GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of December 30, 2024 – January 3, 2025

SPOTLIGHT:

Evaluating Vegan and Mediterranean Diets Effects on Weight Loss and Cardiometabolic Risks

Evaluating Vegan and Mediterranean Diets: Effects on Weight Loss and Cardiometabolic Risks

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

A Mediterranean Diet and Low-Fat Vegan Diet to Improve Body Weight and Cardiometabolic Risk Factors: A Randomized, Crossover Trial

Barnard ND, Alwarith J, Rembert E, et al. A Mediterranean Diet and Low-Fat Vegan Diet to Improve Body Weight and Cardiometabolic Risk Factors: A Randomized, Cross-over Trial. *J Am Nutr Assoc*. 2022;41(2):127-139. doi:10.1080/07315724.2020.1869625

KEY TAKEAWAY: A low-fat vegan diet leads to significant improvements in body composition and blood lipids (except triglycerides), compared to a Mediterranean diet. However, the vegan diet had varying effects on insulin resistance and glucose tolerance.

STUDY DESIGN: Randomized crossover trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Diet can have a significant role in weight loss and cardiometabolic risk factors. About 70% of US adults are overweight, and nearly half have cardiovascular disease. There have been few studies that study the role of Mediterranean and vegan diets without confounding factors like increasing exercise or calorie restriction. This study aimed to assess the impact each diet may have on weight loss and cardiometabolic risks.

PATIENTS: Adults with body mass index (BMI) 28–40 kg/m^2

INTERVENTION: Vegan diet

CONTROL: Mediterranean diet

PRIMARY OUTCOME: Body composition, blood lipids, insulin resistance, and glucose sensitivity

METHODS (BRIEF DESCRIPTION):

- Adult non-pregnant women and men who were not currently on a vegan or Mediterranean diet were included.
- Patients were excluded if they had type 1 diabetes mellitus (T1DM), were pregnant or lactating, currently vegan or Mediterranean diet, smoked, used alcohol, or had drug abuse issues.
- Patients were randomized 1:1 to one of the following treatments:
  - Mediterranean diet for 16 weeks, four-week washout period, followed by vegan diet for 16 weeks
  - Vegan diet for 16 weeks, four-week washout period, followed by Mediterranean diet for 16 weeks
- The Mediterranean diet included daily servings of ≥2 vegetables and ≥2–3 fresh fruits and weekly servings of ≥3 legumes, ≥3 fish or shellfish, and ≥3 nuts or seeds.
  - Participants were asked to limit or eliminate cream, butter, margarine, processed meats, sweetened beverages, pastries, and processed snacks.
  - Cured ham, red meat, and fatty cheeses were limited to ≤1 serving per week.
  - Participants were asked to use extra virgin olive oil instead of other fats/oils.
- The low-fat vegan diet (approximately 75% of energy from carbohydrates, 15% protein, and 10% fat) consisted of vegetables, grains, legumes, and fruits.
  - Participants were instructed to avoid animal products and added fats.
  - Vitamin B12 was supplemented (500 mg per day) during the vegan phase of the study.
- Dietary intake data were collected and analyzed by a registered dietitian, or a staff member certified in the nutrition data system for research, who were not blinded.
- All measurements were performed at baseline and week 16 after a 10-hour overnight fast.
- Body composition, blood lipids, insulin resistance, and glucose sensitivity were measured as the primary outcome using the following.
  - Body composition was composed of body weight, total fat mass, and total lean mass.
  - Blood lipid concentrations including total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides were measured using enzymatic colorimetric methods.
  - Insulin resistance and glucose tolerance were determined using HbA1c, fasting insulin

resistance, predicted insulin sensitivity, and post-prandial insulin sensitivity.

INTERVENTION (# IN THE GROUP): 31

COMPARISON (# IN THE GROUP): 31

FOLLOW-UP PERIOD: 36 weeks

RESULTS:

Primary Outcome –

- The vegan diet improved body composition compared to the Mediterranean diet.
  - Body weight loss (mean difference [MD] –6.0 kg; 95% CI, –7.5 to –4.5)
  - Total fat mass (MD –3.4 kg; 95% CI, –4.7 to –2.2)
  - Total lean mass (MD –2.3 kg; 95% CI, –3.3 to –1.4)
- The vegan diet had varying effects on lipid concentrations compared to the Mediterranean diet.
  - Reduced total cholesterol (MD –11 mg/dL; 95% CI, –22 to –0.3)
  - Increased triglycerides (MD 21 mg/dL; 95% CI, 4.4–37)
  - Reduced HDL cholesterol (MD –4.4 mg/dL; 95% CI, –7.7 to –1.1)
  - Reduced LDL cholesterol (MD –11 mg/dL; 95% CI, –21 to –0.6)
- The vegan diet had varying effects on insulin resistance and glucose tolerance compared to the Mediterranean diet.
  - Decreased HbA1c (MD –0.13%; 95% CI, –0.22 to –0.03)
  - No difference in fasting insulin resistance (MD –0.68; 95% CI, –1.8 to 0.39)
  - No difference in predicted insulin sensitivity (MD 0.6 mg/min/kg; 95% CI, –0.2 to 1.4)
  - Improved post-prandial insulin sensitivity (MD 36 mL/min/m^2; 95% CI, 13–58)

LIMITATIONS:

- The adherence to diet was self-reported, making it impossible to know the certainty of participants' adherence.
- Self-reported energy intake was lower on both diets in the first period compared to the second period.
- There were more pronounced body weight and cardiometabolic outcomes seen in the first study period compared to the second study period.
- The study had a short duration of only 36 weeks.
- The results do not address patient-oriented outcomes.

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Demystifying RPOCs: Echogenic Mass Detection Reduces Diagnostic Uncertainty on Ultrasound

The Accuracy of Ultrasound Scan in Diagnosing Retained Products of Conception: A Systematic Review and Meta-Analysis

Sundararajan S, Roy S, Polanski LT. The accuracy of ultrasound scan in diagnosing retained products of conception: a systematic review and meta-analysis. *Am J Obstet Gynecol*. 2024;230(5):512-531.e3. doi:10.1016/j.ajog.2023.11.1243

KEY TAKEAWAY: Echogenic mass (EM) is more reliable as a sonographic indicator of retained products of conception (RPOC) in women after any pregnancy-related event compared to endometrial thickness (ET) and color Doppler imaging.

STUDY DESIGN: Systematic review and meta-analysis of 11 prospective, retrospective, cross-sectional, or cohort studies (N=1,567)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to high heterogeneity)

BRIEF BACKGROUND INFORMATION: Establishing standard diagnostic factors to identify RPOC in any pregnancy-related event remains unclear. RPOCs are currently diagnosed through ultrasound and clinical presentation, impacting decision-making related to management on a case-by-case basis. Prompt use of standardized predictors of RPOCs through ultrasound leads to more accurate diagnosis and management of RPOCs, thus minimizing complications and ensuring reproductive ability for future pregnancies. This study aimed to establish a standard diagnostic factor for identifying RPOCs on ultrasound accurately to improve medical decision-making and management of RPOC in any pregnancy-related event.

PATIENTS: Women with RPOCs after any pregnancy-related event

INTERVENTION: Ultrasound using EM

CONTROL: Ultrasound with ET or ultrasound with color Doppler flow imaging

PRIMARY OUTCOME: Accuracy of diagnosis

METHODS (BRIEF DESCRIPTION):

- Studies that utilized ultrasounds and histopathologic results of RPOC at all gestational ages were included.
- Women with signs and symptoms of RPOC after full-term, preterm, vaginal, or cesarean delivery, miscarriage, or termination of pregnancy with sonographic identification of RPOC (echogenic mass, endometrial thickness, color Doppler flow) were included.
- The average age of participants was 28–32 years old, with the time interval between ultrasound and surgical intervention (0–8 days) reported in three studies and gestational age (reported in 8 out of 11 cases) ranging between 9.2–39 weeks, and mode of delivery (cesarean, term or vaginal delivery, miscarriage or termination of pregnancy.)
- Nine studies used ultrasound with EM as a predictor of RPOC in any pregnancy-related event. At present, there is no consensus to describe EM, but generally, the definition includes, a hyperechoic or irregular, mixed echogenic endometrium or a well-circumscribed mass.
- Four studies used ultrasound with ET as an RPOC predictor, based on studies using 10 mm as a standardized cutoff, while five studies used ultrasound with color Doppler flow to identify RPOCs in any pregnancy-related event.
- The gold standard for this review used histopathologic confirmation of RPOCs as a reference.
- The accuracy of diagnosis was determined by calculating the sensitivity, specificity, diagnostic odds ratios (DOR), positive likelihood ratio (PLR), and negative likelihood ratio (NLR) of nine of 11 studies reporting EM as a diagnostic factor.
- The sensitivity and specificity were pooled separately to obtain the Cochran Q value and calculate the heterogeneity between studies to determine the diagnostic precision of RPOC.

INTERVENTION (# IN THE GROUP): 1,237

COMPARISON (# IN THE GROUP):

- Ultrasound with ET: 504
- Ultrasound with color Doppler imaging: 425

FOLLOW-UP PERIOD: Not available

RESULTS:

Primary Outcome –

- Echogenic mass is a strong diagnostic predictor of RPOC (n=9).
  - Sensitivity (0.90; 95% CI, 0.87–0.92; I^2=78%)
  - Specificity (0.87; 95% CI, 0.84–0.89; I^2=96%)
  - Diagnostic accuracy (diagnostic odds ratio [DOR] 60; 95% CI, 13–193; I^2=87%)
  - PLR (5.5; 95% CI, 2.4–12; I^2=96%)
  - NLR (0.15; 95% CI, 0.08–0.28; I^2=74%)
- Endometrial thickness may be a poor predictor of RPOC (n=4).
  - Sensitivity (0.43; 95% CI, 0.36–0.50; I^2=98%)
  - Specificity (0.81; 95% CI, 0.76–0.85; I^2=96%)
  - Diagnostic accuracy (DOR 7.3; 95% CI, 0.17–308; I^2=94%)
  - PLR (1.7; 95% CI, 0.33–8.4; I^2=92%)
  - NLR (0.41; 95% CI, 0.08–2.0; I^2=98%)
- Color Doppler imaging may not be a reliable diagnostic indicator for diagnosing RPOC (n=5).
  - Sensitivity (0.82; 95% CI, 0.77–0.87; I^2=67%)
  - Specificity (0.44; 95% CI, 0.37–0.52; I^2=93%)
  - Diagnostic accuracy (DOR 3.9; 95% CI, 0.91–17; I^2=84%)
  - PLR (1.6; 95% CI, 0.91–2.8; I^2=93%)
  - NLR (0.41; 95% CI, 0.51–1.1; I^2=78%)

LIMITATIONS:

- The study design, participants, and methodologies of each study contributed to the high heterogeneity.
- The results did not report the number of participants in the statistical analysis for each outcome.
- The use of only sonographic RPOC findings as descriptors in creating the study design eliminates pertinent clinical findings (vaginal bleeding, pyrexia, or pain) related to RPOC.

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Orexin Receptor Agonists Headline Only Three Working Medication for Insomnia

Effectiveness of Arts Interventions to Reduce Mental-Health-Related Stigma Among Youth: A Systematic Review and Meta-Analysis

Gaiha SM, Salisbury TT, Usmani S, Koschorke M, Raman U, Petticrew M. Effectiveness of arts interventions to reduce mental-health-related stigma among youth: a systematic review and meta-analysis. *BMC Psychiatry*. 2021;21(1):364. Published 2021 Jul 22. doi:10.1186/s12888-021-03350-8

KEY TAKEAWAY: Orexin receptor antagonists (ORAs), melatonin receptor agonists (MRAs), and benzodiazepine-like drugs (Z-drugs) reduce sleep latency (SL). ORAs and Z-drugs reduce awake time after sleep onset (WASO). Z-drugs increase the frequency of adverse effects, resulting in medication discontinuation.

STUDY DESIGN: Systematic review and meta-analysis of 69 randomized controlled trials (RCTs) (N=17,319)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to high heterogeneity and unclear risk of bias)

BRIEF BACKGROUND INFORMATION: Insomnia involves trouble initiating or maintaining sleep, which can lead to significant daytime impairment. Nearly half of all insomnia patients in the United States choose pharmacotherapy, but we lack well-designed trials evaluating the efficacy and tolerability of the major classes of sleep medications. This study assessed which classes are effective and well-tolerated.

PATIENTS: Adults with a primary diagnosis of insomnia

INTERVENTION: Various insomnia medications

CONTROL: Placebo

PRIMARY OUTCOME: SL and WASO

Secondary Outcome: Discontinuation for adverse events (AED)

METHODS (BRIEF DESCRIPTION):

- Double-blinded, placebo-controlled RCTs of adults ≥18 years old with a primary diagnosis of insomnia, based on a literature search that included trials with unpublished data, were included.
- Study populations came from North America, Asia, and Europe. Sample sizes of the included studies sranged from 10–669 participants.
- Study duration varied considerably (range 2–365 days) and was ≤4 weeks for most studies (44 RCTs), while 25 studies lasted longer. Nine studies provided follow-up.
- Patients were randomized to monotherapy with one of 20 drugs within seven classes and were compared to placebo.
- Classes include benzodiazepines (BZDs), Z-drugs, ORAs, MRAs, antidepressants (ADP's), antihistamines, and the anticonvulsant, tiagabine.
- The authors selected SL and WASO as efficacy primary objective outcomes, and AED to assess tolerability.
    - SL and WASO were measured in minutes via polysomnographic or actigraphic recordings.
    - AED was measured as a percentage.
- The authors compared drug classes with placebo using standard mean differences to calculate effect size for SL and WASO while using an odds ratio for AED.
- An SMD size of >0.70 represents a large effect, <0.40 is a small effect, while SMD values between the two represent moderate effects.

INTERVENTION (# IN THE GROUP): 10,321

COMPARISON (# IN THE GROUP): 6,997

FOLLOW-UP PERIOD: Most studies included no follow-up and when reported follow-up varied widely

RESULTS:

Primary Outcome –

- Three classes of medications moderately improve SL compared to placebo.
    - ORAs (standardized mean difference [SMD] –0.67; 95% CI, –1.1 to –0.26)
    - MRAs (SMD –0.47; 95% CI, –0.83 to –0.11)
    - Z-drugs (SMD –0.38; 95% CI, –0.69 to –0.07)
- BZDs, ADPs, antihistamines, and tiagabine do not improve sleep latency.
- ORAs largely improved WASO compared to placebo (SMD –1.6; 95% CI, –2.2 to –1.0).
- Z-drugs moderately improved WASO compared to placebo (SMD –0.54; 95% CI, –0.96 to –1.1).
- BZDs, ADPs, anticonvulsants, MRAs, and tiagabine do not improve WASO compared to placebo.

Secondary Outcome –

- Of all the seven above groups of medications, only Z-drugs were more likely than placebo to be

discontinued for adverse effects (odds ratio [OR] 1.7; 95% CI, 1.3–2.2).

LIMITATIONS:

- High heterogeneity was present among studies comparing SL and WASO (both I^2>50%).
- The number of trials, number of patients, and I^2 measure of heterogeneity were not supplied for any of the outcomes.
- Different criteria (DSM, ICD, or ICSD) were used to diagnose insomnia.
- Doses and treatment durations varied in studies.
- Some drugs compared only had a few studies.
- Some secondary outcomes such as sleep quality involved subjective interpretations.
- Investigators excluded participants with psychotic or physical illness.
- The short duration of some studies might not have been long enough to note medication side effects.
- The variable number of RCTs in each class did not allow comparisons of individual drugs (only a few drugs had enough RCTs to demonstrate efficacy compared to placebo).
- Almost half of the studies (49%) had an unclear risk of bias.
- Presenting the outcomes as SMD allowed comparison of a variety of RCTs, however using "minutes reduction in SL and WASO" would be more useful to clinicians and patients.

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Overtreating Asymptomatic Hypertension in the Hospital

Clinical Outcomes of Intensive Inpatient Blood Pressure Management in Hospitalized Older Adults

Anderson TS, Herzig SJ, Jing B, et al. Clinical Outcomes of Intensive Inpatient Blood Pressure Management in Hospitalized Older Adults. *JAMA Intern Med*. 2023;183(7):715-723. doi:10.1001/jamainternmed.2023.1667

KEY TAKEAWAY: Treatment of asymptomatic high blood pressure is associated with harm in hospitalized patients, including increased risk of intensive care unit (ICU) transfer, acute kidney injury (AKI), cardiac marker elevations, and increased discharge to a skilled nursing community rather than home.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Elevated blood pressure in hospitalized patients is common, though there are no guidelines for the management of hypertension (HTN) in these patients. Despite scarce evidence of benefit from treating asymptomatic HTN in comorbid and hospitalized patients, "treating the numbers" remains a common practice. Recent evidence suggests that treating asymptomatic high blood pressure in the inpatient setting not only provides little to no benefit but may worsen outcomes. This study investigated the impact of inpatient asymptomatic HTN management on several clinical outcomes.

PATIENTS: Hospitalized adults ≥65 years old with asymptomatic HTN

INTERVENTION: Intensive treatment

CONTROL: No treatment

PRIMARY OUTCOME: Composite of inpatient mortality, ICU transfer, stroke, AKI, and cardiac marker elevations (B-type natriuretic peptide [BNP] and troponin).

Secondary Outcome: Each component of the primary composite outcome, hypotensive episodes, hospital length of stay, stage two AKI, and disposition at discharge.

METHODS (BRIEF DESCRIPTION):

- Participants included hospitalized ≥65 years old adults admitted to a Veterans Administration (VA) hospital for non-cardiac related diagnoses between 10/1/2015 and 12/31/2017 and were found to have ≥2 elevated systolic blood pressure readings >140 mmHg within the first 48 hours from admission.
- Exclusion criteria included those who experienced a study outcome within the first 48 hours after admission and those discharged within 48 hours
- Included patients had a mean age of 74 years old, 98% male and 2.6% female, 17% Black, 1.7% Hispanic, and 76% White.
- Participants were subsequently divided into those who received intensive antihypertensive treatment (intervention) and those who did not.
    - Intensive treatment included any administration of intravenous (IV) antihypertensive of any class and administration of any class of oral antihypertension that was not prescribed prior to admission
- All outcomes were measured after the initial 48 hours until discharge from the hospital and included:
    - Elevated BNP >900 mg/mL
    - Elevated troponin measured as >0.029 ng/mL for troponin T and >0.045 ng/mL for troponin I
    - AKI was measured as a creatinine increase of 0.3 mg/dL or 1.5 times the maximum recorded in the first 48 hours
    - Stage 2 AKI was measured as a creatinine increase of 0.5 mg/dL, or two times the maximum recorded in the first 48 hours
- A propensity score overlap weighting approach was utilized to address confounding by indication.

INTERVENTION (# IN THE GROUP): 14,084

COMPARISON (# IN THE GROUP): 52,056

FOLLOW-UP PERIOD: Not available

RESULTS:

Primary Outcome –

- Intensive asymptomatic blood pressure management was associated with an increased risk of the primary composite outcome compared to those who did not receive intensive blood pressure management (odds ratio [OR] 1.3; 95% CI, 1.2–1.4).

Secondary Outcome –

- Intensive asymptomatic blood pressure management was associated with an increased risk

of the following compared to no blood pressure management:
    - ICU transfer (OR 1.2; 95% CI, 1.1–1.4)
    - AKI of any stage (OR 1.4; 95% CI, 1.3–1.6)
    - BNP elevation (OR 1.8; 95% CI, 1.2–2.8)
    - Hypotension (OR 1.2; 95% CI 1.2–1.3)
    - Disposition to a skilled nursing facility (OR 1.1; 95% CI, 1.04–1.2)
- Intensive asymptomatic blood pressure management was not associated with stroke or mortality compared to no blood pressure management.

LIMITATIONS:

- The study results may not be generalizable since it consisted of a study population of mostly comorbid patients who are predominantly white elderly men.
- The study did not measure actual clinical cardiac injury events but rather used laboratory correlates of such, and so may have missed patients where those markers were not measured.
- The observational design does not exclude unquantified confounders.

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Could a Single Dose of a Subcutaneous Injection Help Control Hypertension Long Term?

Zilebesiran, an RNA Interference Therapeutic Agent for Hypertension

Desai AS, Webb DJ, Taubel J, et al. Zilebesiran, an RNA Interference Therapeutic Agent for Hypertension. *N Engl J Med*. 2023;389(3):228-238. doi:10.1056/NEJMoa2208391

KEY TAKEAWAY: Zilebesiran does not demonstrate a higher rate of adverse events compared to placebo. Dose-dependent decreases in serum angiotensinogen are noted, and blood pressure-lowering effects are sustained after a single subcutaneous dose of ≥200 mg.

STUDY DESIGN: Multi-part, multicenter, phase I trial

- Part A and B: Double-blind, randomized, placebo-controlled
- Part E: Open-label

LEVEL OF EVIDENCE: STEP 3 (downgraded due to a mismatch between the PICO of the research question and the methodology)

BRIEF BACKGROUND INFORMATION: Hypertension (HTN) is a common condition managed by primary care providers. Zilebesiran, a novel RNA interference agent, is expected to decrease serum angiotensinogen, thereby decreasing blood pressure (BP). Its safety and potential efficacy were previously unknown.

PATIENTS: Adults with HTN

INTERVENTION: Zilebesiran

CONTROL: Part A and B: Placebo, Part E: Zilebesiran coadministration with irbesartan

PRIMARY OUTCOME: Safety, pharmacokinetic, and pharmacodynamic parameters

Exploratory Outcome: BP

METHODS (BRIEF DESCRIPTION):

- The study took place at four sites in the United Kingdom.
- The study included parts A, B, and E. Part C was removed and part D is ongoing.
- The study included 107 patients with the following pooled baseline characteristics:
  - The mean age was 55 years old
  - 62% male
  - 25% Black
  - Mean BP was 140 ± 9.0 mmHg
- Interventions and comparisons were:
  - Part A: Randomized in a 2:1 ratio to receive a single subcutaneous injection of zilebesiran at various doses (ranging from 10–800 mg) or placebo. Endpoint assessments were measured at weeks six, eight, 12, and 24.
  - Part B: Participants consumed a low salt diet (0.23 grams per day) followed by a high salt diet (5.75 grams per day) before randomization in a 2:1 ratio to receive either a single dose zilebesiran 800 mg or a placebo. The previous dietary protocol was repeated in correlation with zilebesiran's anticipated peak effect. Endpoint assessments were monitored before and after dose administration.
  - Part E: Participants received a single 800 mg zilebesiran dose. At week six, if systolic BP was ≥120 mmHg, oral irbesartan 300 mg daily was administered for two weeks. Endpoint assessments were checked before and after irbesartan administration.
- Endpoint assessments included monitoring the frequency of adverse events (fAE), serum angiotensinogen levels, and 24-hour ambulatory BP.

INTERVENTION (# IN THE GROUP):

- Part A: 56
- Part B: 8
- Part E: 6

COMPARISON (# IN THE GROUP):

- Part A: 28
- Part B: 4
- Part E: 10

FOLLOW-UP PERIOD: Until angiotensinogen levels returned to ≥50% of baseline or one year after the final zilebesiran dose, whichever was earlier

RESULTS:

Primary Outcome –

- Adverse events occurred in 88% of patients receiving placebo and 72% of patients receiving zilebesiran (no statistical analysis completed).
- Zilebesiran was associated with a decrease in angiotensinogen levels at eight weeks (r –0.56; 95% CI, –0.69 to –0.39).

Exploratory Outcome –

- Part A: The decrease in mean BP measured via (± standard error [SE]) at 24 weeks was 23 ± 5.1 mmHg (systolic) and 11 ± 2.7 mmHg (diastolic) among those who received zilebesiran 800 mg.
- Part B: The decrease in mean (±SE) BP reduction was 19 ± 4.3 mmHg (systolic) and 8.4 ± 2.5 mmHg (diastolic) after a low-salt diet following administration of zilebesiran 800 mg.
- Part E: A mean (±SE) BP reduction of 6.3 ± 3.1 mmHg (systolic) and 3.0 ± 1.9 mmHg (diastolic) occurred at eight weeks for those with systolic BP readings ≥120 mm Hg after the addition of irbesartan to zilebesiran 800 mg.

LIMITATIONS:

- The multi-part study design was not appropriately focused on assessing the primary outcome.
- Didn't enroll older adults or those with robust medical conditions.
- Difficult to extrapolate results given the small sample size and short follow-up duration secondary to the phase I trial design.
- Investigators didn't assess zilebesiran's teratogenicity.

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Head to Head: MRI vs PSA for Prostate Cancer Screening

Prostate MRI vs PSA Screening for Prostate Cancer Detection (The MVP Study): A Randomized Clinical Trial

Nam R, Patel C, Milot L, et al. Prostate MRI versus PSA screening for prostate cancer detection (the MVP Study): a randomized clinical trial. *BMJ Open*. 2022;12(11):e059482. Published 2022 Nov 8. doi:10.1136/bmjopen-2021-059482

KEY TAKEAWAY: Prostate magnetic resonance imaging (MRI) alone detects similar rates of adenocarcinoma of the prostate as compared to prostate-specific antigen (PSA).

STUDY DESIGN: Randomized controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to unblinded study design)

BRIEF BACKGROUND INFORMATION: PSA has been the gold standard for prostate cancer screening, but new imaging and tests are being evaluated as adjunct modalities to improve screening outcomes. This study compared stand-alone prostate MRI screening to PSA rather than as an adjunct to PSA testing.

PATIENTS: Men ≥50 years old

INTERVENTION: Prostate MRI

CONTROL: Serum MRI

PRIMARY OUTCOME: Prostate cancer

Secondary Outcome: Rate of prostate biopsy, unnecessary biopsies, and clinically significant prostate cancer detection

METHODS (BRIEF DESCRIPTION):

- This was an open-label, phase three randomized controlled trial at a single center conducted in Toronto, Canada.
- Males ≥50 years old were recruited through general media advertisement and could enroll if life expectance was ≥10 years and had no exclusion criteria.
- Exclusion criteria included any prior prostate biopsy, PSA test within the last three years, current urinary difficulty symptoms, family history of prostate cancer in any first-degree relatives at age <50, urinary International Prostate Symptom Score >7, five-alpha reductase inhibitor use or prior use, claustrophobia/medical condition incompatible with undergoing MRI, or abnormal digital rectal exam at enrollment visit.
- Participants had a mean age of 68 years old and most identified as White (>84%).
- Patients were randomized 1:1 to one of the following screening tests:
  - Prostate MRI
  - Serum PSA
- Biopsies with 12 core samples were recommended for patients with PSA levels ≥2.6 ng/mL.
- Biparameteric prostate MRI (bpMRI) was graded by PI-RADS scoring, and biopsy was recommended for a Prostate Imaging and Data System (PIRADS) score of four or five. Scores range from 1–5, with five being most suspicious for malignancy.
- An experienced neuroradiologist read the bpMRIs and poor-quality exams were repeated.
  - 12 core biopsy samples with an additional four cores were taken from primary targets and up to four cores from secondary identified targets.
- At the end of the study, PSA testing was recommended for MRI arm subjects.
- The primary outcome was the relative risk of prostate biopsy showing adenocarcinoma of the International Society of Urological Pathology (ISUP) grade group ≥1. Scores of the ISUP range from 1–5, with higher scores indicating high-grade dysplasia. The analysis was compared between the two groups using intention-to-treat analysis.
- Secondary outcomes included the rate of recommendation and completion of prostate biopsy and detection of clinically significant prostate adenocarcinoma, defined as:
  - Gleason score ≥7. Scores range from 2–10, with higher scores indicating higher-grade cancer
  - ISUP score ≥2.
- Additional analysis evaluated the concordance of the MRI arm outcome with end-of-study PSA testing in that arm.

INTERVENTION (# IN THE GROUP): 246

COMPARISON (# IN THE GROUP): 248

FOLLOW-UP PERIOD: Not applicable

RESULTS:

Primary Outcome –

- There was no difference in adenocarcinoma detection in the MRI vs. PSA group (relative risk [RR] 1.9; 95% CI, 0.82–4.4).

Secondary Outcome –

- There was no difference in clinically significant cancer detection in the MRI compared to the PSA group.
- MRI resulted in a significantly lower likelihood to recommend a prostate biopsy compared to PSA screening (10% vs 19%, respectively; RR 0.52; 95% CI, 0.33–0.82) and higher acceptance of recommendation for biopsy (96% vs 58%, no statistics reported).
- A total of 117 (48%) patients in the MRI arm had PSA labs drawn after the study:
  - 13% of those with PSA values <2.6 had PIRADS scores of four or five and 27% of these (3 patients) were found to have biopsy-proven cancer, which would have been missed with PSA screening.
  - Of those with abnormal PSA values 62% had a PIRADS score of 1–3 (no need for biopsy).
- PSA screening was associated with a greater risk of potentially missing prostate cancer compared to prostate MRI (RR 1.7; 95% CI, 1.6–10).
- PSA screening was associated with more unnecessary biopsies compared to MRI (RR 2.4; 95% CI, 1.4–4.1).

LIMITATIONS:

- The study was terminated early due to COVID-19 pandemic-related shortages and likely underpowered.
- Dropout rate by biopsy refusal was significantly greater in the PSA arm compared to the MRI arm.
- The study was completed at a single center in Canada and MRI results were read by uroradiology experts, which may limit generalizability.
- Recruitment was via newspaper and radio advertisements which may introduce selection bias and response bias.
- Due to the nature of the trial blinding was not possible.
- Additional biopsies were taken from the MRI arm than the PSA arm because the MRI had identifiable target areas, which may lead to detection bias.
- Completion of planned PSA testing for the MRI arm group was limited to <50% due to resource and personnel limitations with the COVID-19 pandemic.
- MRI testing was not completed on all subjects in the PSA group, which would have further strengthened the secondary findings of this trial.

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Don’t Forget to Soak up Some Sunshine! Replenish Your Vitamin D to Keep the Darkness of Stroke at Bay

A Systematic Review and Meta-Analysis of the Linkage Between Low Vitamin D and the Risk as Well as the Prognosis of Stroke

Xiong J, Zhao C, Li J, Li Y. A systematic review and meta-analysis of the linkage between low vitamin D and the risk as well as the prognosis of stroke. *Brain Behav*. 2024;14(6):e3577. doi:10.1002/brb3.3577

KEY TAKEAWAY: Vitamin D deficiency is associated with elevated stroke risk and poor stroke prognosis.

STUDY DESIGN: Systematic review and meta-analysis of 27 studies comprising 19 cohort, six case-control, and one randomized controlled trial (RCT) (N=45,302)

LEVEL OF EVIDENCE: STEP 3 (downgraded due to the design of included studies)

BRIEF BACKGROUND INFORMATION: Vitamin D plays an essential role in cardiovascular health. The specific relationship between vitamin D and cardiovascular health, as well as the potential clinical benefits of vitamin D supplementation, requires additional research.

PATIENTS: Adults 30–83 years old

INTERVENTION: Low vitamin D levels

CONTROL: Normal vitamin D levels

PRIMARY OUTCOME: Risk of stroke

Secondary Outcome: Stroke prognosis

METHODS (BRIEF DESCRIPTION):

- An in-depth analysis of three databases (PubMed, Embase, and Cochrane Library) was performed to study the correlation between insufficient Vitamin D levels and the risk of cerebrovascular accident.
- The majority of studies selected were from the USA, Brazil, China, and several European countries, including Sweden, Finland, Denmark, and Germany.
- Adults 30–83 years old with or without comorbidities were included in the study.
- The meta-analysis focused on the effects of low vitamin D levels, instead of assessing the role of vitamin D supplementation as an intervention.
- In a meta-analysis of 27 studies, 20 evaluated the effects of vitamin D levels and stroke incidence. Serum vitamin D levels were studied in patients with stroke to analyze the correlation.
- Seven studies were analyzed to evaluate the impact of vitamin D levels on stroke outcomes.
- The results were assessed using relative risk and confidence interval.
- The potential confounding effects of comorbidities on this relationship were not directly studied.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Not available

RESULTS:

Primary Outcome –

- Vitamin D deficiency was associated with an increased risk of stroke compared to no vitamin D deficiency (20 trials, n=44,218; relative risk [RR] 1.5; 95% CI, 1.2–1.7; I^2=92%).
- Vitamin D deficiency was associated with an increased risk of ischemic stroke compared to normal vitamin D levels (7 trials, n=39,302; RR 1.7; 95% CI, 1.1–2.7; I^2=98%).
- Vitamin D deficiency was not associated with an elevated risk of hemorrhagic stroke compared to normal vitamin D levels (6 trials, n=4,987; RR 1.9; 95% CI, 0.95–4.0; I^2=95%).
- Vitamin D deficiency was associated with an increased risk of nonspecific stroke compared to optimal vitamin D levels (11 trials, n=2,945; RR 1.3; 95% CI, 1.1–1.5; I^2=29%).

Secondary Outcome –

- Vitamin D deficiency was associated with a less favorable prognosis in ischemic stroke (7 trials, n=7,857; RR 3.0; 95% CI, 1.9–4.6; I^2=72%).

LIMITATIONS:

- The majority of cases (34,217 out of 45,302) in this meta-analysis are from a single study conducted in Sweden, which might affect the generalizability of the findings and produce skewed results.
- Publication bias was recognized with the help of funnel plot analysis. This was linked to small sample sizes in case-control studies and the RCT. However, the funnel plot was found to be symmetrical when the analysis was limited to cohort studies, indicating the observed bias was likely due to smaller sample sizes in the case-control studies and the RCT.
- A high level of heterogeneity was noted, which was due to variations in sample size and gender distribution.

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