormone therapy (MHT; generally regarded as estrogen plus progesterone in women with a uterus and as estrogen alone in women without a uterus), Crawford et al analyzed survey data from up to 14 approximately annual visits collected between 1996 and 2013 from 3,018 participants in the NIH's multicenter Study of Women's Health Across the Nation (SWAN). Investigators wished to determine the effect of the initial 2002 report[1] of data from the Women's Health Initiative (WHI), which involved administration of estrogen-progestin therapy to postmenopausal women and ended prematurely because of significant concerns about safety on initiation and continuation of MHT. SWAN included women of diverse ethnicities 42-52 years of age with an intact uterus and one or two ovaries to examine the changes that occur longitudinally across the menopausal transition. MHT initiation declined from 8.6% before publication of the WHI results to 2.8% post-WHI ($P < 0.0001$), with a decrease in continuation as well from 84.0% to 62.0% ($P < 0.0001$). Although the magnitude of the lower initiation and continuation varied among ethnic groups, it occurred in all and tended to be greater in women who might be expected to benefit more from MHT based on current guidelines, specifically younger women with severe vasomotor flushes. More frequent vasomotor symptoms were associated with greater initiation of MHT, both pre- and post-WHI ($P < 0.001$ for both), but the largest decrease (9.4% decline) occurred in women who reported the most frequent hot flashes. Similarly, young postmenopausal women were less apt to begin MHT and were more likely to discontinue use despite current guidelines. Reasons for initiating MHT changed after publication of WHI, with the largest declines for use among those who wished to reduce the risk of osteoporosis and heart disease. The most commons reasons for discontinuing MHT were for media reports and provider advice.

■ COMMENTARY

The initial report that the WHI was ending early because of safety concerns changed our views on MHT forever. MHT should not be used for prevention of coronary heart disease, breast cancer, or dementia. Despite subsequent studies and guidelines promoting appropriate use of MHT in certain symptomatic postmenopausal women, providers who are not gynecologists are significantly less likely to recommend use of MHT (as noted in this report), regardless of patient symptomatology. I have been frustrated when patients who clearly would benefit from MHT were advised not to begin or to discontinue therapy after seeing another provider. Yet, another large cohort study, this time from Denmark, documented that long-term follow-up (median, 17.6 years) of almost 30,000 women between the ages of 50 and 64 years representing 7% of the Danish female population enrolled between 1993 and 1997 showed no association of MHT and overall mortality.[2] This squares with a recent reanalysis of the data from the WHI documenting the safety of MHT when begun within five years of menopause and documenting no increase in all-cause mortality.[3]

American women have had their reproductive lives turned topsy-turvy three times in the last 50 years. In the 1960s, they witnessed the publicity surrounding combination oral contraceptive agents and the higher risks for several significant diseases, including deep venous thrombosis, stroke, and myocardial infarction. The far greater risks of pregnancy compared to the use of oral contraceptives were not emphasized in press releases. Many women discontinued use of this contraception only to suffer unintended pregnancies. Then followed the debacle related to the Dalkon Shield intrauterine device (IUD), which resulted in a dramatic decline in IUD usage in the United States; today, this usage remains lower than in most other industrialized countries. More recently, women were subjected to incompletely analyzed findings from the WHI, which has lowered MHT use rates — even when it is indicated.

Clinicians counseling women on the risks and benefits of MHT should remain positive. We need to emphasize to patients and less-informed providers that MHT is extremely useful in improving quality of life and is

warranted for women with vasomotor flushes,[4] plays a role in protection against fracture risk,[5] and can improve sexual function.[6] Moreover, we have long known that MHT is warranted to prevent coronary heart disease,[7] as well as to prevent symptoms associated with estrogen deficiency following bilateral oophorectomy in premenopausal women and in those with premature menopause.[8]

Both the North American Menopause Society and the Endocrine Society have created guidelines for the use of MHT.[9,10] Both effectively agree that MHT is the most effective therapy for vasomotor symptoms and the genitourinary syndrome of menopause (GSM) and can prevent bone loss. Both emphasize the need to individualize therapy based on clinical factors and patient preference and note that benefits may exceed risks for most women < 60 years of age. Both note that low-dose vaginal estrogen therapy is effective for treatment of GSM in women without indications for systemic MHT.

For those not desiring local estrogen, several vaginal moisturizers and lubricants are available. Neither guideline recommends a firm age by which MHT must be discontinued, focusing on shared decision-making with the patient. All women should embrace healthy lifestyle measures. It is these recommendations that we must emphasize in counseling patients and in educating other providers. ■

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PHARMACOLOGY UPDATE

PrabotulinumtoxinA-xvfs Injection (Jeuveau)

By William Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Assistant Clinical Professor of Medicine, University of California, San Francisco.
Dr. Chan is Associate Clinical Professor, School of Pharmacy, University of California, San Francisco.

Drs. Elliott and Chan report no financial relationships relevant to this field of study.

The FDA has approved a botulinum neurotoxin type A for the treatment of glabellar lines (wrinkles between eyebrows). PrabotulinumtoxinA-xvfs will be launched as an alternative to onabotulinumtoxinA (Botox) for this indication. PrabotulinumtoxinA-xvfs was developed in South Korea from wild-type *Clostridium botulinum*, resulting in a product of higher purity than onabotulinumtoxinA (> 98% vs. 95%).[1] The new product will be marketed as Jeuveau.

INDICATIONS

PrabotulinumtoxinA-xvfs is indicated for temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adults.[2]

DOSAGE

The recommended dose is 0.1 mL (four units) by intramuscular injection into each of five sites for a total of 20 units.[2]

PrabotulinumtoxinA-xvfs is available as a single-dose vial containing 100 units of vacuum-dried powder.

POTENTIAL ADVANTAGES

PrabotulinumtoxinA-xvfs is expected to be cheaper than onabotulinumtoxinA for the treatment of glabellar lines.

POTENTIAL DISADVANTAGES

The label states that prabotulinumtoxinA-xvfs is not interchangeable with other botulinum toxin A products.[2]

COMMENTS

The efficacy and safety of prabotulinumtoxinA-xvfs were evaluated in two randomized, double-blind, placebo-controlled trials of identical design.[2-4] Adults with glabellar lines of at least moderate severity at maximum frown were randomized to a single treatment of prabotulinumtoxinA-xvfs (n = 246) or placebo (n= 84). The primary endpoint, assessed on day 30, was defined as the proportion of subjects achieving ≥ 2-grade improvement from baseline at maximum frown. This was assessed by both the investigator and the subject using a four-point grading scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). Composite responder rates were 67% and 71% for prabotulinumtoxinA-xvfs and 1% in both studies for placebo. Headache was the most common adverse reaction, which occurred at a frequency of 12% in both the drug and placebo groups.[2] In a comparative, noninferiority study that included 265 patients, prabotulinumtoxinA-xvfs was noninferior to onabotulinumtoxinA.[1] The Responder rates were 94% for prabotulinumtoxinA-xvfs and 89% for onabotulinumtoxinA. There were no differences in the incidence of adverse events between the two neurotoxins (20% vs. 18%).

CLINICAL IMPLICATIONS

PrabotulinumtoxinA-xvfs is a neurotoxin that produces a denervation and muscle inactivation. It has been available since 2002. Its approved indications (other than for cosmetic use) include axillary hyperhidrosis, cervical dystonia, chronic migraine prophylaxis, lower limb spasticity, overactive bladder, strabismus/blepharospasm associated with dystonia, upper limb spasticity, and urinary incontinence due to detrusor overactivity. It also has been used off label for conditions such as sialorrhea and achalasia.

PrabotulinumtoxinA-xvfs is the first competitor for onabotulinumtoxinA approved for glabellar lines. It is expected to be priced 20-25% lower and to be available in spring 2019.[5] ■

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CME QUESTIONS

1. Which of the following now carries a Class IA recommendation in the new atrial fibrillation guidelines?
a. Apixaban for hemodialysis patients
b. New oral anticoagulants for nonvalvular atrial fibrillation patients
c. Catheter ablation for heart failure with reduced ejection fraction patients
d. Atrial appendage occlusion in patients who cannot take anticoagulants

2. In the trial by Krag et al, compared to placebo, ICU patients assigned to pantoprazole:
a. demonstrated lower 90-day mortality.
b. demonstrated a lower rate of clinically important gastrointestinal bleeding.
c. demonstrated a higher rate of pneumonia.
d. demonstrated a higher rate of *Clostridium difficile* infection.

3. In the trial by Krag et al, which subgroup of patients showed a higher risk of 90-day mortality associated with pantoprazole?
a. Those who scored > 53 on the Simplified Acute Physiology Score II scale
b. Those with mechanical ventilation at randomization
c. Those in shock at randomization
d. Those who presented with a history of liver disease

4. Dual antiplatelet treatment for acute ischemic stroke, combining cilostazol with aspirin, carries a high risk of long-term hemorrhagic complications.
a. True
b. False