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INSIDE

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The Broken Heart: It CAN Be Mended

ABSTRACT & COMMENTARY

By Barbara A. Phillips, MD, MSPH

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Dr. Phillips serves on the speakers bureaus for Cephalon, Resmed, and Respironics.

Synopsis: *The authors advocate that cardiovascular magnetic resonance imaging using specific criteria may be useful as a diagnostic tool for patients with stress cardiomyopathy at the time of acute clinical presentation.*

Source: Eitel I, et al. Clinical characteristics and cardiovascular magnetic resonance findings in stress (takotsubo) cardiomyopathy. *JAMA* 2011;306:277-286.

These investigators set out to learn more about the clinical presentation and outcomes of stress cardiomyopathy (also known as Takotsubo cardiomyopathy) in a multicenter study in Europe and North America. Potential patients for inclusion in the study were recruited at the time of initial hospitalization. The evaluation included electrocardiogram (ECG), transthoracic echocardiogram, blood sample analysis, coronary angiogram and ventriculogram, as well as cardiovascular magnetic resonance imaging. The diagnosis of stress cardiomyopathy was defined as: 1) an acute cardiac event typically presenting with chest pain and/or shortness of breath; 2) transient systolic dysfunction with marked left ventricular (LV) contraction abnormality extending beyond a single coronary perfusion bed; 3) absence of significant (> 50%) obstructive coronary artery disease or angiographic evidence of acute plaque rupture; 4) new ECG abnormalities (either ST elevation or T-wave inversion) or modest elevation in cardiac troponin level; 5) absence of pheochromocytoma; and 6) absence of myocarditis or typical ischemic transmural late gadolinium enhancement (LGE) on cardiovascular magnetic resonance imaging.[1] One to 6 months after the acute event, patients with suspected stress cardiomyopathy were

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readmitted for clinical evaluation and cardiovascular magnetic resonance imaging follow-up in order to confirm that diagnosis. Some participants chose not to undergo repeat imaging, and had echocardiography instead, but the cohort is remarkably well-studied.

Over a 5-year period, 256 patients were recruited, and most (93%) had cardiovascular resonance imaging performed shortly after admission. Patients who were ultimately diagnosed with stress cardiomypathy had a mean age of 69 years, and 89% were women. Most (207) of these women were postmenopausal. Men accounted for 11% of cases, and there were no age differences between men and women. Most (88%) of the patients reported symptoms consistent with acute coronary syndrome (ACS) at their initial presentation. Among those who did not, the acute event was most likely characterized as either syncope (n = 9 [4%]) or asystole (n = 3; [1%]). The rest were admitted for suspected ACS detected during monitoring of noncardiac conditions because of new ECG abnormalities, acute onset of chest pain, and/or positive troponin levels.

Most of the patients (71%) could identify a significant stressful event that happened within 48 hours of clinical symptoms. These events were emotional stress in 77 (30%) and physical stress in 105 (41%).

At initial presentation, ECGs showed abnormalities in 222 patients (87%). The initial troponin T level was typically only mildly increased in 231 patients (90%). No relation was evident between ballooning patterns seen on the imaging studies and troponin levels, age, sex, or reported stress trigger.

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

All 256 patients underwent cardiac catheterization at initial presentation. Left ventriculography revealed typical apical ballooning in 210 (82%), midventricular ballooning in 44 (17%), and an inverted, basal pattern in 2 (1%). Of note, most (75%) patients had healthy coronary arteries. Of the remainder, only 6% had coronary artery stenosis of 75% or more; and the areas of coronary artery stenosis did not correspond to the area of wall motion abnormality seen on magnetic resonance imaging. The remaining 47 patients (18%) had only mild coronary atherosclerosis. Two patients (1%) had spontaneous coronary spasm. No patient had cardiovascular plaque rupture.

Cardiovascular magnetic resonance imaging detected ballooning patterns with moderate to severe reduction of LV function in all patients (mean LV ejection fraction, 47.7%). Biventricular ballooning was observed in 81 patients (34%). Interestingly, LV ejection fraction was lower than in patients without RV involvement. Patients with biventricular ballooning were older (mean, 73.4 vs 66.5 years) and had significantly more frequent preceding stressful events. Myocardial edema was visible on cardiovascular resonance imaging in 162 of 199 patients (81%) with the regional distribution pattern matching the distribution of LV dysfunction. LGE (thought to be a marker of subtle fibrosis) was uncommon and did not correlate with clinical presentation. Pleural effusions were common (33%), as were pericardial effusions (43%).

Initially, most patients were treated using standard cardiovascular medications for ACS (aspirin, clopidogrel, heparin, beta-blockers, angiotensin-converting enzyme inhibitors, vasodilators, and diuretics). After exclusion of coronary artery stenosis, the patients received standard supportive care for congestive heart failure with beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, diuretics, and aldosterone antagonists. In seven patients (3%) with severe hemodynamic compromise, an intra-aortic balloon pump was implanted. Four patients had thrombi, and were treated with warfarin with no subsequent events. Four patients (3 women and 1 man) died in the hospital. Causes of death in these patients were ventricular fibrillation (n = 2), cardiogenic shock (n = 1), and hypoxic brain injury (n = 1). Of these, three patients had apical and one patient had midventricular ballooning. No relation was evident between in-hospital outcome and ECG pattern, troponin level, or clinical features. Another four patients died during the follow-up period.

Among the remaining 248 patients, a complete clinical follow-up including imaging and/or echocardiography for confirmation of LV function recovery was available.

Follow-up echocardiography and cardiovascular magnetic imaging showed normalization of LV ejection fraction in all patients, and end-diastolic and end-systolic volume decreased.

■ **COMMENTARY**

This study was largely focused on cardiovascular magnetic resonance imaging in stress cardiomyopathy, but the authors helped us to expand our knowledge of this newly-described syndrome. Stress cardiomyopathy was first reported in Japan as takotsubo cardiomyopathy. It is characterized by acute, profound, but reversible left ventricular dysfunction in the absence of significant coronary artery disease, triggered by acute emotional or physical stress.[1-4] This phenomenon is identified by a distinctive imaging pattern of "apical ballooning" and has previously been reported to primarily affect postmenopausal women. Most patients have a clinical presentation similar to that of ACS. Recent studies revealed a prevalence of approximately 2% of patients presenting with ACS in the United States and Europe.[1,4] Enhanced sympathetic activity is believed to play a causal role in the transient myocardial dysfunction, and the prognosis is generally considered favorable.[1,4]

The current study is a large multicenter trial which used exquisite imaging techniques and careful follow-up. This carefully-described group of patients had a considerably broader clinical profile than previously reported, including men, some younger individuals, and some patients who could not identify a precipitating physical or emotional stress. The authors also advocate that cardiovascular magnetic resonance imaging using specific criteria may be useful as a diagnostic tool for patients with stress cardiomyopathy at the time of acute clinical presentation; they note that those with biventricular ballooning were more likely to have longer hospitalizations, markers of heart failure (as reflected by a lower LV ejection fraction and a high incidence of bilateral pleural effusions), and older age, and thus biventricular ballooning may be an important prognostic marker.

An important take home message from this study is that the absence of an identifiable stressful event does not rule out the diagnosis of stress cardiomyopathy. And, in this study, many more patients had a physical than an emotional stress as the precipitating event, contrary to the common notion that emotional stress is generally the trigger. The authors note, "…preceding stress is not evident in every case, and it would therefore seem inappropriate to assume a common trigger among all...patients." Clearly, we still have much to learn about the Broken Heart Syndrome. ■

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Beware of the Single Blood Pressure

ABSTRACT & COMMENTARY

By Joseph E. Scherger, MD, MPH

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

Synopsis: *Single blood pressure (BP) measurements are not reflective of the average BP 20% of the time. A series of BPs should be averaged for medical decision making. A series of home BP recordings is more accurate than those in the office for assessing the control of BP among hypertensive patients.*

Source: Powers BJ, et al. Measuring blood pressure for decision making and quality reporting: Where and how many measures? *Ann Intern Med* 2011;154:781-788.

HYPERTENSION IS THE MOST COMMON CHRONIC ILLNESS IN adults and arguably the most important risk factor for coronary heart disease and stroke. Unlike other chronic diseases, hypertension has no laboratory measurement for diagnosis — we rely on taking blood pressures (BPs).

BPs vary moment to moment and many factors can result in an abnormal reading, usually with higher values, such as the "white coat" effect, patients not being at rest, and poor technique. In the office, as patients come for preventive care and return visits, we are often in the situation of making medical decisions on their treatment based on one recording. Recent studies have shown that all patients with proven or suspected hypertension should obtain a series of BP recordings away from the medical office, referred to as ambulatory blood pressure monitoring, to guide medical decision making.[1]

This study done at the VA Medical Center associated with Duke University followed 444 veterans with hypertension, mostly men, over 18 months. A total of 111,181 BP measurements were obtained in three settings: the office, at home, and as part of the research protocol. All measurements were made using automated equipment. Each setting showed substantial variation in the results, such as a range between 120 and 157 in systolic BP. The patients "true" BP was calculated by taking the average BP over time. Regardless of setting, a single BP recording was considered inaccurate about 20% of the time.

Interestingly, the patients' BPs were considered under control 68% of the time in the research setting, 47% based on the home recordings, and only 28% based on the clinic measurements.

■ **COMMENTARY**

Measuring the quality of care in chronic disease is of vital importance in primary care. Compared with diabetes and hyperlipidemia, measuring outcomes in hypertension is fraught with error due to the unreliability of BP recordings. As shown in this study, our clinic recordings may be the worst for proper medical decision making.

All patients with known or suspected hypertension should have equipment at home for measuring BPs with training and evaluation of the equipment for accuracy. Medical decision making should be made by looking at a series of BPs over time and not on the single recording we obtain in the medical office. It is time for this practice to become axiomatic in primary care. ■

Reference

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Something's Fishy — DHA and Prostate Cancer

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD

Clinical Assistant Professor, School of Medicine, University of North Carolina, Chapel Hill, NC, and Visiting Assistant Professor, University of Arizona, College of Medicine, Tucson, AZ; he reports no financial relationships relevant to this field of study.

This article originally appeared in the August 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, WA. Dr. Kiefer reports no financial relationships relevant to this field of study.*

Synopsis: *In a shocking series of findings, this well-done prospective study showed that in men older than age 55 years a higher proportion of serum omega-3 fatty acids, specifically DHA, actually may increase the risk for high-grade prostate cancer.*

Source: Brasky TM, et al. Serum phospholipid fatty acids and prostate cancer risk: Results from the Prostate Cancer Prevention Trial. *Am J Epidemiol* 2011;173:1429-1439.

DATA SUGGEST THAT THE OMEGA-3 FATTY ACIDS FOUND in fish oils may help prevent a variety of cancers, including prostate cancer, with the most likely mechanism being modulation of inflammation. The researchers behind this prospective, nested case-control trial were interested in furthering investigation in this area, working from the hypothesis that higher serum omega-3 fats would be associated with a lessened incidence of prostate cancer, and that high serum concentrations of omega-6 and *trans* fatty acids would be tied to an increased risk.

The study comes out of the Prostate Cancer Prevention Trial, a randomized, placebo-controlled trial that evaluated the effect of finasteride on prostate cancer risk (of note, results suggested that finasteride reduced the risk of prostate cancer; however, cancers that developed in those on the medication were more aggressive). Subjects were men older than 55 years with no history of antecedent cancer (save for non-melanoma skin cancer) or severe benign prostatic hyperplasia; prostate-specific antigen concentrations of ≤ 3.0 ng/mL; and normal digital rectal examination. Nearly 19,000 men receiving care out of 221 U.S. medical centers were randomized to receive either finasteride or placebo. Over the course of the 7-year study, men underwent annual prostate-specific antigen and digital rectal examination testing. Men who had an abnormal digital rectal examination or finasteride-adjusted prostate-specific antigen result ≥ 4.0 ng/mL were recommended for prostate biopsy. At the final study visit, all men who had not been diagnosed with prostate cancer also were requested to undergo prostate biopsy. Pathology specimens were reviewed for adenocarcinoma by both the pathologist at the local study site and at a central pathology laboratory, with concordance achieved in all cases. Clinical stage was assigned locally, and grade was assigned by a single pathologist at the central laboratory. Non-fasting blood was collected 3 months prior to randomization and then annually until either the end of the study or a diagnosis of prostate cancer was made. Total lipids were extracted from serum, and phospholipids were separated from other lipids by one-dimensional thin-layer chromatography. Proportions of fatty acids were categorized into quartiles on the basis of the distribution in the controls.

Excluding men without baseline serum available for analysis, cases (n = 1809) were men with biopsy-confirmed invasive prostate cancer identified before the study was unblinded, and controls (n = 1809) were selected from subjects who had no cancer detectable at the end-of-study biopsy. Controls were frequency matched to cases on distributions of age (± 5 years), treatment group (finasteride or placebo), and other factors. All models were adjusted for the matching variables of age, family history of prostate cancer, and race, and additionally adjusted for risk factors including history of diabetes, alcohol consumption, and body mass index.

Results were sobering — proportions of DHA were *higher* among high-grade cases of prostate cancer (Gleason score 8-10) compared with controls, whereas *trans* fatty acid levels were significantly *lower* among high-grade cases compared with controls. Higher quartile levels of percent serum DHA were associated with an almost doubling of the risk for high-grade disease compared with the lowest quartile; on the other hand, a significant inverse relationship was found between the percent serum *trans* fatty acid level and risk of high-grade prostate cancer. Associations for DHA + EPA were similar to those for DHA alone. There were no other significant findings for the remaining phospholipids between control and cancer groups, including for EPA alone or linoleic acid, and no association identified for any fatty acid with low-grade disease (Gleason score 2-7).

The researchers concluded that, in this large prospective investigation of inflammation-associated phospholipid fatty acids and prostate cancer risk, omega-3 fatty acids do not reduce prostate cancer risk, and *trans* fatty acids do not increase prostate cancer risk — in fact, just the opposite. The authors are frank about being "disconcerted" by their findings, noting that the results illustrate the complexity of research on nutrition and chronic disease risk.

■ COMMENTARY

Good research has a way of turning things topsy-turvy and making us revisit long-held assumptions previously deemed fact. This paper represents good research. The study authors entered into their protocol fully expecting to find that higher serum levels of omega-3 fats would be protective against prostate cancer, and that the presence of those evil *trans* fats in high concentrations would be shown yet again to be harbingers of ill health. Oops…

A wealth of research strongly suggests that inappropriate inflammation may contribute to the development of carcinogenesis, and studies that examine dietary omega-3 fatty acid intakes have supported the general inflammation–cancer hypothesis. Simply put, omega-3s are anti-inflammatory or at least *less* pro-inflammatory (good), while omega-6s and *trans* fatty acids are *more* pro-inflammatory (bad). It's been pretty easy, pretty linear, but like few studies before, these investigators looked at things differently — actual serum levels of phospholipid fatty acids. And they found the opposite of what was anticipated — increased risk with higher proportions of DHA, lowered risk with increased proportions of *trans* fats, and no identifiable association with omega-6s or EPA. These findings, when taken together with those from the large EPIC trial that suggested an increased risk of both high- and low-grade prostate cancer in the highest quintile of DHA blood levels, as well as an increased risk of prostate cancer with increasing blood levels of EPA (unlike what is reported in the current study),[1] must give us pause when considering the overall benefits, and risks, associated with omega-3 fatty acids. The authors themselves state it is possible that omega-3 fatty acids *promote* tumorigenesis.

This was an extremely well-done bit of research, which makes the conclusions all the more concerning. The researchers even analyzed the results on the basis of whether subjects received finasteride or not (cases of high-grade prostate cancer were more likely to have been randomized to treatment with finasteride). Yes, there was over-sampling with respect to the frequency of prostate biopsy, as evidenced by the fact that almost all cases of prostate cancer detected were local stage (although high-grade disease was detected). In addition, the study authors point out that they looked at fatty acid as a proportion (%) rather than by concentrations. Regardless, across an array of statistical analyses the findings held true.

Now what? DHA is often thought of as the "eye and memory fatty acid" with its cousin, EPA, typically considered the "heart and joint fatty acid." Practitioners should discuss the risks and benefits of fish oils with individual patients based upon their unique clinical circumstances. For those using fish oil supplements for general health purposes, especially men, it may be worthwhile taking products that contain a significantly higher percentage of EPA compared to DHA. Clarity on this topic demands further data. Considering how many people make a habit of eating fatty, cold water fish for health reasons or who take fish oil supplements, here's hoping those data come soon. ■

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Pharmacology Update

Ticagrelor Tablets (Brilinta™)

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 relationship to this field of study.

A THIRD ORAL ANTIPLATELET INHIBITOR HAS BEEN APPROVED by the FDA to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS). Ticagrelor is an adenosine diphosphate receptor P2Y12 inhibitor similar to clopidogrel and prasugrel. It is marketed by AstraZeneca as Brilinta.

Indications

Ticagrelor is indicated to reduce the rate of thrombotic cardiovascular events in patients with ACS.[1] These include unstable angina (UA), ST (STEMI), or non-ST (NSTEMI) elevation myocardial infarction.

Dosage

The recommended dose is 180 mg as a loading dose along with 325 mg of aspirin,[1] followed by ticagrelor, 90 mg twice daily and aspirin (75-100 mg) daily.

Ticagrelor is available as 90 mg tablets.

Potential Advantages

Ticagrelor is more effective than clopidogrel in reducing the combined endpoint of cardiovascular death, myocardial infarction, or stroke.[1] In contrast to clodidogrel, ticagrelor is not a prodrug and is not dependant on gene-based metabolism to activate the drug.

Potential Disadvantages

Ticagrelor is associated with a higher rate (compared to clopidogrel) of non-coronary artery bypass surgery (CABG)-related major bleeding (4.5% vs. 3.8%, P = 0.03) and more episodes of intracranial bleeding (0.3% vs. 0.2%, P = 0.06), including fatal intracranial bleeding (0.1% vs 0.01%, P = 0.02).[2] Dyspnea is reported more frequently with ticagrelor (13.8% vs 7.8%, $P < 0.001$). Ticagrelor is dosed twice daily compared to once daily dosing for clopidogrel and ticagrelor.

Comments

Ticagrelor is a reversible adenosine diphosphate receptor P2Y12 inhibitor compared to clopidogrel and prasugrel which are irreversible inhibitors. Ticagrelor has a higher maximum inhibition of platelet aggregation than clopidogrel but a faster offset leading to faster platelet recovery.[1,3] After 6 weeks of therapy, the mean maximum inhibition of platelet aggregation (IPA) was 88% for ticagrelor and 62% for clopidogrel. Twenty-four hours after the last dose, mean IPA was similar between drugs, but after 48 hours, mean IPA was significantly lower with ticagrelor.

The efficacy and safety of ticagrelor compared to clopidogrel was studied in a large, randomized, double-blind study (n = 18,624; the Study of Platelet Inhibition and Patient Outcome [PLATO]).[2] Patients hospitalized for an ACS were randomized to clopidogrel (300 mg loading dose followed by 75 mg daily) or ticagrelor (180 mg loading dose followed by 90 mg twice daily) for 12 months. All patients received aspirin (75-100 mg daily) unless they were intolerant (97% were on aspirin after randomization). The primary efficacy endpoint was time to the first occurrence of a composite of death from vascular causes, myocardial infarction, or stroke. A secondary efficacy analysis included the subgroup in which invasive management was planned at randomization. The ACS breakdown was 43% for NSTEMI, 38% STEMI, and 17% UA. The primary safety endpoint was the first occurrence of any major bleeding event (e.g., fatal bleeding, intracranial bleeding). At 12 months, the composite endpoint occurred in 9.8% of patients randomized to ticagrelor and 11.7% of patients randomized to clopidogrel (hazard ratio [HR], 0.84, 95% CI, 0.77, 0.92, $P < 0.001$). There was no difference in major bleeds (11.6% and 11.2%, respectively). There was a higher rate of major bleeds not associated with CABG and intracranial bleeds as well as fatal intracranial bleeds with ticagrelor. Benefit was seen for patients who planned for invasive management as well as noninvasive (medical) management. HRs (95% CI) were 0.84 (0.75, 0.94) and 0.85 (0.73, 1.00).[4,5]

A retrospective analysis of subjects who underwent CABG suggested that total and cardiovascular mortality were reduced with ticagrelor compared to clopidogrel.[6] In the United States subgroup of the PLATO trial (n = 1413), subjects on ticagrelor had a higher rate of composite endpoints compared to clopidrogrel (12.6% vs 10.1), HR 1.27 (0.92, 1.75). A similar trend was observed in Canadian subjects (n = 401).[5] FDA reviewers speculated that use of higher aspirin doses may be an explanation for the conflicting results although they suggest that there may potentially be multiple confounders and/or effect modifiers, including different baseline factors.[5]

Clinical Implications

Both ticagrelor and prasugrel have been shown to be more effective than clopidogrel in large studies, PLATO and TRITON TIMI.[2,7] While there are no head-to-head comparisons between ticagrelor and prasugrel, an indirect comparison suggests similar efficacy between the two drugs.[8] The conflicting North American results cast some concern about ticagrelor. ■

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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.

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To earn credit for this activity, follow these instructions:

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5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly. You will no longer have to wait to receive your credit letter! ■

CME Questions

12. Stress cardiomyopathy (Takotsubo cardiomyopathy) is characterized by:

a. a higher incidence in men than in women.
b. severe, irreversibly myocardial damage.
c. a presentation similar to acute coronary syndrome.
d. lack of wall motion abnormalities on echocardiography.

13. For the assessment of control of blood pressure in patients with hypertension, what is the most accurate for medical decision making?

a. A carefully obtained blood pressure measurement in the office
b. A blood pressure reading from home
c. A series of blood pressure readings in the office over time
d. A series of blood pressure readings from home

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

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

What Things are Making us Gain Weight?

Source: Mozaffarian D, et al. *N Engl J Med* 2011;364:2392-2404.

Since two-thirds of Americans are overweight or obese, most of us should probably be trying to better understand why. Perhaps the observation that the daily number of calories per capita continues to increase, while daily energy expenditure dwindles, is enough to satisfy the casual observer. Or is the character of caloric intake — such as high glycemic index carbohydrate vs low — a critical factor? As yet, despite simple answers (just reduce calories), there are few simple solutions (folks cannot/will not adhere to calorie-based dietary restrictions).

Might it help to identify commonplace "culprit" foods — that is, dietary components associated most often with weight gain, rather that just total calorie counts?

Based on follow-up of healthy U.S. adults during observational periods lasting as long as 20 years (n = 120,877), Mozaffarian et al determined that several commonplace dietary and lifestyle factors were associated with weight gain. For instance, over a 4-year interval, for every additional daily serving of potato chips, there was a 1.69 lb weight gain. Sugar-sweetened beverages were next on the list of items associated with weight gain. Perhaps, not surprisingly, physical activity, fruits, grains, nuts, and vegetables were inversely associated with weight.

Despite widespread public awareness of the health consequences of being overweight and obesity, most are not able — using currently advised methods — to reverse the trend for weight gain. Whether targeting elimination of specific dietary components (e.g., sugar-sweetened beverages) and/or the augmentation of selected favorable components (e.g., nuts, grains, fruits) will prove to be effective remains to be determined. ■

The Ipswich Touch Test for Diabetic Peripheral Neuropathy

Source: Rayman G, et al. *Diabetes Care* 2011;34:1517-1518.

Type 2 diabetes (DM2) remains the #1 cause of atraumatic limb amputation in the United States. The primary cause of foot ulcers that progress to limb loss is diabetic neuropathy, which decreases sensory awareness of tissue trauma, allowing destruction to progress without warning signs that would otherwise stimulate seeking care for injuries or infections. Albeit consistently recommended by consensus guidelines, routine examination of the feet remains markedly suboptimal by both clinicians and patients alike. Although monofilament and tuning fork testing are highly effective in identifying the presence of diabetic neuropathy, they also remain underutilized.

The Ipswich Touch Test (named after the United Kingdom Hospital in which it was developed) is performed by "lightly touching/resting the tip of the index finger for 1-2 seconds on the tips of the first, third, and fifth toes and the dorsum of the hallux." The presence of neuropathy is defined by this method as having two or more of the eight sites (four sites on each foot) being insensate.

The gold-standard for identification of diabetic neuropathy in this trial was vibration perception threshold as determined by a neurothesiometer. Both monofilament and the Ipswich Touch Test were highly sensitive and had strong positive-predictive value for the presence of neuropathy. When the Ipswich Touch Test was compared with monofilament testing, there was near-perfect agreement. As discussed by the authors, perhaps the lack of requirement for specialized measurement tools will prompt clinicians to be more consistently proactive in seeking to define diabetic neuropathy in the feet. ■

Disease-Modifying Antirheumatic Drugs and Risk for Developing Diabetes

Source: Solomon DH, et al. *JAMA* 2011;305:2525-2531.

Prior to the advent of disease-modifying antirheumatic drugs (DMARDs), the possibilities for remission of disorders like rheumatoid arthritis (RA) and severe psoriasis (PSOR) were remote. Along with the welcome dramatic clinical improvements seen with DMARDs, concerns about adverse effects — such as adversities associated with either the consequences of their immunomodulatory activity or direct toxic effects — require a high level of vigilance. Recently, however, there has been recognition that biologic DMARDs such as TNF inhibitors or hydroxychloroquine, when used in RA or PSOR, might be associated with a lesser risk of diabetes.

Solomon et al performed a retrospective study of RA/PSOR patients who began treatment with a DMARD (n = 121,280) in the United States and Canada. Compared with nonbiologic DMARDs (examples include sulfasalazine, leflunomide, cyclosporine, and others), use of biologic DMARDs was associated with a 23%-46% lesser risk of new-onset diabetes. Because cardiovascular (CV) risk is magnified in persons with RA, treatment choices may be influenced by consideration of agents less likely to further augment CV risk through induction of diabetes. ■

In Future Issues:

Sleep-Disordered Breathing, Hypoxia, and Risk of Mild Cognitive Impairment and Dementia in Older Women