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Internal Medicine

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ABSTRACT & COMMENTARY

Another Reason to Recommend Smoking Cessation

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

Synopsis: In a study of patients with atrial fibrillation, there was a higher risk of severe bleeding in smokers, mainly in those treated with vitamin K antagonists.

Source: Angoulvant D, et al. Effect of active smoking on comparative efficacy of antithrombotic therapy in patients with atrial fibrillation: The Loire Valley Atrial Fibrillation Project. *Chest* 2015 Mar 26. doi: 10.1378/chest.14-3006. [Epub ahead of print].

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice, affecting an estimated 2.7 million individuals in the United States.[1] The proportion of strokes attributable to AF increases strikingly from 1.5% at 50-59 years of age to 23.5% at 80-89 years of age.[2] Approximately 15-20% of all strokes are due to AF. To predict the thromboembolic risk in the individual patient, risk models used most frequently are CHA2DS2-VASc and CHADS2 scores. The CHA2DS2-VASc score may be the better option since both the 2014 American Heart Association, American College of Cardiology, Heart Rhythm Society AF guidelines, and the 2012 European Society of Cardiology AF guidelines prefer it when evaluating the individual thromboembolic risk associated with AF and to determine the risk:benefit ratio of antithrombotic therapy.[3]

Anticoagulation has been shown to substantially reduce the risk of ischemic stroke by up to 60%. However, this is at the expense of an increase in risk of bleeding, including intracranial hemorrhage, which may be disabling or fatal. To assess the risk

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for anticoagulation-induced bleeding, risk models for patients with AF include the HEMORR2HAGES risk index and the HAS-BLED risk score.[4] Each includes a number of risk factors, including age, renal or hepatic dysfunction, hypertension, bleeding tendency, and stroke.

Interestingly, active smoking is a frequent cardiovascular risk factor that is usually associated with a higher risk of thrombotic events. Smoking has been shown to independently influence poor INR control in patients with AF (SAMe-TT2R2 score) initiated on vitamin K antagonists (VKA).[5] Therefore, active smoking could influence the risks of stroke and bleeding in AF patients treated with VKA or with antiplatelet therapy (APT).

In their study, Angoulvant and colleagues compared the clinical outcomes of 7809 consecutive patients with a diagnosis of AF seen at a French hospital from 2000 to 2010 with relation to their smoking status. Of those, 62% were male, with mean age of 71 ± 15 years. Smokers tended to be younger, more males than females, and have more comorbidities compared to non-smokers. Overall, 1034 (13%) participants were actively smoking. APT was prescribed for 2761 patients (35%) and VKA in 4534 (57%).

Smokers were found to have higher HAS-BLED and SAMe-TT2R2 scores, while the CHA2DS2-VASc score was similar in the smokers and non-smokers. After a follow-up of 929 ± 1082 days (median = 463 days), researchers found that smoking was not independently associated with a higher risk of stroke or thromboembolism in AF patients (hazard ratio [HR], 0.95; 95% confidence interval [CI], 0.78-1.22; $P = 0.66$). However, on conducting the multivariate analysis, smoking was independently associated with a worse prognosis for the risk of severe bleeding (HR, 1.23; 95% CI, 1.01-1.49; $P = 0.04$) and for the risk of major bleeding (HR, 1.40; 95% CI, 1.02-1.90; $P = 0.03$). In comparing the use of VKA with APT, smoking was independently associated with a higher risk of bleeding in patients treated with VKA (HR, 1.32; 95% CI, 1.04-1.67; $P = 0.02$), while the risk was statistically non-significant in patients treated with APT (HR, 1.28; 95% CI, 0.94-1.74; P = 0.11).

■ COMMENTARY

In this study, researchers found that while actively smoking AF patients did not have a higher risk of thromboembolic events, they did exhibit a significantly higher risk of severe bleeding risk, particularly in patients treated with VKA such as warfarin. This is an especially interesting finding since the risk of bleeding in AF patients with anticoagulation therapy increases with age and the active smoking status AF patients in the study were significantly younger. Previous studies in this field have demonstrated a variety of effects of smoking on VKA use. A meta-analysis suggested that smoking may potentially cause significant interactions with warfarin by enhancing its clearance, leading to reduced warfarin effects.[6]

Other studies have demonstrated that smoking cessation is associated with increased INR values. Perhaps, based on current and previous findings, it would be fair to draw the conclusion that smoking induces INR instability, which may lead to increased bleeding risk and, therefore, would require closer monitoring of the INR in such an AF patient being treated with VKA. This study did not include the newer non-vitamin K oral anticoagulants. Regardless of the choice of agent for use, this is yet another reason to recommend smoking cessation in our patients. ■

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ABSTRACT & COMMENTARY

Is it Worth it? Do "Healthy" Dietary Guidelines Lower the Risk of Heart Disease?

By Martin S. Lipsky, MD

Adjunct Professor, Institute on Aging, School of Community Health, Portland State University; Dean Emeritus, University of Illinois College of Medicine, Rockford

Dr. Lipsky is a retained consultant for Health Solutions & Strategies.

SYNOPSIS: Following a diet consistent with current United Kingdom dietary guidelines lowers blood pressure and lipid levels. Based on the observed changes, the study authors estimate a risk reduction of cardiovascular disease by one-third in healthy middle-aged and older men and women.

SOURCE: Reidlinger DP, et. al. How effective are current guidelines for cardiovascular disease prevention in healthy middle-aged and older men and women? A randomized controlled trial. *Am J Clin Nutr* 2015: doi: 10.3945/ajcn.114.097352 accessed March 31.

Recent controversy surrounds diet and its impact on cardiovascular disease (CVD). In this study, Reidlinger and her colleagues sought to assess diet by comparing the effects on vascular and lipid CVD risk factors of adhering to a diet consistent with United Kingdom (UK) dietary guidelines (DG group) to a traditional British diet (control group).

Using a randomized trial of 165 healthy, non-smoking middle-aged men and women (age 40-70), the researchers measured baseline blood pressure, vascular function, and other CVD risk factors. Treatment was allocated by minimization for age, sex, ethnicity, and body mass index (BMI) using a custom-designed computer database. If two participants cohabited, both were allocated to the same treatment group (17 couples).

The dietary guideline (DG) group were counseled about a heart-healthy diet, including eating oily fish once a week, increasing fruit and vegetable intake, replacing refined with whole grain cereal, swapping high-fat dairy products and meat for low-fat alternatives, and restriction of both salt and simple sugars. The control diet was a nutritionally balanced British diet without salt or sugar restriction and included unrefined cereals (e.g., white bread, pasta), potatoes with meat, a limited intake of both oily fish (< 1x/per month), and whole grain cereals. The control group was also advised to eat three servings of full-fat dairy products and at least one serving of fruit and two servings of vegetables each day. Both groups were asked to limit their consumption of confectionary and snack foods and to drink alcohol within safe limits. Compliance to guidelines was confirmed using both dietary records and by measuring biomarkers. These markers included measurements such as urine sodium and potassium, sucrose and fructose excretion, eicosapentoic and docosahexaenoic acid in erythrocyte lipids, and plasma alkyrescorcinol concentration.

Outcome measurements included height, weight, blood pressure (BP), lipids, glucose, insulin, high-sensitivity C-reactive protein (hsCRP), arterial stiffness using pulse wave velocity, and vasodilation using a flow-mediated dilation technique. These were measured at the beginning of the trial and after 12 weeks.

The DG groups experienced a 1.3 kg weight loss while the control group gained 0.6 kg. Waist circumference was 1.7 cm lower in the DG group. The DG group also experienced a significant drop in blood pressure: 4.2/2.5 mmHg for daytime readings and 2.9/1.9 mmHG for night-time readings. Cholesterol levels fell by 8%, although changes in the total cholesterol:high-density lipoprotein (TC:HDL) ratio were modest. The C-reactive protein dropped by 36%, and pulse wave velocity also fell. Changes in insulin sensitivity and flow-mediated dilation were not significant.

The authors concluded that following dietary guidelines lowers BP and cholesterol. They estimated a CVD risk reduction of up to one-third for healthy men and women aged 40 and older who adapt a heart healthy diet.

■ COMMENTARY

Changes in dietary recommendations and recent publications make it difficult for the primary care physician to know exactly how to advise patients. The American Heart Association (AHA) recommends a dietary pattern that emphasizes fruits, vegetables, whole grains, low-fat dairy products, poultry, fish, and nuts, while limiting red meat and sugary foods and beverages.[1] As the study authors note, the AHA guidelines are similar to the UK recommendations. Despite the similarity in guidelines and the long-held belief that limiting saturated fats reduces risk, recent publications have cast doubt on these traditional opinions. Notably, a meta-analysis by Chowdhury et al[2] in the *Annals of Internal Medicine* concluded that the current evidence does not clearly support cardiovascular guideless that encourage consumption of polyunsaturated fatty acids and lower consumption of saturated fats.

In light of this recent meta-analysis, it is reassuring to see that what has long been viewed as a healthy dietary lifestyle does seem to work. For primary care physicians who recommend that patients follow AHA guidelines, it should be gratifying to see evidence that this diet does improve risk factors such as BP and lipid levels. As the authors note, study strength is that it evaluates the impact of changing a whole dietary pattern which mimics the clinical world where providers typically provide whole diet counseling rather than advice limited to individual dietary components. One limitation is that the study measured surrogate markers rather than clinical outcomes such as reduced mortality. However, both BP and lipid levels are well accepted as modifiable risk factors that favorably impact CV outcomes. ■

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ABSTRACT & COMMENTARY

Statins After an MI: Does it Happen?

By Martin S. Lipsky, MD

SYNOPSIS: Following hospital discharge for a heart attack, the majority of Medicare patients do not get recommended high-intensity statin therapy.

SOURCE: Rosenson RS, et al. Underutilization of high-intensity statins therapy after hospitalization for coronary artery disease. *J Am Coll Cardiol* 2015;65: 270-275.

Following a hospitalization for coronary heart disease (CHD) or acute coronary syndrome (ACS), randomized trials demonstrate that high-intensity atorvastatin is more effective than either placebo or low- to moderate-intensity therapy with either pravastatin or atorvastatin.[1-3] Based on this evidence, the American College of Cardiology and the American Heart Association guidelines recommend high-intensity therapy in cases of an acute cardiac event and that therapy be initiated before discharge.

Previous studies indicate that more than 80% of patients receive a statin after a myocardial infarction (MI) or coronary revascularization.[4-5] However, few studies examined the percentage of individuals who met guidelines and were prescribed and filled a script for high-intensity statins. One previous study demonstrated that only about one in three filled a high-intensity statin script[6] and that the only correlation with taking a high-intensity statin after 1 year was being prescribed a high-intensity statin at discharge.

The authors used a random sample of Medicare beneficiaries between ages 65 and 74 who filled a statin script after being hospitalized for a MI or for bypass surgery from 2007-2009. Of the more than 8000 who filled a statin script, only 27% of the first post-discharge scripts were for a high-intensity statin such as 40-80 mg of atorvastatin or 80 mg of simvastatin. The percentage filling a high-intensity statin post-discharge was 23.1%, 9.4%, and 80.7 % for beneficiaries not taking statins pre-hospitalization, taking low- to moderate-intensity statins, and taking high-intensity before the CHD event, respectively.

Only 11.5% of beneficiaries whose first post-discharge fill was for a low- to moderate-intensity statin eventually filled a high-intensity statin within 365 days of discharge. The authors conclude that the majority of Medicare beneficiaries do not fill high-intensity statin after hospitalization for CHD.

■ COMMENTARY

Despite evidenced-based guidelines supporting the use of high-intensity statins in a high-risk population, Rosenson and colleagues found that only about one in four individuals hospitalized for a coronary event receive high-dose statins.

To no great surprise, the greatest predictor of who fills a high-intensity statin was being on one prior to hospitalization. Even though one might argue that physicians are reluctant to use a high dose initially, and prefer to titrate the dose up if tolerated, by year's end, the percentage on high-intensity therapy only increased to about 35%. Unfortunately, the Medicare dataset used did not allow an analysis of the characteristics, such as liver disease, dose intolerance, or renal disease that might account for such low compliance with the guidelines.

So why are doctors reluctant to use these medicines as recommended? One explanation may be that physicians are unaware of the recommendation, although physicians participating in the care of patients with myocardial infarctionss or bypass surgery likely would be familiar with this recommendation. It is possible that despite their physician's recommendation, patients might be reluctant to fill these scripts. However, in the face of a significant cardiac event, most patients will at least follow their physician's initial advice.

So what explains such a low level of compliance with a recommended guideline? It likely relates to concerns about the risk of using high-dose statins in an older postulation who are the most vulnerable to side effects. Early on statins may have gotten a bad rap, with some early studies reporting the risk of adverse effects as high as 20%. However, a recent Johns Hopkins review of 20 years of research concluded that the risks linked to statins, including muscle toxicity, diabetes, and dementia, were very low and far outweighed by a statin's benefits.

The authors found little evidence of significant myalgias and only a modest increase in myositis. Rhabdomyolysis was primarily associated with regimens that are no longer recommended. Regarding blood sugar elevations, this evidence-based review found only a modest increase in the risk of type 2 diabetes with statins. However, this association was found only among people with other risk factors for diabetes, raising the question of whether diabetes might have inevitably developed even without statin use.

Another meta-analysis by Macedo et al found an increase in muscle complaints and creatine phosphokinase (CPK) levels with statin use, but also concluded that the absolute excess risk of side effects with statins is very small compared to its beneficial effects in patients whose risks exceed a certain threshold of cardiovascular risk. The findings by Rosenson suggest that physicians might be underestimating the benefit:risk ratio for high-intensity statins in those with a coronary event.

So what is the take home message for the primary care physician? Consider reviewing how well you adhere to the guidelines recommending high-dose statin therapy. If you are not prescribing these medications as recommended, then perhaps the next step is to determine why not. If it is because of the concern about adverse effects, then I would encourage you to review the cited meta-analyses and decide if you agree with their assessments. If it is because you want to use the strategy in older patients of "start low, go slow," then consider a tracking system to allow you to remember to increase the dose in patients without significant side effect. ■

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Are Atrial Premature Complexes Benign?

By Michael H. Crawford, MD

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Dr. Crawford reports no financial relationships relevant to this field of study. This article originally appeared in the April 2015 issue of *Clinical Cardiology Alert*.

SYNOPSIS: The presence of APCs on a routine ECG is associated with AF and cardiovascular death

SOURCE: Murakoshi N, Xu D, et al. Prognostic impact of supraventricular premature complexes in community-based health checkups: The Ibaraki Prefectural Health Study. *Eur Heart J* 2015;36:170-178.

Atrial premature complexes (APCs) are commonly observed on routine ECGs and believed to be harbingers of atrial fibrillation, especially in patients with cardiovascular disease. However, little is known about the long-term prognosis of APCs in the general population. Thus, these investigators from Japan analyzed the database of a large community-based cohort from 1993 to 2008 to determine the risks of APCs seen on the subjects' baseline ECGs. There were 63,197 subjects without heart disease or atrial fibrillation (AF) who were followed for at least 1 year (20,492 men and 42,705 women, mean age 58 years at baseline). The primary endpoint was mortality and the secondary endpoint was AF. The mean follow-up was 14 years, but if censured by AF occurrence on the yearly follow-up exam, it was 6 years. In addition to analyzing the raw data, the data were adjusted for age and other potential confounders such as blood pressure, body mass index, alcohol use, and other ECG findings. Also, a propensity-matched analysis was done matching subjects with APCs to those without.

APCs were observed in 6%, and these subjects were more likely to be older and have other risk factors for AF and mortality. APCs were significantly associated with death from stroke, cardiovascular death, and all-cause mortality in women, but only cardiovascular death in men. AF occurred in 1 per 1000 person years, and APCs were a significant predictor of AF (hazard ratio [HR], 4.87 men and 3.87 women). In the propensity score-matched subjects, APCs were significantly associated with AF and cardiovascular death in all subjects and stroke death in women, but not all-cause mortality. The authors concluded that in a general population free of AF or cardiovascular disease, the presence of APCs on a routine ECG is associated with AF and cardiovascular death.

■ COMMENTARY

This study affirms what has been seen in smaller studies of higher-risk patients, that APCs predict future AF. Why APCs would predict cardiovascular death in a general population is not clear from this study. It could be simply that by being associated with AF, you are more likely to have a stroke or develop heart failure. On the other hand, APCs may be markers of underlying cardiovascular disease. This makes sense since in the baseline data, APC subjects were older and had more risk factors for cardiovascular disease. That APCs are strong predictors of AF is not surprising. Pathophysiology studies show that APCs originating in the pulmonary vein orifices can trigger AF. Also, when the number of APCs per ECG was evaluated, more APCs increased the risk of AF. This is remarkable given that we are talking about a routine ECG, approximately 15 seconds of monitoring. Since APCs are frequently seen on ambulatory ECG monitoring done for a variety of reasons, one wonders if there is some threshold for APCs 24 hours above which the risk of AF and cardiovascular disease increases significantly in a general population.

In addition to the limitations of an ECG as a monitoring device for APCs, it was also the way AF was confirmed. Thus, asymptomatic intermitten AF was unlikely to be detected. Also, the subjects were not extensively evaluated for cardiovascular disease on the yearly exams, so some subclinical disease may have been present and unaccounted for in the propensity analysis. In addition, there were twice as many women as men in the study. The authors don't offer an explanation for this, but since subjects with known cardiovascular disease were excluded in this older middle-aged population, many men may have been excluded. The main clinical message of this study is that patients with APCs on a routine ECG should undergo screening for heart disease and asymptomatic intermitten AF. ■

Clinical Briefs

By Louis Kuritzky, MD

Chronobiology and Insulin Glargine

SOURCE: Porcellati F, et al. *Diabetes Care* 2015; 38:503-512.

The "Indications" labeling for insulin glargine (Lantus) simply says, "Administer subcutaneously once daily at any time of day, but at the same time every day." Some patients and clinicians prefer morning administration, some prefer evenings, and some even prefer twice-daily injections, although the latter is clearly off-label. The important question is, then, does it make any difference when you give insulin glargine, or is it just personal preference?

The pharmacokinetics and pharmacodynamics of insulin glargine were studied in 10 subjects with type 2 diabetes who had already been receiving insulin glargine as part of their therapeutic regimen. Subjects were randomized in a crossover design to dose insulin glargine at either 10:00 a.m. or 10:00 p.m., with dose optimization attained during a 2-week run-in period to achieve fasting blood glucose (FBG) ≤ 100 mg/dL without experiencing nocturnal hypoglycemia (glucose < 72 mg/dL).

Several interesting results were noted. First, the actual dose needed for optimization of FBG was slightly greater when glargine was administered at 10:00 a.m. than 10:00 p.m. Second, morning administration of glargine had less glucagon-suppression effect in the second half of the 24-hr cycle than evening administration had in the second half of its 24-hr cycle. Evening administration also limited lipolysis more than morning, resulting in lower levels of plasma fatty acids.

The differences between morning and evening glargine administration demonstrated here are quite modest, but do suggest that overall, evening administration may be superior in reference to some dysregulations seen in type 2 diabetes such as glucagon and fatty acids. ■

Dual Add-on Therapy for Type 2 Diabetes When Metformin is Not Enough

SOURCE: Rosenstock J, et al. *Diabetes Care* 2015; 38:376-383.

The current (2015) American Diabetes Association (ADA) guidance for progression of treatment when A1c goals are not attained with metformin imply stepwise initiation of additional monotherapies. But would it make sense to consider dual add-on?

Rosenstock et al studied patients with type 2 diabetes (T2DM) whose A1c was 8.9% at baseline on monotherapy with metformin. Subjects were randomized to add either a DPP4 inhibitor (saxagliptin), an SGLT2 inhibitor (Dapagliflozin), or both and were followed for 24 weeks.

All three regimens were successful to reduce A1c from baseline, and it probably comes as no surprise that the addition of two drugs (DPP4 inhibitor AND SGLT2 inhibitor) to metformin outperformed the addition of either monotherapy. The addition of an SGLT2 to metformin demonstrated substantially better A1c reductions than the addition of a DPP4 inhibitor (-0.9% vs -0.59%), but the three-drug combination was far more effective, providing a -1.5% A1c reduction.

The simultaneous addition of two drugs to metformin monotherapy is probably an uncommon step for clinicians, who are more accustomed to progressive monotherapeutic step advancements. The fact that there were no episodes of major hypoglycemia during the 6 months of the trial is reassuring that similar therapeutic steps may be safely taken in practice settings where patients continue to have an elevated A1c on metformin. Because of the very potent A1c reduction, however, it is equally important to select patients with a sufficiently elevated A1c on metformin (at least 8.9%) so that the addition of dual add-on treatment does not lead to problematic hypoglycemia. ■

Might Long-term Dual Antiplatelet Therapy Be Better? Not

Elmariah S, et al. *Lancet* 2014;385:792-798.

Risk reduction provided by dual antiplatelet therapy (DAT) in the short-term interval (3-12 months) after coronary stenting is well established, and published guidelines provide consistent advice about appropriate duration of such therapy. In essentially every large randomized trial that has compared DAT to monotherapy, bleeding risks go up to a sufficient level that it counterbalances any risk reduction in reference to cardiovascular events. Indeed, two major mega-trials comparing DAT to monotherapy in stable patients with established vascular disease failed to demonstrate beneficial reduction in stroke (the MATCH trial) or stable coronary disease (the CHARISMA trial), but did find more bleeding risk.

Elmariah et al performed a meta-analtsis of randomized controlled trials employing DAT post coronary stenting to compare "short duration therapy" (i.e., 6 months or less) or aspirin alone with longer treatment.

Based on data from 14 clinical trials (n = 69,644), they found no evidence of improved outcome associated with longer duration treatment. While this may appear disappointing, one rationale for the investigation was the finding in the large DAPT Study (Dual Antiplatelet Therapy Study, n = 11,648) that non-cardiovascular deaths were actually increased if DAT was extended beyond 12 months, which was not confirmed in the meta-analysis. ■

CME INSTRUCTIONS

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CME QUESTIONS

1. Based on the study by Angoulvant et al, which of the following is *not true* in patients with atrial fibrillation on oral anticoagulation?

a. Smoking was not independently associated with a higher risk of stroke or thromboembolism.

b. Smoking was independently associated with a worse prognosis for the risk of severe bleeding.

c. Smoking was independently associated with a higher risk of bleeding in patients treated with vitamin K antagonists.

d. Smoking was independently associated with a higher risk of bleeding in patients treated with anti-platelet therapy.

2. Following an acute coronary event, the benefits of high-intensity statins outweigh their risk in a 70-year-old woman.

a. true

b. false

3. When compared to controls Individuals that followed the UK heart healthy dietary guidelines experienced all except:

a. weight loss

b. lowered blood pressure

c. improved lipids

d. improved insulin sensitivity.

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]

Angiotensin Receptor Blockade

Steroids for Severe Community-acquired Pneumonia