AHC Media

Internal Medicine

Evidence-based summaries of the latest research in internal medicine [ALERT]

Vol. 36, Issue 18, September 29, 2014
www.ahcmedia.com

ABSTRACT & COMMENTARY

Stopping Colonoscopy at Age 75 — Even With a History of Colon Cancer

By Joseph E. Scherger, MD, MPH

Vice President, Primary Care, Eisenhower Medical Center; Clinical Professor, Keck School of Medicine, University of Southern California, Los Angeles

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

SYNOPSIS: The incidence of colorectal cancer is much less in people > 75 years of age compared with ages 50-74, even in patients with a personal history of colon cancer or adenomatous polyps. Complication rates for colonoscopy are high in the elderly ≥ age 75 and in patients with comorbidities. Surveillance colonoscopy may be stopped in the advanced elderly and in comorbid elderly patients.

SOURCE: Tran AH, et al. Surveillance colonoscopy in elderly patients: A retrospective cohort study. *JAMA Intern Med* 2014; Aug 11. doi: 10.1001/jamainternmed.2014.3746. [Epub ahead of print.]

This robust study comes from Kaiser Permanente Southern California, an integrated delivery system and health plan caring for 3.6 million residents in Southern California. A Kaiser team of investigators performed a retrospective cohort study from 2001 through 2010 of patients undergoing surveillance colonoscopy with a history of colorectal cancer (CRC) or adenomatous polyps. A total of 27,763 racially diverse patients were identified and put into two groups, 22,929 in the group ages 50-74 years and 4834 in the group ages ≥ 75 years. The mean age of the younger group was 63 years and the older group was 79 years. Men and women were well represented. About 20% of the patients in both groups had a prior CRC history as opposed to a history of adenomatous polyps.

Cancers were found on colonoscopy in 368 patients in the younger group and in 5 patients among the older group. The rate of cancer detection was 3.61 per 1000 person years in the younger group compared with only 0.24 per 1000 person years in the older group ($P < 0.001$), showing that colon cancer was far less likely in the advanced elderly.

Financial Disclosure: *Internal Medicine Alert*'s editor, Stephen Brunton, MD, is a retained consultant for Abbott, AstraZeneca, Boehringer Ingelheim, Janssen, Lilly, Meda Pharmaceuticals, Novartis, Novo Nordisk, Sanofi, and Teva; he serves on the speakers bureau of AstraZeneca, Boehringer Ingelheim, Janssen, Lilly, 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.

Internal Medicine
Evidence-based summaries of the latest research in internal medicine [ALERT]

Internal Medicine Alert,
ISSN 0195-315X, is published monthly by
AHC Media, LLC
One Atlanta Plaza
950 East Paces Ferry Road NE, Suite 2850
Atlanta, GA 30326.
www.ahcmedia.com

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 550669,
Atlanta, GA 30355.

SUBSCRIBER INFORMATION
1-800-688-2421
customerservice@ahcmedia.com
www.ahcmedia.com

Editorial E-Mail: neill.kimball@ahcmedia.com
Questions & Comments
Please call Neill Kimball, Managing Editor, at (404) 262-5404.

Subscription Prices
United States:
Print: 1 year with free *AMA PRA Category 1 Credits*™: $349
Add $19.99 for shipping & handling.
Online only: 1 year (Single user) with ***free*** *AMA PRA Category 1 Credits*™: $299
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.
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.

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 48 *AMA PRA Category 1 Credits*™. Physicians should only claim 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 credits by the American Academy of Family Physicians. AAFP certification begins January 1, 2014. Term of approval is for one year from this date with the option of yearly renewal. Each issue is approved for 1 Prescribed credit. 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.

The American Osteopathic Association has approved this continuing education activity for up to 48 AOA Category 2-B credits.

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

A colonoscopy-related hospitalization within 30 days of the procedure occurred in 711 patients, with 527 patients in the older group compared with 184 patients in the younger group, a highly significant difference ($P < 0.001$). Hospitalizations were also common among patients with more comorbidities as measured by a Charlson index of 2 or more.

The authors conclude that future recommendations for colonoscopy surveillance in elderly patients should be individualized, with strong consideration given to advanced age and comorbidities.

■ COMMENTARY

Currently, the American College of Physicians recommends against further colonoscopy screening for adults ≥ age 75 years.[1] The U.S. Preventive Services Task Force guideline recommends individualized decision making about colorectal cancer screening between ages 75 and 85 years.[2] Colonoscopy is universally recommended for surveillance of patients with a personal history of adenomatous polyps or CRC. That may change based on this study.

Determining what screening should be done in elderly populations is especially important since this age group is rapidly growing, projected to double in the United States between 2012 and 2060.[3] Given the variability in patient health at age 75, decision making should be individualized. These guidelines are helpful, especially for patients who want information for shared decision making. Patients and physicians are still getting comfortable with the concept of discontinuing cancer screening based on age.

I find that some patients are relieved to hear that they no longer need screening while others are very concerned about stopping, especially if they are in good health. Now that DNA stool testing has been approved by the FDA for colon cancer screening, there is another option to be considered rather than the expensive and invasive colonoscopy. Most physicians use common sense and do not perform cancer screening in nursing home patients and those with dementia. Where to draw the line with cancer screening in the advanced elderly will always be individualized, but it is very helpful to have high-quality research and clinical guidelines that justify and even encourage restraint. ■

REFERENCES
1. Qaseem A, et al. Screening for colorectal cancer: A guidance statement from the American College of Physicians. *Ann Intern Med* 2012;156:378-386.
2. U.S. Preventive Services Task Force. Screening for colorectal cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2008;149:627-637.
3. U.S. Census Bureau Projections Show a Slower Growing, Older, More Diverse Nation a Half Century from Now. http://www.census.gov/newsroom/releases/archives/population/cb12-243.html. Accessed Sept. 5, 2014.

ABSTRACT & COMMENTARY

Bring on the Butter and the Eggs

By Barbara A. Phillips, MD, MSPH

Professor of Medicine, University of Kentucky; Director, Sleep Disorders Center, Samaritan Hospital, Lexington

Dr. Phillips serves on the speakers bureau for PotomaCME.

SYNOPSIS: People who were randomized to a low-carbohydrate diet lost more weight than those who were randomized to a low-fat diet over a year. They also had greater improvements in risk factors for cardiovascular disease.

SOURCE: Bazzano LA, et al. Effects of low-carbohydrate and low-fat diets: A randomized trial. *Ann Intern Med* 2014;161:309-318.

These Louisiana investigators recruited 148 people from the general population for this study. To be included, participants had to be obese (body mass index [BMI] > 30 kg/m^2) and could not have cardiovascular disease, type 2 diabetes, or kidney disease, or be using prescription weight-loss medications. On

average, the participants were about 49 years old and their mean BMI was about 35 kg/m^2. A large majority (88%) were women, and 51% were black.

People in the low-carbohydrate diet group were asked to maintain an intake of digestible carbohydrates (total carbohydrate minus total fiber) of < 40 g/day. Those on the low-fat diet were told to get < 30% of their daily energy intake from total fat (with < 7% from saturated fat) and 55% from carbohydrates, based on National Cholesterol Education Program guidelines. Importantly, neither diet included a specific calorie goal. Participants were told not to change their physical activity levels during the intervention. All participants got nutritional counseling with a dietician, as well as a handbook that included recipes, sample menus, food lists, shopping lists, meal planners, and guides on reading nutrition labels. They also got one low-carbohydrate or low-fat meal replacement (bar or shake) per day for the entire study.

Data collection included a detailed medical history. Anthropometric measures and blood and urine samples were collected at the screening visit and each follow-up visit. Follow-up visits were at 3, 6, and 12 months, and retention rates were high. Body weight, height, body composition, and blood pressure were precisely measured.

Dietary logs demonstrated that although baseline reported dietary composition in the two groups was similar, the reported intake of total carbohydrates was indeed significantly higher and fat intakes were significantly lower in the low-fat group at 12 months. Physical activity and total calorie intake levels were similar throughout the study for both groups.

The low-carbohydrate group lost more weight than the low-fat group at 3, 6, and 12 months. At 12 months, those in the low-carbohydrate group lost 3.5 kg (about 7 pounds) more than those in the low-fat group. They also had larger reductions in fat mass and greater proportional increases in lean mass. Although all participants had significantly reduced waist circumference, reductions were greater in the low-carbohydrate group at 3 and 6 months.

At 12 months, high-density lipoprotein (HDL) cholesterol increased significantly more in the low-carbohydrate group than in the low-fat group and ratios of total/HDL cholesterol decreased significantly only among participants in the low-carbohydrate group. Serum levels of triglycerides also decreased significantly in both groups, but the decrease was greater in the low-carbohydrate group. Similarly, participants in the low-carbohydrate group had significantly greater decreases in C-reactive protein levels than those in the low-fat group. Participants in the low-carbohydrate group had significant decreases in estimated 10-year Framingham risk score for coronary heart disease at 6 and 12 months, whereas those in the low-fat group did not.

Serum levels of insulin and creatinine decreased significantly and approximately equally in each group. There were no significant changes in either group for blood pressures, glucose, total cholesterol, and LDL cholesterol. There were no significant adverse events, and very little difference in reported adverse events between the groups, except more people on the low-fat diet reported headaches at 3 months.

■ COMMENTARY

The big news here is that the low-carbohydrate diet trumped the low-fat diet, not just in the amount of weight lost over a year's time, but also in most measures of risk factors for cardiovascular disease. Is it possible that the days of blood-letting and leaches are still with us? For years, venerable organizations within the medical establishment have been promulgating low-carbohydrate diets for weight loss and presumable reduction in cardiovascular risk.[1-3] (And over that same period of time, rates of overweight and obesity in this country have soared).

Nearly coincident with the publication of this paper, a meta-analysis appeared in *JAMA* of 48 trials including more than 7000 people.[4] This analysis found that low-carbohydrate diets were associated with greater weight loss than low-fat diets, but the difference in weight loss between proprietary low-carbohydrate diets was small.

This study from Bazzano et al is consistent with several other trials.[4,5] What accounts for differences in weight loss by diet is not understood, but a recent study showed that low-carbohydrate diets may have a more favorable effect on resting energy expenditure and total energy expenditure (i.e., calorie burning) than low-fat diets.[6] The current study supports this notion, since dietary recall between the two groups found no difference in overall caloric intake between the two groups.

The current study is particularly important because of the inclusion of a large number of black participants, who have a higher prevalence of both obesity and cardiovascular disease than whites.[7] There were no important differences in the responses to the diets in blacks and whites in this study.

This paper also helped to debunk the prevalent concern that low-carbohydrate diets have the potential to elevate LDL cholesterol levels. This study also found no change in LDL cholesterol level among

participants in either group, with no significant difference between the groups.

In contrast to many previous studies of this issue, this trial included people without diabetes or cardiovascular disease at baseline. While it is possible that the two different dietary approaches might have different effects or outcomes than were found here in sicker patients (i.e., when the horse is already out of the barn), it is unlikely. And prevention is preferable to palliation.

Because cardiovascular disease is the leading cause of death in the United States, this study has important public health implications. Perhaps first among them is to stop recommending a low-fat diet. The authors of the recent meta-analysis in *JAMA* concluded, "This supports the practice of recommending any diet that a patient will adhere to in order to lose weight."[4] Indeed. ■

REFERENCES

1. Krauss RM, et al. AHA Dietary Guidelines: revision 2000: A statement for healthcare professionals from the Nutrition Committee of the American Heart Association. *Circulation* 2000; 102:2284-2299.
2. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;106:3143-3421.
3. Stone NJ, Van Horn L. Therapeutic lifestyle change and Adult Treatment Panel III: Evidence then and now. *Curr Atheroscler Rep* 2002;4:433-443.
4. Johnston BC, et al. Comparison of weight loss among named diet programs in overweight and obese adults: A meta-analysis. *JAMA* 2014;312:923-933.
5. Hu T, et al. Effects of low-carbohydrate diets versus low-fat diets on metabolic risk factors: A meta-analysis of randomized controlled clinical trials. *Am J Epidemiol* 2012;176 Suppl 7:S44-54.
6. Ebbeling CB, et al. Effects of dietary composition on energy expenditure during weight-loss maintenance. *JAMA* 2012;307: 2627-2634.
7. http://www.cdc.gov/obesity/data/adult.html. Accessed Sept. 7, 2014.

ABSTRACT & COMMENTARY

Good Ol' Vitamin C: Does It Deserve Another Look for Your Heart?

By David Kiefer, MD

Research Fellow, Department of Family Medicine, University of Wisconsin; Clinical Assistant Professor of Medicine, Arizona Center for Integrative Medicine, University of Arizona

Dr. Kiefer reports no financial relationships relevant to this field of study. This article originally appeared in the August 2014 issue of *Integrative Medicine Alert*.

SYNOPSIS: A meta-analysis and systematic review found vitamin C supplementation improved endothelial function in patients with diabetes, atherosclerosis, and heart failure.

SOURCE: Ashor AW, et al. Effect of vitamin C on endothelial function in health and disease: A systematic review and meta-analysis of randomised controlled trials. *Atherosclerosis* 2014;235:9-20.

This meta-analysis and systematic review was undertaken to investigate the clinical effects of supplemental vitamin C on endothelial function. Vitamin C's effect as a free radical scavenger and, through its activity as an enzyme co-factor, maintaining the vasodilator nitric oxide's blood levels, created a compelling mechanistic connection to vascular health and disease, underpinning the rationale for this analysis.

The authors used Cochrane's methodology to review four major databases (PubMed, Embase, Scopus, and Cochrane Library) up to May 2013 for randomized, controlled trials in adults that examined the effect of vitamin C on a variety of search terms to capture cardiovascular effects and endothelial function. To assess endothelial function, this meta-analysis analyzed parameters from the clinical trials including flow-mediated dilation, forearm blood flow, and pulse wave analysis. All told, 9685 studies were located from the database searches plus four from other sources, though 9458 were excluded after title and abstract screening. Of the remaining 231 studies, 179 did not meet the inclusion criteria of adult subjects, randomized controlled trial, vitamin C as the intervention, and an endothelial functional measurement using ultrasound, venous occlusion plethysmography, pulse wave velocity, iontophoresis, or pulse amplitude tonometry. The remaining 52 studies were included in the qualitative analysis of

the systematic review. Seven of these studies did not have endothelial measurements that were applied appropriately, so only 44 trials were included in the quantitative aspect of the meta-analysis.

The 52 studies (27 orally dosed vitamin C, 18 intravenous, and 7 not detailed) represented 1324 research subjects (75% male, median age 51.1 years). Qualitatively, two-thirds of the studies reported a significant improvement in endothelial function with the administration of vitamin C; one-third did not. The quantitative analysis of the 44 studies corroborated the significant improvement in endothelial function with a standardized mean difference of 0.50 (95% confidence interval [CI], 0.34-0.66; $P < 0.001$), though there was a moderate amount of heterogeneity between the studies. Subgroup analyses showed no effect of vitamin C supplementation in studies on healthy volunteers (smokers and non-smokers) or people with hypertension. However, supplementation benefited people with diabetes, atherosclerosis, heart failure, and those who underwent experimentally induced endothelial dysfunction using glucose, lipids, endotoxins, organic nitrite, insulin, and methionine.

With respect to doses, lower doses (90-500 mg daily) of vitamin C supplementation did not affect endothelial function ($P < 0.1$), whereas higher doses (501-4000 mg daily) did lead to a statistically significant improvement in endothelial function ($P <$ 0.01-0.001), a correlation that was also seen in the regression analysis on vitamin C dose and magnitude of effect. With respect to safety, none of the studies analyzed that used a vitamin C dose > 2 g daily (the Institute of Medicine upper limit) reported any adverse effects. In the discussion, the authors tie their results into known mechanisms of action, namely the lessening of oxidative damage and vascular inflammation that leads to healthy endothelial function and a lowering of the risk of cardiovascular disease.

■ COMMENTARY

This is an important analysis, extending the findings from observational studies showing a connection between vitamin C intake and improved cardiovascular health;[1] for example, the authors quote results affirming that 700 mg of vitamin C daily is associated with a 25% decrease in the risk of coronary heart disease, likely by affecting the inflammatory process and the pathophysiology of atherosclerotic plaque disruption. However, also quoted is the fact that randomized controlled trials generally have been negative, possibly due to genetic effects, vitamin C status, and confounding effects that were unaccounted for. The results here — a dose-dependent effect on the vessels themselves — adds to mechanistic data and begins the process of trying to determine who might benefit most from vitamin C therapy.

What can we conclude from who might benefit most from vitamin C therapy? The results presented here point toward those with experimentally induced endothelial dysfunction, not usually the demographic seen in most clinics. In those studies, supraphysiologic dosing (240-2600 mg) was used short-term, another uncommon intervention. Healthy individuals, presumably with normal endothelial function and/or adequate vitamin C status, did not benefit from supplementation. The authors suggest a focus on vitamin C dosing of 500 mg daily or more in people with endothelial dysfunction, low vitamin C status, or increased oxidative stress; again, clinically it may be difficult to know definitively who falls into that category. Also, this meta-analysis focused on randomized controlled trials of supplemental, not dietary, vitamin C. As with other vitamins, the clinical results seen for supplementation can differ significantly from a reliance of vitamins and minerals in food as shown in dietary studies. Interestingly, in this study, studies involving healthy smokers did not show an endothelial benefit, even given the oxidative stress imparted by tobacco smoke. It is true, as the authors conclude, that teasing out all of these effects would require a well-designed, randomized, controlled trial, but, until then, given its relative safety and affordability, there seems to be little reason not to recommend this well-known nutrient to most, if not all, of the population. ■

REFERENCE

1. Mangge H, et al. Antioxidants, inflammation and cardiovascular disease. *World J Cardiol* 2014;6:462-477.

PHARMACOLOGY UPDATE

Empagliflozin Tablets (Jardiance®)

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 sodium glucose co-transporter 2 (SGLT2) has been approved by the FDA. Empagliflozin follows canagliflozin (Invokana) and dapagliflozin (Farxiga)as the third entry in this group. These drugs reduce plasma glucose levels by reducing renal absorption of filtered glucose. Empagliflozin is marketed by Boehringer Ingelheim as Jardiance.

INDICATION

Empagliflozin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[1]

DOSAGE

The recommended dose is 10 mg once daily in the morning.[1] It may be taken without regard to meals. The dose may be increased to 25 mg. The drug should not be initiated if eGFR is below 45 mL/min/1.73 m^2 and it should be discontinued if the eGFR falls below 45 mL/min/1.73 m^2.

POTENTIAL ADVANTAGES

Empagliflozin does not appear to have any important clinical interactions with CYP450 isoforms, UGT1A1, P-glycoprotein and breast cancer resistant protein (BCRP), and human uptake transporters.[1] Empagliflozin may be used in patients with hepatic impairment.[1]

POTENTIAL DISADVANTAGES

As a class, the SGLT2 inhibitors cause intravascular volume contraction. Symptomatic hypotension may occur particularly in the elderly, those with renal impairment, those with low systolic blood pressure, and those on diuretics.[1]

COMMENTS

Empagliflozin was studied as monotherapy as well as in combination with metformin, sulfonylurea, pioglitazone, and insulin.[1] In the monotherapy study, subjects with type 2 diabetes (n = 676) with an HbA1c between 7-10% were randomized to empagliflozin 10 mg, 25 mg, or placebo. At week 24, empagliflozin showed a difference from placebo of 0.7% (97.5% confidence interval [CI], -0.9 to -0.6) for 10 mg and -0.9% (97.5% CI, -1.0 to -0.7) for 25 mg. Fasting plasma glucose showed a difference from placebo of -31 mg/mL (95% CI, -37 to -26), and -36 mg/mL (95% CI, -42 to -31), respectively. There was a significant loss in body weight of 2.5-2.8 kg with the drug. Systolic blood pressure was significantly reduced by 2.6 mmHg relative to placebo. The addition of empagliflozin to metformin, metformin plus sulfonylurea, pioglitazone, or insulin showed a HbA1c difference from placebo of about -0.6% in previously inadequately controlled diabetics. In a 52-week study, there was no significant difference in reduction of HbA1c between empagliflozin or glimepiride when added to metformin in previously inadequately controlled subjects. The most common adverse events were urinary tract infections (7-9% vs 7.6% for placebo) and female genital mycotic infections (5.4-6.4% vs 1.5% for placebo).

CLINICAL IMPLICATIONS

Empagliflozin is the third SGLT2 inhibitor to come on the market. These drugs provide a new mechanism of action to improve glycemic control with modest decreases in systolic blood pressure and body weight. There are no published comparative studies among the three agents. An indirect comparison of monotherapy studies suggests that the magnitude of effect (reduction in HbA1c and fasting glucose) may be similar to dapagliflozin but numerically less than canagliflozin.[2,3] This may be related to the additional inhibition of SGLT1 with canagliflozin, delaying intestinal glucose absorption.[4] Dapagliflozin has been linked to possible bladder cancer risk. Canagliflozin is not recommended in patients with severe hepatic impairment. Empagliflozin is being evaluated in an international study in type 2 diabetics with high cardiovascular risk for long-term cardiovascular safety as well as potential benefits on macro-/microvascular outcomes with results expected in 2015.[5] Empagliflozin has the lowest wholesale cost at $301 per 30-day supply compared to $312 for dapagliflozin and $374 for canagliflozin. ■

REFERENCES

1. Jardiance Prescribing Information. Ridgefield, CT: Boehringer Ingelheim; August 2014.
2. Invokana Prescribing Information. Titusville, NJ: Janssen Pharmaceuticals, Inc.; May 2014.
3. Farxiga Prescribing Information. New York City, NY: Bristol-Myers Squibb; August 2014.
4. Polidori D, et al. Canagliflozin lowers postprandial glucose and insulin by delaying intestinal glucose absorption in addition to increasing urinary glucose excretion. *Diabetes Care* 2013; 36:2154-2161.
5. Zinman B, et al. Rationale, design, and baseline characteristics of a randomized, placebo-controlled cardiovascular outcome trial of empagliflozin. *Cardiovasc Diabetol* 2014;13:102.

By Louis Kuritzky, MD

Clinical Assistant Professor, University of Florida, Gainesville

Dr. Kuritzky is a retained consultant for AbbVie, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Chelsea, Daiichi Sankyo, Forest Pharmaceuticals, Janssen, Lilly, Novo Nordisk, Pfizer, and Sanofi.

High-dose Influenza Vaccine vs Standard-dose for Seniors

Source: DiazGranados CA, et al. *N Engl J Med* 2014;371:635-645.

The highest morbidity and mortality consequences of influenza occur in senior citizens. The efficacy of "standard" flu vaccine varies depending on the outcome that is examined. For instance, as has been best demonstrated in nursing home trials, even when standard-dose flu vaccine fails to prevent clinical disease, it mitigates disease severity enough to reduce mortality. Evolving vaccines, such as the high-dose influenza vaccine, are trying to improve on the already impressive results of earlier versions.

High-dose influenza vaccine (HDVax) contains four times the amount of hemagglutinin as standard-dose vaccine (SDVax). It has already been established that higher antibody titers are achieved with HDVax than SDVax, but whether that translates into improved protection from influenza has not been fully clarified.

This very large randomized, double-blind, active-controlled trial (n = 31,989) compared HDVax vs SDVax through two influenza seasons in North America. Both vaccines were highly effective, since < 2% of recipients of either vaccine contracted clinical influenza. HDVax was found to be superior to SDVax for the primary trial endpoint (acquisition of documented clinical influenza), showing a 24% lower frequency than SDVax. As previously demonstrated, higher antibody levels were also achieved with HDVax.

Before we celebrate the 24% risk reduction with HDVax, recall that this is a *relative* risk reduction. The *absolute* risk reduction was *very small* (0.5%), translating into a number needed to treat of 200. Whether using HDVax instead of SDVax is a worthwhile investment — since this trial indicates that 200 persons must be treated with HDVax instead of SDVax to prevent one case of clinical influenza — will require further consideration, especially since there was no difference in mortality between the groups. ■

Is Type 2 Diabetes Induced by Psychological Stressors?

Source: Virtanen M, et al. *Diabetes Care* 2014;37:2091-2097.

Although the commonly recognized primary predictors of type 2 diabetes (T2DM) include obesity and insulin resistance, it is less clear why some folks with obesity and/or insulin resistance progress to T2DM and others do not. Could psychological stress be a predictor? Results from the Whitehall II Cohort Study suggest that this is indeed the case.

The Whitehall II Cohort Study is comprised of adults employed by the London, England, department of civil service (n = 6895 men and 3413 women) followed prospectively. Data were obtained from a subpopulation of this cohort during various cycles (average observation cycle = 5.46 years) from 1991-2009 to ascertain incidence of T2DM in previously non-diabetic subjects. Psychological stress was measured with the General Health Questionnaire (GHQ-30); a GHQ-30 score > 4 was categorized as "stressed." Proclivity to develop diabetes was further stratified into quartiles by the Framingham Offspring T2DM Risk Score (FOTRS).

Among prediabetic adults in the highest quartile of FOTRS, the adjusted odds ratio for developing T2DM was more than 2-fold greater in stressed individuals than in persons with low stress scores. The mechanism(s) by which stress increases progression to T2DM is not understood. The authors posit that interventions designed to prevent progression from prediabetes to diabetes might well show greater consideration for the potential impact of emotional stressors like depression and anxiety. ■

Distinguishing Malignant Melanoma from Benign Lesions with a Skin Patch Test

Source: Gerami P, et al. *J Am Acad Dermatol* 2014;71:237-244.

All of us in primary care who have been faced with the dilemma of ascertaining whether a particular lesion on the skin of a patient is benign or malignant know that, in the absence of a biopsy, we can rarely respond with certainty. Of course, we would rather *not* biopsy a benign lesion unnecessarily because of time, expense, discomfort, and cosmetic concern for the patient. On the other hand, we don't *ever* want to mistakenly allow a cutaneous malignancy, particularly malignant melanoma, to stay on the skin without being identified.

Gerami et al report on the use of a skin patch to diagnose melanoma on the basis of mRNA profiles. Having obtained mRNA "signatures" from multiple prior cases of malignant melanoma in their study sample, subjects had an adhesive patch placed above the lesion in question, which was vigorously rubbed to create adhesion of skin cells to the patch, which were then analyzed for mRNA. After removing the patch, lesions were biopsied to confirm their pathology.

The sensitivity of skin patch-retrieved mRNA diagnosis for melanoma was 97.6%. Hence, having a negative skin patch mRNA test essentially excluded melanoma. The authors point out that such technology could meaningfully reduce unnecessary skin biopsies for questionable lesions. ■

CME INSTRUCTIONS

To earn credit for this activity, please follow these instructions:
1. Read and study the activity, using the provided references for further research.
2. Scan the QR code to the right or log on to **www.cmecity.com** to take a post-test; tests can be taken after each issue. 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 test, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.

CME QUESTIONS

1. The Kaiser Permanente Southern California study of surveillance colonoscopy in elderly patients showed which of the following?

a. Colonoscopy should be discontinued in patients with a history of colorectal cancer or polyps starting at age 80 years.

b. Patients < age 75 should be screened for colon cancer regardless of comorbidities.

c. Patients with a previous history of colorectal cancer should have colonoscopy screening indefinitely.

d. Even in patients with a history of colorectal cancer or polyps, colonoscopy screening may be stopped at age 75 and in patients with significant comorbidities.

2. In a recent randomized, controlled trial of low-fat vs low-carbohydrate diets and cardiovascular risk, the low-carbohydrate diet, compared with the low-fat diet, resulted in which of the following at 12 months?

a. Greater weight loss

b. Greater reduction in blood pressure

c. Greater prevalence of adverse events

d. Greater reduction in LDL levels

3. Which of the following research participants did not benefit from vitamin C supplementation?

a. Smokers

b. People with diabetes

c. People with atherosclerosis

d. People with heart failure

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.

[IN FUTURE ISSUES]

OnabotulinumtoxinA for Treatment of Chronic Migraines

Prognostic Value of Fasting vs Nonfasting Low-Density Lipoprotein Cholesterol Levels on Long-Term Mortality: Insight from the National Health and Nutrition Examination Survey III (NHANES-III)