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ABSTRACT & COMMENTARY

Blood Pressure Concordance Between SPRINT and Routine Clinical Practice

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SYNOPSIS: Blood pressures obtained in routine clinical practice frequently vary from research-quality blood pressure measurements, highlighting the importance of proper techniques and clinician awareness.

SOURCE: Drawz PE, Agarwal A, Dwyer JP, et al. Concordance between blood pressure in the Systolic Blood Pressure Intervention Trial and in routine clinical practice. *JAMA Intern Med* 2020;180:1655.

The authors of SPRINT, published in 2015, reported that intensive blood pressure (BP)-lowering in patients with elevated cardiovascular risk (but without diabetes) resulted in lower rates of a composite outcome, including myocardial infarction, other acute coronary syndromes, heart failure, stroke, or death from cardiovascular causes.[1] However, BP measurement during the trial was based on an American Heart Association-recommended protocol: BP was measured after five minutes of rest with an automatic oscillometric device, proper patient and BP cuff positioning was ensured, and the obtained BP reading was the mean of three measurements.[2] Often, clinicians do not follow these procedures in routine practice, possibly resulting in higher BP readings than would be found using more rigorous protocols.[3] This could result in an overestimation of BP level and subsequent overtreatment of hypertension.[3]

Drawz et al sought to determine the concordance between BP measurements reported in SPRINT under those authors' protocol and BP measurements for the same patients in routine clinical practice. In this prospective study, the authors evaluated 3,074 patients with three or more trial BP measurements recorded and three or more outpatient BP measurements available in the electronic health record (EHR). The mean age was 68.5 years. Compared with the overall SPRINT population, these patients were more likely to be white, less likely to be women, more likely to be treated with a statin or aspirin, and recorded a lower baseline

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BP. During the time from the six-month SPRINT visit to the end of the trial, the mean systolic BP was 7.3 mmHg (95% CI, 7.0-7.6 mmHg) and 4.6 mmHg (95% CI, 4.4-4.9 mmHg) lower at trial visits compared with the corresponding outpatient visits for the intensive treatment group and the standard treatment group, respectively. BP differences varied by individual and clinic site, but results generally were consistent for subgroups. However, mean BP differences between outpatient EHR and trial measurements were larger in women compared with men. The authors concluded systolic BP measurements in the routine clinical setting were 5 mmHg to 8 mmHg higher, on average, than systolic BP measurements at SPRINT visits. Additionally, there was a larger systolic BP difference for patients in the intensive treatment group, and variability of BP differences fluctuated at the patient and clinic levels.

■ COMMENTARY

This study highlights the need for proper BP monitoring techniques, which tends to be difficult in routine clinical practice for various reasons, including time constraints, lack of staff training or knowledge, limited clinic space, and lack of proper equipment.[3] BP measurements are important data points to determine diagnosis and adequate control of hypertension. Patients may be incorrectly diagnosed or treated if clinicians use improper methods. Thus, physicians should be aware of these limitations and consider that without rigorous BP measurement protocol implementation, many routine clinic BP readings can prompt overdiagnosis and overtreatment of hypertension.

Additionally, Drawz et al identified substantial variability between different clinics' BP measurements and between individual patients' BP measurements, leading the authors to question the overall validity of using 10 mmHg in national guidelines as a correction factor to approximate clinical trial measurements. In addition to awareness of guideline recommendations and clinical evidence for hypertension management, accounting for patient characteristics, such as comorbid conditions and treatment preferences, can help determine an optimal BP target and treatment regimen. ■

REFERENCES

1. The SPRINT Research Group; Wright JT Jr, Williamson JD, Whelton PK, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015;373:2103-2116.
2. Muntner P, Shimbo D, Carey RM, et al. Measurement of blood pressure in humans: A scientific statement from the American Heart Association. *Hypertension* 2019;73:e35-e66.
3. Drawz PE, Ix JH. BP measurement in clinical practice: Time to SPRINT to guideline-recommended protocols. *J Am Soc Nephrol* 2018;29:383-388.

ABSTRACT & COMMENTARY

Prodromal Alzheimer's Disease and Nutritional Interventions

By Lisa Mosconi, PhD

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SYNOPSIS: Over a 36-month period, patients with prodromal Alzheimer's disease who consumed Fortasyn Connect (Souvenaid), a nutraceutical drink, demonstrated a slower decline in cognitive functions vs. the control group.

SOURCE: Soininen H, Solomon A, Visser PJ, et al. 36-month LipiDiDiet multinutrient clinical trial in prodromal Alzheimer's disease. *Alzheimers Dement* 2020; Sept. 13. doi: 10.1002/alz.12172. [Online ahead of print].

Late-onset Alzheimer's disease (AD) is the most common cause of dementia in the elderly, affecting 5.7 million patients in the United States alone. The consensus is AD progresses on a spectrum with three stages: an early, preclinical stage with no symptoms; a middle stage of mild cognitive impairment (MCI); and a final stage marked by symptoms of dementia. Although MCI is heterogeneous, in approximately 50% of cases it

represents a state between regular aging and dementia. Diagnosing AD in the MCI prodromal stage early is a chance to implement interventions to strengthen cognitive functioning or brain health and to handle modifiable risk factors associated with disease progression.

Experts believe more attention on modifying risk factors connected to lifestyle could slow the progression from MCI to dementia.[1] Diet and nutritional status are recognized as important factors for healthy brain aging and dementia, which has provided a rationale for the investigation of nutritional supplements to improve cognitive function in patients with MCI or AD. Although several observational studies reported positive associations between the intake of several single-agent nutrient supplements — mainly vitamin E, vitamin C, some B vitamins, carotenoids, and omega-3 fatty acids — clinical trial evidence for the effectiveness of single nutritional interventions in MCI and AD remains limited. However, it is possible that a combination of nutrients might be more beneficial than any single nutrient taken in isolation, a concept known as "nutritional synergy."

Fortasyn Connect (Souvenaid) is a once-daily drink that contains nutrients associated with a lower risk of age-related cognitive decline. Chiefly, these include cofactors and precursors that help the formation and function of neuronal membranes and synapses, such as B vitamins, vitamin C, vitamin E, long-chain omega-3 fatty acids, choline, uridine, and selenium. Research has shown the mixture of nutrients in Fortasyn Connect reduces AD brain pathology. The authors of previous clinical studies in humans reported some benefits on memory tests in patients with mild AD, but not in patients with moderate to severe AD.[1-3] Based on available clinical trial results, an expert consensus opinion stated Fortasyn Connect should be considered as an option for patients with mild AD dementia or MCI caused by AD pathology (e.g., prodromal AD).

The European LipiDiDiet trial was a randomized, double-blind, placebo-controlled trial designed to investigate the effects of Fortasyn Connect on cognition in a cohort of patients with a diagnosis of prodromal AD. A previous analysis of the first 24-month intervention period showed favorable effects on secondary endpoints, including Clinical Dementia Rating-Sum of Boxes (CDR-SB) and hippocampal atrophy on MRI scans, but not on the primary endpoint (Neuropsychological Test Battery [NTB] five-item composite).[4] In this study, the authors extended the time to follow-up to 36 months to test whether a longer intervention duration might lead to improvement on the primary endpoint. The authors recruited 311 patients with prodromal AD using the International Working Group-1 criteria and assigned patients to active product (125 mL once-a-day drink) or an isocaloric, same-tasting, placebo-control drink. The main outcome was a change in cognition (NTB five-item composite) over 36 months. Analyses were by modified intention-to-treat, excluding (i.e., censoring) data collected after the start of open-label active product and/or AD medication.

Of the 311 patients, 162 participants completed the 36-month study, including 81 with 36-month data eligible for efficacy analysis. Over 36 months, significant reductions in decline were observed for the NTB five-item composite (-60%; between-group difference, 0.212 [95% CI, 0.044-0.380]; $P = 0.014$), CDR-SB (-45%; $P = 0.014$), memory scores (-76%; $P = 0.008$), and brain atrophy measures, with small to medium Cohen's d effect size (0.25-0.31) similar to established clinically relevant AD treatment.

This was the first randomized clinical trial of a nutritional intervention in prodromal AD over 36 months. The authors offered that positive results on the CDR-SB, along with other measures of cognition and function (including some that appeared only after long-term intervention), suggest disease-modifying potential. However, the effects of Souvenaid became statistically significant only after 36 months of intervention, highlighting the need for a long treatment duration.

■ COMMENTARY

Experts recently concluded some lifestyle, medical, nutritional, and psychosocial interventions may prevent or slow the progression from MCI to dementia. However, researchers do not recommend pharmacologic interventions with AD drugs for those with MCI. Those drugs could be considered if clinicians see biomarker evidence of AD, although researchers based this on limited clinical trial evidence.[5] Generally, researchers have not observed significant benefits with pharmacologic therapies, such as memantine and cholinesterase inhibitors.

Medical and lifestyle interventions are encouraged more consistently. The *Lancet* Commission on Dementia Prevention suggested 21.7% of dementia cases progressing from MCI may be preventable by eliminating diabetes, poor diets, and neuropsychiatric symptoms. Therefore, pay attention to modifiable risk factors for those diagnosed with MCI. The best evidence indicates managing patients with an MCI diagnosis likely requires a multipronged approach that includes changing lifestyle habits to reduce the effects of modifiable risk factors (hypertension, smoking, hearing loss, obesity, physical inactivity, depression, social isolation, and diabetes mellitus) and to promote healthy diets.

The most compelling data so far concern the role of exercise in reducing the risk of dementia. However, mounting evidence points to dietary and nutritional interventions as part of broader lifestyle changes that

may contribute to improved cognitive performance among individuals at risk of progression to dementia. Epidemiological studies have revealed a connection between diets with high antioxidant content (e.g., the Mediterranean diet) and a lower risk of MCI, dementia, and cognitive decline in older patients. The evidence also suggests multipronged modifications of lifestyle risk factors may be better than focusing on individual parameters. Likewise, although single nutritional supplements are not recommended because of a lack of evidence showing clinical benefit, combinations of specific nutrients seem to yield more encouraging results.

Souvenaid is a nutraceutical preparation that includes several nutrients with AD risk-lowering properties. The authors of randomized, controlled trials investigated Souvenaid across a spectrum of patients with AD, ranging from prodromal AD to mild-moderate AD dementia, and the data showed the benefits are greater when the product is used early in the disease course. In the LipiDiDiet study, the benefits of Souvenaid on memory, hippocampal volume, and cognition were more helpful to individuals with mild AD dementia and prodromal AD, but not in mild-moderate AD dementia. These data, along with high rates of long-term product adherence, indicate Souvenaid is a useful tool in early-stage disease, including AD-induced MCI.

Patient experience programs and real-world data also have indicated benefits for Souvenaid in those with mild AD and MCI, including more social engagement and motivation; mental and physical resilience; higher energy levels; and improvements in memory, cognition, and mood connected to a return to functional hobbies and tasks. Although these data are not as reliable as those from randomized, controlled trials, they provide important information on quality of life for the patient and the family.

A major limitation to using Souvenaid is the need for biomarker support of the diagnosis of MCI caused by AD (prodromal AD). In fact, the only randomized, controlled trial data showing clinical benefit were obtained in MCI patients who exhibited evidence for underlying AD pathology based on positive findings from at least one diagnostic biomarker test (cerebrospinal fluid, MRI, and fluorodeoxyglucose F 18 PET). No studies are available regarding the effects of Souvenaid on MCI patients with a different diagnostic type. These data also speak to the importance of biomarker testing for clinical trials as well as clinical practice. The success of techniques to delay progression of MCI to dementia depends in large part on early and accurate identification of people at risk of AD. Finally, it remains unclear whether simply taking multivitamin supplements containing similar doses of the same nutrients included in Souvenaid would yield similar results.

Identifying individuals at risk of progression from MCI to AD dementia early is vital to facilitate patient management when clinical deficits and pathological changes are not too severe yet. Physicians play an important role in encouraging patients to adopt a healthy diets and lifestyles to support cognitive function, which is a crucial first step in MCI management. In addition, MCI patients with AD pathology should be provided with information about nutritional supplementation, including Souvenaid. ■

REFERENCES

1. Scheltens P, Kamphuis PJ, Verhey FRJ, et al. Efficacy of a medical food in mild Alzheimer's disease: A randomized, controlled trial. *Alzheimers Dement* 2010;6:1-10e1.
2. Scheltens P, Twisk JWR, Blesa R, et al. Efficacy of Souvenaid in mild Alzheimer's disease: Results from a randomized, controlled trial. *J Alzheimers Dis* 2012;31:225-236.
3. Shah RC, Kamphuis PJ, Leurgans S, et al. The S-Connect study: Results from a randomized, controlled trial of Souvenaid in mild to moderate Alzheimer's disease. *Alzheimers Res Ther* 2013;5:59.
4. Soininen H, Solomon A, Visser PJ, et al. 24-month intervention with a specific multinutrient in people with prodromal Alzheimer's disease (LipiDiDiet): A randomised, double-blind, controlled trial. *Lancet Neurol* 2017;16:965-975.
5. Cummings J, Passmore P, McGuinness B, et al. Souvenaid in the management of mild cognitive impairment: An expert consensus opinion. *Alzheimers Res Ther* 2019;11:73.

ABSTRACT & COMMENTARY

Fruits and Vegetables Lower the Risk of Type 2 Diabetes

By Ricardo Hood, MD, and Nancy Selfridge, MD

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SYNOPSIS: Researchers concluded an increase in dietary consumption of fruits and vegetables is beneficial in reducing the risk of diabetes mellitus type 2, regardless of the current level of consumption.

SOURCE: Zheng JS, Sharp SJ, Imamura F, et al. Association of plasma biomarkers of fruit and vegetable intake with incident type 2 diabetes: EPIC-InterAct case-cohort study in eight European countries. *BMJ 2020*;370:m2194.

The estimated risk of developing diabetes continues to increase throughout the world. The average risk of developing type 2 diabetes (T2D) for persons born in the United States in 2000 is 32.8% for men and 38.5% for women. The estimated risk for Hispanic persons born in the United States is 45.4% for men and 52.5% for women, the highest in the country.[1] Any effective technique for risk reduction and prevention carries significant public health implications.

Citing inconsistent, weak evidence from prospective studies and sparse randomized, controlled trials linking fruit and vegetable intake with T2D risk reduction, Zheng et al aimed to examine the association of baseline levels of circulating vitamin C and carotenoids with incident T2D. The investigators used data collected in the European Prospective Investigation into Cancer and Nutrition (EPIC), an ongoing, multicenter, prospective, cohort study designed to investigate the links between nutrition and cancer risk in more than 500,000 community-based adult subjects from eight European countries.[2]

According to the case-cohort study design, and after exclusions for missing or inadequate blood samples, the authors included data from a population of 22,833 subjects from the EPIC-InterAct subcohort (more than 340,000 participants) nested within the EPIC study. The population consisted of 9,754 participants with incident T2D and 13,662 randomly selected subcohort participants, with an average follow-up of 9.7 years across 26 study centers in eight European countries. Nonfasting blood samples, collected from subjects at the EPIC study's baseline visit, were used to obtain plasma levels of vitamin C, and several carotenoids (alpha-carotene, beta-carotene, lycopene, lutein, zeaxanthin, and beta-cryptoxanthin) were measured via the high-performance liquid chromatography-ultraviolet method. Additional baseline data included weight, height, and waist circumference. Baseline physical activity, smoking status, sociodemographic factors, and medical history were obtained by study staff from self-administered questionnaires. The authors used primary and secondary care registers, drug registers, and hospital and mortality records to ascertain self-reported diabetic status.

Using averages of the standardized values of vitamin C and individual carotenoid levels in the subcohort, Zheng et al calculated a composite biomarker score and applied it to analyses, along with analyses of the effect of individual biomarker levels. They correlated the composite biomarker score with subject self-report of fruit and vegetable intake. The authors determined differences in total intake for each one standard deviation increase in composite biomarker score using linear regression. They adjusted for confounding factors, including age, sex, sociodemographic factors (marital status and education), physical activity, smoking, BMI, energy intake, alcohol, waist circumference, and diet (cereals, potatoes, soft drinks, legumes, nuts, eggs, fish, red meat, and vitamin supplementation).

Composite biomarker scores were divided into five categories, correlating with lowest consumption of fruits and vegetables (Group 1) to highest consumption (Group 5). Researchers correlated these categories with incident T2D, continuing to adjust for other confounding risk factors, including obesity, family history of T2D, insulin resistance, cardiovascular disease, cancer, stroke, menopausal status, and diet quality. Additionally, to investigate the association between incident T2D and current "five a day" recommendations for fruit and vegetable serving consumption, the authors used composite biomarker levels to identify subjects in two groups: those meeting or exceeding five servings a day (> 400 g) and those not meeting current recommendations.

Results focused on incident T2D and composite biomarker scores from Groups 2, 3, 4, and 5 vs. Group 1. They were applied in a primary reference statistical model, 1a, adjusting for age, sex, and research center. Two additional models adjusted for confounding risk factors: model 1b, further adjusting for physical activity, smoking, alcohol, total energy intake, sociodemographic factors, high-density lipoprotein and low-density lipoprotein levels; and model 2, additionally adjusting for BMI and adiposity. Although adjustments in these models attenuated the magnitude of the inverse association trends, all remained statistically significant ($P < 0.001$).

Subjects with incident T2D recorded lower mean concentrations of plasma vitamin C and total carotenoids vs. the subcohort population. There was an inverse association between incident T2D and composite biomarker scores, as well as total vitamin C and total carotenoids. Additionally, Zheng et al noted an inverse association with incident T2D for all individual plasma carotenoids, except for zeaxanthin. The hazard ratios comparing Groups 2, 3, 4, and 5 of the composite biomarker score with Group 1 were 0.77 (95% CI, 0.68-0.87), 0.66 (95% CI, 0.54-0.80), 0.59 (95% CI, 0.48-0.72), and 0.50 (95% CI, 0.40-0.62), respectively, for model 2, which included adjustments for all confounding risk factors. An analysis comparing "five or more servings per day" to fewer than five servings

daily and incident T2D resulted in a hazard ratio of 0.69 (95% CI, 0.63-0.76). A single standard deviation difference in the composite biomarker score, equivalent to approximately 66 g difference in daily fruit and vegetable intake, was associated with a hazard ratio of 0.75 (95% CI, 0.67-0.83; $P < 0.001$).

■ COMMENTARY

The strengths of this study include its case-cohort design, the large number of subjects with complete data sets from the EPIC database, the use of quantitative measures of fruit and vegetable consumption biomarkers that correlated well with subject self-report of daily intake, and the care the researchers took to statistically adjust dietary association results for other confounding risk factors for incident T2D. This study supports the current nutrition recommendation by several national and international organizations (American Heart Association, U.S. Department of Agriculture, CDC, World Health Organization, et al) to consume five total servings of fruits and vegetables daily. It also provides evidence for encouraging patients with low intake to add daily servings toward meeting these recommendations, with each increase of about 66 g in daily consumption of fruits and vegetables appearing to significantly reduce the risk of developing T2D.

For patients who adhere to this recommendation, evidence exists for further risk reduction when consumption exceeds the five recommended servings per day. Further, as noted in previous studies, vitamin supplements are not similarly associated with risk reduction as whole fruits and vegetables. Thus, it is unlikely these vitamins identified as biomarkers for fruits and vegetables are solely biophysiologically responsible for risk-mitigating effects.

Encourage patients to increase their intake of fruits and vegetables and assure them even small increments make a difference. The 66-g increment associated with a standard deviation in biomarker plasma level amounts to about half of a medium apple, one medium raw carrot, one cup of chopped broccoli, or one cup of chopped kale. When patients ask if they can take a vitamin, we can cite this study as ongoing evidence that the value of whole food is much more than the vitamins contained therein. The common wisdom reflected in author Michael Pollan's aphorism rings loud and clear in these study results: "Eat food, not too much, mostly plants."[3] ■

REFERENCES

1. Narayan KMV, Boyle JP, Thompson TJ, et al. Lifetime risk for diabetes mellitus in the United States. *JAMA* 2003;290:1884-1890.
2. Riboli E, Hunt KJ, Slimani N, et al. European Prospective Investigation in Cancer and Nutrition (EPIC): Study populations and data collection. *Public Health Nutr* 2002;5:1113-1124.
3. Pollan M. *In Defense of Food: An Eater's Manifesto*. Penguin Press;2009.

PHARMACOLOGY UPDATE

Tirbanibulin Ointment (Klisyri)

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 a first-in-class topical drug for the treatment of actinic keratosis (AK). Tirbanibulin is a microtubule inhibitor with antiproliferative activity. It is distributed as Klisyri.

INDICATIONS

Tirbanibulin is indicated for the topical treatment of AK on the face and scalp.[1]

DOSAGE

Apply a single-dose packet to the treatment field (up to 25 cm^2) on face or scalp once daily for five consecutive days.[1] Tirbanibulin 1% ointment is available as a single-dose packet.

POTENTIAL ADVANTAGES

Tirbanibulin offers a new mechanism of action. Its short treatment regimen (five days) may improve adherence. Local reactions were mostly mild and transient.[2]

POTENTIAL DISADVANTAGES

The most frequently reported adverse reactions compared to the vehicle were moderate erythema (63% vs. 6%) and moderate flaking/scaling (47% vs. 9%).[1] AK lesions tend to recur at 12 months.[1]

COMMENTS

The efficacy of tirbanibulin was established in two double-blind, vehicle-controlled trials in adult subjects with AK on the face or scalp.[1] Subjects (mainly white men with Fitzpatrick skin types II and III) exhibited four to eight clinically typical, visible, and discrete AK lesions on the face or scalp with a contiguous area of 25 cm^2. They were randomized to tirbanibulin (n = 175 in study

1 and n = 178 in study 2) or vehicle (n = 176 and 173, respectively). Subjects received five consecutive days of treatment. The primary endpoint was the proportion of subjects with complete (100%) clearance of AK. The secondary endpoint was partial clearance (≥ 75%). Subjects with complete clearance returned for assessment of recurrence every three months for 12 months after day 57.

Complete clearance rates were 44% (study 1) and 54% (study 2) at day 57 vs. 5% and 13% for vehicle, respectively, showing treatment differences of 40% and 42%. Tirbanibulin was more effective on face lesions compared to scalp lesions (50% and 54% vs. 30% and 41%, respectively). The recurrence rate at 12 months was 73%.[1] Partial clearance rates (vs. placebo) were 68% vs. 16% for study 1 and 76% vs. 20% for study 2. Cost information is not available yet.

CLINICAL IMPLICATIONS

AK is a common skin lesion in older, fair-skinned individuals resulting from cumulative sun exposure.[2] A portion may progress to invasive squamous cell carcinoma.[3-5] The treatment goal is to eradicate both clinical and subclinical AK lesions and maintain a disease-free interval as long as possible.[4] Spontaneous resolution is reported to occur in 15% to 63% of lesions after one year.[5] Treatment/removal modalities include nondrug (e.g., cryotherapy, curettage,) that are lesion-directed or topical treatment (e.g., fluorouracil, imiquimod, ingenol mebutate, diclofenac gel, or photodynamic therapy) for field-directed treatment of multiple lesions.[6,7] For topical options, fluorouracil and imiquimod represent 80% of the market, with ingenol mebutate and diclofenac with 10% each.[4] The authors of a randomized trial compared four treatments in 624 subjects with AK (five or more lesions on the head, approximately 50% of the face) with one continuous area of 25 cm^2 to 100 cm^2.[8] Fluorouracil was applied twice daily for four weeks. Imiquimod was applied once daily three days per week for four weeks. Ingenol mebutate was applied once daily for three consecutive days. Some subjects also underwent methyl aminolevulinate photodynamic therapy (PDT). All patients could receive a maximum of two courses of assigned treatment. Treatment success was assessed at 12 months after last treatment. The cumulative probabilities of treatment success were 75% for fluorouracil, 54% for imiquimod, 38% for PDT, and 29% for ingenol mebutate. The lower rate for imiquimod may be because a shorter treatment duration is recommended. Fluorouracil was not associated with higher frequency of adverse events than other treatments. Diclofenac, not included in the study, requires treatment for two to three months.[6] Fluorouracil may be less preferable for the face because of skin reaction (e.g., local inflammation).[6] Tirbanibulin may be an option for the face because of its mild to moderate local reaction and short treatment duration. The potential downside is a high recurrence rate. ■

REFERENCES

1. Almirall, LLC. Klisyri prescribing information. December 2020. https://bit.ly/3sdJfnv
2. Kempers S, DuBois J, Forman S, et al. Tirbanibulin ointment 1% as a novel treatment for actinic keratosis: Phase 1 and 2 results. *J Drugs Dermatol* 2020;19:1093-1100.
3. Rosen T, Lebwohl MG. Prevalence and awareness of actinic keratosis: barriers and opportunities. *J Am Acad Dermatol* 2013;68:S2-S9.
4. Cramer P, Stockfleth E. Actinic keratosis: Where do we stand and where is the future going to take us? *Exp Opin Emerg Drugs* 2020;25:49-58.
5. Center for Drug Research and Evaluation. NDA 213189 Multidisciplinary review and evaluation. Oct. 12, 2018. https://bit.ly/3nE7veI
6. American Academy of Dermatology Association. Actinic keratosis: Diagnosis and treatment. http://bit.ly/2LGtPXW
7. Goldenberg G. Treatment considerations in actinic keratosis. *J Eur Acad Dermatol Venereol* 2017;31:12-16.
8. Jansen MHE, Kessels JPHM, Nelemans PJ, et al. Randomized trial of four treatment approaches for actinic keratosis. *N Engl J Med* 2019;380:935-946.

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CME QUESTIONS

1. Which is true about blood pressure (BP) concordance in patients evaluated from the SPRINT trial?
a. On average, patients recorded lower outpatient BP than trial visit BP.
b. On average, patients recorded higher outpatient BP than trial visit BP.
c. On average, there was no difference between outpatient BP and trial visit BP.
d. On average, the difference between outpatient BP and trial visit BP was the same for the intensive control group and standard control group.

2. In the Soininen et al study, which lifestyle intervention is recommended to delay the progression of prodromal Alzheimer's disease?
a. Massage therapy
b. Controlling hypertension
c. Taking up more hobbies
d. Completing sudoku puzzles

3. Which best describes the association between daily fruit and vegetable intake and incident type 2 diabetes in the Zheng et al study?
a. Vitamin C and carotenoid biomarkers correlated poorly with subjects' self-reported intake.
b. A 66 g per day increase in total daily intake was associated with statistically significant risk reduction.
c. Individual vitamin C and carotenoid levels were not associated with significant risk reduction.
d. Adjustments of risk calculation for other known risk factors negated all inverse risk associations.

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.