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ABSTRACT & COMMENTARY

Can a Brain Condition Affect the Heart?

By Seema Gupta, MD, MSPH

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

SYNOPSIS: A large, prospective cohort study in women with more than two decades of follow-up indicated a consistent link between migraine and cardiovascular disease events, including cardiovascular mortality.

SOURCE: Kurth T, Winter AC, Eliassen AH, et al. Migraine and risk of cardiovascular disease in women: Prospective cohort study. *BMJ* 2016;353:i2610.

Migraine is a widely prevalent and disabling primary headache disorder. Globally, it is ranked as the third most common disorder and seventh highest specific cause of disability.[1] In the United States, migraine headaches affect roughly one out of every seven Americans annually, with more than twice the prevalence in women.[2] Current evidence supports an association between migraine, specifically migraine with aura, and ischemic, as well as, to a lesser extent, hemorrhagic stroke risk.[3] The risk is higher for women, young people, and those who suffer from frequent headaches. Smoking habits and oral contraceptives, especially together, also increase stroke risk. However, while potential pathways for a cardiovascular disease event in migraine sufferers can be hypothesized, none of the postulated mechanisms has been confirmed as a pathophysiological explanation linking stroke and migraine. Nevertheless, it is possible that in migraineurs, the same underlying mechanism(s) may be responsible for other types of cardiovascular events, including ischemic heart disease and cardiovascular death.[4] Because of its high socioeconomic and personal effects, such an association could present significant global public health implications.

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Kurth et al conducted a large, prospective cohort study among Nurses' Health Study II participants. They analyzed data from 115,541 enrolled women who were 25-42 years of age and free from angina and cardiovascular disease. Researchers followed participants from 1989-2011. The primary outcome of the study was major cardiovascular disease, a combined endpoint of myocardial infarction, stroke, or fatal cardiovascular disease.

Researchers observed that 17,531 participants reported a physician's diagnosis of migraine at baseline in 1989. An additional 6,389 women newly reported a physician's diagnosis on subsequent questionnaires and were classified as experiencing migraine during follow-up. During 20 years of follow-up, 1,329 major cardiovascular disease events occurred, and 223 women died from cardiovascular disease. After adjustment for potential confounding factors, researchers found that migraine was associated with an increased risk for major cardiovascular disease (hazard ratio [HR], 1.50; 95% confidence interval [CI], 1.33-1.69), myocardial infarction (HR, 1.39; CI, 1.18-1.64), stroke (HR, 1.62; CI, 1.37-1.92), and angina/coronary revascularization procedures (HR, 1.73; CI, 1.29-2.32) compared with women without migraine. Furthermore, migraine was found to be associated with a significantly increased risk for cardiovascular disease mortality (HR, 1.37; CI, 1.02-1.83). This association was similar across subgroups of women, including subgroups defined by age, smoking status, hypertension, postmenopausal hormone therapy, and oral contraceptive use.

■ COMMENTARY

When compared to women who did not suffer from migraines, study results demonstrated that women who reported a migraine were at greater risk for major cardiovascular disease, including heart attacks, strokes, and angina/coronary revascularization procedures. Although all the findings may not be new, they certainly strengthen the evidence supporting migraine as a risk factor for vascular disorders beyond the brain. Migraine already has been known to be associated with a roughly twofold increase in the risk of ischemic stroke and a 1.5-fold increase in the risk of hemorrhagic stroke.[5] With the presence of other risk factors, such as smoking, hyperlipidemia, or the use of oral contraceptives, this risk is further elevated in women experiencing migraines. Although Kurth et al did not ask if participants experienced an aura, these findings, which included a higher risk for cardiovascular mortality, are noteworthy. While the risk may be small at the level of the individual patient, it is significant at a population level because of the wide prevalence of migraines.

[The prudent clinical next step may be to understand that migraine could be a potential risk factor for cardiovascular disease.]

Therefore, these findings really should make clinicians consider adding migraine as perhaps an important risk marker for cardiovascular disease, at least in women. Since some patients presenting with migraines may be subject to lifelong preventive pharmacological therapy, it also is important to consider the role of cardiovascular disease in such patients and how that may interact with other risk factors. Furthermore, future research should evaluate the complex relationship of migraine with other cardiovascular risk factors as well as the role of preventive therapies in possible reduction of cardiovascular events in migraine sufferers.

The prudent clinical next step may be to understand that migraine could be a potential risk factor for cardiovascular disease. Optimizing management of existing cardiovascular risk factors remains the most judicious approach until investigators conduct more research. ■

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ABSTRACT & COMMENTARY

Should Lipid Measurements Be Obtained in the Fasting or Nonfasting State?

By Harold L. Karpman, MD, FACC, FACP

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

SYNOPSIS: When attempting to determine whether fasting or nonfasting lipid measurements are most appropriate in an individual patient, it is important to first think carefully about the clinical scenario and consider what question the results answer.

SOURCE: Driver SL, Martin SS, Gluckman TJ, et al. Fasting or nonfasting lipid measurements: It depends on the question. *J Am Coll Cardiol* 2016;67:1227-1234.

Requiring patients to fast before obtaining a lipid panel is of concern for some patients because of the potential inconvenience of prolonged fasting before, for example, an afternoon visit. Because of the inconvenience of obtaining fasting lipid studies on frequent occasions, Driver et al re-examined the need for obtaining fasting lipid and lipoprotein measurements in various clinical scenarios.[1]

Rather than focusing on the best answer (i.e., fasting or nonfasting), the authors suggested that it was more important first to think carefully about what question is to be answered with the results. The authors concluded that different questions arise depending on the clinical scenario presented by the patient. Different factors to consider include: 1) is the acquired data to be used for estimating the initial global risk from atherosclerotic cardiovascular disease (ASCVD) in the typical primary prevention patient; 2) screening for familial hypercholesterolemia in a patient with a strong family history of premature ASCVD or other genetic dyslipidemia; 3) attempting to clarify a diagnosis of metabolic syndrome; 4) assessing residual risk in a treated patient; 5) diagnosing and treating patients with suspected hypertriglyceridemic pancreatitis; or 6) diagnosing hypertriglyceridemia. Fasting lipid results initially were required when hypertriglyceridemia was studied in 1967, and fasting lipid measurements still were recommended in the third report of the national cholesterol education program.[2,3]

Driver et al concluded that when estimating the ASCVD risk in untreated primary prevention patients or when clarifying the diagnosis of a metabolic syndrome, nonfasting lipid studies were acceptable. However, fasting lipid studies were preferred or required when screening or following patients with a family history of genetic hyperlipidemia or premature ASCVD, when estimating residual risk for a treated patient, when assessing patients with or at risk for pancreatitis, or when diagnosing or following patients with hypertriglyceridemia. If a nonfasting triglyceride level is > 200 mg/dL, perform a follow-up fasting lipid panel.

■ COMMENTARY

When attempting to determine whether fasting or nonfasting lipids are most appropriate, it is important to first review the clinical scenario in individual patients and consider exactly what question is to be answered with the results. If a clinician follows the 2013 American College of Cardiology/American Heart Association guidelines, which suggested using a fixed dose of statin drugs for each risk category, minor differences in lipid results are not of great concern and, therefore, it makes little difference if these results are obtained in the fasting state.[4] However, if the ATP III guidelines are followed, the treat-to-target strategy is to treat to achieve certain goals (i.e., low-density lipoprotein cholesterol < 100 mg/dL for primary prevention in high-risk individuals, < 130 mg/dL for those at intermediate risk, and < 160 mg/dL for low-risk individuals). Therefore, clinicians must obtain fasting lipid measurements. Finally, it is important to recognize that there is

never a benefit to obtaining nonfasting lipid studies except for a minor convenience to the patient on occasion. Therefore, it would seem appropriate to recommend that all lipid studies be obtained in the fasting state unless it is inconvenient or impossible to do so in the individual patient under study. ■

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ABSTRACT & COMMENTARY

Reduced Cardiac Index Is Not Correlated with Renal Function in Heart Failure Patients

By Van Selby, MD

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

SYNOPSIS: In a retrospective analysis of patients with acute decompensated heart failure who received a pulmonary artery catheter, there was no significant correlation between cardiac index and markers of renal function, contradicting the importance of cardiac output in renal dysfunction among patients with heart failure.

SOURCE: Hanberg JS, Sury K, Wilson FP, et al. Reduced cardiac index is not the dominant driver of renal dysfunction in heart failure. *J Am Coll Cardiol* 2016;67:2199-2208.

Renal dysfunction is common among patients hospitalized for heart failure (HF) and associated with a worse prognosis. Many believe reduced cardiac index (CI) is the primary cause of worsening renal function. However, several small studies have suggested CI is not correlated with renal function in HF. No study has thoroughly evaluated the relationship between CI and markers of renal dysfunction in a large, heterogeneous, acute HF population.

Investigators analyzed data from 575 patients enrolled in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) study who received a pulmonary artery catheter (PAC) to guide management of acute decompensated HF. Patients were included whether they were enrolled through the randomized ESCAPE trial or the concurrent PAC registry. The mean ejection fraction was 23%, mean CI was 2.3 L/min/m^2, and mean estimated glomerular filtration rate (eGFR) at baseline was 52.4 mL/min/1.73 m^2. Researchers measured the correlation between CI and eGFR at baseline and evaluated the relationship between changes in CI and eGFR over time.

The overall correlation between baseline CI and eGFR was weak, and higher CI was actually correlated with lower eGFR (r = -0.12; P = 0.02). There was no correlation between CI and eGFR in a broad range of subgroups, including patients with advanced symptoms, worse renal function, or inotrope dependence. Longitudinal changes in renal function were not associated with individual measurements of CI or change in CI over time. In a multivariate analysis, both higher right atrial pressure and higher CI were associated with lower GFR, although hemodynamic predictors accounted for a tiny amount of the observed eGFR variability. The authors concluded that low cardiac output is not the predominant driver for renal dysfunction in patients with decompensated HF.

■ COMMENTARY

The complex relationship between the heart and kidneys in HF patients remains incompletely understood. The concept of decreases in CI driving worsening renal function seems intuitive to many clinicians. The eGFR is related to the product of renal blood flow and the filtration fraction. There-

fore, any factor that reduces overall perfusion (i.e., cardiac index) should reduce the eGFR. This is the largest and one of the most thorough studies to date evaluating the relationship between CI and renal dysfunction and demonstrates convincingly that CI is not the primary driver of renal dysfunction in HF. This is primarily due to renal autoregulation that maintains renal perfusion over a wide range of hemodynamic conditions. Changes in the CI do not have a strong effect on renal blood flow, therefore maintaining eGFR.

The authors impressively used subgroup analyses and longitudinal changes in CI to re-enforce the finding that low CI does not drive renal dysfunction. There was not a single clinical or hemodynamic subset of patients in whom CI and eGFR were positively correlated, including patients with very low CI. Additionally, it also is worth noting the lack of a relationship between CI and renal dysfunction observed in patients referred for PAC placement specifically to evaluate and manage oliguric renal failure. Furthermore, researchers demonstrated that neither baseline nor changes in CI predicts worsening renal function during hospitalization for HF.

So which hemodynamic factors drive renal function in HF? Several studies have identified systolic blood pressure, an important determinant of renal blood flow, as the strongest predictor of renal dysfunction, with the relationship maintained independent of CI. Both the central venous pressure and intra-abdominal pressure contribute to renal venous pressure, and also have been identified as important determinants of GFR in HF. Therefore, factors that alter the perfusion pressure across the kidneys, whether it be lower arterial pressure or higher renal venous pressure, appear to be much more important than the CI in determining eGFR. Increased neurohormonal activation, particularly the sympathetic and renin-angiotensin systems, also plays a role.

There are several limitations to this study. Serum creatinine, which was used to estimate GFR for the primary outcome, is an imperfect measure of renal function. This may be true especially in the decompensated HF population. Creatinine also primarily reflects glomerular filtration and does not account for changes in other components of renal function, such as tubular function.

Although this was not a study of treatment strategies for acute HF, we can make several conclusions based on the findings. First, the practice of starting or uptitrating inotropes to correct renal dysfunction in HF may not be an effective strategy. Similarly, right heart catheterization should not be used indiscriminately to evaluate worsening renal function in patients with acute HF. Rather, efforts to avoid or minimize hypotension and decrease the central venous pressure are more likely to restore perfusion pressure and improve renal function. ■

[Factors that alter the perfusion pressure across the kidneys, whether it be lower arterial pressure or higher renal venous pressure, appear to be much more important than cardiac index in determining estimated glomerular filtration rate.]

PHARMCOLOGY UPDATE

Sofosbuvir and Velpatasvir Tablets (Epclusa)

By William Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Medical Director, Pharmacy, Northern California Kaiser Permanente, and Assistant Clinical 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 FDA has approved the first drug combination for the treatment of all six major genotypes of hepatitis C virus (HCV) infections. The combination contains a previously approved nucleotide analog NS5B polymerase inhibitor, sofosbuvir (SOF), and a newly approved HCV NS5A inhibitor,

velpatasvir (VEL). SOF/VEL is marketed as Epclusa.

INDICATIONS

SOF/VEL is indicated for the treatment of adult patients with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infections.[1] It is approved for patients without cirrhosis, with compensated cirrhosis, or with decompensated cirrhosis (in combination with ribavirin).

DOSAGE

For patients without cirrhosis or with compensated cirrhosis, the recommended dose is one tablet once daily for 12 weeks.[1] For patients with decompensated cirrhosis, the recommended dose is one tablet with weight-based ribavirin for 12 weeks. No dose adjustments are needed for mild-to-moderate renal impairment or mild, moderate, or severe hepatic impairment. Each tablet of SOF/VEL contains 400 mg of sofosbuvir and 100 mg of velpatasvir.

POTENTIAL ADVANTAGES

This is the first drug/drug combination approved for the treatment of the six most prevalent HCV genotypes, as well as for patients with or without cirrhosis.

POTENTIAL DISADVANTAGES

Coadministration of sofosbuvir and amiodarone is not recommended because of potential risk of serious symptomatic bradycardia.[1] Concomitant use with P-gp inducers or moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 also is not recommended. Take precautions with concomitant administration with antacids or histamine-2 receptor antagonists. Avoid proton pump inhibitors unless medically necessary.[1]

COMMENTS

The safety and efficacy of SOF/VEL were evaluated in three trials in patients without cirrhosis or with compensated cirrhosis.[1,2,3] A fourth included subjects presenting with decompensated cirrhosis.[1,4] The primary endpoint was no detectable virus at 12 weeks post-treatment (SVR12).

In the first study, subjects with genotype 1, 2, 4, 5, and 6 were randomized to SOF/VEL for 12 weeks (n = 624) or placebo (n = 116).[1,2] SVR12 ranged from 97% to 100%, compared to 0% for placebo.

Study two compared SOF/VEL for 12 weeks (n = 134) to SOF + ribavirin for 12 weeks (n = 132) in subjects with genotype 2.[1,3] SVR12 rates were 99% vs. 94%. Relapse rates were 0% vs. 5%, respectively.

Study three compared SOF/VEL for 12 weeks (n = 277) and SOF + ribavirin for 24 weeks (n = 275) in subjects with genotype 3.[1,3] Overall, SVR12 rates were 95% compared to 80% (treatment difference of 14.8%; 95% confidence interval, 9.6-20%). SOF/VEL was more effective in treatment-naïve and treatment-experienced without cirrhosis (98% vs. 90%; 94% vs. 71%, respectively). In those with compensated cirrhosis, SVR12 rates were 93% vs. 73%, and 89% vs. 58%, respectively.

Study four compared three regimens: SOF/VEL for 12 weeks, SOF/VEL + ribavirin for 12 weeks, or SOF/VEL for 24 weeks in subjects with genotype 1, 2, 3, 4, and 6 with decompensated cirrhosis.[1,4] Overall, SVR12 rates were 83%, 94%, and 86%, respectively. The most frequently reported adverse events for monotherapy included headache (22%) and fatigue (15%).[1] In combination with ribavirin, adverse events included fatigue (32%), anemia (26%), nausea (15%), headache (11%), insomnia (11%), and diarrhea (10%).

CLINICAL IMPLICATIONS

SOF/VEL has been highly anticipated, as it is the first combination that provides an effective treatment for all genotypes as well as patients presenting with moderate-to-severe cirrhosis. The cost of SOF/VEL (without ribavirin) is $74,760 for 12 weeks of therapy. ■

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Internal Medicine [ALERT]

Clinical Briefs

By Louis Kuritzky, MD

Treatment Selection for Older Adults with Atrial Fibrillation

SOURCE: Garwood CL, Chaben AC. *Ann Longterm Care* 2016;24:31-39.

Risk of stroke in patients with atrial fibrillation (AF) is predicted well by the $CHADS_2$ or CHA_2DS_2-VASc scores. Anticoagulant treatment should be celebrated since clinical trials document a ≥ 60% reduction in stroke, as well as a ≥ 25% mortality reduction compared to placebo. The addition of four so-called novel anticoagulants (NOACs) in recent years for AF requires that clinicians become more astute about individualizing anticoagulant choices, because there are factors that may have a substantial effect on which agent is best for a particular patient. Newer agents may appear at first glance to have enough superiority over warfarin that they generally should be preferred; to the contrary, it has been shown that for warfarin patients who are consistently (at least 66% of the time) within the desired therapeutic range, the risk-reduction performance of warfarin and the novel anticoagulants is essentially the same.

Additionally, compliance may turn out to be more important for patients taking novel anticoagulants than warfarin. For instance, missing a NOAC dose has a much more prompt and greater effect on risk reduction than missing a single dose of warfarin. Twice-daily dosing required for dabigatran and apixaban might be problematic for some but can be solved by utilizing rivaroxaban or edoxaban instead. Many warfarin patients find that dietary modulation is difficult for them and welcome NOACs, which are free of food interactions. Finally, regular blood monitoring required for warfarin is burdensome for some patients; some cost-effectiveness studies have opined that NOACs, despite their much greater up-front costs at the time of purchase, are no more expensive than warfarin over the long term because clinician visits, international normalized ratio monitoring, and travel for these events are eliminated. The decision to begin anticoagulant therapy is a very important one. The diversity of choices now requires closer attention to individual patient characteristics and preferences to ensure best outcomes. ■

Sublingual Desensitization Against House Dust Mites

SOURCE: Virchow JC, et al. *JAMA* 2016;316:1715-1725.

As many as half of asthmatics are sensitized to house dust mites (HDM). Decades of implementation of subcutaneous allergy desensitization have demonstrated two important facts: 1) subcutaneous desensitization can improve asthma in some patients, and 2) although serious adverse reactions to subcutaneous desensitization are rare, asthmatics are the group in which such reactions most often occur. Because of the time and effort necessary to achieve allergen desensitization, only a small minority of asthmatics currently participate in any form of allergen desensitization.

Sublingual immunotherapy is a newer format for allergen desensitization. It can be performed at home and may be preferred by patients who are avoidant of injectable desensitization, but data on asthmatic exacerbations previously has not been studied. Adult asthmatics (n = 834) were randomized to a single sublingual HDM tablet (or placebo) each morning for 18 months. Inclusion required that asthma not be well controlled on inhaled steroids (ICS) or combination inhaled products. Beginning at month 12 of the study, ICS dosing was reduced by half, and at month 15, patients discontinued ICS entirely. The primary endpoint was time to first asthma exacerbation during the ICS-withdrawal phase of the study. HDM sublingual tablets reduced the risk of moderate/severe asthma exacerbations by approximately 30% compared to placebo. HDM was well tolerated, and no serious adverse systemic events occurred. Among the minor adverse effects, oral pruritus was most commonly reported (20% of the high dose HDM treatment group vs. 3% placebo), but all reports of oral pruritus occurred at initiation of treatment onset, and all had disappeared by day five of the clinical trial. Sublingual HDM desensitization is a promising tool for asthmatic patients not well controlled on ICS. ■

Updated Guidelines on Acne Management

SOURCE: Zaenglein AL, et al. *J Am Acad Dermatol* 2016:74:945-973.

There are updated guidelines on the management of acne in adolescents and adults from the American Academy of Dermatology. A multidisciplinary team, which included representatives from dermatology, primary care, pediatrics, and an acne patient participant, generated the guidelines. While it's not possible to adequately summarize this lengthy document in a few words, several noteworthy principles merit sharing with all primary care clinicians who address acne in their practices.

For mild acne, recommended first-line treatments include benzoyl peroxide, topical retinoids, and topical antibiotics (clindamycin preferred), with topical dapsone considered an alternative. Topicals may be used as monotherapy, dual, or even triple combination, except for topical antibiotics, which are not recommended as monotherapy due to emergence of bacterial resistance. For moderate acne, monotherapy is not considered first line; rather, dual or even triple combination topicals (benzoyl peroxide, antibiotics, retinoids), oral antibiotics plus dual/triple topicals, or (for women) oral contraceptives and spironolactone are options. Although not a usual treatment, isotretinoin becomes a consideration when moderate-to-severe acne has not responded to first-line treatments. Systemic antibiotics (e.g., doxycycline, TMP/SMX, azithromycin, cephalexin) are useful in moderate-to-severe acne, and are recommended to be used in combination with benzoyl peroxide and topical retinoids (but not in combination with topical antibiotics). Tetracycline is the preferred antibiotic class. The new guidelines provide a useful template on which to plan management of acne at all levels of severity. ■

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CME QUESTIONS

1. **Based on the study by Kurth et al, researchers found that compared to women without migraine, those with migraine had an approximately __% increased risk for major cardiovascular disease:**

   a. 20

   b. 30

   c. 50

   d. 60

2. **When deciding whether to obtain fasting or nonfasting lipid studies:**

   a. nonfasting studies should never be obtained.

   b. it is important to think about the clinical scenario and consider what question is to be answered with the results.

   c. only fasting studies should ever be obtained.

   d. None of the above

3. **The major determinant of renal function in acute heart failure patients is:**

   a. cardiac index.

   b. renal perfusion pressure.

   c. atrial natriuretic protein levels.

   d. cardiac inotropic state.

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]

Intensive vs. Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults ≥ 75 Years of Age