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ABSTRACT & COMMENTARY

New Dietary Guidance to Improve Cardiovascular Health: Meeting People Where They Are

By Seema Gupta, MD, MSPH

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SYNOPSIS: The American Heart Association emphasizes the importance of an overall lifetime heart-healthy diet and the vital role of nutrition early in life.

SOURCE: Lichtenstein AH, Appel LJ, Vadiveloo M, et al. 2021 dietary guidance to improve cardiovascular health: A scientific statement from the American Heart Association. *Circulation* 2021;144:e472-e487.

Poor diet is considered one of the leading causes of negative health outcomes, including diet-related cancers, cardiovascular disease, diabetes, and obesity.[1] In the United States, researchers estimate dietary factors account for more than 650,000 deaths annually and 14% of all disability-adjusted life-years lost.[2] Therefore, it is critical to focus on the aspects of diet that improve cardiovascular health.

To enhance cardiovascular health, Lichtenstein et al analyzed the available evidence to provide guidance in their scientific statement to reduce the rates of cardiovascular morbidity and mortality. The stated purpose of the guidance included emphasizing the importance of dietary patterns, not just individual foods or nutrients; the significance of initiating heart-healthy dietary habits early in life; and discussing dietary patterns that not only promote cardiometabolic health but also benefits beyond cardiovascular health. For the first time, the authors included information about food-related sustainability and structural challenges that may impede the adoption of heart-healthy diets. The guidance includes 10 central points:

- To maintain a healthy weight, patients should adjust energy intake and expenditure. Portion control and engaging in at least 150 minutes of moderate physical activity each week are essential.
- Diets should include a high volume of a variety of vegetables and fruits (excluding white potatoes).

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This CME activity is intended for the internist/family physician. It is in effect for 36 months from the date of the publication.

• Cull refined grains and replace them with more whole grains.
• Regularly consuming plant-based food, fish, and low-fat or fat-free dairy products can boost cardiovascular health. Avoid processed meats; choose lean cuts.
• Avoid tropical oils, (e.g., coconut and palm), animal fats, and partially hydrogenated fats; replace with liquid plant oils. Monounsaturated and polyunsaturated fats can benefit cardiovascular health.
• Avoid ultra-processed foods, which are tied to several negative health outcomes.
• Minimize added sugars, especially sugar-sweetened beverages.
• Use little or no salt when preparing food. Avoiding excess sodium intake helps blood pressure stay at a normal level.
• Patients should not start drinking alcohol if they have never consumed any. Patients who already drink alcohol should limit their intake. Alcohol intake at any level to improve cardiovascular health is no longer recommended.
• Policies should encourage making the healthier choice the easy choice.

The highest-quality diet scores may be associated with a lower risk of all-cause mortality, cardiovascular disease incidence or mortality, cancer incidence/mortality, type 2 diabetes, and neurogenerative diseases. However, the statement recognizes significant challenges to adherence to heart-healthy dietary patterns. This includes socioeconomic factors, food insecurity, structural racism, and targeted marketing of unhealthy foods and beverages. Overall, the guidance calls for creating an environment that promotes rather than hinders the adherence to heart-healthy dietary patterns among all individuals.

■ COMMENTARY

Even with advances in healthcare, the cardiovascular disease mortality rate has leveled off in recent years and may appear to be trending upward.[3] Although dietary modification is a cornerstone of cardiovascular health, implementation often can be complicated to practice, time-consuming, expensive, or sometimes just unappealing to patients. The American Heart Association's latest dietary guidance to improving cardiovascular health aims to emphasize the importance of healthy eating throughout one's life. Based on most current research, it is designed to accommodate today's diverse eating habits and food choices. There are a few noteworthy aspects that make these guidelines unique or at least cognizant of the reality we face. This includes focusing on the value of an overall heart-healthy diet throughout one's lifetime, rather than thinking in terms of "good" or "bad" foods, as well as the critical role of initiating heart-healthy dietary habits early in life. The guidelines also underline additional benefits of heart-healthy dietary patterns beyond cardiovascular health. Finally, the authors highlighted structural challenges that impede the adoption of heart-healthy dietary patterns.

Most importantly, these guidelines aim to meet people where they are. Whether someone predominantly eats at restaurants or is a truck driver who lives on a tight budget, everyone can benefit from a heart-healthy dietary pattern. The guidelines emphasize that a one-size-fits-all approach may no longer be needed. A heart-healthy dietary pattern can be for everyone and be consistent with personal preferences, lifestyles, and religious and cultural customs. ■

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ABSTRACT & COMMENTARY

Infections Before Age 20 Years Increase the Risk of Multiple Sclerosis

By Hai H. Hoang, MD

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SYNOPSIS: Researchers found patients diagnosed with infection in adolescence were at higher risk for multiple sclerosis, even after exclusion of infectious mononucleosis, pneumonia, and central nervous system infection.

SOURCE: Xu Y, Smith KA, Hiyoshi A, et al. Hospital-diagnosed infections before age 20 and risk of a subsequent multiple sclerosis diagnosis. *Brain* 2021;144:2390-2400.

There are many theories on the etiology of multiple sclerosis, including the role infections might play in disease development. Two meta-analyses revealed infectious mononucleosis, a clinical manifestation of Epstein-Barr virus infection, in adolescents and young adults more than doubled multiple sclerosis risk. Other infectious pathogens that have been linked with multiple sclerosis include human herpesvirus 6 (HHV-6) and *Chlamydia pneumoniae*.

However, the underlying mechanism between infections and an increased risk of multiple sclerosis is unknown. One theory includes the molecular mimicry hypothesis, which suggests infectious agents with homologous sequences or structures to a host's myelin antigens could trigger cross-activation of autoreactive T cells to attack host tissue. Another theory suggests macrophages and natural killer cells activated by infectious agents elsewhere in the body, such as the lungs, can result in pro-inflammatory cytokine production and nonspecific activation of pre-primed T cells. This allows them to cross the blood-brain barrier, causing inflammation in the central nervous system (CNS), and inducing multiple sclerosis pathogenesis by triggering autoimmune responses against myelin.

Xu et al used a large population-based cohort in Sweden to assess the risk of a multiple sclerosis diagnosis from age 20 years associated with hospital-diagnosed infection in adolescence (ages 11-19 years) and earlier childhood (between birth and age 10 years). Researchers hypothesized that during adolescence, environmental exposures are likely to be more causally associated with an increased risk of a subsequent diagnosis of multiple sclerosis and that exposures in earlier childhood are less likely to contribute to such a diagnosis.

A total of 462,157 and 338,352 individuals contracted hospital-diagnosed infections between birth and age 10 years and between ages 11 and 19 years, respectively. Only infections before age 20 years were considered in patients older than age 25 years with first multiple sclerosis diagnosis. There was a delay of at least five years between exposure and multiple sclerosis diagnosis.

Any infection from birth to 10 years of age was not statistically significantly associated with an increased risk of a subsequent diagnosis of multiple sclerosis when compared to no infection from birth to age 10 years. Those at greater risk of a multiple sclerosis diagnosis were individuals with any infection in adolescence, defined as between ages 11 and 19 years. Infectious mononucleosis in adolescence, between ages 11 and 19 years, increased the risk of a multiple sclerosis diagnosis after adjustment for pneumonia, sex, and parental socioeconomic status. Viral infection (excluding infectious mononucleosis in adolescence) did not statistically significantly increase the risk of a subsequent multiple sclerosis diagnosis vs. no viral infection. However, there was a higher risk of a multiple sclerosis diagnosis associated with bacterial infection in adolescence, which remained statistically significant when individuals with bacterial infection but without CNS infection, infectious mononucleosis, and pneumonia diagnoses were compared with those without bacterial infection. The authors concluded any hospital-treated infection in adolescence increased the risk of a multiple sclerosis diagnosis from age 20 years, although the effect size was small (hazard ratio, 1.33).

■ COMMENTARY

Considering this study relied on patients hospitalized for an infection, the total number of infections in adolescence and earlier childhood was underestimated, because infections diagnosed in outpatient clinics were not included. Another limitation was the inability to analyze the risk of multiple sclerosis associated with specific types of CNS infection, because of small numbers of patients with multiple sclerosis and earlier CNS infections. Although the authors identified multiple infectious pathogens rather than a single pathogen contributing to the risk of a multiple sclerosis diagnosis, they did not consider whether multiple infectious pathogens act independently or interact with each other in an additive or multiplier effect.

Overall, this was a well-designed cohort study, which further supports the theory that infections during childhood and adolescence may play a role in the underlying cause for multiple sclerosis. ■

ABSTRACT & COMMENTARY

Plant-Based Diets and Menopausal Hot Flashes

By Rebecca H. Allen, MD, MPH

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SYNOPSIS: In this clinical trial, women randomized to a low-fat, vegan diet including one-half cup of cooked whole soybeans daily experienced a reduction in total hot flashes of 79% vs. 49% in the control group over 12 weeks of observation.

SOURCE: Barnard ND, Kahleova H, Holtz DN, et al. The Women's Study for the Alleviation of Vasomotor Symptoms (WAVS): A randomized, controlled trial of a plant-based diet and whole soybeans for postmenopausal women. *Menopause* 2021;28:1150-1156.

This study was conducted to evaluate the effectiveness of whole soybeans and a plant-based vegan diet in reducing the frequency and severity of menopausal hot flashes. Previous studies have revealed some indication that soy (phytoestrogen) supplements can modestly reduce hot flashes, although data are limited.[1] This was a randomized, controlled trial performed over 12 weeks among women with postmenopausal hot flashes. Inclusion criteria were women age 40 to 65 years, moderate to severe hot flashes at least twice a day, last menses within the preceding 10 years, and no menses in the preceding 12 months. Exclusion criteria were use of hormonal medications in the previous two months, smoking, substance abuse, history of an eating disorder, use of weight loss medications in the past six months, attempting to lose weight, body mass index (BMI) of < 18.5 kg/m^2, soy allergy, and current diet already matching the study diet.

The intervention group followed a low-fat vegan diet, including consuming one-half cup of soybeans daily. Intervention participants attended weekly one-hour group sessions, received information on meal planning and food preparation (a pressure cooker was provided for the soybeans), and answered weekly questions about diet adherence. Control group participants followed their usual diet, also used a pressure cooker, and attended four one-hour group sessions. For both groups, alcohol was limited to one drink per day. Data collection was performed at baseline and at 12 weeks and included three-day dietary intake record, body weight and height, health status, medication use, physical activity, menopausal symptoms (hot flashes), and the Menopause-Specific Quality of Life (MENQOL) questionnaire.

The authors considered this a pilot study and aimed to enroll 40 participants. Women were recruited through social media and screened by phone. Ultimately, 38 women were randomized. There was no significant difference between the two groups in terms of age, race, or BMI. Mean body weight decreased by 3.5 kg in the vegan diet group vs. a 0.8-kg gain in the control group (P = 0.002). Total hot flashes decreased by 79% in the intervention group (6.2 vs. 1.3 events per seven days) compared to 49% in the control group (4.9 vs. 2.5 events per seven days; P = 0.01). Moderate-to-severe hot flashes decreased 84% in the intervention group vs. 42% in the control group (P = 0.013). From 0 to 12 weeks, 59% of intervention-group participants reported becoming free of moderate-to-severe hot flashes compared to no change in the control group (P = 0.0003). The MENQOL questionnaire showed significant reductions in all the vasomotor, psychosocial, physical, and sexual domains in the intervention group vs. the control group.

■ COMMENTARY

Hot flashes are common in the perimenopausal transition and menopause. The most effective treatment for hot flashes is systemic estrogen therapy. For women who do not want to use hormones, there are a few nonhormonal medications that have proven effective: selective serotonin reuptake inhibitors, selective serotonin-norepinephrine reuptake inhibitors, clonidine, and gabapentin.[2] However, the goal of this study was to evaluate the usefulness of whole soybeans because many women are seeking nonhormonal and nonpharmacological options to treat menopausal symptoms. Phytoestrogens are plant-derived substances with estrogenic biologic activity. Examples include the isoflavones genistein and daidzein, which are found in high amounts in soybeans, soy products, and red clover. Previous studies have shown soy products may be modestly useful in treating menopausal hot flashes.[1] However, current evidence has not been strong enough to recommend soy products on a routine basis.[2]

Barnard et al showed a vegan diet with whole soybeans reduced hot flashes significantly and almost eliminated moderate-to-severe hot flashes. The control group also experienced a decrease in hot flashes. The authors speculated this was because the control group also was aware of the vegan diet in the intervention group and possibly followed it. However, the study was limited by the small sample size and short duration. But the findings were

dramatic and deserve further study. Certainly, there may be other health benefits to a plant-based vegan diet, and there is no downside to eating soybeans. Therefore, this may be an option for patients who do not want to use medications and do not find enough benefit from regular lifestyle changes, such as layering clothing, lowering ambient temperatures, and consuming cool drinks. ■

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ABSTRACT & COMMENTARY

Adverse Effects of Electronic Cigarettes on the Disease-Naïve Oral Microbiome

By Lindsey N. Clark, MD, and Taimur K. Mian, MD

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SYNOPSIS: A robust metagenomic comparison study of the effects of electronic cigarettes on oral microbiomes suggested that the unique aerosol component of electronic cigarettes poses increased risk to development of oral cavity disease.

SOURCE: Ganesan SM, Dabdoub SM, Nagaraja HN, et al. Adverse effects of electronic cigarettes on the disease-naïve oral microbiome. *Sci Adv* 2020;6:eaaz0108.

The oral cavity hosts a diverse group of bacterial communities, with more than 1,000 species across seven phyla. Imbalances in the oral microbiome communities and increased inflammatory responses to oral bacteria have been associated with diseases, such as periodontitis, dental caries tooth loss, and oropharyngeal cancer.

The effects of cigarette use, chewing tobacco, and alcohol consumption on the oral cavity have been studied widely, with results showing these habits offset the healthy balance of oral bacterial communities and create the potential for harmful bacterial species to be introduced into the oral cavity, increasing the risk for disease development.[1,2] However, the effects of e-cigarettes on the oral microbiome, and their potential for harm, remain understudied. Considering e-cigarettes are relatively novel because they deliver nicotine in a unique heated aerosol component, more insight into their effects on the oral microbiome is needed to determine their risk for oral cavity illness.

Ganesan et al analyzed the subgingival microbiomes across e-cigarette users, smokers, and nonsmokers. They recruited 123 individuals considered systemically and periodontally healthy. Periodontal health, or gingival inflammation assessment, was defined as attachment loss of < 1, fewer than three sites with 4 mm of probe depths, and a bleeding index of < 20%. Systemic health was established using the American Society of Anesthesiologists Physical Status Classification. Participants were placed in one of five groups based on their tobacco use status: smoker, nonsmoker, e-cigarette user, former smoker currently using e-cigarettes, and concomitant cigarette and e-cigarette user. Current smoking was defined as at least a five-pack-year history. Nonsmokers were defined as people who consumed fewer than 100 cigarettes in their lifetimes. Those in the e-cigarette category used the product daily for at least three months, with at least one cartridge per day, or 1 mL of liquid per day. Sample size was determined to have at least an 80% chance of detecting clades of bacterial genes that differed in abundance by 1%. Exclusion criteria consisted of presence of controlled or uncontrolled diabetes; HIV infection; use of immunosuppressant medication, bisphosphonates, steroids, antibiotic therapy, or oral prophylactic procedures within the past three months; and fewer than 20 teeth in dentition.

Subgingival plaque samples using sterile endodontic paper points and gingival crevicular fluid collections were taken from each participant at 15 sites within the oral cavity. Bacterial DNA was isolated from the paper point samples and quantified using Qiagen DNA Mini-Amp kits and Qubit fluorometers. Phylogenetic profiles for each participant's oral microbiome were created using Kraken v1.1 software and complete genome data lists from the Human Oral Microbiome Database. Each phylogenetic profile then was tested for alpha (within-group) and beta (between-group) genetic diversity using PhyloToAST v1.4 and QIIME v1.9.

For quality control, all DNA samples were sequenced in two runs, and samples were randomly assigned to each run. Each participant's gingival crevicular fluid samples also were used to determine cytokine assays, measuring

levels of interferon-gamma (INF-gamma), interleukin 2 (IL-2), IL-4, IL-6, IL-8, IL-10, granulocyte-macrophage colony stimulating factor (GM-CSF), and tumor necrosis factor-alpha (TNF-alpha). To assess and compare the genetic variability and gene clustering in the oral microbiome community between each participant cohort, Ganesan et al generated principal coordinate analysis (PCoA) plots using the software PhyloToAST (PcoA.py). The significance of identified genetic clustering in participant cohorts was determined using permutational multivariate analysis of variance (MANOVA) (adonis function, vegan package for R). Additionally, the relative abundance of functional genes across participant cohorts was assessed using linear discriminant analysis (LDA) (scikit-learn v0.18.0). Wilk's lambda was used to test for significance of LDA identified functional gene clustering.

Overall, Ganesan et al compared oral microbiomes of 20 e-cigarette users, 25 nonsmokers, 25 current cigarette smokers, 25 former smokers, and 25 dual users. E-cigarette users were age 21 to 35 years, predominantly white, and reported using e-cigarettes products with 6 mg to 18 mg of nicotine. Interpretation of PCoA and LDA plots revealed three significantly different oral microbial profiles of e-cigarette users, smokers, and nonsmokers ($P = 0.008$, MANOVA/Wilks). There was no significant microbial profile difference between e-cigarette users, dual users, and former smokers who had switched to e-cigarettes ($P = 0.27$ and 0.35).

Further nonmetric multidimensional scaling analysis of variance in the user groups showed the duration of e-cigarette use (< 6 months vs. > 10 months) was the strongest source of variation, with nicotine concentration and type of flavoring not contributing to variations seen in the oral microbial profiles. Furthermore, 70% of the metagenome in e-cigarette users was shared by more than 80% of subjects, whereas the smoker and nonsmoker cohorts only shared 40% and 50% of their metagenomes, respectively. This presence of a large, core microbiome present in most e-cigarette users that differed significantly from the microbiome of smokers and nonsmokers suggests the aerosol effects of e-cigarettes alters the oral cavity bacterial community via different mechanisms than traditional cigarettes.

Additionally, the metagenome profile of e-cigarette users showed more genes related to virulence factors vs. smokers and nonsmokers ($P < 0.05$), including cell wall and capsular polysaccharides, peptidoglycan, and lipopolysaccharide biosynthesis, stress response, quorum sensing and biofilm formation, and resistance to antibiotics and toxic compounds. These findings suggest the unique oral bacterial community found in e-cigarette users could increase exposure to bacterial factors that cause disease in human hosts. Further analysis of the cytokine assays taken from the participant's gingival crevicular fluid showed those who used e-cigarettes had significantly higher levels of proinflammatory cytokines IL-2, IL-6, GM-CSF, TNF-alpha, and INF-gamma, and lower levels of anti-inflammatory cytokine IL-10 ($P < 0.05$, Dunn's test). These findings suggest the e-cigarette user microbial profile creates a higher inflammatory burden and response vs. cigarette users and nonsmokers.

Cigarette users showed a similar increase in proinflammatory cytokines vs. never-smokers as well with increases in cytokines IL-2, IL-6, and IL-8, TNF-alpha, and INF-gamma, and lower levels of IL-10. The authors noted this difference may suggest that while both e-cigarette and cigarette use increase inflammatory response cytokines in the oral microbiome, different biological pathways are involved.

■ COMMENTARY

Ultimately, this study shows e-cigarette use can shift the oral microbiome community to a state with more exposure to bacterial virulence factors and increased host inflammatory response, both states that can predispose an individual to oral cavity diseases. The authors noted while no e-cigarette users had been diagnosed with periodontitis, the functional genetic profile of their oral microbiome "bore remarkable resemblance to individuals with periodontitis."[3,4] Ganesan et al hypothesized the glycerol and glycol components of e-cigarette aerosol may serve as a nutrient source for bacteria, altering the microbial profile and biofilm structures in the oral cavity of e-cigarette users.

While e-cigarettes have been on the market for 17 years, and studies have begun to show the potential for harmful effects on the respiratory system, little remains known about their effect on the oral cavity and the oral microbiome.[5,6] Because the heated aerosol contains fewer harmful chemicals than an ignited tobacco device, it has been suggested their use is safer than cigarettes, and they often have been advertised as a smoking cessation device.[7] However, studies show the biggest user group of e-cigarettes is a young population taking up e-cigarette use as a new habit vs. a tool for smoking cessation. One study revealed 20% of high schoolers in the United States admitted to trying e-cigarettes at least once a month.[8] Considering these numbers, physicians are incredibly likely to encounter a young patient who is using e-cigarettes recreationally. Physicians should consider the results of the Ganesan et al study, along with the growing body of literature, which demonstrate that e-cigarettes expose users to a unique aerosol-nicotine compound that may increase the risk for oral cavity disease. Talking to patients about e-cigarette use and the effects on their oral health may be beneficial for reducing the risks of developing oral cavity diseases associated with e-cigarette use. ■

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PHARMACOLOGY UPDATE

Inclisiran Injection (Leqvio)

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.

The FDA has approved the first small interfering RNA (siRNA) to lower low-density lipoprotein cholesterol (LDL-C). Inclisiran acts by inhibiting the synthesis of proprotein convertase subtilisin-kexin type 9 (PCSK9). Inhibition of PCSK9 increases LDL-C receptors, lowering LDL-C levels. It is distributed as Leqvio.

INDICATIONS

Inclisiran can be prescribed as an adjunct to diet and maximally tolerated statin therapy for adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD) who required additional LDL-C lowering.[1]

DOSAGE

The recommended dose is a single injection given subcutaneously into the abdomen, upper arm, or thigh initially, then again in three months, and then every six months. Inclisiran should be administered by a healthcare professional.[1] It is available as a single-dose prefilled syringe containing 284 mg/1.5 mL.[1]

POTENTIAL ADVANTAGES

Inclisiran provides another option that targets PCSK9 via inhibiting its synthesis as opposed to monoclonal antibodies that bind directly to PCSK9. Its long pharmacological action permits dosing every six months after the first two doses.[2] Inclisiran was reported to be well-tolerated, with a safety profile comparable to placebo.[3,4]

POTENTIAL DISADVANTAGES

The use of a siRNA is a new therapeutic approach. Long-term safety has not been established. In contrast to monoclonal antibodies, the effect of inclisiran on cardiovascular morbidity and mortality has not been established. Adverse reactions were primarily injection site reactions (8.2% vs. 1.8% for placebo).[1]

COMMENTS

Inclisiran lowers LDL-C levels by inhibiting the synthesis of liver-derived PCSK9. The siRNA, once taken up by hepatocytes, inhibits PCSK9 mRNA translation. The efficacy of inclisiran was demonstrated in three randomized, 18-month, double-blind, placebo-controlled trials — two in subjects with ASCVD and one in subjects with HeFH.[1-4] Both subject groups were on maximally tolerated statin therapy. Users of PCSK9 inhibitors were excluded. In the two studies in patients with ASCVD, subjects were randomized to inclisiran (n = 781) or placebo (n = 780) in study 1 and n = 712 and n = 702, respectively, in study 2. Baseline LDL-C levels were 105 mg/dL and 101 mg/dL, respectively. The primary efficacy endpoint was change in LDL-C from baseline to day 510. Changes were -52% vs. +1% in study 1 and -46% vs. +4% in study 2. Total cholesterol, non-HDL cholesterol, and ApoB values also were lower, ranging from a difference from placebo of -30% to -47%. Results were similar across subgroups, including age, sex, race, and disease characteristics. In a similarly designed study of subjects with HeFH (74% on high-intensity statin therapy), inclisiran reduced LDL-C by 40% vs. an increase of 8% for placebo.

CLINICAL IMPLICATIONS

Inclisiran takes a different approach to targeting PCSK9 in contrast to monoclonal antibodies that bind to extracellular PCSK9. The magnitude of LDL-C reduction is roughly similar to that produced by alirocumab and evolocumab. In a systematic review and network meta-analysis, PCSK9 inhibitors added to medium- to high-intensity statin therapy lowered LDL-C by 54% to 74% vs. placebo.[5] There are no

head-to-head comparisons between inclisiran with a PCSK9 inhibitor. In contrast to alirocumab and evolocumab, inclisiran is not FDA-approved for reducing CV risk (e.g., myocardial infarction, stroke) in patients with homozygous familial hypercholesterolemia. Numerous studies are registered in ClinicalTrial.gov to address these indications: VICTORION-2P (NCT05030428), testing whether inclisiran plus high-intensity statin therapy can cut the risk of three-point major adverse cardiovascular events (CV death, non-fatal myocardial infarction, and non-fatal ischemic stroke); and ORION-4 (NCT03705234) as secondary prevention of myocardial infarction or stroke. Inclisiran may offer significant out-of-pocket cost advantages for patients, as it is administered by a healthcare provider vs. an anti-PCSK9 monoclonal antibody, which is administered by the patient or caregiver. The cost of inclisiran is $3,250 per dose, resulting in the first year of treatment costing $9,750 and $6,500 for subsequent years. ■

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CME QUESTIONS

1. **The new dietary guidelines from the American Heart Association:**
   a. emphasize the importance of dietary patterns, not just individual foods or nutrients.
   b. suggest a vegan diet is best for overall health.
   c. highlight dietary patterns that only promote cardiometabolic health.
   d. indicate drinking one glass of white wine per day is good for heart health.

2. **Multiple sclerosis developing after age 25 years may be associated with:**
   a. traumatic brain injury during adolescence.
   b. bacterial infections in early childhood, from birth to age 10 years.
   c. any non-viral infection (excluding infectious mononucleosis) from ages 11 to 19 years.
   d. viral infection, excluding infectious mononucleosis.

3. **The analysis by Ganesan et al suggests e-cigarette use alters the oral microbiome of users by increasing the presence of what bacterial features?**
   a. Species diversity
   b. Virulence factors
   c. Anaerobic metabolism
   d. Anti-inflammatory responses

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.