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ABSTRACT & COMMENTARY

Investigating the Relationship Between Achieved Blood Pressure and Cardiovascular Outcomes

By Harold L. Karpman, MD, FACC, FACP

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

SYNOPSIS: In patients suffering from hypertension and coronary artery disease in routine clinical practice, systolic blood pressure of < 120 mmHg and diastolic blood pressure < 70 mmHg each were associated with adverse cardiovascular outcomes, including mortality, supporting the existence of a J-curve phenomenon.

SOURCE: Vidal-Petiot E, Ford I, Greenlaw N, et al. Cardiovascular event rates and mortality according to achieved systolic and diastolic blood pressure in patients with stable coronary artery disease: An international cohort study. *Lancet* 2016 388:2142-2152.

Lowering blood pressure (BP) in patients suffering from hypertension reduces the risk of cardiovascular events and death,[1,2] but the optimum target BP remains unresolved.[1-4] Some randomized trials have not shown a benefit of BP targets of < 140/90 mmHg. In fact, some published analyses have suggested that the benefits of BP lowering even may be reversed below a certain threshold,[5-9] the so-called J-curve phenomenon.[6] Vidal-Petiot et al studied the association between achieved BP levels and cardiovascular outcomes in a large cohort of patients presenting with stable coronary artery disease treated for hypertension in the CLARIFY study.[11]

The CLARIFY study was a prospective observational, longitudinal registry of patients presenting with stable coronary artery disease and included 32,703 patients receiving standard care for hypertension. The study was conducted in 45 countries, excluding the United States. All eligible patients presented with stable coronary artery disease and were receiving treatment with at least one antihypertensive drug for hypertension, defined as

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BP readings > 140/90 mmHg. BP in the office was measured annually in patients after a rest of five minutes in the sitting position. The primary outcomes measured were the composite of cardiovascular death, myocardial infarction, or stroke, and the measured secondary outcomes were each component of the primary endpoints and all-cause death and hospital admission for heart failure. The results of this very large observational, international cohort study revealed that elevated systolic BP and/or low diastolic BP levels were associated with an increased risk of cardiovascular events in patients suffering from coronary artery disease and hypertension. The authors observed the increased risk both over a threshold of 140/90 mmHg and under a threshold of 120/70 mmHg, resulting in a J-curve phenomenon.

■ COMMENTARY

The results from the CLARIFY trial are consistent with the results from previous analyses conducted in other randomized trials that studied patients with hypertension and coronary artery disease.[7,12] Although the J-curve effect was robust and persisted after multiple adjustment procedures for potential confounders, the study was based on a large cohort from routine clinical practices with no predefined BP intervention, which might confound the analysis.

Of course, the strength of the study lies in the accuracy of the baseline and follow-up BP determinations. Another particular strength of the study is that it included a large international cohort of patients treated under real-life conditions, which might provide greater validity than the highly selected populations studied in numerous published randomized trials.[13]

The benefit of the observations is that they are in agreement with the results of other published studies, which concluded that the benefit of lowering BP to < 140 mmHg remains unquestionable, whereas the benefit of lowering BP to < 130 mmHg is uncertain.[6,7]

Systolic BP > 140 mmHg should be lowered to at least 130 mmHg, but lowering systolic BP to less than that value may actually cause harm. Lowering diastolic BP to 70-79 mmHg is associated with a better outcome than leaving diastolic BP at ≥ 80 mmHg, which is consistent with results from SPRINT.[14] However, trial results stand as strong evidence against lowering diastolic BP to < 70 mmHg.

[Clinicians should be fully aware of the fact that both systolic *and* diastolic BP readings should be carefully managed and, if abnormal, be brought to appropriate levels.]

Clinicians should be fully aware of the fact that both systolic *and* diastolic BP readings should be carefully managed and, if abnormal, be brought to appropriate levels as outlined above, but not to abnormally low or high levels. ■

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ABSTRACT & COMMENTARY

How Is Iron Deficiency Connected to Hearing Loss?

By Seema Gupta, MD, MSPH

Clinical Assistant Professor, Department of Family and Community Health, Joan C. Edwards School of Medicine, Marshall University, Huntington, WV

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

SYNOPSIS: A large-scale retrospective cohort study found that iron deficiency anemia was associated positively with sensorineural hearing loss and combined hearing loss.

SOURCE: Schieffer KM, Chuang CH, Connor J, et al. Association of iron deficiency anemia with hearing loss in U.S. adults. *JAMA Otolaryngol Head Neck Surg* 2016 Dec 29. doi: 10.1001/jamaoto.2016.3631. [Epub ahead of print].

Worldwide, iron deficiency is a major public health challenge, especially in women of childbearing age, children, and those living in poverty. Iron deficiency anemia (IDA) occurs when iron deficiency becomes significant enough to diminish erythropoiesis, resulting in the development of anemia. Although iron deficiency caused solely by diet is uncommon in adults in North America and Europe, it is most common in women of childbearing age and as a manifestation of hemorrhage. In the United States, data indicate 9-11% of women of adolescent and/or childbearing age suffer from iron deficiency, while IDA may exist in approximately 2-5% of these individuals.[1] The prevalence of iron deficiency also correlates with the state of pregnancy as well as with a greater number of pregnancies.[2] In contrast, the prevalence of hearing loss in the United States population is quite widespread. In fact, data estimates show that approximately 12.7% of Americans ≥ 12 years of age suffered bilateral hearing loss from 2001-2008, and this estimate increased to approximately 20.3% when individuals who suffered unilateral hearing loss also were included.[3] Additionally, the prevalence of hearing loss is expected to rise as the population ages. Hearing loss increases with each decade of life, affecting 40-66% of adults > 65 years of age and 80% of those > 85 years of age. Sudden sensorineural hearing loss (SNHL) is a type of permanent hearing loss in which the vestibular cochlear nerve, inner ear, or central processing centers of the brain are suddenly affected, leading to a rapid deterioration of the hearing function in less than a 72-hour period. Risk factors for earlier onset of adult hearing loss may include hypertension, diabetes, and tobacco use. Interestingly, recent research has found a significant association between sudden SNHL and prior IDA.[4]

In their research, Schieffer et al conducted a retrospective study involving 305,339 adults 21-90 years of age living in the United States. Of the patients in the study population, approximately 43% of those patients were men, and the mean age was 50 years. The researchers assessed the prevalence of IDA and hearing loss in this population, including SNHL, conductive hearing loss, and combined hearing loss. The study revealed a 1.6% prevalence of combined hearing loss and 0.7% prevalence of IDA. Both SNHL (present in 1.1% of individuals with IDA; $P = 0.005$) and combined hearing loss (present in 3.4% individuals with IDA; $P < 0.001$) were significantly associated with IDA. Furthermore, a logistic regression analysis confirmed that the overall risk for SNHL in someone with IDA was 82% higher

than for those without IDA (adjusted odds ratio [OR], 1.82; 95% confidence interval [CI], 1.18-2.66). Individuals with IDA also had a 2.4 times greater risk of combined hearing loss (adjusted OR, 2.41; 95% CI, 1.90-3.01) compared to those without IDA, after adjusting for sex.

■ COMMENTARY

With a well-conducted, large retrospective study, the authors made a strong case for the existence of an association between IDA in adults and hearing loss. There may be several potential mechanisms by which IDA may affect hearing health. Although the role of iron in the inner ear has not been clearly established, vascular supply to this area is critical. IDA may exacerbate conditions, leading the cochlear area to become susceptible to ischemic damage. The study results raise concerns about the potential role of iron in the vasculature and nervous system and, thus, the possibility of its association with other common types of adult hearing loss beside SNHL. Although IDA has been demonstrated to be a potential risk factor for ischemic stroke due to lower hemoglobin levels, leading to impaired oxygen-carrying capacity, the increased risk of IDA in patients with reactive thrombocytosis may be another potential vascular mechanism that may relate IDA to hearing loss.[5,6]

As iron deficiency, as well as the resultant anemia, can be treated easily with several months of oral iron supplementation in most cases, the real clinical question remains whether early diagnosis and treatment of IDA or iron deficiency could positively affect the overall health status of adults with hearing loss or even prevent hearing loss. Additional studies surely are needed to determine whether there is a link between iron supplementation and improving the hearing status in adults. Meanwhile, it would make clinical sense to continue to diagnose and treat iron deficiency while knowing that we may be preventing potential hearing loss. For everyone else, we can reiterate that a healthy, well-balanced diet that meets the daily recommended intake of vitamins and nutrients such as iron not only may help in physical and mental well-being but also potentially with hearing health by preventing premature, permanent hearing loss. ■

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ABSTRACT & COMMENTARY

Does Long-term, Low-intensity Smoking Result in Similar Mortality Risks as Heavier Smokers?

By Tim Drake, PharmD, MBA, BCPS, and Martin S. Lipsky, MD

Dr. Drake is Assistant Professor of Pharmacy, College of Pharmacy, Roseman University of Health Sciences. Dr. Lipsky is Chancellor, South Jordan Campus, Roseman University of Health Sciences, South Jordan, UT.

Drs. Drake and Lipsky report no financial relationships relevant to this field of study.

SYNOPSIS: Individuals who smoke fewer than 10 cigarettes per day over their lifetime have a higher risk of mortality than those who have never smoked cigarettes.

SOURCE: Inoue-Choi M, Liao LM, Reyes-Guzman C, et al. Association of long-term, low-intensity smoking with all-cause and cause-specific mortality in the National Institutes of Health-AARP Diet and Health Study. *JAMA Intern Med* 2017;177:87-95.

Smoking cigarettes continues to be a major health problem around the world. Smoking cessation and awareness programs have led to decreased rates of persons smoking cigarettes and decreased intensity of smoking. However, the number of low-intensity smokers is increasing, and from 2005-2014

the percentage of smokers who only smoke between one and 10 cigarettes per day increased 11% (from 16-27%).[1] Although there is a perception that smoking fewer cigarettes is less harmful, the duration of smoking is thought to be a more important contributor to disease risk than the number of cigarettes smoked per day. However, there are little data about the adverse effects from long-term, low-intensity smoking.[2]

This prospective, cohort study examined 290,215 persons 59-82 years of age participating in the National Institutes of Health-AARP Diet and Health Study between 2004-2005. Historical smoking data were obtained by questionnaire. Patients were followed through the end of 2011.

The primary outcome was all-cause mortality, and secondary outcomes included cause-specific mortality. Hazard ratios (HR) were determined for the primary and secondary endpoints through Cox proportional hazards regression models using age as the time metric and adjusting for sex, race/ethnicity, educational level, physical activity, and alcohol intake. Low-intensity smoking was defined as either less than one cigarette per day (CPD) or 1-10 CPD. The average age of study participants was 71 years, and 57.9% were male. Compared to never-smokers, those who smoked less than one CPD demonstrated a 64% higher risk of mortality, and those who smoked 1-10 CPD demonstrated an 87% increase in mortality (HR, 1.64; 95% confidence interval [CI], 1.07-2.51 and HR, 1.87; 95% CI, 1.64-2.13, respectively). These results were similar when looking at individual causes of mortality with a strong association with lung cancer (HR, 9.12; 95% CI, 2.92-28.47, and HR, 11.61; 95% CI, 8.25-16.35 for less than one and 1-10 CPD, respectively). Additionally, former low-intensity smokers also had a higher risk of mortality compared to never-smokers, but a lower risk compared to those who continue to smoke. Finally, mortality risk increases with increased intensity of smoking.

The study concluded that consistent low-intensity smoking increases the risk of premature mortality compared to those who never smoke.[3] There is no "safe" level of cigarette smoking.

■ COMMENTARY

The 2014 Surgeon General's report on smoking states that since 1964, more than 20 million premature deaths are attributable to smoking.[4] Healthcare practitioners spend time with patients counseling them to quit tobacco. If patients do not quit, many physicians congratulate patients if they reduce the number of cigarettes they smoke per day. After all, it does make sense that a lower dose of a toxic substance should substantially reduce its health-associated risks. However, while it appears that less tobacco use lowers risk, even smoking less than one cigarette per day increases mortality risk by 64% over those who never smoked and also increases the risk of lung cancer. For those smoking 1-10 CPD, cancer risk increases by 12% over those who never smoked. These findings by Inoue-Choi et al highlight the need to advise patients that there is no level of "safe" smoking, and that for patients to optimize their health they need to abstain completely from tobacco. Additionally, if there is an increased mortality risk with the consistent use of even less than one CPD, how many patients get the equivalent of one CPD through second-hand smoke, and what is their relative risk to those with no exposure?

[Our guess is that most patients and providers underestimate the risk of low-intensity smoking, and continued education aimed at increasing the awareness of the risk of even low levels of tobacco use is needed for both the public and providers.]

Our guess is that most patients and providers underestimate the risk of low-intensity smoking, and continued education aimed at increasing the awareness of the risk of even low levels of tobacco use is needed for both the public and providers. ■

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PHARMACOLOGY UPDATE

Plecanatide Tablets (Trulance)

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

Dr. Elliott is Assistant Clinical Professor of Medicine, University of California, San Francisco. Dr. Chan is Associate Clinical Professor, School of Pharmacy, University of California, San Francisco.

Drs. Elliott and Chan report no financial relationships relevant to this field of study.

The FDA has approved a new drug for the treatment of chronic idiopathic constipation (CIC) in adults. Plecanatide is the second guanylate cyclase-C agonist (GC-C; after linaclotide) and is marketed as Trulance.

INDICATIONS

Plecanatide is indicated for the treatment of CIC.[1]

DOSAGE

The recommended dose is 3 mg taken orally once daily with or without food.[1] The tablets can be crushed and mixed with applesauce or administered with water via a nasogastric or gastric feeding tube. Plecanatide is available as 3 mg tablets.

POTENTIAL ADVANTAGES

Plecanatide provides another option for the treatment of CIC.

POTENTIAL DISADVANTAGES

Diarrhea is the most common adverse event (5% vs. 1% for placebo).[1] Severe diarrhea was reported in 0.6% (vs. 0.3% for placebo).

COMMENTS

GC-C regulates intestinal fluid and electrolyte homeostasis.[2] Stimulation of the GC-C receptor results in fluid movement into the gut lumen and facilitates defecation. Plecanatide's action is limited to the gastrointestinal tract as the drug is minimally absorbed. The safety and efficacy of plecanatide were evaluated in two randomized, placebo-controlled, 12-week trials.[1,5] Subjects experienced constipation in line with the modified Rome III criteria for at least three months. Subjects basically experienced fewer than three complete spontaneous bowel movements (CSBMs) during each of the last weeks prior to randomization, along with straining during defecation, lumpy or hard stools, and sensation of anorectal obstruction/blockage. A CSBM is a bowel movement that occurs in the absence of laxative use within 24 hours and is associated with the feeling of complete evacuation.[5] Subjects were randomized to plecanatide 3 mg daily (n = 453 and 430) or placebo (n = 452 and 440). Efficacy was assessed based on CSBMs, with a responder defined as having at least three CSBMs in a given week and an increase of at least one CSBM from baseline in the same week for at least nine weeks out of the 12 treatment weeks and at least three of the last four weeks of the study. Response rates were 21% vs. 10% in study one and 21% vs. 13% for study two, with a treatment difference of 11% (6.1, 15.4) and 8% (2.6, 12.4), respectively. The mean change in CSBMs/week from baseline to week 12 was 1.1 CSBMs/week. Stool frequency, stool consistency, and amount of straining generally improved. When plecanatide was discontinued, subjects generally returned to baseline. There currently are no published comparative studies between linaclotide (Linzess) and plecanatide. Treatment difference for linaclotide were 17% (11, 22.8) and 10% (4.2, 15.7) in two similar studies for the treatment of CIC.[4] The cost for plecanatide was not available at the time of this review.

CLINICAL IMPLICATIONS

CIC is persistent constipation for which there is no structural or biochemical explanation.[3,6] Plecanatide is the second GC-C agonist to be approved. In contrast to linaclotide, plecanatide currently is not approved for irritable bowel syndrome with constipation. ■

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Clinical Briefs

By Louis Kuritzky, MD

Identifying Risk for Macrovascular Events in Diabetes Patients

SOURCE: Mohammedi K, Woodward M, Zoungas S, et al. Absence of peripheral pulses and risk of major vascular outcomes in patients with type 2 diabetes. *Diabetes Care* 2016;39:2270-2277.

Cardiovascular disease is the most common cause of death for patients suffering from type 2 diabetes. Even though it is also common for type 2 diabetes patients to suffer from dyslipidemia and hypertension, the cardiovascular disease risk is disproportionate to these burdens. How might we better identify type 2 diabetes patients who are at particularly high risk?

Creators of the ADVANCE trial enrolled type 2 diabetes patients (n = 11,120) and compared tight vs. standard glucose control for cardiovascular disease outcomes. However, the authors were unable to confirm any macrovascular benefit of tight control.

At enrollment into ADVANCE, researchers sought and recorded peripheral pulses (dorsalis pedis and posterior tibial, bilaterally) on physical exam.

Over a median of five years of follow-up, absence of either pulse predicted increased risk for myocardial infarction, stroke, cardiovascular death, heart failure, and all-cause mortality.

The absence of either of the pulses had similar predictive value, and risk of adversity increased with the number of missing pulses.

Diabetic patients deserve our best efforts to prevent, forestall, or mitigate cardiovascular events. The simple clinical maneuver of peripheral pulse palpation can help us identify a subgroup of type 2 diabetes patients who are at measurably increased risk. ■

Atrial Fibrillation Still a Mortal Disorder

SOURCE: Fauchier L, Villejoubert O, Clementy N, et al. Causes of death and influencing factors in patients with atrial fibrillation. *Am J Med* 2016;129:1278-1287.

The advent of warfarin for anticoagulation in patients presenting with atrial fibrillation (AF) provided dramatic risk reductions; more than 60% reduced risk of ischemic stroke, and more than 25% reduced mortality. The addition of novel anticoagulants (factor Xa and antithrombin agents) reduces risk even more.

It may come as a surprise that of the 5.5% annual risk of death noted in a population of AF patients, the three most common causes of death were heart failure (29%), infection (18%), and cancer (12%).

Of course, anticoagulation does not totally eliminate stroke-related deaths in AF, not only because not all strokes may be caused by other disorders besides AF, but also because utilization of anticoagulants, particularly warfarin, also is imperfect.

Stroke and bleeding remain less frequent, but nonetheless important, causes of death in the AF population studied (n = 7,668), each accountable for 7% of deaths.

Although we have much to celebrate in the efficacy of established and novel treatments for stroke prevention in AF, the authors proposed that we might pay greater attention to prevention, identification, and management of heart failure, as it is the most frequent cause of death in patients presenting with AF. ■

Prophylaxis of Genital Herpes Recurrences with Antivirals

SOURCE: Sands-Lincoln M, Goldmann DR. Antiviral drugs to prevent clinical recurrence in patients with genital herpes. *Am J Med* 2016;129:1264-1266.

For now, herpes has outsmarted us. Antivirals can reduce the duration of acute attacks, decrease the number of days of viral shedding, and reduce the frequency of recurrences, but they do not eradicate the latent virus or alter the natural course of disease. Once antiviral treatment ends, the frequency and severity of attacks resumes unaltered.

However, the good news is that the three currently approved antivirals (acyclovir, famciclovir, valacyclovir) can produce a major, albeit imperfect, effect on recurrences when administered daily as prophylaxis. The literature suggests recurrences can be reduced by as much as 70-80% in patients presenting with frequent recurrences.

Long-term data (one to six years) support the safety and efficacy of the antivirals, each of which has demonstrated similar benefit.

In the absence of head-to-head clinical trials, no substantial differences in efficacy or tolerability among the three potential treatments have been demonstrated.

Our experience with antivirals against influenza has taught us that problematic levels of resistance can occur quickly, but similar trends for genital herpes have not been observed. ■

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CME QUESTIONS

1. Use caution in prescribing blood pressure-lowering medication to patients suffering from hypertension and coronary artery disease if:

a. systolic blood pressure drops to < 120 mmHg and/or diastolic blood pressure drops to < 70 mmHg.

b. heart rate increases more than 10%.

c. systolic blood pressure drops to < 135 mmHg.

d. diastolic blood pressure drops to 80 mmHg.

2. Based on the study by Schieffer et al, the overall risk for sensorineural hearing loss in someone presenting with iron deficiency anemia was ____ higher than for those without iron deficiency anemia.

a. 50%

b. 74%

c. 82%

d. 96%

3. Which of the following statements is true regarding smoking and mortality risk?

a. The adverse effects of smoking correlate more closely with the duration of smoking than with the intensity of tobacco use.

b. Smoking less than one cigarette per day doubles the risk of lung cancer.

c. Smoking less than one cigarette per day increases all-cause mortality by about two-thirds compared to those who never smoked.

d. None of the above

e. Both a and c

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]

Amyloid PET Imaging in the Diagnosis of Dementia

Polyneuropathy in the Metabolic Syndrome