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Internal Medicine

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ABSTRACT & COMMENTARY

Efficacy of Folic Acid Therapy in Primary Prevention of Stroke

By Harold L. Karpman, MD, FACC, FACP

Clinical Professor of Medicine, UCLA School of Medicine

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

SYNOPSIS: Among adults with hypertension in China without a history of stroke or myocardial infarction, the combined use of enalapril and folic acid, compared with enalapril alone, significantly reduced the risk of first stroke.

SOURCE: Huo Y, et al. Efficacy of folic acid therapy in primary prevention of stroke among adults with hypertension in China. The CSPPT randomized clinical trial. *JAMA* 2015; 313:1325 – 1335.

Stroke is the leading cause of death in China and the second leading cause of death in the world.[1] Since approximately 77% of all strokes are first events,[2] primary prevention is particularly important. Some of the many published trials evaluating the beneficial effect of folic acid supplementation for the prevention of cardiovascular disease have suggested a specific reduction in stroke risk.[3-5] Polymorphism of the MTHFR gene C677T leads to a reduction in the main regulatory enzyme for folate metabolism, and a large meta-analysis of genetic studies and clinical trials suggested that the effect of gene variants on stroke risk might be modified by folate status. The China Stroke Primary Prevention Trial (CSPPT) was designed to test the efficacy of folic acid therapy in stroke prevention in the context of primary vs secondary prevention and the combined effects of baseline folate levels and MTHFR gene C677T polymorphism.

Yong Huo and his colleagues from the Peking University First Hospital in Beijing, China, designed a study to test whether enalapril–folic acid therapy was more effective in reducing primary stroke incidence then was enalapril alone among adults

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with hypertension in China.[7] A total of 20,702 adults with hypertension and without a history of stroke or myocardial infarction participated in the study. They were randomly assigned to receive a double-blind daily treatment with a single pill combination containing enalapril 10 mg and folic acid 0.8 mg or a tablet containing only enalapril 10 mg. The primary outcome studied was first stroke, and secondary outcomes included first ischemic stroke, first hemorrhagic stroke, myocardial infarction, and the composite of cardiovascular events including cardiovascular death, myocardial infarction, stroke, and, finally, all-cause death. The findings were consistent with benefits from folate use among adults with hypertension and low baseline folate levels, and the authors concluded that among adults with hypertension in China without a history of stroke or myocardial infarction, the combined use of enalapril and folic acid, compared with enalapril alone, significantly reduced the risk of first stroke.

■COMMENTARY

The effectiveness of folic acid supplementation in stroke prevention had not previously been well established[8,9] until a comprehensive meta-analysis in 2012 found that folic acid supplementation significantly reduced the risk of first stroke.[10] The enalapril–folic acid combination in the Huo study also significantly reduced the relative risk of first stroke by 21%, and it should be noted that the result occurred in a population in which there was a very low percentage of concomitant use of lipid-lowering drugs and antiplatelet agents. It was also important to note that since hypertension is a primary risk factor for stroke,[8] in the Huo trial, blood pressure was controlled at baseline and throughout follow-up using enalapril and other antihypertensive agents as needed in both the treatment and control groups. It must be remembered that the study focused on primary prevention of stroke in adults with hypertension and that further studies will be needed to determine if the same results can be obtained in secondary stroke prevention and/or in adults without hypertension. The authors speculated that even in countries with folic acid fortification and widespread use of folic acid supplements, such as in the United States and in Canada, there still may be room to further reduce stroke incidence using more targeted folic acid therapy, in particular among those with low or moderate folate levels.

In summary, Huo[7] and his colleagues demonstrated that among adults with hypertension in China without a history of stroke or myocardial infarction, the combined use of enalapril and folic acid compared with enalapril alone significantly reduced the risk of first stroke. This finding is consistent with the benefit from folate use observed to occur among adults with hypertension and low baseline folate levels, and in time, folate therapy may also be effective in reducing the incidence of recurrent strokes even in patients who have previously suffered a stroke. ■

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ABSTRACT & COMMENTARY

Inpatient and Outpatient Care Providers: Why Can't We Just Work Together?

By Deborah J. DeWaay, MD, FACP

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

SYNOPSIS: The authors of this paper did a qualitative study to analyze the barriers and solutions to care coordination between hospitalists and primary care providers in North Carolina.

SOURCE: Jones C, et al. A failure to communicate: A qualitative exploration of care coordination between hospitalists and primary care providers around patient hospitalizations. *J Gen Intern Med* 2014;30:417-424.

Many problems that occur after a patient is discharged are a direct result of poor coordination of care between hospitalists and primary care providers (PCPs). These issues include, but are not limited to, missed test results, medication errors, inadequate follow-up, and harm to the patient. PCPs are frequently unaware that their patient was hospitalized, and they often do not receive a copy of the discharge summary. The authors of this paper did a qualitative study to analyze the barriers and solutions to care coordination between hospitalists and PCPs in North Carolina.

This exploratory qualitative study involved both hospitalists and PCPs from North Carolina practices, and consisted of eight focus groups between February and May 2013. Three were comprised entirely of PCPs. Four were comprised of hospitalists and one was a hybrid of both PCPs and hospitalists. Each group met and talked for 45 minutes. The discussion was taped and transcribed in its entirety.

The authors purposefully sampled practices from diverse settings. A common theme among the recruits was their active involvement in quality improvement projects regarding care transitions. Only one eligible practice declined to participate because of scheduling issues.

The interview questions were based on the Agency for Healthcare Research and Quality Care Coordination Measurement Framework and included the following themes: care coordination, information exchange, follow-up, medication management, and accountability. The research team developed and used a framework-based code book to code the comments made in the focus groups. A main coder coded all of the transcripts, and a group of additional team members coded portions of the transcripts. The team members and main coder would meet to reconcile any discrepancies. In addition, the members of the focus groups were able to check the key discussion themes from their group.

The eight focus groups included 58 total participants: 34 hospitalists, 22 outpatient PCPs, and two physicians who practiced equally in both settings. Academic and private practices were represented, as were rural and urban areas. All of the participants used an electronic medical record (EMR). The hospitalists were more often male, whereas the PCPs were more often female.

Both hospitalists and PCPs described having a lack of time to communicate with each other. They said that it was often difficult to get the correct phone

number in order to speak with the right physician. Discharge summaries were also a stress point. The hospitalists' systems struggled to share the discharge summaries with the PCPs and to coordinate a follow-up appointment after hours or on the weekends, thus leaving patients responsible to schedule an appointment. Discharge summaries were also often incomplete, not adequately describing the expectations for the follow-up visit, leaving both PCPs and patients in a bad situation.

Both groups had concerns about missing tests with results pending. The PCPs felt that hospitalists should be accountable for hospitalist-ordered tests unless expressly described in the discharge summary or via a phone call. The hospitalists expressed that PCPs should be responsible for follow-up tests that are required after hospitalization. For example, a PCP should order the CT needed 6 months after finding a lung nodule. In addition, there was an unclear accountability dispute regarding home health services. Both groups agreed the hospitalists should oversee the initial order set, but there was a difference of opinion regarding follow-up orders.

The hospitalists and PCPs agreed that a greater effort is needed from both sides with high-risk patients. There was a shared sentiment regarding the benefits of a personal relationship between the two physicians and sharing an EMR. The hospitalists wanted a centralized scheduling system for PCP follow-up appointments or to have a hospitalist-run follow-up clinic, while the PCPs wanted follow-up appointments to be scheduled before discharge.

This study found that both types of physicians had similar concerns regarding the important transition from inpatient to outpatient care. Often, the discrepancies in opinions had to do with issues that clinicians in the opposite setting didn't realize were a problem. Both groups believe improving personal relationships between physicians and using the EMR would be helpful. Further studies need to be performed to see if more formal accountability with pending tests, future tests, and home health would be helpful.

■COMMENTARY

The discharge process is more complex than ever. This paper outlines some good starting places for hospitals and physicians to begin their quality improvement processes regarding inpatient to outpatient transitions of care.

This study's biggest limitation was its generalizability. All participants were from North Carolina, and the authors chose groups that were very active in quality improvement within their systems. Thus, these findings may not represent experiences elsewhere. Discharge planning and transitions of care will continue to be a major issue that hospitals and physicians must address as payments change to be based on quality measures.

The discharge process is very complex, and trying to improve the transition proves daunting. Creating better phone directories and increased access to paging systems would be a great place to increase PCP/hospitalist communications. Increased automation with respect to EMRs will be helpful, especially regarding sending discharge summaries, as well as laboratory and imaging studies. More automation and earlier arrangement of PCP appointments might also be helpful. ■

PHARMACOLOGY UPDATE

Liraglutide Injection (Saxenda®)

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.

The glucagon-like peptide (GLP-1) receptor agonist, liraglutide is now approved for weight management in adults. The drug is also approved for the treatment of diabetes (Victoza®) but at a lower dose. Liraglutide is marketed by Novo Nordisk as Saxenda® for the weight-loss indication.

Liraglutide is indicated as an adjunct to a reduced-caloric diet and increased physical activity for chronic weight management in adults with initial body mass index (BMI) ≥ 30 kg/m^2 (obese) and BMI of 27 kg/m^2 (overweight) with at least one weight-related comorbidity such as hypertension, type 2 diabetes, or

dyslipidemia.[1]

DOSAGE

The recommended dose is 3 mg subcutaneously daily. The dose is initiated at 0.6 mg daily and titrated on a weekly basis until 3 mg is reached. Liraglutide is available as a 6mg/mL (3 mL) pre-filled, multi-dose pen that delivers 0.6 mg, 1.2 mg, 1.8 mg, or 3 mg.

POTENTIAL ADVANTAGES

Liraglutide provides another treatment option with a different mechanism of action for weight management.

POTENTIAL DISADVANTAGES

Liraglutide is contraindicated in patients with a personal or family history of medullary thyroid carcinoma.[1] It should not be used in patients taking insulin or any other GLP-1 receptor agonist. Most frequent adverse events are nausea, diarrhea, constipation, vomiting, hypoglycemia, and decreased appetite.[1] Acute pancreatitis (fatal and nonfatal) has been observed in postmarking surveillance. Less frequent adverse events include suicidal ideation (0.2%), cholelithiasis (1.5%), and cholecystitis (0.2%).

COMMENTS

The safety and efficacy of liraglutide were studied in three 56-week, randomized, double-blind, placebo-controlled clinical trials. Subjects were randomized to liraglutide 3 mg or placebo. All patients were instructed on a reduced-calorie diet and received exercise counseling throughout the trial. The primary efficacy endpoints were mean percent change in body weight and the percentage of patients achieving ≥ 5% and 10% weight loss from baseline to week 56. Study 1 included obese subjects or overweight subjects with hypertension or dyslipidemia. Study 2 included obese and overweight type 2 diabetics. The mean baseline weights were 106 kg. Least square percent mean change from baseline were -7.4% for liraglutide compared to -3.0% for study 1 (difference -4.5%; 95% confidence interval [CI], -5.2% to -3.8%) and -5.4% vs -1.7% for study 2, difference of -3.7% (-4.7%; -2.7%). The percentage of patients losing 5% of body weight compared to placebo was 62.3% vs 34.4% (study 1) and 49% vs 16.4% (study 2), and for losing 10% of body weight, 24% vs 15% (study 1) and 22% vs 6% (study 2). Difference (in ≥ 5% or weight loss) from placebo was 28% and 33% for the two studies. All these were statistically significant. Study 3 included subjects who achieved weight loss of at least 5% of their screening body weight in the run-in period of 4-12 weeks while on liraglutide. These subjects were then randomized to liraglutide or placebo for 56 weeks. Those randomized to liraglutide showed additional mean weight loss from placebo of 5.2 kg with 44% losing ≥ 5% compared to 22% for placebo (difference 23%; 95% CI, 14%; 31%) and for weight loss of ≥ 10%, 25% vs 7%. Improvements in some cardiovascular disease-risk factors were also observed (HbA1c, fasting plasma glucose, fasting insulin, systolic blood pressure). In a 2-year extension study, the prevalence of prediabetes and metabolic syndrome decreased by 52% and 59% for pooled doses of 2.4 and 3.0 mg.[3]

CLINICAL IMPLICATIONS

Liraglutide is the most recent drug or drug combination approved for weight management. Lorcaserin and topiramate/phentermine were approved in 2012 and bupropion/naltrexone and liraglutide in 2014. The FDA benchmarks for weight loss efficacy are made up of two criteria: mean weight loss between drug and placebo is at least 5% (and statistically significant), and the proportion of subjects who lose ≥ 5% of baseline weight in the drug group is at least 35% and approximately double the proportion in the placebo-treated group (and the difference is statistically significant). Liraglutide fell a little short with the first criteria, -3.7% and -4.5%. For the second criteria, the proportion achieving 35% was met in the two studies (62% and 49%) but was double the placebo only in the study with type 2 diabetics. The wholesale cost for Saxenda is $231.66 for a 3 ml pen (18 mg). ■

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Clinical Briefs

By Louis Kuritzky, MD

Carbon Monoxide Toxicity in the Elderly

SOURCE: Muo IM, et al. Carbon monoxide poisoning: Safety tips for practitioners in the long-term care setting. *Ann Long-Term Care* 2015;23:35-38.

The signs of carbon monoxide toxicity (CMT) may be subtle and easily mistaken for other disorders, simply because clinicians may not think of it. Symptoms such as change in mental status, chest pain, dizziness, headache, nausea, seizure, and syncope do not necessarily bring CMT to front-of-mind status. Most episodes of CMT occur in colder climates during winter, but CMT can occur in any environment, at any time of year.

Typical presentations of CMT include sinus tachycardia, tachypnea, and focal neurologic deficits. Because pulse oximeters do not detect carboxyhemoglobin levels, pulse oximetry is usually normal. Because the affinity of carbon monoxide for hemoglobin is several hundred-fold greater than oxygen, once carbon monoxide has bound to hemoglobin, oxygen binding is markedly reduced and tissue hypoxia ensues. Acute MI, angina, and heart failure may all represent CMT. Chronic CMT can lead to neurologic damage, including Parkinsonism and frontal lobe dysfunction, sometimes presaged by admission for altered mental status.

Hyperbaric oxygen treatment is generally considered the optimum treatment resource for CMT, although a Cochrane review did not confirm the superiority of hyperbaric oxygen over treatment with normobaric oxygen. When clinicians encounter syndromes reflecting potential tissue ischemia, CMT should sometimes be among the differential diagnoses. Prompt intervention may prevent important neurologic sequelae. ■

Does Hypovitaminosis D Increase Risk of Atrial Fibrillation in Hypertensive Patients?

SOURCE: Ozcan OU, et al. Relation of vitamin D deficiency and new-onset atrial fibrillation among hypertensive patients. *J Am Soc Hypertens* 2015;9:307-312.

If you have been practicing medicine for 5 years or longer, you probably have already been assailed by literature from all compartments of medicine claiming that low levels of vitamin D are associated with almost anything bad that can happen to almost anyone. Just in case your dossier of hypovitaminosis D crimes is insufficiently full, you might consider adding "New Onset Atrial Fibrillation" to the rap sheet.

Ozcan et al evaluated 227 hypertensive patients, among whom 137 had new onset atrial fibrillation (AFIB). When they compared the levels of vitamin D in persons with new onset AFIB to controls (the hypertensive patients who *didn't* have AFIB), they found that low vitamin D levels (< 20 ng/mL) were essentially twice as common in the AFIB group (67% vs 33%). The odds ratio for incurring AFIB was almost 70% greater for patients with low vitamin D levels than vitamin D-replete individuals.

Explanations for how vitamin D might be related to AFIB include the observation that activation of the renin-angiotensin-aldosterone system is heightened in vitamin D deficiency states. Whether vitamin D supplementation would result in reduced incidence of AFIB has not yet been determined. ■

Reflections on the Consequences of Morning BP Surge

SOURCE: McMullan CJ, et al. Racial impact of diurnal variations in blood pressure on cardiovascular events in chronic kidney disease. *J Am Soc Hypertens* 2015;9:299-306.

The circadian rhythm of blood pressure (BP) in healthy individuals, as well as most persons with hypertension, is characterized by a 10-20% decline in BP overnight, followed by an early (pre-awakening) rise maintained through much of the day. The change from lowest overnight BP to sustained morning BP is called the morning "surge," remembering that timing of BP changes is actually relative to sleep cycle rather than time of day.

It has been noted that deviations from the "typical" circadian BP pattern of healthy individuals — for instance, failure to experience a dip in overnight BP (non-dipping) — is associated with increased risk of cardiovascular (CV) endpoints. Additionally, CV events tend to cluster with the morning surge in BP in the population at large, including those with hypertension.

McMullan examined diurnal variations in BP among patients with CKD to see whether ethnicity factors into outcomes. Their study population included Japanese (n = 197) and African-American (n = 197) men.

McMullan determined that the morning BP surge was associated with increase CV risk in Japanese, but not African-American, men. Whether BP treatment that specifically affects morning BP surge might provide specific risk reduction independent of overall BP control remains to be determined. ■

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CME QUESTIONS

1. **Among adults with hypertension in China, the combined use of enalapril and folic acid:**

   a. improved nutrition and digestion.

   b. had no significant effect on blood pressure.

   c. significantly reduced the risk of first stroke.

   d. significantly reduced the risk of recurrent stroke and MI.

2. **In the study by Jones et al, both PCPs and hospitalists think that all of the following are barriers to smooth patient transitions from the inpatient to the outpatient setting *except*:**

   a. a lack of clarity as to which provider should follow up on test results.

   b. a lack of time for communication.

   c. difficulty finding the appropriate phone number for the appropriate doctor to discuss the case.

   d. a lack of pertinent information in the discharge summary.

   e. a lack of a personal relationship between PCPs and hospitalists.

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]

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Internal Medicine [ALERT]

ECG Review

By Ken Grauer, MD

Professor Emeritus in Family Medicine, College of Medicine, University of Florida

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

Is There Complete AV Block or Any Block at All?

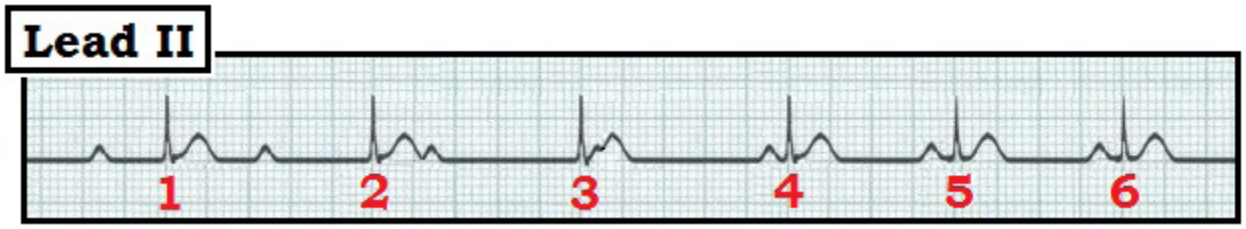

Figure: Lead II rhythm strip with non-conducted beats.

There are non-conducted *P* waves in the rhythm above. Is there AV block? If so, what type? Why is this not complete AV block?

Interpretation: At first glance, it appears that none of the *P* waves in this tracing are being conducted to the ventricles. That said, the best approach for assessing the AV blocks is to return to the basics. We summarize the five parameters to assess in the interpretation of *any* cardiac rhythm by the saying, "Watch your Ps and Qs — and the 3Rs." We look for: i) Presence and nature of atrial activity (*P* waves); ii) QRS width; iii) and iv) Rate and regularity of both the atrial and ventricular rhythm; and v) If *P* waves are present, are they related to a neighboring QRS complex?

- The QRS complex is clearly narrow in this tracing. Therefore, the rhythm is supraventricular.
- Upright sinus *P* waves are present in this lead II rhythm strip. They are regular throughout the tracing at a rate of 75/minute.
- It is obvious that *P* waves for the initial part of this tracing are not related to their neighboring QRS (i.e., there is AV dissociation — at least for the first few beats). If all we had were the first 4 beats, one would think the degree of AV block was complete.

The key to interpreting this rhythm is to appreciate that the ventricular rhythm is not regular over the entire tracing! Instead, beat #5 comes early. Most of the time when there is complete (i.e., third-degree) AV block, the ventricular rhythm will be regular throughout. This is because with complete AV block, no atrial impulses are able to penetrate the AV node. As a result, an escape pacemaker arises from either the AV node or from the ventricles, and the rate of most escape pacemakers is at least fairly regular. The fact that beat #5 occurs early and is preceded by a P wave with a normal PR interval suggests that this beat is being conducted. Support for this theory is forthcoming from the fact that beat #6 follows with a similar R-to-R interval and with a similar preceding PR interval.

In summary, assessment of AV blocks is best accomplished by use of the same "Ps, Qs, 3R Approach" as for any other rhythm. AV dissociation may be transient (as it is here for the first three beats in this tracing). An important clue that despite transient AV dissociation, the degree of AV block is not complete — is when the ventricular rhythm is not regular. Attention to the beats that follow this change in rhythm regularity will usually be revealing. In this case, the rhythm is a form of high-grade second-degree AV block (since several of the regularly occurring P waves that should conduct do not conduct) — but the degree of AV block is clearly not complete.

NOTE: For review of the basics of AV Block, go to: http://www.avblockecg.com.