INTERNAL MEDICINE ALERT

A twice-monthly update of developments in internal and family medicine

Providing Evidence-based Clinical Information for 35 Years

AHC Media Home Page—www.ahcmedia.com

CME for Physicians—www.cmeweb.com
www.cmecity.com

AHC Media

INSIDE

Financial Disclosure: *Internal Medicine Alert's* editor, Stephen Brunton, MD, serves on the advisory board for Abbott, Boehringer Ingelheim, Janssen, Novo Nordisk, Sanofi, Sunovion, and Teva; he serves on the speakers bureau of Boehringer Ingelheim, Kowa, Novo Nordisk, and Teva. Peer reviewer Gerald Roberts, MD; executive editor Leslie Coplin; and managing editor Neill Kimball report no financial relationships relevant to this field of study.

Daily Coffee Consumption: A New Frontier in Diabetes Prevention!

ABSTRACT & COMMENTARY

By Rahul Gupta, MD, MPH, FACP

Clinical Assistant Professor, West Virginia University School of Medicine, Charleston, WV

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

Synopsis: *Regardless of the caffeine status, coffee intake was associated with reduced risk of type 2 diabetes while sugar-sweetened beverages were associated with a higher risk.*

Source: Bhupathiraju SN, et al. Caffeinated and caffeine-free beverages and risk of type 2 diabetes. *Am J Clin Nutr* 2013;97:155-166.

In the United States, type 2 diabetes (T2D) has become a major cause of heart disease and stroke. In fact, death rates for heart disease and the risk of stroke for a patient with diabetes are about 2-4 times higher than those of a non-diabetic. Additionally, two-thirds of adults who report having diabetes also report being hypertensive. It is estimated that the average medical expenses for someone with diabetes are more than twice that of someone without diabetes. Since 1990, the annual number of new cases of diagnosed diabetes in U.S. adults has more than tripled.[1] Overall, 25.8 million people or 8.3% of the total U.S. population suffers from diabetes. However, another 33% of U.S. adults have prediabetes, a condition where individuals have blood glucose levels that are higher than normal, but not high enough to be diagnosed as diabetes. Unfortunately, we now know that prediabetes can also place people at increased risk of developing T2D, heart disease, and stroke. However, less than 10% of U.S. adults with prediabetes report that they have ever been told of having prediabetes.

Development of T2D in patients with prediabetes is not inevitable. Studies have shown that people with prediabetes can prevent or delay the onset of diabetes by dietary modifications and physical activity leading to 5-7% weight loss.[2] While several prospective epidemio-

VOLUME 35 • NUMBER 1 • JANUARY 15, 2013 • PAGES 1-8

INTERNAL MEDICINE ALERT IS AVAILABLE ONLINE
www.internalmedicinealert.com

logic studies in the past have concluded that ingestion of caffeinated and decaffeinated coffee can reduce the risk of diabetes, some short-term studies have paradoxically shown that glucose tolerance is reduced shortly after ingestion of caffeine or caffeinated coffee and suggest that coffee consumption could increase the risk of diabetes. Additionally, while it is known that the consumption of caffeinated sugar-sweetened beverages (SSBs), such as soft drinks, energy drinks, and iced tea, may increase the risk of T2D, it is not well known whether artificially sweetened beverages (ASBs) may have the same impact.

In their research, Bhupathiraju et al used data from the Nurses' Health Study (NHS) and the Health Professionals Follow-Up Study (HPFS), two research projects that followed more than 74,000 women and 39,000 men for 24 and 22 years, respectively. The NHS was initiated in 1976 as a prospective cohort study of female registered nurses aged 30-55 years from 11 states and HPFS was initiated in 1986 as a prospective cohort study of male health professionals aged 40-75 years from all 50 states. Researchers documented 7370 new cases of T2D in the NHS population and 2865 new cases of T2D in the HPFS population during the follow-up period. Controlling for major lifestyle and dietary risk factors, analysis revealed that SSB intake was associated with statistically significant increased risk of T2D in both population groups. In the NHS group, caffeinated SSBs were associated with a 13% increased risk while non-caffeinated SSBs were associated with an 11% increased risk for T2D per serving consumed. Similarly, in the HPFS group, caffeinated SSBs were associated with a 16% increased risk while non-caffeinated SSBs were associated with a 23% increased risk for T2D. For ASBs, only caffeine-free intake was associated with a 6% higher risk of T2D. In contrast, consumption of coffee (regardless of caffeine presence) was associated with a lower risk of T2D. Specifically, in the NHS group, both caffeinated and decaffeinated coffee were associated with an 8% decreased risk while in the HPFS group, the decreased risk was 4% for caffeinated and 7% for decaffeinated coffee. Caffeinated tea (but not decaffeinated) was associated with a 5% lowered risk of T2D in the NHS population only.

■ COMMENTARY

It is no surprise that sugary beverages, irrespective of the caffeine content, would lead to an increase in the incidence of T2D. However, in this study, the increased incidence remained even after adjusting for confounders, which may suggest a direct biological effect of sugars used in sodas, such as high-fructose corn syrup and sucrose. This study was noteworthy to find that whether one likes his or her coffee caffeinated or decaffeinated, the benefits now include the reduction in risk of developing T2D. Interestingly, in men, the study found greater benefits from decaffeinated than caffeinated. For tea drinkers, only women derived similar benefits with caffeinated tea. Coffee is the leading worldwide beverage after water. Collectively, results from this and several other epidemiological studies suggest that coffee consumption may help prevent several chronic diseases, including T2D, Parkinson's disease, and liver disease (cirrhosis and hepatocellular carcinoma).[3] The health-promoting properties of coffee are often attributed to its rich phytochemistry, including caffeine, chlorogenic acid, caffeic acid, hydroxyhydroquinone, and others. However, coffee consumption is associated with increases in several cardiovascular disease risk factors, including blood pressure, cholesterol, and homocysteine as well as side effects from caffeine overindulgence. Traditionally, drinking coffee is often thought to be linked to unhealthier habits, such as smoking and low levels of physical activity. However, for most adult patients, research suggests that consuming moderate amounts of coffee may have some evidence of health benefits, especially when taken without cream or sugar. So, the next time you find yourself recommending strategies, such as dietary modification and physical activity, to prevent the development of T2D in your patients, you may want to consider adding the recommendation for two to three cups of coffee per day (providing 200-300 mg/d of caffeine), which may be associated with an almost 25% lower risk. Compared with many other less healthy beverages in an average diet, coffee may seem like a healthy beverage these days. ■

Internal Medicine Alert, ISSN 0195-315X, is published monthly by AHC Media, a division of Thompson Media Group LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

EXECUTIVE EDITOR: Leslie Coplin.
MANAGING EDITOR: Neill L. Kimball.
SENIOR VICE PRESIDENT/GROUP PUBLISHER: Donald R. Johnston.

GST Registration Number: R128870672.

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to ***Internal Medicine Alert,*** P.O. Box 105109, Atlanta, GA 30348.

Back Issues: $21. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Subscriber Information

Customer Service: 1-800-688-2421.
Customer Service E-Mail: customerservice@ahcmedia.com
Editorial E-Mail: neill.kimball@ahcmedia.com
Online: www.ahcmedia.com

Subscription Prices

United States
1 year with free AMA Category 1 credits: $319
Add $17.95 for shipping & handling.
(Student/Resident rate: $125)

Multiple Copies
Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482.

Canada
Add 7% GST and $30 shipping.

Elsewhere
Add $30 shipping.

Accreditation

AHC Media is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media designates this enduring material for a maximum of 45 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This enduring material activity, *Internal Medicine Alert*, has been reviewed and is acceptable for up to 24 Prescribed credit(s) by the American Academy of Family Physicians. AAFP certification begins January 15, 2013. Term of approval is for one year from this date with the option of yearly renewal. Each issue is approved for 1 Prescribed credits. Credit may be claimed for one year from the date of each issue. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This CME activity is intended for the internist/family physician. It is in effect for 36 months from the date of the publication.

AHC Media

Questions & Comments
Please call **Neill Kimball**, Managing Editor, at (404) 262-5404.

References

1. Centers for Disease Control and Prevention. Diabetes Report Card. 2012. http://www.cdc.gov/diabetes/pubs/pdf/DiabetesReportCard.pdf. Accessed December 17, 2012.
2. Knowler WC, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346:393-403.
3. Higdon JV, Frei B. Coffee and health: A review of recent human research. *Crit Rev Food Sci Nutr* 2006;46:101-123.

Using Low-Dose Aspirin to Prevent Recurrent Venous Thromboembolism

ABSTRACT & COMMENTARY

By Harold L. Karpman, MD, FACC, FACP

Clinical Professor of Medicine, UCLA School of Medicine

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

Synopsis: *Aspirin therapy, as compared with placebo, significantly reduced the rate of major vascular events with improved net clinical benefit and also reduced the rate of recurrent venous thromboembolism.*

Source: Brighton TA, et al. Low-dose aspirin for preventing recurrent venous thromboembolism. *N Engl J Med* 2012;367:1979-1987.

It is well known that patients who have had an episode of unprovoked venous thromboembolism are at high risk for recurrence after anticoagulant therapy is discontinued.[1-2] Long-term warfarin anticoagulant therapy has proven to be very effective in preventing a recurrence of venous thromboembolism, but is associated with an increased risk of bleeding and is inconvenient from the patient's point of view.[3-6] As a result, many patients will discontinue their warfarin therapy after 3-6 months despite recommendations for prolonged therapy.[5]

Brighton and his colleagues evaluated the efficacy of low-dose aspirin compared to placebo in preventing a recurrence of venous thromboembolism in patients who had completed initial anticoagulation therapy with warfarin after a first unprovoked episode of venous thromboembolism. They performed the Aspirin to Prevent Recurrent Venous Thromboembolism (ASPIRE) study,[7] which was a double-blind, randomized, placebo-controlled study of 822 patients who had completed initial anticoagulation therapy with heparin followed by warfarin or another effective anticoagulant therapy after the first episode of unprovoked venous thromboembolism. A target INR of 2.0-3.0 was recommended while on warfarin therapy that was maintained for 6 to 12 months. Subjects were randomly assigned to receive a 100 mg dose of aspirin or placebo. The patients on aspirin demonstrated a large, although not significant, reduction in the rate of recurrence of venous thromboembolism. Most importantly, the patients also demonstrated a significant reduction in the rate of occurrence of other major vascular events, including myocardial infarction, stroke, or cardiovascular death.

■ COMMENTARY

Although the results of the trial performed by Brighton et al did not demonstrate a significant reduction in the primary outcome of recurrent venous thromboembolism with aspirin as compared to placebo therapy in patients who had suffered a first unprovoked venous thromboembolic incident and had been treated with 6-12 months of warfarin therapy, they did demonstrate that aspirin therapy significantly reduced the secondary composite outcome of major vascular events by 34% without increased bleeding. With fewer patients recruited than originally planned, the trial by itself was not sufficiently powered to show a significant reduction in the primary outcome, but when combined with the WARFASA study[8] results, in which patients had baseline characteristics that were similar, a clear effect was evident. The combined results of the two trials revealed a highly significant reduction of 32% in the rate of recurrent venous thromboembolism and a reduction of 34% in the rate of major vascular events with no excess bleeding.

It is well known that the risk of late reoccurrence of venous thromboembolism after a first unprovoked event remains high at approximately 10% in the first year.[1,2] Therefore, it is important to have an alternative form of medical therapy for the many patients who are unwilling to accept extended warfarin therapy because of its inconvenience and the increased risk of developing significant bleeding. Although aspirin is less effective than warfarin, this study by Brighton et al suggests that aspirin therapy is an attractive alternative to warfarin because it is simple, inexpensive, and has a well-documented safety profile. Aspirin has now been demonstrated to be effective by producing a significant overall reduction in the risk of major thrombotic events and cardiovascular death and a large, although not statistically significant, reduction in the rate of recurrent venous thromboembolism.

In summary, low-dose aspirin therapy appears to be

beneficial in preventing recurrent venous thromboembolism and major vascular events in patients who had a first episode of unprovoked venous thromboembolism. It also appears to be an attractive therapeutic option for these patients after they have completed an initial course of warfarin therapy. ■

References

1. Prandoni P, et al. The long-term clinical course of acute deep venous thrombosis. *Ann Intern Med* 1996;125:1-7.
2. Rodger M, et al. Unprovoked venous thromboembolism: Short-term or indefinite anticoagulation? Balancing long-term risk and benefit. *Blood Rev* 2010;24:171-178.
3. Kearon C, et al. Antithrombotic therapy for VTE: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141: e419S-e494S.
4. Schulman S, et al. The duration of oral anticoagulant therapy after a second episode of venous thromboembolism. *N Engl J Med* 1999;341:298.
5. Agnelli G, et al. Three months versus one year of oral anticoagulant therapy for idiopathic deep vein thrombosis. *N Engl J Med* 2001;345:165-169.
6. Agnelli G, et al. Extended oral anticoagulant therapy after a first episode of pulmonary embolism. *Ann Intern Med* 2003;139:19-25.
7. Brighton TA, et al. Low-dose aspirin for preventing recurrent venous thromboembolism. *N Engl J Med* 2012; 367:1979-1987.
8. Prandoni P, et al. An association between atherosclerosis and venous thrombosis. *N Engl J Med* 2003;348: 1435-1441.

At Last…Type 1 Diabetes Can Be Prevented (But Only in Rats)!

ABSTRACT & COMMENTARY

By Jeff Unger, MD

Director, Metabolic Studies, Catalina Research Institute, Chino, CA

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

Synopsis: *The author reviewed the strategies of predicting and preventing type 1 diabetes across the different stages of development of the disorder. Not only can risk for type 1 diabetes be predicted, but the approximate age of diabetes onset in children can be ascertained. Although diabetes can be prevented in animal models, clinical trials in humans have demonstrated only the ability to delay loss of insulin secretion. To date, no clinical trial has resulted in complete reversal and restoration of pancreatic beta-cell function in human subjects.*

Source: Eisenbarth GS. Prevention of type 1A diabetes mellitus. *Endocr Pract* 2012;18:745-749.

Type 1 diabetes (T1D) is a chronic progressive autoimmune disorder affecting more than 500,000 Americans. The pathogenetic stages of T1D begin with genetic susceptibility, followed by a triggering of autoimmunity marked by the appearance of islet autoantibodies (autoantibodies to insulin, glutamic acid decarboxylates, insulinoma-associated antigen, and the islet zinc transporter), followed by progressive beta-cell death (apoptosis) and overt hyperglycemia. The initial and primary antigenic target in humans is endogenous insulin. The levels of insulin autoantibody appearance correlate with the rate of progression toward hyperglycemia. Interestingly, some patients who have had T1D for more than 50 years demonstrate histologic evidence within some islets of complete destruction, whereas other islets appear to be normal.[1] Pathologic examinations of pancreases from islet autoantibody-positive cadaver donors have shown both insulinitis and areas of psuedoatrophic islets consistent with a chronic-progressive autoimmune beta-cell destructive process.[2]

The results of clinical trials that have been designed to address each of the phases of autoimmune pathogenesis in T1D are listed in Table 1 (*see Table 1*).

In summary, no effective and safe antigen-specific immunologic therapy exists for reversing type 1 diabetes in high-risk patients. Newly diagnosed patients with T1D should be made aware of screening and intervention studies such as T1D TrialNet through the National Institutes of Health (http://www.diabetestrialnet.org). Ultimately, preventive therapies for T1D will require combinations of interventions to fully mitigate one's dysregulated immunity. ■

References

1. Keenan HA, et al. Residual insulin production and pancreatic b-cell turnover after 50 years of diabetes: Joslin Medalist Study. *Diabetes* 2010;59:2846-2853.
2. In't Veld P, et al. Screening for insulitis in adult autoantibody-positive organ donors. *Diabetes* 2007;56:2400-2404.

Table 1
Clinical Trials Designed to Prevent T1D*

Stage	Stage Pathogenesis	What We Know	Results of Studies to Date
I	Genetic susceptibility	People heterozygous for HLA alleles DR3-DQ2 and DR4-DQ8 have a 5% risk of developing T1D. 30% of T1D have this genotype vs 2% of the general U.S. population.	Therapeutic interventions provided to "high-risk" patients have failed to slow or reverse pancreatic beta-cell loss. Therapies attempted have included nicotinamide, low-dose subcutaneous insulin, GAD vaccination, immunostimulant bacillus Calmette-Guerin vaccine, oral or nasal insulin, and immune modulation.
II	Appearance of islet autoantibodies	The presence of two of four autoantibodies in children is associated with 90% development of T1D by age 20. Patients testing positive for a greater number of autoantibodies tend to experience a faster course of disease progression. The absence of autoantibodies in children may indicate the presence of monogenetic diabetes.	Financial barriers exist in screening high-risk patients. The estimated cost spent for a single case of identifying a low-risk T1D patient who is likely to progress based on antibody screening is $73,000. Widespread clinical testing for low-risk patients is not recommended by the American Diabetes Association.
III	Beta-cell apoptosis	We have yet to define the most effective measurement of beta-cell mass and function in vivo. In some cases, beta-cell injury or apoptosis occurs rapidly, whereas in others the destruction of islets is protracted as in latent autoimmune diabetes of adulthood. Flatbush diabetes patients present with acute onset of diabetic ketoacidosis, yet recover nearly complete beta-cell insulin secretion.	T1D may be predicted in individuals based on both the presence of one or more autoantibodies and the titers of those antibodies obtained at the time of testing.
IV	Overt clinical type 1 diabetes	T1D occurs in individuals in whom genetic susceptibility outweighs genetic protection. As islet cell destruction occurs, autoantibodies are delivered into pancreatic lymph nodes where destructive T-effector cells are produced that outnumber the stabilizing T- regulator cells. Initially, the decline in beta-cell function and loss of beta-cell mass presents clinically as loss of first phase insulin response to an intravenous glucose challenge. Over time, patients progress to frank hyperglycemia.	Studies have shown that hyperglycemia begins at least 2 years prior to the time of diagnosis of T1D, after which glucose levels continue to increase gradually until 6 months prior to diagnosis. Fasting C-peptide levels are preserved at normal levels longer than post-prandial C-peptide secretion. Attempts to "re-boot" the immune system using monoclonal antibodies have not proven successful at reversing the trend toward T1D in high-risk patients.

*A comprehensive summary of the pathogenesis and prevention of type 1 diabetes (including references for this table) may be found in "Type 1 diabetes in adults." In: Unger Jeff. *Diabetes Management in Primary Care - Second Edition*. Philadelphia: Lippincott, Williams and Wilkins; 2012. 413-452.

Pharmacology Update

Ingenol Mebutate Gel (Picato)

By William T. 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.

A NEW TOPICAL AGENT IS AVAILABLE FOR THE TREATMENT OF actinic keratosis (AK). Ingenol mebutate is a macrocyclic diterpene ester found in the sap of *Euphorbia peplus*, a common plant found in Africa, Europe, and Asia. It is a novel agent with a postulated dual mechanism of action, rapid lesion necrosis followed by specific neutrophil-mediated antibody dependent cellular cytotoxicity.[1] It is marketed as a topical gel by Leo Pharma as Picato.

Indications

Ingenol mebutate is indicated for the topical treatment of AK.[1]

Dosage

For AK of the face and scalp, the 0.015% gel is applied once daily for 3 consecutive days. For lesions on the trunk and extremities, the 0.05% gel is applied once daily for 2 consecutive days.

Ingenol mebutate is available as 0.015% and 0.05% gel for two or three unit dose tubes.

Potential Advantages

Ingenol mebutate treatment is for 2-3 days compared to prolonged treatment (14-60 days) required for current therapy (e.g., 5-FU, imiquimod, diclofenac). This reduces the duration of adverse reactions and likely improves adherence.

Potential Disadvantages

The most common local skin reactions (> 60%) were erythema, flaking/scaling, crusting, and swelling. Less frequently reported reactions include vesiculation/pustulation and erosion/ulceration (26-56%).[2]

Comments

The safety and efficacy of ingenol mebutate were evaluated in four double-blind, vehicle-controlled trials, two involving lesions on the face or scalp and two involving the trunk or extremities.[2,3] Subjects with AK on the face or scalp were randomized to ingenol mebutate 0.015% (n = 277) or vehicle gel (n = 270) applied once daily for 3 consecutive days. Those with AK of the trunk or extremities were randomized to 0.05% (n = 226) or vehicle (n = 232) once daily for 2 consecutive days. The primary endpoint was complete clearance of all clinically visible AK in the treatment area; partial clearance was reduction of 75% on day 57. Pooled results for face and scalp were 42.2% complete and 63.9% partial clearance compared to 3.7% and 7.4%, respectively, for the vehicle. Complete and partial clearance were 34.1% and 49.1% for trunk and extremities, and 4.7% and 6.9% for the vehicle. The median reductions of lesions were 83% and 75% for face/scalp and trunk/extremities compared to 0% for the vehicle. For those with complete clearance, there was a roughly 50% recurrence in the previously treated area. There are currently no comparative studies with other topical agents. The magnitude of success appears similar to that reported for 5-fluorouracil, diclofenac gel, and imiquimod cream.[4-6]

Clinical Implications

AK is a premalignant lesion that can progress to squamous cell carcinoma. The prevalence of AK is estimated to be 27% in men and 10% in women. Currently recommended topical treatment by the American Academy of Dermatology includes 5-fluorouracil cream, diclofenac gel, imiquimond cream, and now ingenol mebutate gel.[4] The latter offers a significantly shorter duration of treatment and appears to be comparable in effectiveness to the other agents. The wholesale acquisition cost of ingenol mebutate is $590, which is similar to diclofenac gel (Solaraze, $621) and imiquimod (Zyclara, $598), but more expensive than 5-fluorouracil (Efudex, Fluroplex) which is $230 and $350. ■

References

1. Rosen RH, et al. Dual mechanism of action of ingenol mebutate gel for topical treatment of actinic keratoses: Rapid lesion necrosis followed by lesion-specific immune response. *J Am Acad Dermatol* 2012;66:486-493.
2. Picato Prescribing Information. Parsippany, NJ: LEO Pharma, Inc.; February 2012.
3. Lebwohl M, et al. Ingenol mebutate gel for actinic keratosis. *N Engl J Med* 2012;366:1010-1019.
4. Rhavar M, et al. Randomized, vehicle-controlled trials of topical 5-fluorouracil therapy for actinic keratosis treatment: An overview. *Immunotherapy* 2012;4:939-945.
5. Aldara Prescribing Information. Bristol, TN: Graceway Pharmaceuticals; February 2007.
6. Solaraze Gel Prescribing Information. Florham Park, NJ: PharmaDerm.
7. http://www.aad.org/skin-conditions/dermatology-a-to-z/actinic-keratosis/diagnosis-treatment/actinic-keratosis-diagnosis-treatment-and-outcome. Accessed Dec. 23, 2012.

CME Questions

1. **In the study by Bhupathiraju et al, which of the following drinks was not associated with reduced risk for type 2 diabetes?**
   a. Caffeinated coffee
   b. Decaffeinated coffee
   c. Caffeinated tea
   d. Decaffeinated tea
   e. All of the above

2. **When compared to placebo therapy, aspirin:**
   a. had no significant effect on the rate of major vascular events.
   b. significantly reduced the rate of recurrence of venous thromboembolism.
   c. did not significantly reduce the rate of recurrence of venous thromboembolism but did result in a significant reduction in the rate of major vascular events with improved net clinical benefit.
   d. None of the above

3. **Which of the following statements is true about diabetes?**
   a. The initial presentation of diabetic ketoacidosis indicates that the patient is unlikely to recover any beta-cell function over time.
   b. Screening low-risk patients for type 1 diabetes is cost effective and recommended by the American Diabetes Association.
   c. Children who present with diabetes, yet lack autoantibodies, may have monogenetic diabetes.
   d. Vaccines against GAD autoantibodies appear to be an effective means to prevent progression of insulinitis in high-risk patients.

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville

Dr. Kuritzky is an advisor for Endo, Kowa, Pricara, and Takeda.

Does Screening for Type 2 Diabetes Pay Off?

Source: Simmons RK, et al. Screening for type 2 diabetes and population mortality over 10 years (ADDITION-Cambridge): A cluster-randomised controlled trial. *Lancet* 2012;380:1741-1748.

It is easy to envision that earlier diagnosis of type 2 diabetes (DM2) might lead to an opportunity for earlier, intensified interventions that might translate into improved outcomes. So far, however, we only *think* that, we don't actually *know* it. Simmons et al followed patients from general practices in England (n = 11,737) who enrolled in pathways of 1) screening for DM2 plus intensive multifactorial interventions, 2) screening for DM2 plus routine care, and 3) a "no screening" population. The mean age of the population was 58 years.

The practices in which multifactorial intervention groups were enrolled received educational and logistical support for attaining glucose, blood pressure, and lipid goals. Recent data in the United States suggest that currently fewer than 15% of type 2 diabetics are achieving simultaneous goal attainment in all three of these.

Over an interval of approximately 10 years' follow-up, there were no significant differences seen between unscreened vs screened subjects in regards to all-cause mortality, cardiovascular mortality, cancer mortality, or diabetes-related death.

Explanations for failure to reduce risk include the following: 1) screening for diabetes became more routine in the non-screened group over time; 2) routine care is improving, such that intensive intervention may not be as dramatically different than routine care, and 3) the duration of follow-up was insufficient. ■

Surgical Treatment of Diabetes

Source: Vetter ML, et al. Comparison of bariatric surgical procedures for diabetes remission: Efficacy and mechanisms. *Diabetes Spectrum* 2012;25:200-210.

The link between obesity and type 2 diabetes (DM2) is widely acknowledged. Certainly, weight gain is associated with increased incidence of DM2, and weight loss improves insulin sensitivity, as well as other cardiovascular risk factors. Surgery produces prompt and dramatic reductions in excess body weight, yet it appears that rebalancing of the disturbed metabolic homeostasis seen in DM2 varies among the different bariatric surgical interventions. Additionally, it appears that weight loss alone cannot fully explain the metabolic restorations seen post-surgically. Favorable metabolic changes are especially prompt, intensive, and durable when surgery involves bypassing or elimination of much of the small intestine from the digestive path.

In their review of the DM2 bariatric surgery trials, Vetter et al conclude that the primary driving force for DM2 remission appears to be weight loss. Since diversionary procedures are associated with greater and more durable weight loss, they would be anticipated to produce greater benefits for DM2 and they do. Overall adjustable gastric bypass is reported to result in remission in 57% vs 95% in biliopancreatic diversion surgery. The long-term relapse rate is not insubstantial: One very long follow-up of diversionary surgery (up to 16 years) noted relapse in 43%.

There are distinct hormonal changes that differ between the surgical interventions. For instance, gastric banding does not affect incretin activity, but bypass surgeries are associated with increased secretion of incretins. Evidence continues to accumulate that corroborates the efficacy, safety, and durability of bariatric surgical intervention for DM2. ■

Benefits and Consequences of Aldosterone Antagonists for HF

Source: Hernandez AF, et al. Associations between aldosterone antagonist therapy and risks of mortality and readmission among patients with heart failure and reduced ejection fraction. *JAMA* 2012;308:2097-2107.

Clinical trial data have conclusively demonstrated improved mortality and cardiovascular outcomes in chronic heart failure (CHF) patients who receive aldosterone blockade (ALD) with spironolactone or eplerenone in addition to standard of care treatment. Clinical trial populations, however, are different from practice settings in which patients may not enjoy the same risk:benefit balance as the often highly selected subjects who enroll in clinical trials.

To evaluate outcomes among patients with newly administered ALD not enrolled in a clinical trial, Hernandez et al reviewed 2005-2010 Medicare data on older (mean age, 78 years) patients who had received a new ALD prescription on discharge from the hospital for CHF (n = 5887). They looked at all-cause mortality, cardiovascular readmission, heart failure readmission, and hyperkalemia.

Although there was no difference in total mortality, the addition of ALD to the treatment regimen was associated with lower heart failure readmission. On the other hand, patients treated with ALD were statistically significantly more likely to be readmitted with hyperkalemia over the next year (1.5-2.5 times more likely). ALD treatment offers some positive outcomes, but clinicians must be vigilant for hyperkalemia when ALD treatment is chosen. ■

Early Repolarization or Anterior STEMI?

By Ken Grauer, MD, *Professor Emeritus in Family Medicine, College of Medicine, University of Florida*

Dr. Grauer is the sole proprietor of KG-EKG Press, and publisher of an ECG pocket brain book.

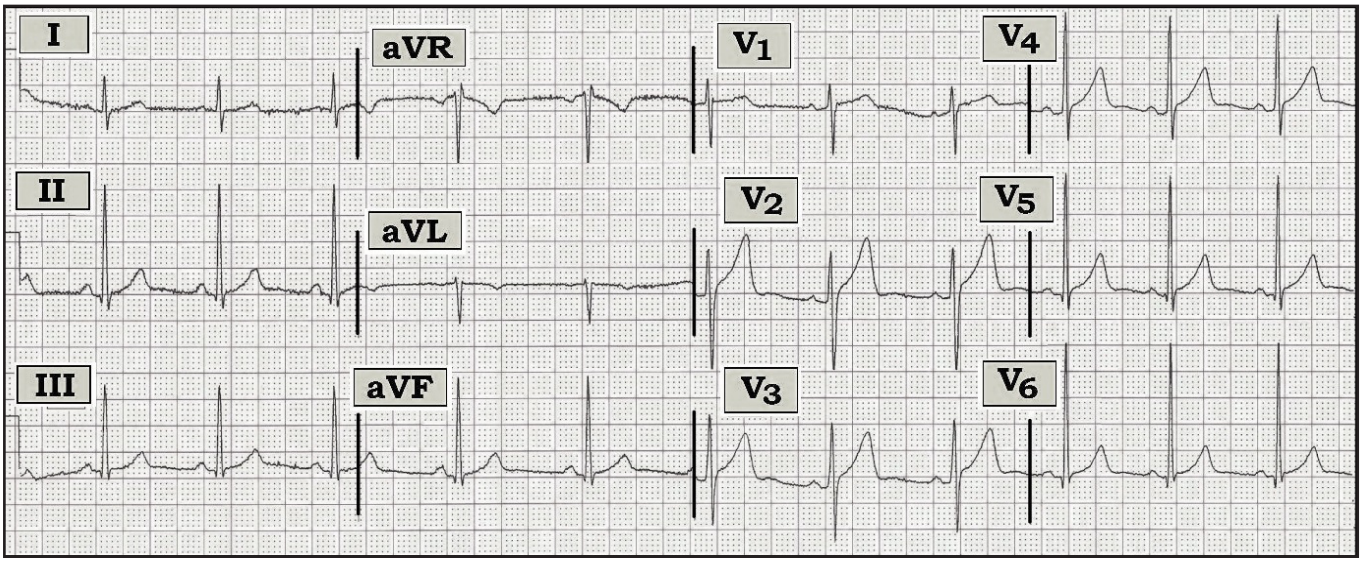


Figure — 12-lead ECG from a 50-year-old man with new-onset chest pain.

Scenario: The 12-lead ECG shown above was obtained from a 50-year-old man with new-onset chest pain. Is this ECG likely to represent a benign early repolarization pattern or the early stage of acute anterior ST elevation myocardial infarction (STEMI)?

Interpretation: The ECG shows sinus arrhythmia with normal intervals and axis, and voltage for left ventricular hypertrophy. There are small q waves in the inferior and lateral precordial leads. R wave progression is normal, with transition occurring between leads V3-to-V4. T waves are peaked. There is some J-point ST segment elevation with upward concavity in virtually all precordial leads, with ST elevation attaining at least 2 mm in lead V2. In addition, there is shallow symmetric T wave inversion in lead aVL.

The significance of the findings identified in the above tracing depends greatly on the clinical setting. Overall, this ECG has the appearance of early repolarization pattern (ERP) because:

1) ST segments manifest an upward concavity ("smiley" configuration) rather than a coved (downward convexity or "frowny" pattern) that would be suggestive of acute injury.

2) ST segment elevation is not marked in amount.

3) The q waves that are seen are small and narrow, which is consistent with normal septal q waves.

4) Other than isolated shallow T wave inversion in lead aVL (which may be a normal finding, especially given the predominantly negative QRS complex in this lead), there are no reciprocal ST-T wave changes.

Despite the above factors in favor of ERP, one *cannot* rule out the possibility of early anterior STEMI on the basis of this single ECG because there is ST segment elevation, and the patient is a 50-year-old man with *new-onset* chest pain. Early changes of anterior STEMI may be subtle, and ST segment elevation may (at least initially) manifest an upward concavity. Clinical follow-up is urgently needed. Search for a prior tracing on this patient, repeating the ECG in short order (to see if there is evolution), serial troponins, and close observation over ensuing hours should be revealing as to what (if anything) is occurring.

For more information on ERP and how to distinguish ERP from anterior STEMI, please visit: https://www.kg-ekgpress.com/ecg_-_early_repolarization/. ■

In Future Issues:

Persistent Subclinical Hypothyroidism and Cardiovascular Risk in the Elderly: The Cardiovascular Health Study

Dear *Internal Medicine Alert* Subscriber:

This issue of your newsletter marks the start of a new continuing medical education (CME) semester and provides us with an opportunity to remind you about the **procedures for earning CME and delivery of your credit letter.**

Internal Medicine Alert, sponsored by AHC Media, provides you with evidence-based information and best practices that help you make informed decisions concerning treatment options and physician office practices. Our intent is the same as yours — the best possible patient care.

The objectives of *Internal Medicine Alert* are:
- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens; and
- explain the advantages and disadvantages of new disease screening procedures.

The American Medical Association, which oversees the Physician's Recognition Award and credit system and allows AHC Media to award *AMA PRA Category 1 Credit*™, has changed its requirements for awarding *AMA PRA Category 1 Credit*™. Enduring materials, like this newsletter, are now required to include an assessment of the learner's performance; the activity provider can award credit only if a minimum performance level is met.

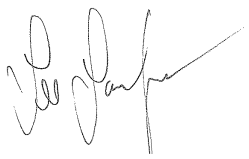
Here are the steps for earning credit for this activity:
1. Read and study the activity, using the provided references for further research.
2. Log on to **www.cmecity.com** to take a post-test; tests can be taken after each issue or collectively at the end of the semester. *First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice, or renewal notice.*
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the evaluation is received, a credit letter will be sent to you.

This activity is valid 36 months from the date of publication for ACCME credit and 12 months from the date of publication for AAFP credit. The target audience for this activity includes internist/family physicians.

If you have any questions about the process, please call us at (800) 688-2421, or outside the U.S. at (404) 262-5476. You can also fax us at (800) 284-3291, or outside the U.S. at (404) 262-5560. You can also email us at: customerservice@ahcmedia.com.

On behalf of AHC Media, we thank you for your trust and look forward to a continuing education partnership.

Sincerely,



Lee Landenberger
Continuing Education Director
AHC Media

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

Zolpidem and Risk of Falls in Hospitalized Patients

In this issue: Zolpidem and risk of falls; AVR and anticoagulation; statins in cancer patients; and FDA actions.

Zolpidem and risk of falls

Zolpidem (Ambien) increases the risk of falls in inpatients, according to a new study from the Mayo Clinic. The records of hospitalized patients who were not in the intensive care unit were reviewed in this retrospective cohort study. The rate of falls was compared in those who were administered zolpidem vs those for whom it was prescribed but not administered. After controlling for age, gender, insomnia, delirium, dose of zolpidem, Charlson comorbidity index, Hendrich's fall risk score, length of stay, visual impairment, gait abnormality, dementia/cognitive impairment, and concomitantly administered meds, the rate of falls was four times higher in those administered zolpidem (n = 4962) vs those who were prescribed but did not receive zolpidem (adjusted odds ratio 4.37, 95% confidence interval [CI], 3.34-5.76; $P < 0.001$). The authors conclude that zolpidem was a strong, independent, and potentially modifiable risk factor for inpatient falls. The authors suggest that changing order sets so that zolpidem use is not encouraged could potentially reduce fall rates in hospitalized patients. They also suggest that there is limited evidence to recommend other hypnotic agents as safer alternatives (*J Hosp Med* published online Nov. 19, 2012. doi: 10.1002/jhm.1985). ■

Anticoagulation and AVR

Bioprosthetic valves are preferred to mechanical valves for aortic valve replacement (AVR) in the elderly because of lack of need for anticoagulation in the long-term, but short-term anticoagulation is required. The duration of anticoagulation after valve replacement has been unclear. Now, a new study from Denmark suggests 6 months is optimal. Using the Danish National Patient Registry, more than 4000 patients who had a bioprosthetic AVR between 1997 and 2009 were identified. Rates of stroke, thromboembolic events, cardiovascular death, and bleeding were assessed along with warfarin treatment duration. Rates of events per 100 person-years in patients not treated vs those treated with warfarin for 3 months were 7 vs 2.7 for stroke, 13 vs 4 for thromboembolic events, 11.7 vs 5.4 for bleeding, and 32 vs 3.8 for cardiovascular death. The rate of cardiovascular death was 6.5 vs 2.0, favoring warfarin from 90 days to 179 days. The authors conclude that stopping warfarin within 6 months of bioprosthetic AVR surgery was associated with increased cardiovascular death. These findings challenge the current guidelines that recommend 3 months of antithrombotic treatment after AVR surgery suggesting that "patients will gain from an additional 3 months of warfarin treatment in terms of reduced cardiovascular death without risking significant increase in bleeding events" (*JAMA* 2012;308:2118-2125). An accompanying editorial states that this study provides important information to help clinicians understand the benefits and risks of warfarin use after bioprosthetic aortic valve implantation, but it

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5404. E-mail: neill.kimball@ahcmedia.com.

does not address the issue of adjunctive aspirin or the role of new novel oral anticoagulants (*JAMA* 2012;308:2147-2148). ■

Statins in patients with cancer

Patients taking a statin when diagnosed with cancer have a better prognosis than patients who are not taking statins, according to a new study. This study also used the Danish Registry in which all patients with a cancer diagnosis between 1995 and 2007 were evaluated. Roughly 19,000 patients were on a statin prior to diagnosis and 277,000 were not. Those taking statins were 15% less likely to die of any cause and 15% less likely to die of cancer (hazard ratio 0.85, 95% CI, 0.82-0.87 for cancer). The benefit was present regardless of statin dose or cancer type. The authors suggest that this is biologically plausible since cholesterol is needed for cell proliferation. They suggest "a need for trials of statins in patients with cancer" (*N Engl J Med* 2012;367:1792-1802). Previous studies have suggested reduced cancer mortality with statins in patients with prostate cancer and reduced recurrence rates in breast cancer patients. ■

FDA actions

The FDA has concluded a safety review of dabigatran (Pradaxa) and found that the drug is not associated with more serious bleeding events than warfarin. The review was done using insurance claims and data from the FDA's Sentinel Initiative. According to the FDA, the bleeding rates are consistent with the observations from large clinical trials, including RE-LY, which showed that bleeding rates in patients newly started on dabigatran were similar to rates associated with new use of warfarin. Therefore, the FDA has not changed its recommendation regarding dabigatran (FDA Drug Safety Communication, Nov. 2, 2012). The next day, *The New York Times* published an article reporting that dabigatran has been associated with more than 500 deaths in the United States since it was introduced. It also detailed several tragic cases of bleeding deaths associated with the drug. The article indicts the FDA stating "… the approval process was not sufficiently rigorous because it allowed a potentially dangerous drug to be sold without an option for reversing its effects." The article also mentions more than 100 lawsuits that have been filed in federal courts "…and thousands more are expected" (*The New York Times* Nov. 3, 2012:B1).

The FDA has expanded the approval of rivaroxaban (Xarelto) to include treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), both for acute treatment and prevention of recurrence. The drug is already approved for prevention of DVT and PE after knee and hip replacement surgery and for prevention of stroke in patients with non-valvular atrial fibrillation. It is the first oral drug approved to treat DVT and PE since warfarin was approved 60 years ago; but unlike warfarin, rivaroxaban can be used as monotherapy from diagnosis until treatment is discontinued. Approval was based on three studies of nearly 9500 patients with DVT or PE randomized to rivaroxaban, enoxaparin/vitamin K antagonist, or placebo. Rivaroxaban was equivalent to enoxaparin/vitamin K antagonist and superior to placebo for preventing recurrent DVT or PE.

The FDA has approved a new egg-free flu vaccine for adults. The vaccine is manufactured using cultured mammalian cells instead of fertilized chicken eggs. The manufacturer claims that the cell culture technology enables a rapid response to public health needs, such as a pandemic, since cell culture technology allows vaccines to be manufactured within weeks as opposed to traditional flu vaccines that depend on a large number of fertilized chicken eggs to grow the virus. Cell culture technology is used for several other vaccines including polio, rubella, and hepatitis A vaccines. Approval was based on a randomized, controlled clinical study of 7700 adults ages 18-49. The new vaccine was 83.8% effective in preventing influenza when compared to placebo. Injection site reactions are the most common side effects. The new vaccine is marketed as Flucelvax by Novartis.

The FDA has approved the first Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis (RA). Tofacitinib, dosed orally twice a day, is approved for RA patients who have failed methotrexate. The drug will compete with the parenteral RA drugs adalimumab (Humira), etanercept (Enbrel), and infliximab (Remicade). Tofacitinib carries a boxed warning regarding the increased risk of opportunistic infections, tuberculosis, cancers, and lymphoma; increases in cholesterol and liver enzymes; and decreases in blood counts. Approval was based on seven clinical trials in which the drug showed improvements in clinical response and physical function compared to placebo in patients with moderate-to-severe RA. Tofacitinib will be marketed by Pfizer as Xeljanz. The cost is projected to be just over $2000 per month, similar to other non-methotrexate biologic treatment options. ■