GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

Volume 5 - Issue 14

FPIN
Family Physicians Inquiries Network

What's in this week's issue?

Week of April 7 - April 11, 2025

SPOTLIGHT:

Doesn’t Bear Repeating: Using Aspirin to Prevent Recurrence of Breast Cancer

- Intensive Blood Pressure Control Improves Cardiovascular Risk in Patients with Diabetes
- Comparing Weight Loss Medication Among Adults with Obesity
- AI in Action: Reducing Neck, Shoulder, and Back Pain From the Comfort of Home

Doesn't Bear Repeating: Using Aspirin to Prevent Recurrence of Breast Cancer

Aspirin vs Placebo as Adjuvant Therapy for Breast Cancer: The Alliance A011502 Randomized Trial

Chen WY, Ballman KV, Partridge AH, et al. Aspirin vs Placebo as Adjuvant Therapy for Breast Cancer: The Alliance A011502 Randomized Trial. *JAMA*. 2024;331(20):1714-1721. doi:10.1001/jama.2024.4840

KEY TAKEAWAY: Daily aspirin use does not improve invasive disease-free survival (IDFS) in people with a history of breast cancer.

STUDY DESIGN: Multicenter, double-blinded, randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Prior observational studies have shown a correlation between aspirin use and a decreased rate of breast cancer recurrence and mortality, though a causative effect was not able to be determined. This study aimed to determine the effect of aspirin on cancer recurrence.

PATIENTS: Adult breast cancer survivors

INTERVENTION: 300 mg aspirin daily

CONTROL: Placebo

PRIMARY OUTCOME: IDFS

Secondary Outcome: Overall survival

METHODS (BRIEF DESCRIPTION):

- Participants 18–70 years old with a history of ERBB2-negative breast cancer who had completed all local therapy and chemotherapy were included in the study.
  - Participants were taken from 534 sites throughout the United States and Canada between January 2017 and December 2020.
  - The median age of participants was 53 years old, and 84% identified as White.
- Endocrine therapy was allowed to continue, but any nonsteroidal anti-inflammatory drug use was discontinued at least 30 days before enrollment.
- Patients with hormone-positive tumors must have been enrolled within 10 years of diagnosis, while those with hormone-negative tumors must have been enrolled within 18 months.
- Exclusion criteria included participants >70 years old, long-term steroid use, use of specific anticoagulation medications, or history of gastrointestinal bleeds, stroke, myocardial infarction, atrial fibrillation, or grade four hypertension.
- Participants were randomized 1:1 to either aspirin or placebo and stratified for hormone receptor status, body mass index (BMI), cancer staging, and time since diagnosis.
  - The intervention group received oral aspirin 300 mg daily.
  - The control group received a placebo tablet by mouth daily.
- Both aspirin and control groups were given the treatment for five years, though the study was terminated early at a median treatment time of 20 months due to meeting a prespecified futility boundary.
- The primary outcome of IDFS was defined as the first occurrence of any one of the following: Distant or regional recurrence, ipsilateral or contralateral breast cancer, a second primary cancer, or death from any cause that occurred after randomization.
- The secondary outcome was defined as death from any cause.

INTERVENTION (# IN THE GROUP): 1,510

COMPARISON (# IN THE GROUP): 1,510

FOLLOW-UP PERIOD: Median 34 months

RESULTS:

Primary Outcome –

- Aspirin did not significantly impact IDFS compared to placebo (hazard ratio [HR] 1.3; 95% CI, 0.99–1.6).

Secondary Outcome –

- There was no statistically significant difference in death from any cause in the aspirin group compared to placebo.

LIMITATIONS:

- Follow-up duration was limited at a median of 34 months due to futility identified at a pre-determined time point.
- Due to inadequate power, researchers were unable to evaluate for impact by breast cancer phenotype.
- Participants were mostly White, with very limited representation from other races, limiting the generalizability of results.

Kiley R. Schlortt, MD

St Louis University Southwest Illinois FMRP
O'Fallon, IL

The views expressed herein are those of the author and do not necessarily reflect the official policy of the Department of the Air Force, Defense Health Agency, Department of Defense, or the US Government.

Intensive Blood Pressure Control Improves Cardiovascular Risk in Patients with Diabetes

Intensive Blood-Pressure Control in Patients with Type 2 Diabetes

Bi Y, Li M, Liu Y, et al. Intensive Blood-Pressure Control in Patients with Type 2 Diabetes. *N Engl J Med*. Published online November 16, 2024. doi:10.1056/NEJMoa2412006

KEY TAKEAWAY: Intensive blood pressure control in patients with type 2 diabetes mellitus (T2DM) reduces the risk of major cardiovascular events.

STUDY DESIGN: Multi-center, parallel-group randomized clinical trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Patients with T2DM frequently have elevated systolic blood pressure (BP), increasing their risk of cardiovascular disease (CVD). Reduction in BP can decrease CVD risk in these patients, but the optimal systolic BP goal remains unclear. This trial compared the impact of intensive and standard BP control on cardiovascular outcomes in patients with T2DM.

PATIENTS: Adults with T2DM and elevated BP

INTERVENTION: Intensive BP treatment

CONTROL: Standard BP treatment

PRIMARY OUTCOME: Cardiovascular events

Secondary Outcome: Individual cardiovascular events, death, adverse events

METHODS (BRIEF DESCRIPTION):

- Participants ≥50 years old with T2DM, elevated systolic BP, and increased CVD risk were enrolled across 145 clinical sites in China.
  - Systolic BP elevation was defined as >130 mmHg in patients taking antihypertensive medications and >140 mmHg in patients not taking these medications.
  - Patients were considered to have an increased risk of CV disease if they had a history of clinical or subclinical CV disease, ≥2 CVD risk factors, or chronic kidney disease (CKD).
    - Clinical CVD was defined as stroke, myocardial infarction (MI), coronary or carotid artery surgeries or stenting, or acute coronary syndrome at least three months prior to enrollment.
    - Subclinical CV disease was defined as microalbuminuria, ≥50% stenosis of a coronary, carotid, or lower extremity artery, coronary artery calcium score ≥400, ankle brachial index ≤0.9, or left ventricular hypertrophy at least three years prior to enrollment.
    - CV disease risk factors included cigarette smoking, elevated body mass index (BMI) or waist circumference, use of lipid-lowering medications, elevated low-density lipoprotein (LDL) or triglycerides, or low high-density lipoprotein (HDL).
- Participants had a mean age of 64 years old, 45% were women, the mean baseline systolic BP was 140 mmHg, and the mean hemoglobin A1C (HbA1c) was 7.6%.
- Participants were randomly assigned to receive intensive treatment with a goal systolic BP of <120 mmHg or standard treatment with a goal systolic BP of <140 mmHg.
  - After five minutes of seated rest, blood pressure was measured three times with one minute between measurements, and a mean of the three measurements was recorded.
  - Appropriate cuff size was chosen based on arm circumference
- Participants and clinical staff were aware of the treatment assignments, but study personnel were blinded.
- Antihypertensive regimens were adjusted based on patient BP levels and treatment goals.
- Participants were seen monthly for the first three months, then every three months once systolic BP targets were achieved.
  - During the COVID-19 pandemic, telephone calls and automated home BP measurements were utilized.
- Clinical outcome data collection was initiated three months after randomization and conducted quarterly.
- The primary outcome was a composite of CV outcomes, including the first occurrence of nonfatal

stroke, nonfatal MI, heart failure treatment or hospitalization, and death from CV cause.

- The secondary outcomes included individual assessment of fatal or nonfatal stroke and MI, heart failure treatment or hospitalization, death from CV or any cause, progression or development of chronic kidney disease, and adverse events.

INTERVENTION (# IN THE GROUP): 6,414
COMPARISON (# IN THE GROUP): 6,407

FOLLOW-UP PERIOD: 4.2 years

RESULTS:

Primary Outcome –

- Intensive treatment reduced the risk of primary cardiovascular events compared to standard treatment (hazard ratio [HR] 0.79; 95% CI, 0.69–0.90).

Secondary Outcome –

- Intensive treatment reduced the risk of fatal or nonfatal stroke compared to standard treatment (HR 0.79; 95% CI, 0.67–0.92).
- Intensive and standard treatment groups had similar rates of fatal or nonfatal MI, heart failure requiring treatment, CKD progression or development, death from cardiovascular causes, all-cause mortality, and serious adverse events.

LIMITATIONS:

- Telephone interviews and automated home blood pressure monitoring were used to collect data due to the pandemic.
- Measuring BP three times after 5 minutes of rest may limit feasibility in the office setting.
- Only about 60% of patients in the intensive-treatment group met the target BP after 1 year, potentially reducing treatment impact.
- Diastolic BP between the two groups was different, potentially confounding results.
- All clinical sites were in China, potentially limiting generalizability to other ethnic groups.

Justin Walters, MD
St Joseph's University Medical Center FMRP
Paterson, NJ

Comparing Weight Loss Medication Among Adults with Obesity

Semaglutide vs Tirzepatide for Weight Loss in Adults with Overweight or Obesity

Rodriguez PJ, Goodwin Cartwright BM, Gratzl S, et al. Semaglutide vs Tirzepatide for Weight Loss in Adults With Overweight or Obesity. *JAMA Intern Med*. 2024;184(9):1056-1064. doi:10.1001/jamainternmed.2024.2525

KEY TAKEAWAY: Tirzepatide, a dual glucagon-like peptide-1 receptor (GLP-1) agonist and gastric inhibitory polypeptide (GIP) receptor agonist, leads to greater weight loss than semaglutide (GLP-1 alone).

STUDY DESIGN: Retrospective, observational cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: The prevalence of overweight and obese adults in the United States (US) is on the rise. Historically, pharmacologic treatments for weight loss were limited, not well tolerated, and had a modest effect. However, newer pharmacologic options, such as GLP-1 agonists (semaglutide) and GLP-1/GIP agonists (tirzepatide), have demonstrated greater effects. This study aimed to compare tirzepatide and semaglutide in populations with obesity, as no direct comparison had been conducted before this publication.

PATIENTS: Overweight or obese adults

INTERVENTION: Tirzepatide

CONTROL: Semaglutide

PRIMARY OUTCOME: Weight loss

Secondary Outcome: Gastrointestinal (GI) adverse events

METHODS (BRIEF DESCRIPTION):

- Adults ≥18 years old with a BMI of ≥27 who are new users of tirzepatide or semaglutide were included.
- New users had no previous exposure to any GLP-1 or GLP-1/GIP and regular interactions (at least 1 year before the initiation date) with the health care system.
- Exclusions included a diagnosis of type 1 diabetes mellitus, gestational diabetes, or diabetes with retinopathy.
- Patients were categorized via brand medication dispensed, and patient weights were standardized (within 60 days of index date).
- Treatment groups were balanced using propensity scores as a function of demographic and clinical characteristics.
- The primary outcome measured weight loss of ≥5%, ≥10%, and ≥15% at one year and the percentage change in weight at three, six, and 12 months.
  - The percentage change in body weight was calculated as (follow-up weight – baseline weight)/baseline weight.
- Moderate to severe GI adverse events were identified from the electronic records. The incidence rate for each per 1,000 person-years at risk was calculated.

INTERVENTION (# IN THE GROUP): 5,140

COMPARISON (# IN THE GROUP): 4,823

FOLLOW-UP PERIOD: 12 months

RESULTS:

Primary Outcome –

- Tirzepatide resulted in greater weight loss compared to semaglutide.
  - ≥5% weight loss (hazard ratio [HR] 1.8; 95% CI, 1.7–1.8)
  - ≥10% weight loss (HR 2.5; 95% CI, 2.4–2.7)
  - ≥15% weight loss (HR 3.2; 95% CI, 2.9–3.6)
- Tirzepatide resulted in greater body weight reductions compared to semaglutide at:
  - Three months (mean difference [MD] –2.4%; 95% CI, –2.5 to –2.2)
  - Six months (MD –4.3%; 95% CI, –4.7 to –4.0)
  - 12 months (MD –6.9%; 95% CI, –7.9 to –5.8)

Secondary Outcome –

- There was no difference between tirzepatide and semaglutide for GI adverse events.

LIMITATIONS:

- Weight loss is directly observable to patients, which may result in censoring.
- Unmeasured confounding variables for weight loss may exist (degree of motivation).
- EHR data has inherent limitations, and adverse events are likely underreported relative to protocolized trials.
- Observed event times are likely delayed relative to true times.

- The geographic distribution was not representative of the entire US, which limits generalizability.
- The study included medications labeled for the treatment of type 2 diabetes mellitus only.

Natalie Ohlde, DO
Peacehealth Southwest Medical Center FMRP
Vancouver, WA

AI in Action: Reducing Neck, Shoulder, and Back Pain From the Comfort of Home

Effects of an Artificial Intelligence-Assisted Health Program on Workers with Neck/Shoulder Pain/Stiffness and Low Back Pain: Randomized Controlled Trial

Anan T, Kajiki S, Oka H, et al. Effects of an Artificial Intelligence-Assisted Health Program on Workers With Neck/Shoulder Pain/Stiffness and Low Back Pain: Randomized Controlled Trial. *JMIR Mhealth Uhealth*. 2021;9(9):e27535. Published 2021 Sep 24. doi:10.2196/27535

KEY TAKEAWAY: An artificial intelligence (AI)-assisted health program improves neck, shoulder, and low-back pain for white collar workers.

STUDY DESIGN: Unblinded randomized controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to lack of blinding)

BRIEF BACKGROUND INFORMATION: Neck, shoulder, and low-back pain are common among sedentary white-collar workers, impacting productivity and quality of life. An AI-assisted health program could provide an innovative solution for managing these issues.

PATIENTS: Adults with neck, shoulder, or low-back pain

INTERVENTION: AI-assisted health program

CONTROL: Usual care

PRIMARY OUTCOME: Pain

METHODS (BRIEF DESCRIPTION):

- Japanese men 20–65 years old with frequent or nearly constant neck, shoulder, or low back pain for at least one week in the past month were included in the study.
- Those who disagreed with the study, were pregnant, had cardiopulmonary diseases, participated in other trials, had disabilities, or had exercise restrictions were excluded from the study.
- Participants were randomized into one of the following groups:
  - 12-week AI-assisted health program with personalized recommendations via daily use of a smartphone application.
  - Usual care of regular workplace exercise routines.
- Pain severity was measured on a scale with scores ranging from 1 to 5, with higher scores indicating worse pain.
  - Pain severity was assessed at baseline and follow-up.
- Participants rated pain improvement as "improved," "slightly improved," "unchanged," "slightly worse," or "worse."
- "Improved" or "slightly improved" was considered as improvement.
- All responses were collected through a web-based form.

INTERVENTION (# IN THE GROUP): 48

COMPARISON (# IN THE GROUP): 46

FOLLOW-UP PERIOD: 12 weeks

RESULTS:

Primary Outcome –

- An AI-assisted health program resulted in improved pain severity compared to usual care (odds ratio [OR] 6.4; 95% CI, 2.6–16).
- An AI-assisted health program resulted in significant subjective pain improvement compared to usual care (OR 43; 95% CI, 11–164).

LIMITATIONS:

- The sample size was small, which may limit the robustness of the findings.
- Patient adherence to the AI program was based on self-reported measures, which could introduce response bias.
- The generalizability of findings to different occupational and ethnic settings remains uncertain.
- Researchers relied on self-reported measures for pain, which could have resulted in measurement bias.

Patrick Bevans MD, Capt USAF
Northside Hospital Gwinnett Program FMRP
Lawrenceville, GA