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## INSIDE



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# Looks Like the Ear Lobe Crease is Here to Stay

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:*** *In this study of patients imaged with CT angiography, finding of the presence of diagonal earlobe creases was independently and significantly associated with increased prevalence, extent, and severity of coronary artery disease.*


**Source:** Shmilovich H, et al. Relation of diagonal ear lobe crease to the presence, extent, and severity of coronary artery disease determined by coronary computed tomography angiography. *Am J Cardiol* 2012;109:1283-1287.

THE DIAGONAL EAR LOBE CREASE (DELC) IS A WRINKLE-LIKE LINE EXtending diagonally from the tragus across the lobule to the rear edge of the auricle of the ear, and its presence has been demonstrated not to be related to sleeping position or wearing earrings. Over the years, it has been intermittently associated with coronary artery disease (CAD), and is referred to as the "Frank" sign because of an article published by Frank in 1979,[1] in which he first associated the presence of the DELC with CAD. The association has remained controversial with some published papers supporting the observation[2-4] and other studies disputing it.[5-6]

Shmilovich and his colleagues performed a study intended to assess whether the presence of DELC correlates to the presence, extent, and severity of CAD as determined by coronary computed tomography (CT) angiography.[7] They studied 430 consecutive patients without a history of coronary artery intervention who underwent CT angiography on a dual-source CT scanner. The presence of DELC was confirmed in the individual patients by two blinded observers, and the CT angiography images were interpreted by two blinded readers who evaluated the CT angiograms for the presence of CAD and for sig-


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nificant (i.e., defined as > 50% stenosis) CAD narrowing. Multivariable logistic regression was performed to adjust for CAD confounders including age, gender, symptoms, and CAD risk factors. In this study of patients imaged with CT angiography, finding DELC was independently and significantly associated with increased prevalence, extent, and severity of CAD.

## ■ COMMENTARY

Over the many years since the relationship between DELC and CAD was described, many concerns have surfaced regarding the different and varying definitions of CAD.[3] For example, in some instances, the diagnosis of CAD was made solely by determining the presence of significant risk factors and/or electrocardiographic abnormalities at rest. Necropsy studies have supported the association between DELC and CAD finding that the presence of DELC often predicted coronary artery plaques causing more than 75% luminal stenosis.[8-12] As a result of these multiple studies, some observers have even recommended that observing DELC to be present should be used as a screening tool for atherosclerosis in young patients.[10] It must be carefully recognized that despite the many published papers, a definite pathophysiologic explanation for this association has not been ascertained. It had been suggested that the presence of DELC is linked to atherosclerosis by common genetic factors,[3] that it may be an acquired physical sign due to vascular disease, skin atrophy, or changes in connective tissue matrix,[3] or is due to the loss of elastin and elastic fibers reflecting microvascular disease in the coronary bed.[13,14] Some authors have concluded that the presence of DELC predicts all-cause and cardiac-cause morbidity and mortality and is associated with a lower 10-year cardiac event-free survival rate.[15] The data from the Shmilovich study support the concept that increased CAD risk in subjects with DELC may be associated with a greater underlying CAD burden in these patients for uncertain reasons.[7]

Although the reasons for the association between DELC and CAD remain unclear, the Shmilovich study[7] is the first study using the robustly validated power of CT angiography to identify the presence and severity of CAD in subjects with DELC. This finding of an association between DELC and significant CAD would suggest that clinicians should take a moment to examine their patients for DELC and should even consider screening patients in the younger age groups. The finding of DELC in asymptomatic patients with a low cardiovascular risk profile may lead to more intensive evaluation of these patients for occult CAD, which could lead to much earlier and effective CAD preventive therapy. ■

## References


1. Frank S, et al. Aural sign of coronary artery disease. *N Engl J Med* 1973;289:327-328.
2. Elliott WJ. Ear lobe crease and coronary artery disease. 1000 patients and review of the literature. *Am J Med* 1983;75:1024-1032.
3. Evrengul H, et al. Bilateral diagonal ear lobe crease and coronary artery disease: A significant association. *Dermatology* 2004;2009:271-275.
4. Jorde LB, et al. Lack of association of diagonal earlobe crease with other cardiovascular risk factors. *West J Med* 1984;140:220-223.
5. Davis TM, et al. The diagonal ear lobe crease (Frank's sign) is not associated with coronary artery disease or retinopathy in type II diabetes; the Fremantle Diabetes Study. *Aust NZ J Med* 2000;30:573-577.
6. Motamed M, et al. The predictive value of diagonal earlobe crease sign. *Int J Clin Pract* 1998;52:305-306.
7. Shmilovich H, et al. Relation of diagonal ear lobe crease to the presence, extent, and severity of coronary artery disease determined by coronary computed tomography angiography. *Am J Cardiol* 2012;109:1283-1287.
8. Cumberland GD, et al. Earlobe creases and coronary atherosclerosis. The view from forensic pathology. *Am J Forensic Med Pathol* 1987;8:9-11.
9. Edston E. The earlobe crease, coronary artery disease, and sudden cardiac death: An autopsy study of 520 individuals. *Am J Forensic Med Pathol* 2006;27:129-133.
10. Ishii T, et al. Earlobe crease and atherosclerosis. An autopsy study. *J Am Geriatric Soc* 1990;38:871-876.
11. Kirkham N, et al. Diagonal earlobe creases and fatal



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cardiovascular disease: A necropsy study. *Br Heart J* 1989;61:361-364.
12. Patel V, et al. Diagonal earlobe creases and atheromatous disease: A postmortem study. *J R Coll Phys Lond* 1992;26:274-277.
13. Lichtstein E, et al. Letter: Diagonal ear-lobe crease and coronary artery sclerosis. *Ann Intern Med* 1976;85:337-338.
14. Shoenfeld Y, et al. Diagonal earlobe crease and coronary risk factors. *J Am Geriat Soc* 1980;28:184-187.
15. Elliott WJ, et al. Diagonal earlobe creases and prognosis in patients with suspected coronary artery disease. *Am J Med* 1996;100:205-211.

# Use With Caution — Dangers of Common Antibiotics

ABSTRACT & COMMENTARY

***By Joseph E. Scherger, MD, MPH***

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

***Synopsis:*** *Dangers of antibiotics are well known and recent research brings to light new dangers of commonly used medications. Five days of azithromycin results in 47 additional deaths from cardiovascular disease compared with amoxicillin and no antibiotic. One out of 2500 patients treated with a fluoroquinolone (ciprofloxacin, levofloxacin, and norfloxacin) suffer a retinal detachment. These antibiotics should be used only when there is a clear clinical need and with caution.*

**Sources:** Ray WA, et al. Azithromycin and the risk of cardiovascular death. *N Engl J Med* 2012;366:1881-1890. Etminan M, et al. Oral fluoroquinolones and the risk of retinal detachment. *JAMA* 2012;307:1414-1419.

WE ALL KNOW WE MUST USE ANTIBIOTICS WITH CAUTION, especially those with potential complications such as drug resistance and colitis. Allergies from antibiotics can be life-threatening in some extreme cases. These two studies are of particular interest since they are about drugs used very commonly today. Ciprofloxacin is given for many urinary tract infections and as a travel medication on request. Azithromycin, in its convenient Z-pack, is very popular for respiratory infections, including bronchitis, which is usually a self-limited viral infection.

The study of azithromycin was from a Tennessee Medicaid cohort of patients to detect an increased risk of death related to short-term cardiac effects of medications. The cohort that took azithromycin was 347,795 prescriptions and the control group was 1,392,180. More than 1 million patients taking amoxicillin, 264,626 taking ciprofloxacin, and 193,906 taking levofloxacin were also included in the study. For those taking azithromycin, the hazard ratio for cardiovascular death was 2.88, compared with the other groups.

While overall there were 47 additional deaths per 1 million users of azithromycin, those with higher risk of cardiovascular disease were at greater risk of death, with an estimated 245 additional deaths per 1 million users in the highest decile of risk. The additional deaths began to appear within 2 days of the prescription being filled and continued for 10 days.

The fluoroquinolone study was a case-control cohort analysis of patients in British Columbia, Canada, who visited an ophthalmologist between 2000 and 2007 for a retinal detachment. From a cohort of 989,591 patients, 4384 cases of retinal detachment and 43,840 controls were identified. The hazard ratio for retinal detachment with current use of a fluoroquinolone antibiotic was 4.50, with one additional case per 2500 patients.

**■ COMMENTARY**

While both events, cardiovascular death with azithromycin and retinal detachment with a fluoroquinolone, are uncommon, the risk should make us and our patients pause. I have already used these studies to discourage antibiotic use for frivolous reasons, such as an apparent viral infection. Taking the time to counsel patients about antibiotic use pays dividends in patient confidence in our knowledge base and concern for their welfare. Warnings are more patient-centered compared with just saying "no." While some patients may resist taking antibiotics when they really need them, we are best suited to put the risks and benefits of antibiotics into proper perspective. Our role in prescribing is best when we serve as the patient's consultant rather than giving potentially dangerous medications by reflex or simple request. ■

# Soda and Stroke Risk: A Pop Connection?

ABSTRACT & COMMENTARY

***By Susan T. Marcolina, MD, FACP***

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*This article originally appeared in the June issue of* Alternative Medicine Alert. *At that time it was peer reviewed by David Kiefer, MD, Clinical Instructor, Family Medicine, University of Washington, Seattle, Clinical Assistant Professor of Medicine, University of Arizona, Tucson, Adjunct Faculty, Bastyr University, Seattle. Drs. Marcolina and Kiefer report no financial relationships relevant to this field of study.*

***Synopsis:*** *Two large, well-known, U.S. prospective cohort studies, the Nurses' Health Study and the Health Professionals Follow-up Study, evaluated both sugar-sweetened and diet (low-calorie, also called artificially sweetened) soda consumption over 20 years and found one or more daily servings to be associated with a significantly higher risk of stroke. Conversely, alternative beverage choices of either skim milk, caffeinated coffee, or decaffeinated coffee were associated with diminished stroke risk. This association appeared to be stronger for women than men and independent of established dietary and nondietary cardiovascular disease risk factors, including body mass index and energy intake. Beverage choice may be a modifiable risk factor for cerebrovascular events.*

**Source:** Bernstein AM, et al. Soda consumption and the risk of stroke in men and women. *Am J Clin Nutr* 2012;95:1190-1199.

This epidemiologic study evaluated beverage types and amounts consumed by two large representative male and female populations of health professionals over more than two decades in detail via biennial validated food frequency questionnaires (FFQs) in addition to their health status questionnaires. The types of sodas included on the FFQs included low-calorie, caffeinated, and decaffeinated colas; other low-calorie, non-cola carbonated beverages; sugar-sweetened colas with and without caffeine; and other carbonated, caffeinated, and decaffeinated beverages with sugar. Soda was categorized as sugar-sweetened or low-calorie, and then participants were divided into categories of cumulative average serving intake of each type (sugar-sweetened and low-calorie soda consumption), which included none, up to once per week, once per week up to once per day, and once per day or more.

The investigators evaluated the associations between sugar-sweetened and low-calorie soda intake and total stroke (hemorrhagic and ischemic) incidence in both populations. In multivariable analyses adjusted for dietary risk factors (intakes of alcohol, fruit and vegetable servings, cereal fiber, fish, red meat, trans fats) and non-dietary cardiovascular disease risk factors (exercise, smoking, family history, menopausal status [women], aspirin, and multivitamin use), increased consumption of both sugar-sweetened and low-calorie colas and non-cola carbonated beverages was associated with a greater risk of overall stroke. For men, one or more daily servings of sugar-sweetened soda was associated with an insignificant relative risk (RR) of total stroke of 1.08 (95% confidence interval [CI], 0.82-1.41; $P = 0.43$); whereas in women, the statistically significant RR was 1.19 (95% CI, 1.00-1.42; $P = 0.02$). For men who consumed one or more daily servings of low-calorie soda, the RR for total stroke was 1.10 (95% CI, 0.92-1.32; $P = 0.13$) and in women was 1.18 (95% CI, 1.05-1.33; $P = 0.003$). The pooled multivariable risk of stroke among both sexes was 1.12 (95% CI, 1.02-1.24; $P = 0.02$) for one or more daily servings of sugar-sweetened soda and 1.09 (95% CI, 1.04-1.15; $P = 0.0001$) for one or more daily low-calorie soda servings.

Interestingly, compared with men and women who did not consume sugar-sweetened soda, those who consumed one or more daily servings had higher rates of hypertension, hypercholesterolemia, and lower physical activity. Greater consumption of low-calorie soda was associated with higher body mass indices (BMIs) and rates of chronic disease.

The authors evaluated the pooled risk ratios for consumption of alternative beverages in regard to stroke risk and found that compared with one daily serving of sugar-sweetened soda, daily servings of decaffeinated and caffeinated coffees were associated with modest reductions of 10% and 9% in stroke risk, respectively. When compared with one daily serving of low-calorie soda, consumption of one daily serving of skim milk, caffeinated coffee, or decaffeinated coffee was associated with decreases in stroke risk of 11%, 11%, and 13%, respectively. Although the 95% CIs suggested a modest benefit with the water for soda substitution, the authors suggest that the chlorogenic acids, lignans, and magnesium content of coffee and the potassium magnesium and calcium content of milk act both as antioxidants and mediators of glucose metabolism and blood pressure, which may be associated with the reduced stroke risk result seen with these beverages.[1]

## ■ COMMENTARY

Stroke is the third major cause of death and the leading cause of functional impairment, with 15-30% of survivors left with permanent disability and lost independence. It is a major public health concern in the United States. Effective primary prevention remains the optimal way to reduce the burden of disease and disability, since more than 70% of strokes occur as first-time events.[2]

The benefit of information obtained from large, long-term cohort studies such as this one is that it prompts us to consider ways in which individuals, in conjunction with their health care providers in the medical home context, can mitigate risk by virtue of dietary and lifestyle interventions that are low-cost, effective, and achievable.

Over the past 25 years, sugar-sweetened and diet soda consumption has increased 135% in the United States in parallel with the prevalence of obesity.[3] The temporal association has a scientific basis in view of the fact that sodas are nutrient-poor beverages consumed in lieu of potentially nutrient-rich beverages such as enriched non-

dairy milks, milk, calcium-fortified juices, or just plain water, which provides necessary hydration without additional cost or calories. Additionally, the caramel coloring in sugar-sweetened and low-calorie colas has advanced glycation endproducts, which have been linked to inflammatory processes that enhance initiation, growth, and destabilization of atherosclerotic plaques.[4]

Another factor in the soda-stroke linkage may be the fructose content of soda either as sucrose (the "sugar" disaccharide composed of 50% fructose and 50% glucose) or high-fructose corn syrup (55% fructose and 45% glucose). Due to this high volume and content of rapidly absorbable carbohydrates, sodas may increase the risk of metabolic syndrome and type 2 diabetes by increasing dietary glycemic load, leading to insulin resistance, weight gain, beta cell dysfunction, and inflammation. Ingested fructose is metabolized almost entirely in the liver; this hepatic metabolism favors lipogenesis, which increases triglyceride levels and reduces low-density cholesterol lipoprotein particle size. Such alterations in the lipoprotein profile increase atherogenicity. Hepatic metabolism of fructose also increases serum uric acid, which reduces endothelial nitric oxide and can result in blood pressure elevation, a known risk factor for stroke.[5]

Additionally, fructose has different metabolic effects than glucose. It does not increase postprandial insulin and leptin (satiety hormone) or suppress ghrelin (appetite-stimulating hormone) levels, thus suggesting another means by which it promotes weight gain.[6]

Several other epidemiologic studies have shown an association between consumption of sugar-sweetened beverages and the development of metabolic syndrome and type 2 diabetes, both of which contribute to risk of stroke.[7]

Although de Koning et al found no association between low-calorie soda intake and diabetes risk,[8] low-calorie soda consumption of two or more daily servings has been associated with albuminuria and progression of kidney disease.[9]

Another consideration is that many carbonated beverages contain a large amount (> 10 mg in a 12 fluid-ounce serving) of inorganic phosphorus (P) in the form of additives such as phosphoric acid or monosodium phosphate. These P salts readily dissociate and are absorbed to a much greater extent compared to the more tightly protein-bound organic P present in natural sources such as beef, chicken, and egg yolks (> 90% absorption vs 40-60% intestinal absorption, respectively). Such additional bioavailable P increases serum P levels and urinary P excretion and decreases serum and urine calcium concentrations. These changes induce a secondary hyperparathyroidism, with its negative consequences for bone health.[10]

The pitfalls with this study, as with any observational study, is that the soda-stroke association cannot confer causality due to confounding from as yet unidentified and unmeasured factor(s). The association may also be an indirect one, linked by other disease processes that may be mitigated by dietary beverage choice including inflammation, endothelial dysfunction, and dyslipidemia. Further information regarding whether, what type, and how much soda consumption can affect stroke risk will depend upon randomized, controlled trial results.

In the meantime, we can all drink to our health by following the advice offered by Dr. William Osler in his 1893 *Principles and Practices of Medicine* text that "the sugar should be kept to a minimum."[11] ■

**References**


1. Ding EL, Mozaffarina D. Optimal dietary habits for the prevention of stroke. *Semin Neurol* 2006;26:11-23.
2. American Stroke Association. A Division of American Heart Association. AHA/ASA Guidelines for the Primary Prevention of Ischemic Stroke. Available at: http://stroke.ahajournals.org/content/37/6/1583.full.pdf+html. Accessed May 1, 2012.
3. Nielsen SJ, Popkin BM. Changes in beverage intake between 1977 and 2001. *Am J Prev Med* 2004;27:205-210.
4. Malik VS, et al. Sugar-sweetened beverages, obesity, type 2 diabetes mellitus, and cardiovascular disease risk. *Circulation* 2010;121:1356-1364.
5. Johnson RJ, et al. Potential role of sugar (fructose) in the epidemic of hypertension, obesity and the metabolic syndrome, diabetes, kidney disease, and cardiovascular disease. *Am J Clin Nutr* 2007;86:899-906.
6. Havel PJ. Dietary fructose: Implications for dysregulation of energy homeostasis and lipid/carbohydrate metabolism. *Nutr Rev* 2005;63:133-157.
7. Malik VS, et al. Sugar-sweetened beverages and risk of metabolic syndrome and type 2 diabetes: A meta-analysis. *Diabetes Care* 2010;33:2477-2483.
8. de Koning L, et al. Sugar-sweetened and artificially sweetened beverage consumption and risk of type 2 diabetes in men. *Am J Clin Nutr* 2011;93:1321-1327.
9. Lin J, Curhan GC. Associations of sugar and artificially sweetened soda with albuminuria and kidney function decline in women. *Clin J Am Soc Nephrol* 2011;6:160-166.
10. Sullivan CM, et al. Phosphorus-containing food additives and the accuracy of nutrient databases: Implications for renal patients. *J Ren Nutr* 2007;17:350-354.
11. Osler W. *The Principles and Practices of Medicine*. 2nd edition. Appleton NY: 1893:287-295.

# Tazarotene Foam, 0.1% (Fabior™)

***By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD***

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

THE FIRST RETINOID AS A TOPICAL FOAM HAS BEEN APPROVED by the FDA for the treatment of acne. Tazarotene is a synthetic, third-generation, polyaromatic, prodrug that binds to the retinoic acid receptors. Tazarotene is available in both gel and cream formulations. The foam is marketed by Stiefel as Fabior™.

## Indications

Tazarotene foam is indicated for the topical treatment of acne vulgaris in patients 12 years of age and older.[1]

## Dosage

Tazarotene is applied as a thin layer to the affected areas of the face and upper trunk once daily in the evening.[1]

Tazarotene foam is available as a 0.1% foam.

## Potential Advantages

The foam provides another formulation of tazarotene, in addition to the gel and cream.

## Potential Disadvantages

The propellant in the foam is flammable and the patient should avoid the presence of fire, flame, and smoking during and immediately following application. Tazarotene is a photosensitizer; therefore sun (actual or artificial) should be avoided. Most frequently reported adverse events are related to the site of application. These include irritation, dryness, erythema, and exfoliation.[1]

## Comments

The efficacy of tazarotene foam was evaluated in two randomized, double-blind, 12-week, vehicle-controlled studies in patients with moderate-to-severe acne vulgaris.[1] Eighty percent of subjects had moderate acne and 20% had severe acne. The mean number of lesions were 31.9 (inflammatory) and 47.8 (non-inflammatory). Subjects (n = 1485) were randomized to tazarotene foam or vehicle applied once daily. Efficacy endpoints were reduction in inflammatory lesion non-inflammatory lesion counts and the Investigator's Global Assessment (IGA). The latter is a 6-grade scale assessing disease severity. For the two studies, tazarotene reduced inflammatory lesion counts by 55% to 58% compared to 45% for the vehicle. Non-inflammatory lesions were reduced by 55% to 57% compared to 33% to 41% for vehicle. Twenty-eight to 29% of subjects showed a minimum of a 2-grade improvement compared to 13% to 16% for the vehicle. Adverse events were limited to application site. The most frequently reported adverse events compared to placebo were irritation (14% vs 1%), dryness (7% vs 1%), erythema, and exfoliation (6% vs < 1%). There are currently no published comparisons between tazarotene foam and cream or gel formulations or to other retinoids such as adapalene. The benefit compared to vehicle appeared similar to that reported for tazarotene cream and gel.[2,3]

## Clinical Implications

Tazarotene foam provides another formulation of a retinoid for moderate-to-severe acne. The cream and gel formulations have been available for more than a decade. Topical retinoids are mainstays of acne treatment.[4] The American Academy of Dermatology indicated that there is no consensus as to relative efficacy of the various retinoids. However, others have suggested that tazarotene may be more effective than adapalene, but adapalene may be better tolerated.[5-7] ■

## References

1. Fabior™ Prescribing Information. Research Triangle Park, NC: Stiefel Laboratories; May 2012.
2. Tazorac® Cream Prescribing Information. Irvine, CA: Allergan; February 2011.
3. Tazorac® Gel Prescribing Information. Irvine, CA: Allergan; March 2011.
4. Strauss JS, et al. Guidelines of care for acne vulgaris management. *J Am Acad Dermatol* 2007;56:651-663.
5. Thiboutot D, et al. Efficacy and tolerability of adapalene 0.3% gel compared to tazarotene 0.1% gel in the treatment of acne vulgaris. *J Drugs Dermatol* 2008;7(6 Suppl):s3-s10.
6. Thielitz A, et al. Topical retinoids in acne — an evidence-based overview. *J Dtsch Dermatol Ges* 2008; 6:1023-1031.
7. Leyden JJ, et al. Topical retinoids in inflammatory acne: A retrospective, investigator-blinded, vehicle-controlled, photographic assessment. *Clin Ther* 2005;27:216-224.

# CME Objectives

Upon completion of this educational activity, participants should be able to:

- 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;
- explain the advantages and disadvantages of new disease screening procedures.

# CME Questions

1. **Diagonal earlobe creases observed on physical examination:**
   a. are almost certainly of no clinical significance.
   b. appeared to be independently and significantly associated with increased prevalence, extent, and severity of coronary artery disease.
   c. are observed only in patients with type II diabetes mellitus.
   d. are interesting observations but should be ignored, especially in the younger age groups.

2. **Which statement best describes a known risk of taking an antibiotic?**
   a. Fluoroquinolone antibiotics are associated with an increased risk of cardiovascular death.
   b. Azithromycin use increases the risk of sudden cardiovascular death.
   c. Azithromycin use increases the risk of retinal detachment.
   d. The risk of cardiovascular death and retinal detachment from antibiotics is so small we should not be concerned about common use.

3. **Which of the following statements is true regarding metabolic effects of fructose?**
   a. It enhances lipogenesis.
   b. It is largely metabolized by the liver.
   c. It increases serum uric acid levels.
   d. All of the above

4. **Fructose undergoes extensive hepatic clearance.**
   a. True
   b. False

# CME Instructions

To earn credit for this activity, follow these instructions:

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

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

## UTI in Long-Term Care Facilities Among Older Adults

**Source:** Genao L, Buhr GT. *Ann Long-Term Care: Clin Care Aging* 2012;20:33-38.

Unless a dramatic demographic shift occurs, approximately one in four of us will reside in a long-term care facility (LTCF) during our lifetime. Among LTCF residents, 30-50% of antibiotic utilization is for urinary tract infections (UTIs), resulting in substantial expense, adverse drug reactions, and ever-growing populations of resistant bacteria.

The first guidelines for managing UTI in LTCF were issued in 1991. The McGeer criteria included fever, chills, dysuria, frequency, urgency, flank pain, suprapubic pain, change in urine character, worsening of mental or functional status, and new or increased incontinence. Unfortunately, these criteria (and their subsequent modification, known as the Loeb guidelines) had a sensitivity of only 30%, a positive-predictive value of 57%, and negative-predictive value of 61%. Further modifications of the Loeb guidelines have evolved into an algorithm with major and minor symptoms that have been shown to reduce false-positive diagnoses by 30% and antibiotic use by 20%.

Genao and Buhr do not support treatment of asymptomatic bacteriuria in the LTCF setting for older adults. They remind us of the merit of urine dipstick testing because of its strong negative-predictive value: A dipstick urine test negative for leukocyte esterase and nitrate has an essentially 100% negative-predictive value for the presence of UTI. Although not yet in widespread use, other biomarkers of bacterial infection are gaining support. For instance, serum procalcitonin has been studied as a marker of bacterial infection (including UTI) in young adults, and might perform equally well in older adults. ■

## Beyond Glucocentricity: Nonglycemic Effects of Incretin-Based Therapy

**Source:** Brown NJ. *J Am Soc Hypertens* 2012;6:163-168.

Although glucose control in diabetes has been consistently demonstrated to improve microvascular outcomes, no randomized clinical trial has shown favorable effects on macrovascular disease (stroke, MI, overall mortality). Whether the failure to achieve macrovascular risk reduction is secondary to adverse effects like weight gain, hypoglycemia, catecholamine activation, or other factors remains to be determined. In the mean time, clinicians would like to use agents that have favorable effects on glucose/A1c, but — at worst — neutral effects on cardiovascular risk factors.

The incretin class of agents is currently comprised of GLP-1 agonists (e.g., exenatide, liraglutide) and DPP4 inhibitors (e.g., linagliptin, saxagliptin, sitagliptin). Although both subgroups blunt glucagon and induce glucose-dependent insulin secretion, only the GLP-1 agonists have sufficient potency to also increase satiety and slow gastric emptying. Incretins are generally weight neutral (DPP4) or associated with weight loss (GLP-1). Accordingly, favorable lipid or blood pressure effects might be associated with incretins compared to other treatments that increase weight. The DPP4 enzyme has also been shown to be responsible for breakdown of some vasoactive peptides; hence, changes in blood pressure could be a direct effect of DPP4 inhibition. Because GLP-1 enhances endothelial function, any medication that augments GLP-1 would be anticipated to at least potentially favorably affect vascular function. We look forward to incretin clinical trials that will define the cardiovascular outcomes associated with this class of therapy. ■

## Home BP Monitoring May Assist BP Goal Attainment in the Elderly

**Source:** Cushman WC, et al. *J Am Soc Hypertens* 2012;6:210-218.

Although clinic blood pressure (CBP) has been the primary standard by which the majority of major clinical hypertension (HTN) trials have been measured, home BP (hBP) and ambulatory blood pressure monitoring (ABPM) correlate more closely with outcomes and target organ damage. With the advent of reliable, inexpensive, validated devices for home oscillometric BP measurement, national and international agencies now recommend routine inclusion of home BP monitoring for patients with HTN.

Cushman et al report on a trial in elderly hypertensives (men and women > age 70) which compared hBP monitoring with cBP monitoring (n = 128) over 16 weeks. They determined that hBP measurements were consistent with cBP.

Adherence to HTN medications is suboptimal. Utilization of hBP monitoring enables early detection of hypotension, facilitates dose titration (up or down), and may uncover otherwise unidentified insufficient durability of pharmacotherapy (i.e., nighttime measurements showing a waning of antihypertensive effect). As has been demonstrated in other populations, elderly patients can effectively and reproducibly use hBP, which may enhance long-term adherence. ■

**In Future Issues:**

**Drug, Patient, and Physician Characteristics Associated with Off-label Prescribing in Primary Care**