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ABSTRACT & COMMENTARY

Too Little of a Good Thing Can Be a Bad Thing

By Martin Lipsky, MD

Chancellor, South Jordan Campus, Roseman University of Health Sciences, South Jordan, UT

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

SYNOPSIS: A healthy lifestyle may substantially reduce the burden of cancer.

SOURCE: Song M, Giovannucci E. Preventable incidence and mortality of carcinoma associated with lifestyle factors among white adults in the United States. *JAMA Oncol* 2016 May 19. doi: 10.1001/jamaoncol.2016.0843. [Epub ahead of print].

Cancer remains the second leading cause of death in the United States, with 1.6 million new cancers and 600,000 deaths projected for 2016.[1] Although the annual adjusted death rate continues declining, the reduction in cancer deaths is modest when compared to deaths from cardiovascular disease. One explanation for this slower decline comes from a recent study that suggested the number of lifetime cell divisions correlates with the lifetime risk of cancer.[2] This study led some experts to conclude that only one-third of cancer risk is attributable to environmental factors and that cancer mutations may be more closely related to so-called bad luck. To shed more light on the role of environmental factors, Song and Giovannucci estimated the contribution of common lifestyle factors to cancer risk and the effect of lifestyle modification on preventing cases and deaths from carcinoma.

The authors used four criteria to define a healthy lifestyle: never smoking or quit smoking; drinking either no alcohol or a maximum of one drink a day for women and two or less for men; a body mass index (BMI) of > 18.5 kg/m^2 but < 27.5 kg/m^2; and weekly aerobic exercise, either ≥ 150 minutes of moderately intense activity or 75 minutes of vigorous activity. The study population included those enrolled in the Nurses' Health Study (NHS) and the Health Professionals Follow-Up Study. Individuals meeting all lifestyle criteria were considered low risk, while those who did not were defined as high risk. The authors calculated the population-attrib-

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utable risk (PAR) by comparing incidence and mortality of total and major individual carcinomas between the low- and high-risk groups. The researchers further assessed the PAR by comparing the low-risk group to the U.S. population.

The total study group included 89,571 women and 46,339 men from the two cohorts, with 16,531 and 11,731 men assigned to the low-risk group. Within the two cohorts, investigators found that between 20-40% of cancer cases and about 50% of cancer deaths possibly could be prevented if individuals adopted the low-risk group lifestyle. The study also examined specific cancers and found the PAR varied by cancer type in the prospective cohorts from a high of 82% for lung cancer risk in women (78% in men) to lows of 4% for breast cancer and 21% each for endometrial, ovarian, and fatal prostate cancers. The PARs were substantially higher when comparing the health lifestyle group to the U.S. population, ranging from a high of 85% for lung cancer risk in women to a low of 15% for breast cancer.[3]

The authors concluded that a substantial cancer burden may be prevented through lifestyle modification, and that primary prevention should remain a priority for cancer control.

■ COMMENTARY

The study findings certainly should resonate with primary care physicians, adding to the large body of evidence supporting the benefits of a healthy lifestyle. Although the link between lifestyle and cardiovascular disease is well recognized, the connection between cancer and lifestyle may be less appreciated. In terms of return on investment, a healthy lifestyle and primary prevention trump cancer screening strategies that often seem to be more fully embraced by the public and providers. Song and Giovannucci believe their findings reinforce the importance of lifestyle in determining cancer risk and the value of primary prevention strategies.[3] As Colditz and Sutliffe succinctly noted in an accompanying editorial, cancer is not inevitable but should be viewed as a potentially preventable disease.[4] They recommend an array of interventions targeting individuals, clinicians, communities, and society.[3]

Unfortunately for clinicians who embrace primary prevention, there is often little reward or time to support their efforts to counsel patients and families about lifestyle. Although research supports the benefit of counseling, it remains challenging for physicians to find the time to adequately counsel individuals and families in a healthcare environment that may allow only 15 minutes per patient visit. The findings of this study should serve to help both motivate individuals and clinicians to address primary prevention and policy to support these activities from the reimbursement perspective. While no one should ignore the importance of new medical discoveries in cancer treatment and diagnosis, the new moonshot proposal to cure cancer should not overlook the value of prevention in reducing the morbidity and mortality of this dreadful disease.[5] ■

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ABSTRACT & COMMENTARY

Wheat Causes Intestinal Immune Activation in Some Patients Without Celiac Disease

By Joseph E. Scherger, MD, MPH

Vice President, Primary Care, Eisenhower Medical Center; Clinical Professor, Keck School of Medicine, University of Southern California

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

SYNOPSIS: Some patients without celiac disease may exhibit wheat sensitivity with demonstrated intestinal epithelial cell damage.

SOURCE: Uhde M, Ajamian M, Caio G, et al. Intestinal cell damage and systemic immune activation in individuals reporting sensitivity to wheat in the absence of coeliac disease. *Gut* 2016. doi:10.1136/gutnl-2016-311964. Published online July 25, 2016.

A team at Columbia University studied 80 individuals who reported on a standardized questionnaire sensitivity to wheat, rye, or barley. Researchers compared these subjects with 40 individuals suffering from celiac disease and 40 healthy individuals exhibiting no symptoms. Those with non-celiac wheat sensitivity (NCWS) experienced intestinal symptoms (bloating, abdominal pain, diarrhea, epigastric pain, and nausea) and extraintestinal symptoms (fatigue, headache, anxiety, memory and cognitive disturbances, and numbness of the arms or legs). These symptoms improved or disappeared when subjects removed wheat, rye, and barley from their diets for six months. The symptoms recurred when subjects reintroduced these food items for up to one month.

The authors performed serum samples and intestinal biopsies on all the study subjects and controls. Those with NCWS did not exhibit the IgA antibodies or TG2 autoantibodies specific for celiac disease. These subjects also did not have the intestinal histologic findings specific for celiac disease. Those presenting with NCWS showed changes in the serum and intestinal epithelium that researchers did not observe in the healthy controls. These findings include increased levels of soluble CD14 and lipopolysaccharide-binding protein, indicating systemic immune activation. NCWS subjects also showed increased levels of fatty acid-binding protein 2, suggesting compromised intestinal barrier integrity. The intestinal biopsies of subjects with NCWS showed epithelial cell damage not seen in healthy controls and that was different from the changes seen in celiac disease. These abnormalities largely resolved during the six months away from the offending foods.

■ COMMENTARY

This study provides further biologic evidence for the "leaky gut" changes postulated in patients consuming gluten-containing foods of wheat, rye, and barley. Uhde et al chose to use wheat and related grains as the culprits, since other proteins may be involved beyond the gluten complex of gliadins and glutamines. The prevalence of NCWS is unknown, and it is not clear if most patients complaining of "gluten sensitivity" experience any of these changes.

The range of intestinal and extraintestinal symptoms these patients experience — as well as their resolution after removal of the offending foods — is impressive. These results match with my practice experience. I routinely recommend the removal of wheat, rye, and barley from all patients presenting with gastroesophageal reflux (GERD) and irritable bowel syndrome, with clinical improvement or resolution of symptoms in most patients. I am gratified to wean many patients off proton pump inhibitors or H2 blocking medications. I also find that many patients with chronic fatigue and fibromyalgia symptoms improve or recover with elimination of these foods. The full list of symptoms and diagnoses associated with inflammatory grains is quite long.

This study did not address the association of inflammatory grains with a variety of autoimmune diseases. This area and the role of the gut microbiome have been explored in other reports.[1-6]

The specific biologic results shown in this controlled study should help us recognize the importance of understanding how inflammatory grains may be harming our patients. The time is now to use an elimination diet with many of our patients. ■

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ABSTRACT & COMMENTARY

Greater Weight Loss Later in Life Associated with Increased Risk of Mild Cognitive Impairment

By Makoto Ishii, MD, PhD

Assistant Professor of Neuroscience and Neurology, Feil Family Brain and Mind Research Institute, Department of Neurology, Weill Cornell Medical College

Dr. Ishii reports he is a stockholder in Regeneron.

SYNOPSIS: In a population-based, prospective study of subjects ≥ 70 years of age, increasing weight loss per decade from midlife to late-life was associated with an increased risk of incident mild cognitive impairment.

SOURCE: Alhurani RE, Vassilaki M, Aakre JA, et al. Decline in weight and incident mild cognitive impairment: Mayo Clinic Study of Aging. *JAMA Neurol* 2016;73:439-446.

Alzheimer's disease (AD) currently remains an incurable disease. Identifying patients with increased risk or with the earliest clinical manifestations of AD could present a significant effect on finding new strategies for the prevention and treatment of AD. Mild cognitive impairment (MCI) is an early prodromal stage of dementia, where every year approximately 5-15% of patients suffering from MCI will progress to dementia. Previously, weight loss has been reported to increase dementia risk and precedes the cognitive decline, but it remains unclear if greater weight loss from midlife to late-life is a prodromal manifestation of dementia that is associated with incident MCI.

Alhurani et al investigated whether greater weight loss was associated with incident MCI using participants from the Mayo Clinic Study of Aging, an ongoing, prospective, population-based study initiated on Oct. 1, 2004. Eligible subjects, who were 70-89 years of age at study initiation and without dementia or in hospice care, were recruited randomly and underwent follow-up evaluations every 15 months. Inclusion criteria included normal cognition at baseline evaluation, at least one follow-up evaluation, and data available on maximum weight and height in midlife. All participants were administered the Clinical Dementia Rating Scale and the Functional Activities Questionnaire, and underwent extensive neuropsychological and neurological evaluation. A diagnosis of MCI, dementia, or normal cognition was made by consensus. Body mass index (BMI) was computed from the measured height and weight at each evaluation, and the maximum weight and height in midlife were determined from the medical records of each participant. At the baseline visit, researchers obtained all demographic variables, medical history, smoking and alcohol use, and apolipoprotein E4 (APOE4) carrier status by genotyping.

Of the 1,895 cognitively normal participants at baseline (50.3% men; mean age, 78.5 years), 524 (27.7%) participants developed incident MCI over a mean follow-up of 4.4 (standard deviation, 2.4) years. Participants who developed MCI were older, more likely to be APOE4 carriers, and more likely to present with diabetes, hypertension, or coronary artery disease compared with those participants who remained cognitively normal. Furthermore, the mean weight change was greater for those who developed incident MCI than those who remained cognitively normal (-2.0 [5.1] vs. 1.2 [4.9] kg; $P = 0.006$). Men who developed incident MCI had greater mean loss of weight per decade than men who did not (-2.1 [5.3] vs. -1.0 [4.6]; $P = 0.02$), but there was no significant difference in women (-1.9 [4.8] vs. -1.5 [5.3]; $P = 0.12$).

After adjusting for sex, education, and APOE4 carrier status, a greater decline in weight from midlife was associated with an increased risk of incident MCI (hazard ratio [HR], 1.04; 95% confidence interval, 1.02-1.06; $P < 0.001$). A weight loss of 5 kg/decade corresponded to a 24% increased MCI risk (HR, 1.24). Additionally, adjusting simultaneously for potential confounding factors such as alcohol problems, depressive symptoms, statin use, diabetes, hypertension, coronary heart disease, cigarette smoking, and stroke, still resulted in the same association between weight change and MCI. The effect sizes

were greater in men than in women, but they were significant in both sexes. Interestingly, the authors observed a consistent association between weight loss and MCI, regardless of whether the participants were underweight, normal weight, overweight, or obese at midlife.

■ COMMENTARY

This study is consistent with other prospective studies that found a correlation between weight loss and increased dementia risk. Importantly, the authors hypothesized that weight loss may represent a prodromal or early manifestation of MCI, and, therefore, weight loss should occur regardless of midlife weight. Overall, the findings were consistent with this hypothesis and provide further evidence that weight loss is an early clinical manifestation of AD.

The strength of this paper is that it is a well-designed prospective population study with a relatively large cohort that had the ability to assess body weights from medical records of the participants for midlife and from direct measurements in late-life. Therefore, this study avoided confounding factors that may exist in other studies, such as lack of clarity on age at assessment of weight, BMI, and onset of dementia. A limitation of this study is that the diagnosis of MCI or dementia was based on a clinical diagnosis rather than on established pathological markers, leaving the possibility for misclassification. Another limitation is that it was not possible to determine whether the weight loss was intentional or unintentional, although the consistent association of weight loss with incident MCI across all midlife weight classes suggests that it is likely unintentional.

Finally, this study could not address the causal mechanism of the weight loss in prodromal stages of dementia. Clinicians speculate that dysfunction in factors that regulate body weight, such as leptin and other hormones, could contribute. Alternatively, amyloid and/or tau deposition in brain regions that control appetite and/or systemic metabolism, such as the hypothalamus or olfactory bulb, could play a role in weight loss. Future investigations using molecular approaches in mouse models and well-designed human studies are likely to help elucidate the mechanisms underlying weight loss in AD, which may eventually lead to the development of new diagnostic and therapeutic approaches against AD. ■

BRIEF REPORT

Dual Antiplatelet Therapy Appears More Effective Than Single Therapy

By Matthew E. Fink, MD

Professor and Chairman, Department of Neurology, Weill Cornell Medical College; Neurologist-in-Chief, New York Presbyterian Hospital

Dr. Fink reports he is a retained consultant for Proctor & Gamble and Pfizer.

SOURCE: Ge F, Lin H, Liu Y, et al. Duel antiplatelet therapy after stroke or transient ischemic attack – how long to treat? The duration of aspirin plus clopidogrel in stroke or transient ischemic attack: A systematic review and meta-analysis. *Eur J Neurol* 2016;23:1051-1057.

The CHANCE study showed that the combination of aspirin and clopidogrel was superior to aspirin alone for reducing the risk of stroke in the first 90 days after a transient ischemic attack (TIA) or minor ischemic stroke (*N Engl J Med* 2013;369:11-19). In its 2014 guidelines, the American Heart Association recommended initiating the combination of aspirin and clopidogrel within 24 hours for a minor ischemic stroke or TIA and continuing for 90 days. However, the CHANCE trial was performed in China with a discrete ethnic population, and it was not clear if the optimal duration of treatment should be 90 days or longer. In ischemic heart disease, treatment with dual antiplatelet therapy beyond one year is the standard of care in patients who have coronary stents, and this question has been unanswered in patients who suffer a TIA or stroke. Therefore, Ge et al performed a comprehensive literature review and meta-analysis, and identified nine randomized, controlled trials that included 21,923 patients. In review of these trials, short-term dual antiplatelet therapy significantly reduced the risk of ischemic stroke recurrence by 41% and major vascular events by 30%, without an increased risk of intracranial hemorrhage. Prolonged treatment beyond 90 days reduced the risk of ischemic stroke recurrence by 12% and major vascular events by 10%. However, the risk of major bleeding and intracranial hemorrhage increased in those patients treated long term. Therefore, it appears that short-term dual antiplatelet therapy is superior to prolonged treatment. However, this difference in outcome must be confirmed by further well-designed randomized, clinical trials. ■

PHARMACOLOGY UPDATE

Lixisenatide Injection (Adlyxin)

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 fifth glucagon-like peptide-1 (GLP-1) receptor agonist. Lixisenatide is injected once-daily and is marketed as Adlyxin.

INDICATIONS

Lixisenatide is indicated as an adjunct to diet and exercise to improve glycemic control in adults suffering from type 2 diabetes mellitus (T2DM).[1]

DOSAGE

The initial dose is 10 mcg once daily for 14 days. On day 15, increase the dose to 20 mcg once daily. Inject lixisenatide within one hour before the first meal of the day.[1] Lixisenatide is available as 50 mcg and 100 mcg prefilled pens, which provide 14 pre-set doses of 10 mcg and 20 mcg, respectively.

POTENTIAL ADVANTAGES

Lixisenatide provides another GLP-1 receptor agonist.

POTENTIAL DISADVANTAGES

Lixisenatide may be less effective than exenatide. Lixisenatide requires daily dosing one hour before the first meal. There are several medications in the same therapeutic class that are dosed once weekly.

COMMENTS

The safety and efficacy of lixisenatide was evaluated in 10 clinical trials that enrolled 5,400 patients. As with other antidiabetic drugs, its efficacy was evaluated as monotherapy and as an add-on to metformin.[1] As monotherapy, lixisenatide (n = 119) was compared to placebo (n = 122) in a 12-week, double-blind study in subjects suffering from T2DM with a mean baseline HbA1c of 8.07% and a mean fasting plasma glucose (FPG) of 160.4 mg/dL. At week 12, mean change in HbA1c from baseline was -0.83% for lixisenatide 20 mcg daily compared to -0.18% for placebo. Mean changes in FPG from baseline were -15.8 mg/dL and +1.46 mg/dL, respectively. Forty-four percent of subjects achieved HbA1c < 7% for lixisenatide compared to 24% for placebo. Lixisenatide is significantly more effective than placebo when added on to metformin, metformin with or without a sulfonylurea, sulfonylurea with or without metformin, pioglitazone with or without metformin, basal insulin with or without metformin, and insulin glargine with or without metformin. However, lixisenatide was statistically less effective in lowering HbA1c than exenatide administered twice daily and insulin glulisine administered three times daily. Mean differences (i.e., greater reduction with lixisenatide) were 0.17% and 0.23%. Noninferiority was claimed since the differences did not meet the prespecified margin of 0.4%.[1] The most common adverse events (vs. placebo) were nausea (25% vs. 6%), vomiting (10% vs. 2%), and headache (9% vs. 6%). In a randomized, placebo-controlled trial, lixisenatide was compared to placebo in T2DM subjects who experienced an acute coronary event within 180 days (n = 6,008).[2] The primary endpoint was time to the first occurrence of a cardiovascular event (death from cardiovascular cause, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina). After a median follow-up of 25 months, lixisenatide was found to be noninferior to placebo but not superior.

CLINICAL IMPLICATIONS

Lixisenatide is the fifth approved GLP-1 receptor agonist. It appears to have a neutral effect on patients who experienced a recent cardiovascular event. In contrast, in a longer study (3.8 years) in T2DM patients with at least one cardiovascular coexisting condition, liraglutide showed a reduction in a composite first cardiovascular event (death from cardiovascular event, nonfatal myocardial infarction, or nonfatal stroke).[3]

It is not clear if lixisenatide offers any clear clinical advantage over existing GLP-1 receptor agonists. The cost of lixisenatide was not available at the time of this review. The makers of lixisenatide hope to gain FDA approval for a fixed-ratio combination of basal insulin glargine 100 units/mL and lixisenatide in the near future. ■

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Clinical Briefs

By Louis Kuritzky, MD

Vindication of Salmeterol-Fluticasone Single-inhaler Combination

SOURCE: Stempel DA, Raphiou IH, Kral KM, et al. Serious asthma events with fluticasone plus salmeterol versus fluticasone alone. *N Engl J Med* 2016;374:1822-1830.

Monotherapy with salmeterol or other long-acting beta agonists (LABA) is not recommended for asthma treatment, based on the observation in asthma clinical trials that salmeterol monotherapy is associated with increased mortality. Similarly, a meta-analysis of patients who received combination treatment with salmeterol and fluticasone provided in separate inhalers also showed higher asthma-related hospitalizations and death. However, it did not go unnoticed that just because patients received prescriptions for separate salmeterol and fluticasone inhalers does not guarantee that they actually used both devices, hence allowing for the possibility that some patients assigned dual treatment actually were only receiving LABA (or fluticasone) monotherapy.

To better address FDA concerns about LABA safety, researchers performed a randomized, double-blind trial comparing LABA + fluticasone (within the same inhalation device) to fluticasone monotherapy (n = 11,679). The primary endpoint was serious asthma-related events (death, intubation, hospitalization) over 26 weeks.

There was no difference in serious asthma-related events between LABA + fluticasone and fluticasone monotherapy. However, asthma exacerbations were 21% lower in the combination LABA + fluticasone treatment group.

The prescription of LABA monotherapy for asthma patients is still appropriate, but data are reassuring in regard to LABA + fluticasone therapy through which many patients enjoy symptom control and reduced exacerbations. ■

Considering Perioperative Statins in Cardiac Surgery

SOURCE: Zheng Z, Jayaram R, Jiang L, et al. Perioperative rosuvastatin in cardiac surgery. *N Engl J Med* 2016;374:1744-1753.

Based on favorable effect on surrogate markers such as C-reactive protein, as well as small clinical trials that suggested reduced incidence of perioperative atrial fibrillation and other complications, guidelines have endorsed administration of perioperative statin therapy. The Statin Therapy in Cardiac Surgery trial was designed to provide more definitive information.

Patients undergoing elective cardiac surgery (n = 1,922) were randomized to perioperative rosuvastatin 20 mg/d or placebo. The primary outcomes were atrial fibrillation and myocardial infarction within five days of surgery.

As has been previously demonstrated, rosuvastatin treatment reduced low-density lipoprotein levels and C-reactive protein. However, there was no difference in the incidence of atrial fibrillation or myocardial infarction.

Of concern, there was an increased risk for acute kidney injury in the rosuvastatin group; within the first 48 hours postoperatively, the frequency of acute injury of any severity was 24.7% in the rosuvastatin arm vs. 19.3% in the placebo arm. Fortunately, most of the acute kidney injury incurred was stage one (mild intensity).

Despite early data suggesting benefits of perioperative statin treatment, this larger data set fails to confirm benefit and indicates some potential harm. ■

Cocaine Use and Pyoderma Gangrenosum

SOURCE: Jeong HS, Layher H, Cao L, et al. Pyoderma gangrenosum (PG) associated with levamisole-adulterated cocaine: Clinical, serologic, and histopathologic findings in a cohort of patients. *J Am Acad Dermatol* 2016;74:892-898.

Clinicians should view photos of pyoderma gangrenosum. These images can be quite devastating and would likely add to the gravity of the information Jeong et al recently provided in a published report.

Pyoderma gangrenosum classically presents as a rapidly progressive, painful, suppurative cutaneous ulcer. The ulcer most commonly occurs on the legs but can appear anywhere on the body. Pyoderma gangrenosum is most commonly associated with malignancy and inflammatory disorders such as ulcerative colitis and rheumatoid arthritis.

In the United States, as much as 80% of cocaine is adulterated with levamisole, which is known to produce vasculitis. Jeong et al reported on eight consecutive patients presenting with pyoderma gangrenosum, each of whom had used cocaine. The biopsy pathology of cocaine/levamisole-induced pyoderma gangrenosum is indistinguishable from that associated with other disorders mentioned above. In addition to the other obvious concerns about cocaine use, add pyoderma gangrenosum to the list. ■

CME INSTRUCTIONS

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CME QUESTIONS

1. All of the following are part of the lifestyle criteria that could result in about a 50% decrease in U.S. cancer deaths *except*:

a. living in an area with good air quality.

b. never smoking.

c. drinking either no alcohol or a maximum of one drink a day for women and two or less for men.

d. a body mass index of > 18.5 kg/m^2 but < 27.5 kg/m^2.

2. What serum change has been seen in patient with non-celiac wheat sensitivity?

a. Elevated immunoglobulin A antibodies

b. Elevated transglutaminase 2 autoantibodies

c. Elevated lipopolysaccharide-binding protein

d. Human leukocyte antigen markers for celiac disease

3. Which of the following has been associated with an increased risk of mild cognitive impairment or dementia?

a. Apolipoprotein E4 carrier

b. Hypertension

c. Weight loss

d. All of the above

4. Following acute ischemic stroke, treatment with a single antiplatelet agent is just as efficacious as treatment with dual antiplatelet medications, and carries a lower risk of intracranial hemorrhage.

a. True

b. False

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]

Influence of Valsartan/Sacubitril on 30-day Readmission After Heart Failure Hospitalization