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ABSTRACT & COMMENTARY

SGLT2 Inhibitors: Now The Bad News

By Jeff Unger, MD, FACE

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Dr. Unger reports he is a consultant for and serves on the speakers bureau of Janssen Pharmaceuticals.

SYNOPSIS: Sodium-glucose cotransporter-2 inhibitors are approved as adjunctive therapy for the treatment of patients with type 2 diabetes. This drug class has been also used off-label to improve glycemic control in patients with type 1 diabetes. This article describes seven cases of diabetic ketoacidosis in patients with type 1 diabetes and two cases in patients with type 2 diabetes. Although the patients were ketotic their blood glucose levels were not significantly elevated. Thus, patients are referred to as having "euDKA."

SOURCE: Peters AL, et al. Euglycemic diabetic ketoacidosis: A potential complication of treatment with sodium-glucose cotransporter 2inhibition. *Diabetes Care* 2015;38:1687-1693.

Diabetic ketoacidosis (DKA) occurs in approximately 5% of patients with type 1 diabetes and is defined by a triad of hyperglycemia (blood glucose > 250 mg/dL), anion-gap acidosis, and increased plasma ketones. Euglycemic DKA (euDKA) is considered rare, but may be underreported. Risk factors for euDKA include meal skipping, alcohol intake, and inhibition of gluconeogenesis. Patient 1 was a 40-year-old female with type 1 diabetes and a body mass index of 26.5 kg/m^2. Prior to canagliflozin initiation, her A1c was 11.4%. As her glycemic control improved within 2 weeks, the patient reduced her basal insulin dose by 50%. Two weeks later, she developed a febrile illness resulting in reduced oral intake. She was therefore consuming fewer carbohydrates and using less insulin. In the emergency department (ED) her blood glucose was 220 mg/dL and serum ketones were positive. Her blood gas showed a pH of 6.9.

A second patient with type 1 diabetes was prescribed canagliflozin as adjunctive therapy to her insulin pump regimen. Her baseline A1c was 7%. The patient walked through an amusement park for 12 hours before becoming ill. After reducing her basal insulin dose, the patient awoke the next morning with a migraine headache. Over the course

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of 5 days, her headache persisted. A neurologist prescribed steroids. Although her blood glucose was 120 mg/dL, the patient's urine ketone test was positive. She self-managed the euglycemia with oral-glucose-containing fluids, insulin, and antiemetics. As her ketones resolved, so did her migraine, nausea, and vomiting.

■ COMMENTARY

Personally, I have discontinued my off-label use of sodium-glucose cotransporter-2 (SGLT2) inhibitors in patients with type 1 diabetes as I have experienced seven cases of euDKA. Five of my patients required overnight hospitalization and responded to hydration, insulin, and carbohydrate intake. Interestingly, the ED doctors were very confused by their presentation in each case. One 25-year-old patient on an insulin pump and canagliflozin helped a friend move. Knowing that his increased activity would likely result in hypoglycemia, the patient lowered his basal rate by 50% for several hours. Seven hours after the move was completed, the patient developed severe muscle pain, nausea, and vomiting. His blood glucose level in the ED was 184 mg/dL, but he was noted to have positive serum ketones. The ED staff was unfamiliar with the diagnosis of euDKA.

The pathophysiology of euDKA is thought to result from the following sequence of events: 1) As carbohydrate utilization is reduced (i.e., caloric restriction), lipolysis becomes the primary source of energy production for the body. 2) The patients with euDKA typically reduce their exogenous insulin dose, thereby enhancing lipolysis. 3) SGLT2 inhibitors are known to raise serum glucagon levels as a means of glucose counterregulation. 4) Exogenous insulin increases glycosuria, which may also increase glucagon production and secretion. 5) The hyperglucagonemia coupled with increased delivery of free fatty acids (product of lipolysis) to the liver promotes both the oxidation of free fatty acids and the production of ketone bodies. 6) SGLT2 inhibitors, as a class, tend to prevent renal excretion of ketone bodies.

EuDKA may be predictable, detectable, and preventable in patients using SGLT2 inhibitors. Patients using SGLT2 inhibitors (especially those using this class of drug as adjunctive therapy to insulin) should be informed to: 1) minimize their risk of dehydration; 2) avoid reducing insulin doses on "sick days; 3) minimize alcohol intake, which may increase hepatic ketone production; and 4) consume carbohydrates on sick days, which will reduce their dependency on lipolysis.

Finally, patients with type 2 diabetes who develop DKA while on SGLT2 inhibitors should be tested for latent autoimmune diabetes of adulthood. DKA is extremely rare in type 2 diabetes. ■

ABSTRACT & COMMENTARY

Is Low Testosterone Therapy Worth the Hype in the Elderly?

By Seema Gupta, MD, MSPH

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Dr. Gupta reports no financial relationship to this field of study.

SYNOPSIS: Testosterone replacement therapy showed no impact on subclinical atherosclerosis progression in recent study.

SOURCE: Basaria S, et al. Effects of testosterone administration for 3 years on subclinical atherosclerosis progression in older men with low or low-normal testosterone levels. *JAMA* 2015;314:570-581.

In recent years, there has been a dramatic rise in the use of testosterone therapy in healthy middle-aged and older men. In fact, the commercial sales of testosterone replacement therapy have increased substantially. Recent evidence demonstrates that from 2001 through 2011, androgen use among men ≥ 40 years of age increased more than three-fold, with topical gel demonstrating the highest rate of overall use and the highest rate of increase — more than five-fold.[1] Clinical benefits of testosterone therapy in hypogonadal men include the restoration of libido and energy, increased muscle strength, and improvements in bone mineral density. Improvements in mood and cognition also may be observed. However, in older men with age-related declines in testosterone levels, a long-term replacement therapy regimen has not consistently demonstrated clinical benefit. Additionally, there may be risks associated with testosterone therapy in elderly men, including worsening of sleep apnea, gynecomastia, polycythemia, fluid retention, and acceleration of benign or malignant prostate disease. There is also a concern for an increase in the risk of cardiovascular disease associated with testosterone replacement therapy, although the evidence on the matter has been inconclusive. While evidence from a subgroup analysis of men ≥ 65 years of age did not demonstrate an increase in cardiovascular events associated with testosterone replacement, another randomized trial in older men with high prevalence of chronic disease ended early due to higher frequency of self-reported cardiovascular-related adverse events in men designated to the testosterone arm compared with the placebo arm.[2,3] Testosterone levels have been negatively associated with common carotid artery intima-media thickness.

Basaria et al conducted a placebo-controlled, double-blind, parallel-group, randomized trial to determine the effect of testosterone administration on subclinical atherosclerosis progression in older men with low or low-normal testosterone levels. Researchers enrolled a total of 308 men (≥ 60 years of age) with low or low-normal testosterone levels (100-400 ng/dL, free testosterone < 50 pg/mL) at three U.S. centers between 2004 and 2009. One hundred fifty-six participants were randomized to receive 7.5 g of 1% testosterone and 152 were randomized to receive placebo gel packets daily for 3 years. The dose was adjusted to achieve testosterone levels between 500 and 900 ng/dL. Primary outcomes measured were the rate of change in distal right common carotid artery intima-media thickness and coronary artery calcium. Secondary outcomes included sexual function and health-related quality of life.

The researchers found that among older men (mean age 67.6 years) with low or low-normal testosterone levels, 3 years of testosterone gel administration did not result in a significant difference in the rates of change in either common carotid artery intima-media thickness or coronary artery calcium when compared with placebo. The rate of change in intima-media thickness was 0.010 mm/year in the placebo group and 0.012 mm/year in the testosterone group. The mean difference adjusted for age and trial site was 0.0002 mm/year (95% confidence interval [CI], –0.003 to 0.003; $P = 0.89$). The rate of change in the coronary artery calcium score was 41.4 Agatston units/year in the placebo group and 31.4 Agatston units/year in the testosterone group. The adjusted mean difference was -10.8 Agatston units/year (95% CI, -45.7 to 24.2; $P = 0.54$). Additionally, researchers found no improvement in the overall sexual function or health-related quality of life in the testosterone treatment group compared with placebo.

■ COMMENTARY

There is both good and bad news resulting from this well-done study. The good news is that testosterone replacement therapy showed no impact on subclinical atherosclerosis progression in older men with low to low-normal testosterone levels. Although this trial was not specifically designed to determine the effects of testosterone on cardiovascular disease events, it does suggest that the increase in cardiovascular events in previous studies may not be due to the atherosclerosis progression from testosterone treatment. Some previous epidemiological studies have reported the association of low testosterone levels with greater common carotid artery intima-media thickness as well as cardiovascular and all-cause mortality.[4] Therefore, further research is needed to determine whether there may be a reverse causality association in which individuals at high risk for death or cardiovascular events may in fact have resultant lower testosterone levels. However, the study finding that testosterone administration did not significantly improve erectile or ejaculatory function, sexual desire, or health-related quality of life is significant. This contrasts with the efficacy of phosphodiesterase inhibitors in relation to sexual function and perhaps testosterone should not be prescribed for this purpose with the possible exception of clearly low testosterone levels.[5] In summary, testosterone replacement should be restricted to symptomatic men with hypogonadism, which is evident by clinical symptoms and signs consistent with androgen deficiency and a subnormal morning serum testosterone concentration. ■

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ABSTRACT & COMMENTARY

Migraine and Cognitive Dysfunction

By Dara Jamieson, MD

Assistant Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Jamieson reports she is on the stroke adjudication committee for Bayer and is a consultant for Boehringer-Ingelheim.

SYNOPSIS: During an attack of migraine without aura, patients may experience transient cognitive impairment, with predominant involvement of verbal processing speed, learning, and memory, due to reversible cortical dysfunction.

SOURCE: Gil-Gouveia R, et al. Cognitive dysfunction during migraine attacks: A study on migraine without aura. *Cephalalgia* 2015;35:662-674.

Patients often report a sense of confusion and impaired thinking during migraine attacks, including immediately before and after the head pain, but studies designed to validate these observations have produced inconsistent results. The authors used a comprehensive battery of cognitive and behavioral tests to investigate changes in cognitive performance of migraineurs during attacks of migraine without aura. The only allowed daily medications were oral contraceptives and migraine prophylactics, and treatment with acute pain medication was not permitted. This prospective randomized, crossover study compared the within-subject neuropsychological evaluations during a naturally occurring untreated migraine attack and also during a headache-free period. Half the subjects were tested first during the attack, and half were first tested during the headache free-period. There was at least a month between testing during the migraine attack and during a headache-free period to avoid learned testing proficiency. Patients were evaluated with the Headache Impact Test and the Migraine-Specific Quality of Life questionnaires and with the Zung Depression scale and the State-Trait Anxiety Inventory. Pain intensity was scored with a 10-point visual analog scale. Paper and pencil neuropsychological testing was applied by licensed neuropsychologists using a standard battery of tests to test executive functioning, long-term memory, perception, motor control, and language.

Out of 39 patients with episodic migraine without aura (37 females, average age 38 years), 24 completed the study with evaluation at both times. Seven participants (29%) were on preventive medication (two propranolol, two propranolol and amitriptyline, two amitriptyline, and one topiramate and amitriptyline). Migraine impact was moderate to high, with most participants having one to four attacks monthly, with moderate to severe pain intensity. Migraineurs performed worse during the attack of head pain and accompanying symptoms in the majority of cognitive tests, compared to their headache-free period. Testing during the headache periods was impaired in reading and processing speed (word reading speed, $P = 0.013$) as well as verbal memory and learning short-term verbal recall with ($P = 0.01$) and without ($P = 0.013$) semantic cueing and delayed recall with ($P = 0.003$) and without ($P = 0.05$) semantic cues. Differences found in cognitive performance during a migraine attack were unrelated to patient baseline characteristics, including age, gender, literacy, condition order, the interval between the two evaluations, anxiety, pain intensity, or duration of the attack. The authors considered potential mechanisms by which cognitive impairment occurs during an attack of migraine without aura, including a cortical spreading depression — like phenomena, activation of the raphe nuclei and its cortical serotoninergic projections, or activation of the thalamus, with its effect on perception, learning, and cognition.

■ COMMENTARY

Patients' complaints of transient difficulty with verbal and memory processing during a migraine without aura have been validated by this well-designed study. However, the sample size was very small and the patients were mostly female, within a restricted age range, not representing the complete spectrum of migraine sufferers. Confounding conditions, including the effect of pain per se and

of the accompanying gastrointestinal symptoms and environmental sensitivities, have not been completely eliminated in this study. The authors point out that the findings could be induced by the cognitive processes related to the head pain, as opposed to an effect unique to migraine. Neuropsychological changes, with impairment in cognitive function, can be associated with chronic pain with resultant neurochemical and anatomic cerebral changes. Patients in this study had to suffer their migraine attacks without pain relief, as attacks treated with abortive medication in the previous 12 hours were not eligible for investigation in this study. Cognitive functioning needs to be assessed in patients who are taking triptans for acute pain treatment, a real-world environment. Because some daily medications used to decrease the frequency and severity of migraine headaches are well known to have cognitive side effects, further investigation should be restricted to patients who are not on oral preventive medications. The argument could be made that these medications, especially topiramate, could cause decreased memory and verbal fluency equally during the attack and during headache-free periods. However, as side effects vary according to dose escalation, these medications could have a differential effect on cognition over time. Despite the study limitations, the conclusions validate patient experiences. Migraine patients with cognitive complaints during a migraine attack without aura should be advised to avoid bar and board examinations during a headache, and other intellectual challenges, adding to the disability of the attack, as well as to anticipatory anxiety. ■

PHARMACOLOGY UPDATE

Alirocumab Injection (Praluent)

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

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; and Assistant Professor of Medicine, University of California, San Francisco. Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA

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

The FDA has approved the first in class injectable proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor for the treatment of hypercholesterolemia inadequately controlled on standard therapy. Alirocumab is a fully humanized monoclonal antibody produced in Chinese hamster ovary cell culture that targets PCSK9. It is marketed by Regeneron and Sanofi-Aventis as Praluent.

INDICATIONS

Alirocumab is indicated as adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease (CVD) who require additional lowering of LDL-cholesterol (LDL-C).[1]

DOSAGE

The initial recommended dose is 75 mg given subcutaneously once every 2 weeks. The dose may be increased to 150 mg every 2 weeks if the response is inadequate.[1] Response to treatments should be assessed 4 to 8 weeks after initiation or titration.

Alirocumab is available as 75 mg/mL or 150 mg/mL single-dose pens or syringes.

POTENTIAL ADVANTAGES

Alirocumab provides a new mechanism of action for lowering cholesterol in patients who have not achieved adequate lowering on maximum dose of statins.

POTENTIAL DISADVANTAGES

It remains to be established whether alirocumab has any effect on CVD morbidity or mortality. The long-term safety of alirocumab is not known.

COMMENTS

LDL-C receptors function to remove LDL-C from blood. The density of these receptors is modulated by PCSK9.[3] Inhibition of PCSK9 reduces the degradation of these receptors and preserves receptor recycling. As a result, there is greater density of receptors to bind and remove LDL-C. The efficacy of alirocumab was studied in five randomized, placebo-controlled trials in subjects who were receiving a maximally tolerated dose of a statin (with or without other lipid-lowering treatment).[1] Two studies involved subjects primarily with clinical atherosclerotic CVD and three studies included subjects with heterozygous familial hypercholesterolemia (HeFH). All studies were at least 52 weeks in duration, with the primary endpoint (mean % change in LDL-C from baseline) checked at week 24. In study 1, patients mainly with CVD

(69%) and mean baseline LDL-C of 122 mg/dL were randomized to alirocumab 150 mg every 2 weeks (n = 1553) or placebo (n = 788).[1,2] At week 24, the mean difference in reduction of LDL-C between alirocumab and placebo was -58% (95% confidence interval [CI], -61% to -56%). The differences in total-C, non-HDLC, and ApoB were reductions of -36%, -50%, and -51%, respectively. Study two involved CVD subjects (84%) with a mean baseline LDL-C of 102 mg/dL. These subjects were randomized to alirocumab, 75 mg every 2 weeks with the option of titrating to 150 mg (n = 209) or placebo (n = 107). At week 24, the majority of subjects remained on 75 mg (83%). The difference in LDL-C was -43% (95% CI, -50% to -35%). In the two studies with HeFH subjects (45% also with CVD) and mean baseline LDL-C of 141 mg, patients were randomized to 75 mg with the option of titrating to 150 mg (n = 490) or placebo (n = 245). At week 24, 42% were titrated to 150 mg and the difference in LDL-C was -54% (95% CI, -59% to -50%). In the third study in HeFH subjects (50% with CVD) with a mean baseline LDL-C of 198 mg/dL, patients were randomized to alirocumab 150 mg (n = 72) or placebo (n = 35). The LDL-C difference at week 24 was -36% (95% CI, -49% to -24%). The effect was maintained at week 52 in all studies and for 78 weeks in study one.[2] Similar reduction in total-C, non-HDL-C, and ApoB were seen across all studies.

The alirocumab group had a higher frequency of injection site reactions (7.2% vs 5.1%) and anti-drug antibodies (4.8% vs 0.6%). A post-hoc analysis suggests that rates of major CVD events (composite endpoint of death from coronary artery disease, non-fatal myocardial infarction (MI), fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization) were statistically lower in the alirocumab group.[2] However, when all adjudicated CVD events were included (congestive heart failure requiring hospitalization and ischemic-driven coronary revascularization), the difference was not statistically significant. A meta-analysis of study level data from 24 randomized, controlled trials involving alirocumab and the other recently approved PCSK9 inhibitor evoluocumab (n = 10,159) suggested reduced all-cause mortality but no change in CVD mortality.[4] The wholesale cost for alirocumab is $1120 for a 4-week supply (two doses).

CLINICAL IMPLICATIONS

Alirocumab provides additional lowering of LDL-C in patients who have not been able to achieve adequate control with a statin or other lipid-lowering treatments. The FDA recently approvated a second PCSK9 inhibitor, evolocmab. Preliminary evidence suggests potential benefit in CVD morbidity/mortality, but this will need to be validated for alirocumab in the ODYSSEY Outcomes study of more than 18,000 with recent hospitalizations for ACS.[5] The trial started in October 2012 and is expected to be completed by December 2017. The primary endpoint is time from randomization to first occurrence of one of the following clinical events: coronary heart disease death, any non-fatal MI, fatal and non-fatal ischemic stroke, or unstable angina requiring hospitalization. Until the results are available, it is unknown whether alirocumab has an effect on cardiovascular morbidity or mortality. ■

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BRIEF REPORT

Cryptogenic Stroke and Atrial Fibrillation

By Matthew E. Fink, MD

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

SOURCE: Favilla CG, et al. Predictors of finding occult atrial fibrillation after cryptogenic stroke. *Stroke* 2015;46:1210-1215.

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Clinical Briefs

By Louis Kuritzky, MD

Preventing Recurrence of Depression: Cognitive Therapy or Medication?

SOURCE: Kuyken W, et al. Effectiveness and cost-effectiveness of mindfulness-based cognitive therapy compared with maintenance antidepressant treatment in the prevention of depressive relapse or recurrence (PREVENT): A randomised controlled trial. *Lancet* 2015;386:63-73.

After an initial episode of depression, unless preventive treatment is initiated, recurrence is the rule rather than the exception (50-80%). As a result, national guidelines support maintenance treatment, especially for persons with demonstrated recurrence or with other high-risk indicators (e.g., history of bipolar disorder, family history of recurrences, or early age at initial diagnosis). The United Kingdom NICE Guidelines endorse at least 2 years of maintenance antidepressants when depression is recurrent.

PREVENT was a randomized, controlled trial (n = 424) comparing mindfulness-based cognitive therapy (MBCT) to antidepressant pharmacotherapy for prevention of depression recurrence. Inclusion required at least three prior episodes of major depression. Study subjects randomized to MBCT had been on pharmacotherapy, which was tapered/discontinued during the MBCT phase of treatment (71% fully discontinued, 17% reduced dose, 13% no dose reduction [total > 100% due to rounding]).

Over a 24-month interval, slightly fewer than half of the subjects experienced relapse (44-47%), with no significant difference demonstrable between MBCT and pharmacotherapy. The comparable efficacy of MBCT and pharmacotherapy should prompt clinicians to offer patients treatment as per their preference. ■

Predicting Which Patients with Non-alcoholic Fatty Liver Disease Will Progress

SOURCE: Bazick J, et al. Clinical model for NASH and advanced fibrosis in adult patients with diabetes and NAFLD: Guidelines for referral in NAFLD. *Diabetes Care* 2015;38:1347-1355.

The language of progressive steps in liver disease used to be simpler: You had cirrhosis, or you didn't.

But things have gotten much more complicated. Non-alcoholic fatty liver disease (NAFLD) is now reported to be the most common cause of chronic liver disease in the United States, and is present in 50-75% of diabetics, thus representing as many as 18 million people among diabetics alone.

Were NAFLD to simply stay NAFLD, we would have much less to discuss. Unfortunately, 10-22% of NAFLD patients have a progressive type called non-alcoholic steatohepatitis (NASH), which itself may progress to cirrhosis and hepatocellular carcinoma.

One way to identify NAFLD patients with NASH is to perform liver biopsy; appraisal of the degree and pattern of fibrosis seen on liver biopsy provides grounds for staging of NASH. But since there is risk, expense, and discomfort associated with this procedure, identification of other biologic markers indicative of NASH has been sought.

Bazick et al reported on the development of a panel of markers that have suitable sensitivity and specificity to identify which patients with NAFLD are most likely to have NASH, potentially benefitting from referral for liver biopsy and confirmation of degree of fibrosis. The panel includes age, ethnicity, body mass index, waist:hip ratio, liver function tests, international normalized ratio, serum proteins, complete blood count, and serum insulin levels, all of which are obtainable with minimum of patient inconvenience. ■

Tramadol for Premature Ejaculation

SOURCE: Kirby EW, et al. Tramadol for the management of premature ejaculation: A timely systematic review. *Int J Impot Res* 2015;27:121-127.

Premature ejaculation is reported to be the most common sexual dysfunction among men, although it may not appear that way to clinicians since patients often do not seek help for the problem.

Since routine inquiry into sexual health issues often does not occur, and since there are no FDA-approved medications to treat premature ejaculation, it is not surprising that patients fail to bring forward the problem. As late as 1998 (the year of the advent of Viagra), 90% of impotent men reported they did not discuss their sexual health problem with a clinician, citing 1) their complaint might be disregarded, 2) there might not be any remedy, and 3) the clinician might be embarrassed by discussing such issues.

To date, selective serotonin reuptake inhibitors (SSRIs) have been the most commonly used effective treatment for premature ejaculation. SSRIs have shown efficacy on both a scheduled and pro re nata basis. Kirby et al recently reported on the efficacy of tramadol for premature ejaculation.

Based on results from eight articles published in peer-reviewed journals, most of which were placebo-controlled or comparison trials to paroxetine (the most commonly used SSRI for premature ejaculation), the authors concluded that on-demand doses of 25-50 mg tramadol administered 2-4 hours prior to intercourse is effective in prolonging vaginal ejaculatory latency time and compares well with SSRIs in head-to-head trials. ■

Continued from page 142

In large, prospective databases of ischemic stroke, cryptogenic stroke occurs in as many as 30% of all ischemic stroke patients. Many of these patients have the characteristics of cardioembolic stroke, and there has always been a strong suspicion that some of these patients have atrial fibrillation (AF). However, only about 5% of patients with acute ischemic stroke are found to have AF while inpatients. Therefore, there is great interest in performing mobile cardiac outpatient telemetry (MCOT) after discharge, and this study looked at a retrospective cohort of consecutive patients who underwent 28-day MCOT after discharge.

There were 227 patients with cryptogenic stroke (179) or transient ischemic stroke (48), and 14% had AF detected on MCOT. In a multivariate analysis of clinical, echocardiographic, and radiographic features associated with the strokes, the only significant independent predictors of finding paroxysmal AF were age > 60 years (odds ratio [OR] = 3.7) and prior cortical or cerebellar infarction seen on neuroimaging (OR = 3).

No other clinical features, including demographics, $CHADS_2$ score, congestive heart failure, hypertension, age, diabetes, prior stroke or transient ischemic attack, vascular disease, sex, or stroke symptoms, were significant predictors, nor did electrocardiographic findings or radiographic characteristics of the acute infarction have any significant association with the detection of paroxysmal AF.

Therefore, these results would support monitoring patients > 60 years of age with evidence of prior stroke on brain imaging to look for AF. In this series, AF was detected in 33% of patients who had both of these features, but in only 4% of patients with neither. ■

CME QUESTIONS

1. **Risk factors for euglycemic diabetic ketoacidosis include all of the following *except*:**
   a. type 1 diabetes.
   b. alcohol use.
   c. reduction in carbohydrate intake.
   d. reduction in insulin dose.
   e. type 2 diabetes.

2. **When elderly hypogonadal patients are treated with testosterone replacement therapy, there is no change in all of the following compared with placebo *except*:**
   a. common carotid artery intima-media thickness.
   b. coronary artery calcium.
   c. cardiovascular events.
   d. sexual function or health-related quality of life.

3. **Which of the following is associated with an attack of migraine with aura?**
   a. A decrease in word reading speed
   b. An increase in verbal memory
   c. A decrease in animal naming
   d. A transient increase in depression
   e. A transient increase in anxiety

4. **Ambulatory cardiac monitoring after discharge does not improve the sensitivity of diagnosing atrial fibrillation in patients with cryptogenic stroke.**
   a. True
   b. False

[IN FUTURE ISSUES]

Intensification Of Oral Therapy For Type 2 Diabetes

Sleep Patterns Predict Diabetes Risk