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ABSTRACT & COMMENTARY

Making Healthy Lifestyle Choices, Living Longer Without Chronic Diseases

By David Fiore, MD

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

SYNOPSIS: The authors found improving each of four "healthy lifestyle choices" added approximately one year of disease-free life between ages 40 and 75 years. Adopting all four "optimal" lifestyles was associated with nine years of life gained vs. adopting zero optimal lifestyles.

SOURCE: Nyberg ST, Singh-Manoux A, Pentti J, et al. Association of healthy lifestyle with years lived without major chronic diseases. *JAMA Intern Med* 2020;180:1-10.

In a multicohort analysis of 12 European studies, Nyberg et al investigated the relationship between four "lifestyle factors" and the number of years between ages 40 and 75 living without chronic illnesses. Specifically, the authors examined type 2 diabetes, coronary heart disease, stroke, cancer, asthma, and chronic obstructive pulmonary disease. In a subsidiary analysis, Nyberg et al included dementia and heart failure. The four "lifestyles" chosen for inclusion and analysis were smoking, body mass index, physical activity, and alcohol consumption. Each lifestyle factor was scored as 0 (poor), 1 (intermediate), or 2 (optimal), which created 16 "lifestyle profiles" based on dichotomous grouping of each factor as either "optimal" or "intermediate/poor."

The researchers used national registers for outcome data. To be included in the analysis, participants had to be free of any of the chronic conditions listed (as well as type 1 diabetes-free). A total of 116,043 participants were analyzed, with a mean age of 43.7 years at enrollment initiation; 61% were women. The mean follow-up was 12.5 years.

There was a linear association between the number of optimal lifestyle factors and years lived without chronic disease. This relationship held for the six initial chronic diseases as well as when dementia and heart disease were added. In a sensitivity analysis, never drinking (intermediate) was combined with moderate drinking (optimal), and no difference in

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outcomes was found. Compared to the worst lifestyle score (no optimal lifestyles), the best lifestyle score (all four optimal lifestyles), there was a gain of nine disease-free years. Each one-point improvement in lifestyle score was associated with nearly one year of disease-free life gained (0.96 years for men, 0.89 years for women).

■ COMMENTARY

This was a well-designed analysis, with a large enough cohort to strongly support the notion that lifestyle choices can make a difference in overall health, even if the effects are delayed. Previous studies have demonstrated longer life expectancy and longer disease-free life expectancy are associated with various healthy lifestyle choices.

Nyberg et al added to these investigations by quantifying the number of disease-free years gained by making healthy lifestyle choices, both individually and in combination.[1-3] Recently, other authors drew similar conclusions as Nyberg et al when they found that the same four healthy lifestyles were associated with a gain of almost 10 additional years of disease-free life for women and eight more years for men.[4] Importantly, lifestyle choices seemed to be additive. This means patients could be motivated to build on the benefits of each healthy lifestyle choice. Considering its design as a cohort study, the work by Nyberg et al cannot truly lead to definitive conclusions about causation. Also, as with any cohort study, there is the concern of confounding. It is well known that many healthy lifestyles are associated with higher socioeconomic status. Fortunately, Nyberg et al addressed this in one of the electronic supplemental tables, and found that the results held across socioeconomic status.

The evidence from the Nyberg et al investigation and multiple other studies on lifestyle and health is becoming too hard to ignore. This work adds to and supports what most clinicians believe already: A healthy lifestyle is associated with a healthier life. ■

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BRIEF REPORT

Benefits of Targeting LDL Cholesterol Below 70 mg/dL

By Matthew E. Fink, MD

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

SOURCE: Amarenco P, Kim JS, Labreuche J, et al. Benefit of targeting LDL (low-density lipoprotein) cholesterol <70 mg/dL during 5 years after ischemic stroke. *Stroke* 2020;51:1231-1239.

In the SPARCL trial (*N Engl J Med* 2006;355:549-559), treatment of patients with atorvastatin 80 mg per day resulted in a 16% relative risk reduction in stroke during 4.9 years of follow-up, compared to placebo. In a subgroup with carotid artery stenosis, the relative risk reduction was 33%. Patients who had a low-density lipoprotein (LDL) cholesterol less than 70 mg/dL had a 28% relative risk reduction compared to patients who only achieved an LDL cholesterol of 100 mg/dL or above.

Amarenco et al specifically focused on targeting an LDL cholesterol below 70 mg/dL in patients who had ischemic stroke or transient ischemic attack (TIA) with evidence of atherosclerosis. The patients were stratified into two groups, where statins were titrated to reach an LDL cholesterol of less than 70 mg/dL or with an LDL of 100 mg/dL. Investigators were free to use any statin of their choice, and this could be combined with ezetimibe or other medications as needed. This was an open-label trial, and patients and investigators were not blinded to treatments. The primary endpoint was the composite of nonfatal stroke, nonfatal myocardial infarction, unstable angina, TIA, and vascular death. Patients were enrolled from 2010 until 2018. The study ended early, after 277 primary endpoints were accrued, because of a lack of funds. Median follow-up was 3.5 years. The groups achieved mean LDL cholesterol of 66 mg/dL and 96 mg/dL, respectively. The primary endpoint occurred in 9.6% and 12.9% of patients, respectively, with a hazard ratio in favor of lower cholesterol of 0.74 (P = 0.019). Ischemic stroke or urgent carotid revascularization following TIA was reduced by 27%. The primary outcome was reduced by 25%. There was no significant difference in the numbers of intracranial hemorrhages that occurred between the two groups. The investigators concluded that after an ischemic stroke of atherosclerotic origin, targeting LDL cholesterol to less than 70 mg/dL resulted in a significant reduction in subsequent major vascular events and no increase in intracranial hemorrhage. ■

BRIEF REPORT

Disability After Minor Stroke and TIA — Secondary Analysis of the POINT Trial

By Matthew E. Fink, MD

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

SOURCE: Cucchiara B, Elm J, Easton JD, et al. Disability after minor stroke and transient ischemic attack in the POINT trial. *Stroke* 2020;51:792-799.

Early treatment of minor stroke and transient ischemic attacks (TIAs) with antiplatelet medication reduces the risk and severity of recurrent stroke. The POINT trial demonstrated that dual antiplatelet treatment with aspirin and clopidogrel resulted in a lower rate of recurrent stroke than with aspirin alone. The investigators conducted a secondary analysis to determine if disability at 90 days was different between the two groups as well.

At 90 days, 9.6% of patients enrolled with TIA and 18.2% of patients enrolled with minor stroke were disabled. Overall disability was similar between the groups whether assigned to dual antiplatelet therapy or aspirin alone (14.7% vs. 14.3%). However, there were fewer patients with disability in conjunction with the primary outcome event in the dual antiplatelet treatment arm, but this did not reach statistical significance. The investigators also analyzed the combination of the index event with recurrent stroke and thought that there was a decrease in disability in the dual antiplatelet treatment arm. A multivariate analysis was performed and indicated that risk factors for disability following TIA included age, subsequent stroke, serious adverse events, and major bleeding. Although the data from this analysis suggest disability might be less with dual antiplatelet therapy, differences between the groups were small, did not show robust findings, and did not reach statistical significance in most of the analyses. ■

BRIEF REPORT

Type of Provider and Opioid Use in New-Onset Low Back Pain

By Jessica Orner, MD

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

SYNOPSIS: When compared to an initial visit with a primary care physician, patients who initially received care for new-onset low back pain from a chiropractor, physical therapist, or acupuncturist were at lower odds for early and long-term opioid use.

SOURCE: Kazis LE, Ameli O, Rothendler J, et al. Observational retrospective study of the association of initial healthcare provider for new-onset low back pain with early and long-term opioid use. *BMJ Open* 2019;9:e028633.

In this retrospective cohort study, Kazis et al examined the association between types of providers seen for an initial concern of new-onset low back pain (LBP) with subsequent early and long-term opioid use. They examined de-identified outpatient and inpatient claims data from OptumLabs Data Warehouse from 2008 though 2013. Claims included visits to primary care providers (PCPs), specialists, chiropractors, acupuncturists, and physical therapists. In this study, chiropractors, acupuncturists, and physical therapists were considered conservative therapists.[1]

Of the 8.8 million adults who visited with a provider for LBP during the study period, 216,504 met the criteria for inclusion. To be included, patients needed to be continuously enrolled in a health plan for at least 24 months before and following the initial outpatient visit for back pain. Both medical and pharmacy claims data were required for that period. Patients were excluded for: prescription for opioids in the preceding 12 months, diagnosis of neoplasia in the preceding 12 months or within three months after the initial claim date, and LBP diagnosis that typically would not be amenable to conservative therapy. Early opioid use was determined by a filled opioid prescription for a qualifying diagnosis within 30 days of the initial visit. Long-term opioid use was defined as an opioid prescription within 60 days of the initial visit and either ≥ 120 days' supply over 12 months or ≥ 90 days' supply of opioids and ≥ 10 prescriptions over 12 months.[1]

Fifty-three percent of patients initially were seen by a PCP, followed by 23.1% by a chiropractor, 1.6% by a physical therapist, and 0.8% by an acupuncturist. When compared with seeing a PCP, patients who initially saw a conservative therapist were at lower odds for early and long-term opioid use. There were lower odds of early opioid use in those initially seen by orthopedic surgeons, neurosurgeons, and rehab physicians compared to PCPs. There was a significant increase in odds of early opioid use in those who visited emergency physicians and long-term use in those who saw physical rehabilitation physicians. Long-term opioid use odds were not significantly different among those who saw orthopedic surgeons, neurosurgeons, or emergency physicians compared to PCPs. Researchers discussed a few possible reasons for the differences seen in opioid use based on initial provider. Conservative therapists cannot prescribe opioids; therefore, patients seeking conservative therapy for their initial claim of new-onset LBP could not obtain opioids at that visit. Also, it is possible early participation with conservative therapists provides an opportunity to incorporate evidence-based nonpharmacological interventions and lowers the need for pharmacologic intervention. The authors noted causation cannot be inferred because this was a claims-based study.

There were several limitations. A claims-based study would miss cases treated outside the insurance system. Insurance coverage for modalities such as chiropractic care and acupuncture vary. Also, the availability of physical therapy without a referral fluctuates between insurance plans and states.[1] Based on the results, PCPs may want to think about their prescribing habits and nonpharmacologic modalities, such as physical therapy, acupuncture, and/or chiropractic care, early in the treatment of LBP. There is additional evidence to suggest early physical therapy participation is associated with fewer opioid prescriptions.[2] ■

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ABSTRACT & COMMENTARY

How Does Weight Loss Affect Lower Urinary Symptoms and Incontinence in Obese and Overweight Women?

By Chiara Ghetti, MD

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

SYNOPSIS: Weight loss interventions were associated with improvements in urinary incontinence in overweight and obese women at one to 2.9 years.

SOURCE: Yazdany T, Jakus-Waldman S, Jeppson PC, et al. American Urogynecologic Society Systematic Review: The impact of weight loss intervention on lower urinary tract symptoms and urinary incontinence in overweight and obese women. *Female Pelvic Med Reconstr Surg* 2020;26:16-29.

The main objective of this study was to evaluate existing data on how weight loss interventions (behavioral and surgical) affect lower urinary tract symptoms in overweight and obese women. This systematic review was conducted by the American Urogynecologic Society Systematic Review Group and registered at Prospero.

Researchers searched PubMed, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), and the Cochrane Library for English-language articles from Jan. 1, 1990, to Dec. 1, 2018. Full-text articles were selected based on set inclusion and exclusion criteria. Eligible studies included randomized, controlled trials and cohort and case-control investigations. Case series were included only if pre- and post-intervention outcomes were reported. Studies included women ≥ age 18 years whose mean body mass index (BMI) was ≥ 30 kg/m^2 enrolled in behavioral or surgical weight loss programs and with symptoms of urinary incontinence or overactive bladder. Behavioral weight loss interventions included diet modification, exercise programs, medications, and/or counseling. Review articles were excluded, as were studies of subjects with interstitial cystitis, bladder pain syndrome, fistulas, pelvic cancer, urinary retention, neurogenic bladder, spinal cord injury, or subjects who had undergone pelvic irradiation or were pregnant. Only data pertaining to women were included in the reported study.

Evidence for certainty of outcomes was categorized using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) and was rated as high, moderate, low, and very low certainty. A grade of high certainty meant the authors were confident the real outcome or true effect comes close to the estimated, while very low certainty evidence meant the authors were not confident at all in the estimate, and that the real effect was likely to be significantly different from the estimate. The authors found high-certainty evidence that behavioral weight loss (diet and exercise) leads to moderate reduction in the prevalence of stress urinary incontinence and overall urinary incontinence (12% to 18%, collectively). However, there was low-certainty evidence on the long-term effects of behavioral weight loss interventions, and only moderate to low certainty evidence exists regarding the effects of weight loss on urge incontinence and overactive bladder symptoms. To date, there is little evidence about the effect of surgical weight loss on urinary symptoms, and there are no randomized studies.

■ COMMENTARY

Urinary incontinence affects nearly half of all women.[1] Obesity is a strong independent risk factor for the condition.[2] Obesity is a growing public health problem worldwide, with a prevalence of 42.4% in the United States in 2017-2018.[3] Epidemiologic studies indicate a 20% to 70% increase in the risk of incontinence with each five unit increase in BMI. Prior studies have shown improvements in urinary incontinence symptoms with weight loss. The goal of this study was to evaluate the existing evidence supporting weight loss for the treatment of urinary incontinence to aid in treatment recommendations. The authors found strong evidence to support improvement of urinary incontinence in the short term following behavioral weight loss. However, it appears weight loss benefits may diminish over time. In light of this evidence, the authors suggested providers not delay treatment of incontinence in women not interested in weight loss.

The treatment of urinary incontinence often is multimodal and certainly should not be delayed. However, the relationship between obesity and urinary

incontinence treatment is not simple, either. In a retrospective cohort study of 431 subjects undergoing midurethral sling, Elshatanoufy et al found that patients with class 3 obesity (BMI ≥ 40 kg/m^2) were twice as likely to fail treatment and had either postoperative stress urinary incontinence symptoms or required additional treatment for stress urinary incontinence.[4] In another recent study of the British Society of Urogynaecology database of 11,859 women treated with midurethral sling, Bach et al found patient-reported subjective urinary incontinence symptoms, measured by validated measures, worsened as BMI increased.[5]

An earlier systematic review and meta-analysis by Greer et al suggested midurethral sling cure rates were lower in obese women.[6] There are significant knowledge gaps in both understanding the long-term effects of weight loss and the effects of surgical weight loss in the treatment of urinary incontinence. More studies also are needed to better understand the long-term effectiveness of surgical interventions for urinary incontinence in obese patients.

In pondering these relationships between obesity, weight loss, and incontinence, we must acknowledge obesity is the second most common cause of preventable death. Each five-unit increase in BMI confers approximately 30% higher overall mortality.[7,8] Obesity increases the risk of cancer, hypertension, heart disease, diabetes, stroke, sleep apnea, and musculoskeletal disorders. As providers addressing the quality of life burden of urinary incontinence, it is imperative we counsel our patients extensively about the risks of obesity while building a therapeutic partnership to promote changes that will lead to weight loss. Although weight loss may not provide long-term urinary symptom reduction, the consequences of persistent obesity are formidable. ■

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PHARMACOLOGY UPDATE

Selpercatinib Capsules (Retevmo)

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

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

The Food and Drug Administration (FDA) has approved the first oncology treatment that targets rearranged during transfection (RET) alterations in the form of mutations or fusions of certain advanced lung and thyroid cancers.[1] Selpercatinib is a kinase inhibitor that inhibits wild-type RET and multiple mutated RET isoforms, as well as vascular endothelial growth factors 1 and 3 (VEGFR1 and VEGFR3).[2]

The FDA greenlit selpercatinib under the accelerated approval pathway. The agency also approved priority review, breakthrough therapy, and orphan drug designations. It is marketed as Retevmo.

INDICATION

Selpercatinib is indicated for the treatment of adults with metastatic RET fusion-positive, non-small cell lung cancer (NSCLC) and pediatric patients (≥ age 12 years) and adults with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy.[2]

It also is indicated in advanced or metastatic RET fusion-positive thyroid cancer in patients who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate). Accelerated approval was based on duration of

response and overall response rate.[2] Continued approval may be contingent on description and verification of clinical benefit in confirmatory trials.

DOSAGE

The recommended dose is 120 mg orally twice daily (< 50 kg body weight) or 160 mg twice daily (≥ 50 kg body weight).[2] The drug should be taken until disease progression or unacceptable toxicity occurs. Dosage modifications are needed for adverse reactions, hepatic impairment, concomitant use of acid-reducing agents, and strong and moderate CYP3A inhibitors. Selpercatinib is available as 40 mg and 80 mg capsules.

POTENTIAL ADVANTAGES

Selpercatinimb is a selective and potent inhibitor of RET compared to other kinase (including multikinase) inhibitors.[3] It is the first therapy approved that targets RET gene alterations. The drug showed response (i.e., tumor shrinkage) in patients with NSCLC, MTC, and thyroid cancer (e.g., papillary thyroid cancer [PTC]), with overall response rates of 64% to 79% in previously treated patients and 73% to 100% for those naïve to treatment.[1,2]

POTENTIAL DISADVANTAGES

Selpercatinib can cause serious hepatotoxicity, hypertension, hemorrhagic events, and embryo-fetal toxicity.[2] It also can cause concentration-dependent QT prolongation and increase the risk of impaired wound healing. Common adverse reactions (more than 30%) include dry mouth, diarrhea, hypertension, fatigue, and edema; higher aspartate transaminase/alanine aminotransferase, glucose, creatinine, alkaline phosphatase, and total cholesterol levels; and lower albumin and leukocytes levels.[2]

COMMENTS

Selpercatinib was evaluated in open-label trials in the three types of cancer and stratified by treatment-experienced and treatment-naïve status.[2] The major efficacy outcome measures were confirmed overall response rate (ORR) and duration of response (DOR) as determined by a blinded, independent review committee.

In patients with advanced RET fusion-positive NSCLC, previously treated with platinum chemotherapy (55% underwent prior anti-PD-1/PDL-1 therapy; n = 105), ORR was 64%, of which 62% were partial response. Median duration of response was 17.5 months.

For treatment-naïve patients (n = 39), ORR was 85% (all partial), and DOR has not been determined. For RET-mutant MTC previously treated with multikinase inhibitors (cabozantinib or vandetanib; n = 55), ORR was 69% (9% complete, 60% partial), with DOR yet to be determined. However, 76% had DOR ≥ 6 months. For treatment-naïve patients (n = 88), ORR was 73% (11% complete, 61% partial). For RET fusion-positive thyroid cancer (78% PTC) previously treated (n = 19), ORR was 79% (5% complete, 74% partial) and DOR of 18.4 months. For treatment-naïve patients (n = 8), ORR was 100% (12% complete, 88% partial) and 75% with DOR ≥ 6 months.

CLINICAL IMPLICATIONS

RET is a transmembrane receptor protein-tyrosine kinase (proto-oncogene) required for normal tissue development and maturation. The RET rearrangement (i.e., chromosomal rearrangement) gene has been associated with 30% of papillary thyroid cancers and 1-2% of NSCLC, particularly in patients who never smoked or who had lung adenocarcinoma.[4-6] Current therapies are limited in efficacy, with ORR for NSCLC ranging from 18% to 32%.[5] Similarly, for MTC, the ORR is 28% with cabozantinib, a multikinase inbibitor.[7]

Selpercatinib is a first-of-its-kind drug that provides the first effective targeted treatment (in this case, RET) rather than targeting the site (i.e., organ) of the tumor, with ORR of 60% to 100%, including previously treated NSCLC, MTC, and PTC. Approval was based on a small number of patients, but these new gene-based therapies offer potential benefit to patients who previously had few options. The National Comprehensive Cancer Network (Version 5.2020) now lists selpercatinib as the preferred treatment for NSCLC with RET rearrangement. It has not been updated for MTC or PTC. The cost is $20,600 for a 30-day supply at 320 mg/day. ■

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CME QUESTIONS

1. **Each of the four healthy lifestyle choices (nonsmoking, not obese, at least moderate exercise, and moderate or no alcohol consumption) is associated with:**
   a. variable increase and decrease in disease-free longevity.
   b. variable increase in disease-free longevity.
   c. six months increase in disease-free longevity.
   d. one year increase in disease-free longevity.

2. **Lowering low-density lipoprotein cholesterol below 70 mg/dL in patients with ischemic stroke due to atherosclerosis results in a significant reduction in recurrent vascular events, compared to the usual target of 100 mg/dL.**
   a. True
   b. False

3. **After minor stroke or transient ischemic attack, treatment with aspirin alone or dual antiplatelet therapy does not seem to make a significant difference in 90-day disability.**
   a. True
   b. False

4. **Obesity and urinary incontinence are interrelated. Which statement is true?**
   a. Weight loss does not provide long-term improvement in urinary symptoms and should not be emphasized.
   b. Obesity negatively affects patients' long-term health and increases mortality risk.
   c. Obesity does not affect urinary incontinence treatment.
   d. Obesity is not a risk factor for urinary incontinence.

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.

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