

GEMS of the Week

SPOTLIGHT

**Does Teaching as a Stand-Alone Therapy
Treat Tendinopathy?**

Fish Oil

A Simple Defense Against Dialysis Heart Risks?

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B is for Bergamia

Better Cholesterol Control

Fish Oil: A Simple Defense Against Dialysis Heart Risks?

Fish-Oil Supplementation and Cardiovascular Events in Patients Receiving Hemodialysis

Lok CE, Farkouh M, Hemmelgarn BR, et al. Fish-Oil Supplementation and Cardiovascular Events in Patients Receiving Hemodialysis. *N Engl J Med*. 2026;394(2):128-137. doi:10.1056/NEJMoa2513032

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KEY TAKEAWAY: In adults receiving maintenance hemodialysis, daily high-dose (4 g) fish-oil supplementation significantly reduces the rate of serious cardiovascular events compared to a corn oil placebo.

STUDY DESIGN: Multicenter, parallel-group, randomized, placebo-controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Cardiovascular disease affects more than two thirds of patients with end stage renal disease on hemodialysis and accounts for >75% of the associated deaths. Thus, effective cardiovascular disease management in patients on hemodialysis is vitally important, but the efficacy of statin medications has not been established. Prior omega-3 trials to reduce cardiovascular disease in general populations showed mixed results, but the benefits in the hemodialysis population remain uncertain.

PATIENTS: Adults on hemodialysis

INTERVENTION: Fish oil

CONTROL: Corn oil

PRIMARY OUTCOME: Composite of serious cardiovascular events including cardiac arrest, fatal and nonfatal myocardial infarction (MI) or stroke, peripheral vascular disease with amputation

Secondary Outcome: Death from cardiovascular and noncardiac causes, individual components of the primary outcome, safety related to bleeding events

METHODS (BRIEF DESCRIPTION):

- The trial was a multicenter, parallel-group, randomized, double-blind, placebo-controlled trial performed at 26 sites in Canada and Australia from March 2017 through October 2021.
- Participants were clinically stable adults at least 18 years old with end-stage renal disease receiving hemodialysis 3–4 times weekly.

- Those taking omega-3 fatty acid supplements or with allergy to fish, soy or corn were excluded.
- Participants had a mean age of 64 years old, with mean duration of hemodialysis of 3.7 years, and 35% had a previous cardiovascular event.
- Participants were assigned in a 1:1 ratio to receive either:
 - Daily oral fish oil supplementation four 1 g capsules of citrus-flavored, deodorized fish oil, containing 1.6 g of eicosapentaenoic acid (EPA) and 0.8 g of docosahexaenoic acid (DHA)
 - Citrus-flavored corn oil capsules
- To assess adherence, incorporation of omega-3 fatty acids into plasma phospholipids was assessed in a randomly selected sample of participants.
- The primary endpoint was a composite of serious cardiovascular events including cardiovascular death (cardiac arrest, fatal MI, fatal stroke), nonfatal MI or stroke, and peripheral vascular disease with amputation.
- The secondary endpoints included individual components of the primary endpoint, cardiovascular and noncardiac causes of death, and safety outcomes.
- Analysis of primary and secondary end points included all randomly assigned participants who received at least one dose of fish-oil or placebo, according to the intention-to-treat principle.

INTERVENTION (# IN THE GROUP): 610

COMPARISON (# IN THE GROUP): 618

FOLLOW-UP PERIOD: 3.5 years

RESULTS:

Primary Outcome –

- Fish oil decreased the composite rate of serious cardiovascular events compared to corn oil (0.31 vs 0.61 events per 1,000 patient-days; hazard ratio [HR] 0.57; 95% CI, 0.47–0.70).

Secondary Outcome –

- The composite rate of serious cardiovascular events was lower in the fish-oil group than the corn oil group regardless of whether the participant had a previous cardiovascular event (0.43 vs 0.91 events per 1,000 patient-days; HR 0.50; 95% CI, 0.37–0.67)

or did not (0.24 vs 0.45 events per 1,000 patient-days; HR 0.55; 95% CI, 0.40–0.76).

- The composite rate of cardiac and noncardiac death was lower in the fish-oil group than the corn oil group (0.52 vs 0.76 events per 1,000 patient-days; HR 0.77; 95% CI, 0.65–0.90).
- Each individual component of the primary end point was lower in the fish-oil group compared to corn oil
 - Cardiac death (0.12 vs 0.22 events per 1,000 patient-days; HR 0.55; 95% CI, 0.40–0.75)
 - Fatal and nonfatal MI (0.10 vs 0.19 events per 1,000 patient-days; HR 0.56; 95% CI, 0.40–0.80)
 - Peripheral vascular disease with amputation (0.07 vs 0.13 events per 1,000 patient-days; HR 0.57; 95% CI, 0.38–0.86)
 - Fatal and nonfatal stroke (0.02 vs 0.07 events per 1,000 patient-days; HR 0.37; 95% CI, 0.18–0.76)
- There was no significant difference in incidence of serious adverse events, bleeding, or death rate between groups.

LIMITATIONS:

- It is unclear if participants in either group took over the counter omega-3 fatty acid supplements.
- Data from participants that received renal transplant or started peritoneal dialysis was removed.
- The trial was not powered to assess mortality.

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Wherefore ART thou, Arterial Lines? Is Arterial Catheterization Always Necessary in ICU Admissions for Shock?

Deferring Arterial Catheterization in Critically Ill Patients with Shock

Muller G, Contou D, Ehrmann S, et al. Deferring Arterial Catheterization in Critically Ill Patients with Shock. *N Engl J Med*. 2025;393(19):1875-1888.

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KEY TAKEAWAY: Non-invasive blood pressure monitoring (NIBP) was not worse than early arterial catheterization (AC) for all-cause mortality at 28 days in critically ill patients with shock.

STUDY DESIGN: Multicenter, open-label, randomized, non-inferiority trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: AC is often recommended for continuous blood pressure monitoring in intensive care unit (ICU) patients with shock, based on the expert opinion that theorizes it allows for superior hemodynamic management. However, this practice is not supported by evidence from randomized trials and carries risks such as infection and hematoma. This trial aimed to determine if a non-invasive monitoring strategy is noninferior to early AC for managing patients in shock.

PATIENTS: Adults admitted to the ICU for shock

INTERVENTION: NIBP

CONTROL: AC

PRIMARY OUTCOME: 28-day all-cause mortality

Secondary Outcome: Severity of organ failure, days free from ventilator support, renal replacement and vasopressor therapy, catheter-related infections, patient-reported pain

METHODS (BRIEF DESCRIPTION):

- The trial enrolled adults admitted to one of nine ICUs in France within 24 hours of ICU admission for shock.
- Patients were included if they had signs of hypotension (systolic blood pressure [SBP] <90 mmHg or mean arterial blood pressure <65 mmHg) for ≥15 minutes or required low dose vasopressor therapy and had at least one sign of tissue hypoperfusion.
- Patients were excluded if blood pressure readings could not be obtained, they were on high dose vasopressor therapy, body mass index (BMI) >40,

pregnant, had severe traumatic brain injury (TBI), or were receiving extracorporeal membrane oxygenation (ECMO).

- The average participant age was 66 years old, with most participants being male and having a BMI of 27.
- Patients were randomized 1:1 to either the NIBP group (with an automated brachial cuff) or the early AC group (AC placed within 4 hours of randomization).
- The NIBP group was not permitted to have AC placement before 28 days unless certain prespecified safety criteria were met (e.g need for high-dose pressors, inability to display pulse oximetry, need for ECMO).
- The primary outcome was all-cause mortality at day 28, analyzed for noninferiority with a margin of five percentage points.
- The following were measured as the secondary outcomes:
 - Severity of organ failure was measured using the Median Sequential Organ Failure Assessment (SOFA). Scores range from 0–24, with higher scores indicating more severe organ failure.
 - Number of days free from life support interventions (e.g. ventilator support, renal replacement therapy, vasopressor therapy).
 - Catheter-related infections
 - Patient-reported pain using an 11-point numeric scale. Scores range from 0–10, with a score of 10 indicating maximum pain/discomfort.
 - Adverse events

INTERVENTION (# IN THE GROUP): 504

COMPARISON (# IN THE GROUP): 502

FOLLOW-UP PERIOD: 28 days

RESULTS:

Primary Outcome –

- There was no significant difference in all-cause mortality at 28 days for NIBP compared to AC (34% vs 37%, respectively; adjusted risk difference –3.2 percentage points; 95% CI, –8.9 to 2.5).

Secondary Outcome –

- The incidence of arterial catheter-related bloodstream infections was lower in the NIBP group compared to the early AC group (1 vs 3 per 1,000 ICU days, respectively; incidence ratio 0.18; 95% CI, 0.06–0.54).
- There was no significant difference in severity of organ failure at seven days or patient-reported pain from the monitoring device for NIBP compared to AC.
- At 28 days, the median duration of ICU stays and days free from organ support (ventilator, vasopressors, renal replacement therapy) was similar for NIBP compared to AC.

LIMITATIONS:

- The trial was not blinded, which may have introduced bias in the assessment of secondary outcomes.
- Pain assessment was limited as only 22% of the NIBP group and 15% of the early AC group were able to self-report.
- The patient population excluded those with a BMI >40 and had few trauma or post-surgical patients, which may limit generalizability.
- The study did not assess the impact of either strategy on hospital staff satisfaction or workload.

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

Does Teaching as a Stand-Alone Therapy Treat Tendinopathy?

The Efficacy of Education as an Intervention for Improving Core Outcome Domains in People with Tendinopathy: A Systematic Review with Meta-Analysis

Townsend L, Neal BS, Carter H, Cuff A, Mallows A. The Efficacy of Education as an Intervention for Improving Core Outcome Domains in People with Tendinopathy: A Systematic Review with Meta-analysis. *J Orthop Sports Phys Ther.* 2025;55(8):1-15.

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KEY TAKEAWAY: Education alone as an intervention for tendinopathy is comparable to traditional treatments but has no additional benefit when combined with physiotherapy.

STUDY DESIGN: Systematic review and meta-analysis of 11 randomized controlled trials (RCTs) (N=2,094)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to small sample sizes in most RCTs and heterogeneity of interventions)

BRIEF BACKGROUND INFORMATION: Tendinopathy is a common overuse injury that causes pain, swelling, and stiffness, with impaired function of the affected tendon. Common treatment options include physiotherapy, education, and corticosteroid injection. There has been no well-established first-line treatment for management of tendinopathy. A combination of treatments including patient education is often recommended. Although guidelines recommend education as a part of treatment, it remains unclear how effective education is either in isolation or as part of a multimodal treatment strategy. This study compared the efficacy of education as a dependent management option to other treatments and when used in combination with education.

PATIENTS: Adults ≥18 years old with any tendinopathy

INTERVENTION: Standalone education

CONTROL: Physiotherapy, physiotherapy + education, corticosteroid injection, prolotherapy, extracorporeal shockwave therapy, and orthotic devices

PRIMARY OUTCOME: Improvement in tendinopathy

METHODS (BRIEF DESCRIPTION):

- A meta-analysis was conducted of 11 RCTs, with 2,094 individuals ≥18 years old with tendinopathy, to interpret the outcomes of education as a self-reliant means when compared to physiotherapy,

corticosteroid injections, and combined education-physiotherapy studies.

- Four databases (CINAHL, MEDLINE, SPORTDiscus, and EMBASE) were used to search for RCT studies using keywords relevant to tendinopathy from the date of establishment to June 2024.
- Eligible RCTs included adults diagnosed with tendinopathy who received education only and those in the multimodal treatment group.
- Dichotomous outcome data (success/no success) using global rating of change scores (i.e. GROC).
 - GROC scores extracted from six RCTs: Four trials selecting the top two categories from a six-point GROC, one trial selecting the top category from a five-point GROC, and one trial selecting the top three categories from an 11-point GROC.
 - Various numerical rating scales used across RCTs to collect raw data (e.g. modified pain-free function questionnaire).
- These studies were assessed over short-term (≤3 months), medium-term (3–6 months) and long-term (≥12 months). Data collected included age, sample size and symptom duration. Standardized mean differences were calculated using within-group mean changes and standard deviations, with 95% confidence intervals.
- Odds ratios were calculated from outcome data relative to a reference value of one.

INTERVENTION (# IN THE GROUP): 664

COMPARISON (# IN THE GROUP): 1,114

FOLLOW-UP PERIOD:

- Short-term (≤3 months)
- Medium-term (3–6 months)
- Long-term (≥12 months)

RESULTS:

Primary Outcome –

- Standalone education offered similar benefits to traditional treatments in short, medium, and long-term follow-up periods for people with tendinopathy compared to physiotherapy management.
 - Short-term (3 trials, n=222; odds ratio [OR] 0.56; 95% CI, 0.31–1.0; I²=0%)

- Medium-term (2 trials, n=126; OR 0.42; 95% CI, 0.12–1.5; $I^2=44\%$)
- Long-term (2 trials, n=188; OR 0.56; 95% CI, 0.21–1.5; $I^2=0\%$)
- Standalone education offered similar benefits to traditional treatments in short, medium, and long-term follow-up periods for people with tendinopathy compared to education + physiotherapy management.
 - Short-term (2 trials, n=331; OR 0.54; 95% CI, 0.07–4.2; $I^2=93\%$)
 - Medium-term (2 trials, n=333; OR 0.47; 95% CI, 0.12–1.8; $I^2=85\%$)
 - Long-term (2 trials, n=336; OR 0.56; 95% CI, 0.21–1.5; $I^2=70\%$)
- Standalone education offered similar benefits to traditional treatments in short, medium, and long-term follow-up periods for people with tendinopathy compared to corticosteroid injection.
 - Short-term (2 trials; OR 0.32; 95% CI, 0.14–2.3)
 - Medium-term (2 trials; OR 1.8; 95% CI, 0.18–18)
 - Long-term (2 trials; OR 1.9; 95% CI, 0.71–4.8)

LIMITATIONS:

- Education was not standardized across the different trials that were included in the meta-analysis. The term 'Education' could vary widely across the trials in terms of the individual delivering it, the frequency and duration of which it is delivered, and the mode of delivery (verbal, digital, written).
- Attribution bias may exist in multimodal interventions that include education, as improvements may be driven by physiotherapy or joint injections. The effect of education cannot be isolated.
- Multimodal groups may include more severe cases or, conversely, patients who are more involved with their care. These baseline differences may lead to biases in results.

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GLP-1s in Patients with Diabetes and Cardiovascular Disease: We Have Options!

Cardiovascular Outcomes with Tirzepatide vs Dulaglutide in Type 2 Diabetes

Nicholls SJ, Pavo I, Bhatt DL, et al. Cardiovascular Outcomes with Tirzepatide versus Dulaglutide in Type 2 Diabetes. *N Engl J Med*. 2025;393(24):2409-2420. doi:10.1056/NEJMoa2505928

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KEY TAKEAWAY: Tirzepatide is non-inferior to dulaglutide in reducing composite cardiovascular death in patients with combined type 2 diabetes (T2DM) and cardiovascular disease (CVD).

STUDY DESIGN: Active-comparator-controlled, double-blinded, noninferiority trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Glucagon-like peptide-1 (GLP-1) receptor agonists are currently used to treat T2DM and cardiovascular risk. Tirzepatide, a dual agonist of the GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptors, has shown benefits in reducing metabolic risk factors such as A1C and lipid profiles. This study was designed to see if tirzepatide was as effective or superior to dulaglutide at reducing mortality from cardiovascular causes in patients with T2DM and CVD.

PATIENTS: Adults with T2DM and CVD

INTERVENTION: Tirzepatide

CONTROL: Dulaglutide

PRIMARY OUTCOME: Composite of death from CV causes, myocardial infarction (MI) or stroke (CVA)
Secondary Outcome: Death from CV causes; MI; CVA; composite death from CV, MI, CVA, or coronary revascularization; composite death from CV or hospitalization or urgent visit for heart failure (HF); death from any cause; and change in metabolic risk factors

METHODS (BRIEF DESCRIPTION):

- Patients were recruited from 640 sites in 30 countries between May 2020 and June 2022.
- Patients ≥40 years old with T2DM and CVD, glycated hemoglobin (A1C) between 7.0–11%, and body mass index (BMI) ≥25 were included.
- Excluded patients were those with a CV event 60 days prior to screening, use of a GLP-1 or pramlintide three months prior, planned treatment for diabetic eye disease, advanced HF, history of

pancreatitis, abnormal gastric emptying, bariatric surgery, liver disease (not metabolic-associated liver disease), end-stage renal disease (ESRD), or GLP-1 contraindications.

- Patients were randomized 1:1 to tirzepatide and dulaglutide.
- Patients received either tirzepatide up to 15 mg or dulaglutide up to 1.5 mg.
- Glucose-control regimens were adjusted at the discretion of the site investigator according to national guidelines using non-incretin agents. Discontinuation of Dipeptidyl peptidase-4 (DPP4) use was recommended.
- Patients were monitored every four weeks for the first 24 weeks and every three months thereafter.
- Patients were followed for a median of four years or until the primary end point: Death from CV causes, MI, or stroke.
- Secondary outcomes evaluated metabolic risk factors: A1C percentage change from baseline in 36 months, body weight in kgs percentage change from baseline in 36 months, triglyceride level percentage change from baseline at 24 months, systolic blood pressure (SBP) mmHg change from baseline in 36 months, change in median triglyceride level, and change in LDL cholesterol level percentage change from baseline in 24 months.
- Time-to-clinical events were analyzed with Cox proportional hazards and the p values with Wald tests. Non-inferiority to dulaglutide would be met with an upper limit less than 1.1 at the 94% confidence interval (CI).
- Superiority would be met if the upper limit of normal of the CI was <1.0.

INTERVENTION (# IN THE GROUP): 6,586

COMPARISON (# IN THE GROUP): 6,579

FOLLOW-UP PERIOD: Four years

RESULTS:

Primary Outcome –

- Tirzepatide decreased composite death from CV causes, MI, or CVA compared to dulaglutide (12% vs 13%, respectively; hazard ratio [HR] 0.92; 95% CI, 0.83–1.01; meeting non-inferiority).

Secondary Outcome –

- Composite of CV death and individual rates of CV death, MI and CVA all favored tirzepatide, but only the composite of CV death showed statistical significance.
 - Tirzepatide reduced the composite of CV death compared to dulaglutide (17% vs 19%, respectively; HR 0.88; 95% CI, 0.81–0.96).
- Tirzepatide reduced death from any cause compared to dulaglutide (8.6% vs 10%, respectively; HR 0.84; 95% CI, 0.75–0.94).
- Tirzepatide reduced change in eGFR from baseline to 36 months compared to dulaglutide (between-group difference -0.78 ml/min/ 1.73m^2 ; 95% CI, -0.84 to -0.72).
- Tirzepatide reduced A1C compared to dulaglutide (between-group difference -0.78 percentage points; 95% CI, -0.84 to -0.72).
- Tirzepatide reduced body weight compared to dulaglutide (between-group difference -6.8 percentage points; 95% CI, -7.1 to -6.5).
- Tirzepatide reduced triglycerides compared to dulaglutide (between-group difference -16 percentage points; 95% CI, -17 to -14).
- Tirzepatide reduced SBP compared to dulaglutide (between-group difference -2.1 mmHg; 95% CI, -2.6 to -1.5).
- Tirzepatide decreased LDL but not as significantly when compared to dulaglutide.
- Adverse effects occurred at similar rates in both groups except for gastrointestinal symptoms which were more common with tirzepatide.

LIMITATIONS:

- The study lacked a placebo group.
- The population was mostly White males (71% male, 81% White).
- The trial did not assess the effect of tirzepatide on patients with T2DM who were candidates for primary prevention of CV events.
- SLGT-2s could be added after randomization, which could have created imbalances between the groups.
- Adverse events occurred in both groups. Drug discontinuation occurred in 13% of patients in the

tirzepatide group and 10% of patients in the dulaglutide group.

- Although the trial followed standard protocols, the involvement of industry introduces a potential conflict of interest that may affect how the data should be interpreted.

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A Randomized Control Trial of Early Breast Milk Pumping Interventions for Mothers of Moderately Preterm Infants

Yuan S, Wang H, Xu X, Li Q. A Randomized Control Trial of Early Breast Milk Pumping Interventions for Mothers of Moderately Preterm Infants. *Breastfeed Med*. 2025;20(10):722-728. doi:10.1177/15568253251365639
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KEY TAKEAWAY: For mothers of moderate pre-term infants, early use of a hospital-grade electronic breast pump within the first five days postpartum promotes earlier lactation, improves daily milk volume, and supports exclusive breastmilk intake.

STUDY DESIGN: Single-center, three-arm, randomized controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to small sample size)

BRIEF BACKGROUND INFORMATION: Breastmilk has been shown to be the best source of nutrition for infants, especially in premature babies, helping to reduce the burden of high-risk complications such as necrotizing enterocolitis and bronchopulmonary dysplasia. Breastfeeding preterm infants is challenging, and early milk production is crucial for sustaining lactation and improving feeding outcomes. Different breast pump strategies may influence milk volume, lactogenesis timing, and long-term exclusivity.

PATIENTS: Preterm mothers

INTERVENTION: Hospital-grade breast pump

CONTROL: Standard home breast pump

PRIMARY OUTCOME: Milk volume

Secondary Outcome: Time to lactogenesis II, breastmilk proportions

METHODS (BRIEF DESCRIPTION):

- Infants born between 28- and 35-weeks' gestation, infants admitted to the neonatal intensive care unit (NICU) in the first hour of life, mothers >20 years old, and breastfeeding mothers were included in the study.
- Individuals with a severe maternal illness, had breastfeeding contraindications for mother or infant, were hospitalized for <14 days, or were discharged against medical advice were excluded from the study.

- Patients were randomized to one of three groups:
 - Hospital-grade pump for 14 days
 - Hospital-grade for the first five days, then a personal pump until day 14
 - Standard breast pump for 14 days
- The primary outcome measured the daily milk volume, which was recorded via mL/day.
- The secondary outcomes measured the time to lactogenesis II, defined as the number of hours postpartum, and the proportions of infants exclusively using breastmilk.

INTERVENTION (# IN THE GROUP):

- Group 1: 23
- Group 2: 23

COMPARISON (# IN THE GROUP): 23

FOLLOW-UP PERIOD: Seven days, three months, and six months

RESULTS:

Primary Outcome –

- Using a hospital-grade pump for 14 days or a hospital-grade pump for the first five days, then a personal pump until day 14 increased milk volume after five days compared to control (231 vs 232 vs 150 mL, respectively; $p=.001$).

Secondary Outcome –

- Using a hospital-grade pump for 14 days or a hospital-grade pump for the first five days, then a personal pump until day 14 decreased the onset time of lactogenesis II compared to control (48 vs 50 vs 61 hours; $p=.018$).
- Using a hospital-grade pump for 14 days or a hospital-grade pump for the first five days, then a personal pump until day 14 increased the proportion of infants receiving exclusive breast milk at seven days compared to control (91% vs 91% vs 61%, respectively; $p=.004$).
- Using a hospital-grade pump for 14 days or a hospital-grade pump for the first five days, then a personal pump until day 14 increased the proportion of infants receiving exclusive breast milk at three months (83% vs 87% vs 39%, respectively; $p=.002$).
- There was no significant difference in exclusive breastmilk proportions at six months post-discharge

for mothers using early hospital-grade pumps compared to control.

LIMITATIONS:

- This study was conducted at a single center, which may limit generalizability.
 - The sample size was small, potentially weakening statistical power.
 - The lack of blinding in this study may have introduced performance bias.
 - This study only included moderately preterm infants and may not apply to very preterm or term infants.
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GLP-1 Discontinuation and Gestational Weight Gain: Is it Sustainable?

Gestational Weight Gain and Pregnancy Outcomes After GLP-1 Receptor Agonist Discontinuation

Maya J, Pant D, Fu Y, et al. Gestational Weight Gain and Pregnancy Outcomes After GLP-1 Receptor Agonist Discontinuation. *JAMA*. 2025;334(24):2186-2196. doi:10.1001/jama.2025.20951

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KEY TAKEAWAY: Discontinuing GLP-1 receptor agonists (GLP-1RAs) before or in early pregnancy increases gestational weight gain compared to those with no prior GLP-1RA exposure.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: GLP-1RAs are increasingly used for obesity and type 2 diabetes (T2D), conditions that can complicate pregnancy. Since GLP-1RAs are discontinued for pregnancy, and their discontinuation is known to cause weight gain, there is a concern that this could lead to excessive weight gain during pregnancy, which has known adverse outcomes. This study aimed to evaluate the association between pre-pregnancy GLP-1RA discontinuation and gestational weight gain and other pregnancy outcomes.

PATIENTS: Singleton pregnancies

INTERVENTION: GLP-1RA exposure

CONTROL: No GLP-1RA exposure

PRIMARY OUTCOME: Gestational weight gain

Secondary Outcome: Excessive gestational weight gain, preterm delivery, gestational diabetes, hypertensive disorders of pregnancy, large for gestational age (LGA), small for gestational age (SGA), cesarean delivery

METHODS (BRIEF DESCRIPTION):

- This study used electronic medical record (EMR) data from singleton pregnancies delivered between June 2016 and March 2025 in the Mass General Brigham health system in Boston, Massachusetts.
- Pregnancies were excluded for multiple gestations, history of bariatric surgery, or missing/improbable data.
- GLP-1RA exposure was defined as a GLP-1RA order up to three years before or 90 days after conception.
- Baseline characteristics of the exposed group included older maternal age, higher pre-pregnancy

body mass index (BMI), and higher pre-existing diabetes and chronic hypertension (HTN) rates when compared to the unexposed group.

- The exposed group was matched 1:3 with an unexposed control group using propensity score matching based on pre-pregnancy BMI, age, parity, race/ethnicity, and pre-existing conditions.
- For the primary outcome, gestational weight gain was calculated as the difference between pre-pregnancy weight and the last weight before term delivery.
- Secondary outcomes such as excessive weight gain, gestational diabetes, and hypertensive disorders of pregnancy were defined using established American College of Obstetrics and Gynecology (ACOG) and Institute of Medicine guidelines.

INTERVENTION (# IN THE GROUP): 448

COMPARISON (# IN THE GROUP): 1,344

FOLLOW-UP PERIOD: Up to three years prior to conception through delivery

RESULTS:

Primary Outcome –

- GLP-1RAs were associated with higher gestational weight gain compared to control (adjusted mean difference [MD] 3.3 kg; 95% CI, 2.3–4.2).

Secondary Outcome –

- GLP-1RAs were associated with a higher risk of the following compared to control:
 - Excessive gestational weight gain (relative risk [RR] 1.3; 95% CI, 1.2–1.5)
 - Preterm delivery (RR 1.3; 95% CI, 1.1–1.7)
 - Gestational diabetes (RR 1.3; 95% CI, 1.01–1.7)
 - Hypertensive disorders of pregnancy (RR 1.3; 95% CI, 1.1–1.5)
- There was no significant difference in LGA, SGA, or cesarean delivery between the groups.

LIMITATIONS:

- The study was conducted at a single health system, and its population was not fully representative of the broader US population, limiting generalizability.
- Because matching was based on pre-pregnancy BMI, the study could not assess the net effect of pre-conception weight loss from GLP-1RAs vs the risks of discontinuing them.

- Relying on EMR data for medication orders does not confirm patient adherence or the precise timing of discontinuation.
- As an observational study, it is subject to residual confounding despite propensity score matching.

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The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the U.S. Navy Medical Department, the Navy at large, or the Department of Defense.

Polygenic Risk Scoring for Prostate Cancer Screening: A Promising Tool

Assessment of a Polygenic Risk Score in Screening for Prostate Cancer

McHugh JK, Bancroft EK, Saunders E, et al. Assessment of a Polygenic Risk Score in Screening for Prostate Cancer. *N Engl J Med*. 2025;392(14):1406-1417.

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KEY TAKEAWAY: Using a genetic-based polygenic risk score to identify individuals at high risk of prostate cancer appears to detect a higher percentage of clinically significant cancers compared to the screening pathway recommended by the 2024 National Comprehensive Cancer Network (NCCN) criteria.

STUDY DESIGN: Cross-sectional observational study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Studies and clinical data on prostate cancer screening show that current screening methods have low sensitivity, and thus often lead to invasive testing (i.e. biopsy) and intervention (i.e. prostatectomy) for individuals who are low risk. Current screening also fails to identify some individuals with higher risk. This study investigated the utility of polygenic risk scoring to improve screening and identify higher-risk individuals based on genetics.

PATIENTS: Men without history of prostate cancer

INTERVENTION: Polygenic risk scoring for prostate cancer

CONTROL: Current screening pathway (Prostate Specific Antigen (PSA) >3 ug/L, positive magnetic resonance imaging (MRI)

PRIMARY OUTCOME: Detection of intermediate, high or very high-risk prostate cancer and prostate cancers missed by current screening pathway

Secondary Outcome: Rates of overdiagnosis, adverse events

METHODS (BRIEF DESCRIPTION):

- Older men from 69 primary care centers in the United Kingdom (UK) were invited by letter to participate in this study investigating the utility of a polygenic risk score for identifying prostate cancer.
- Inclusion criteria were those who were assigned male at birth, 55–69 years old, reported European ancestry, had no personal history of prostate cancer, or biopsy in the past 12 months

- Patients were excluded if they had a prior history of prostate cancer, contraindication to MRI or biopsy, or for other clinical reasons as determined by the study team.
- The mean age of participants was 61.2 years with 21% reporting a family history of prostate cancer, most were highly educated professionals and reported European ancestry.
- Participant DNA was extracted from saliva, and a polygenic risk score was derived for each participant based on 130 DNA variants known to be associated with increased prostate cancer risk.
- Those with a polygenic risk score in the 90th percentile or higher were offered an MRI and prostate biopsy irrespective of PSA level, and biopsy findings were classified by 2024 NCCN criteria.
- All participants who completed an MRI and biopsy were then assessed by the current screening pathway used in the UK, and researchers identified the proportion of those with high polygenic risk scores and intermediate or higher risk cancer that would have been missed.
- The current screening pathway includes an age-based PSA score with high levels (<50 years old >2.5 ug/L, 50–60 years old 3.5 ug/L, and 60–70 >6.5 ug/L) followed up with MRI and biopsy if concerning findings on imaging.
- Researchers determined overdiagnosis by assessing the proportion of participants with polygenic risk score >90th percentile and screen-detected prostate cancer whose cancer would take longer than their remaining lifetime to progress to clinical cancer.
- The proportion of participants who experienced adverse events as a result of receiving a biopsy was also assessed.

INTERVENTION (# IN THE GROUP): 468

COMPARISON (# IN THE GROUP): The same 468 patients

FOLLOW-UP PERIOD: Not applicable

RESULTS:

Primary Outcome –

- Prostate cancer was detected in 40% of patients who underwent MRI and biopsy. 55% had intermediate or higher risk cancers and 21% had

unfavorable intermediate, high or very high cancer risk.

- 72% of participants were found to have an intermediate or high-risk prostate cancer that would have been missed by current screening pathway.

Secondary Outcome –

- 21% (95% CI, 9.7–34) of those with elevated polygenic risk score had over diagnosed disease.
- One participant (0.2%) developed sepsis, 0.4% developed urinary tract infections (UTIs), and 0.2% required temporary catheterization after biopsy.

LIMITATIONS:

- The study population was very homogenous in ethnicity and education limiting generalizability to the greater population.
- The drop out or withdrawal rate was very high. 22% of individuals invited to participate expressed interest and of those offered an MRI and biopsy, only 63% followed through.
- Participants self-selected into the study allowing for selection bias including 20% of patients who had a family history of prostate cancer.

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Citrus bergamia Extract, a Natural Approach for Cholesterol and Lipid Metabolism Management: A Randomized, Double-Blind Placebo-Controlled Clinical Trial

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KEY TAKEAWAY: Daily supplementation with standardized Citrus bergamia extract lowers low-density lipoprotein (LDL) cholesterol and total cholesterol in adults with untreated dyslipidemia compared to placebo.

STUDY DESIGN: Single-center, randomized, double-blind, placebo-controlled clinical trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to small sample size and single-center design)

BRIEF BACKGROUND INFORMATION:

Hypercholesterolemia is a major risk factor for cardiovascular disease. Statins are first-line therapy but are not tolerated by approximately 7–9% of individuals or preferred by all patients. Flavonoid-rich nutraceuticals, such as Citrus bergamia, have been proposed as alternative lipid-lowering therapies; however, high-quality placebo-controlled data remain limited. Other commonly used nutraceuticals for lipid management include red yeast rice, berberine, and plant sterols.

PATIENTS: Overweight adults 40–70 years with untreated dyslipidemia

INTERVENTION: Bergamot (Citrus bergamia)

CONTROL: Placebo

PRIMARY OUTCOME: LDL-C, total cholesterol, HDL-C, oxidized LDL (ox-LDL), paraoxonase activity (PON1)

Secondary Outcome: Triglycerides, blood pressure BP, weight, hepatic and renal markers, HbA1c

METHODS (BRIEF DESCRIPTION):

- Adults with untreated dyslipidemia were recruited at a single center in Italy.
- Participants were randomized 1:1 to intervention or placebo.

- The intervention consisted of one daily bergamot extract capsule standardized to 150 mg flavonoids taken orally.
- The comparator consisted of a placebo capsule identical in appearance, size, and shape to active treatment administered orally once daily for four months.
- Follow-up visits occurred monthly for four months.
- The primary outcomes measured LDL-C, HDL-C, total cholesterol, ox-LDL, and PON1 using fasting blood samples analyzed using routine laboratory methods.
- The secondary outcomes measured body weight, systolic blood pressure (SBP), hepatic function, renal function, HbA1c, and CRP using fasting blood samples analyzed using routine laboratory methods, a standardized blood pressure cuff, and a standardized scale.
- Lipid parameters and safety labs were measured after overnight fasting.

INTERVENTION (# IN THE GROUP): 30

COMPARISON (# IN THE GROUP): 30

FOLLOW-UP PERIOD: Four months

RESULTS:

Primary Outcome –

- Bergamot decreased LDL-C at four months compared to placebo (–12% vs 2.2%, respectively; $p < .001$).
- Bergamot reduced total cholesterol at four months compared to placebo (–8.8% vs 1.0%, respectively; $p < .01$).
- Bergamot did not significantly affect HDL-C at four months compared to placebo (5.5% vs 0.4%, respectively; $p < .0675$).
- Bergamot did not significantly affect ox-LDL at four months compared to placebo (–2.0% vs 2.7%, respectively; $p > .05$).
- Bergamot increased PON1 at four months compared to placebo (6.5% vs 0.4%, respectively; $p < .001$).

Secondary Outcome –

- Bergamot decreased SBP at four months compared to baseline (114 vs 120 mmHg, respectively; $P = .05$).
- There were no significant changes in hepatic or renal function, HbA1c, weight, or triglycerides for bergamot compared to placebo.

LIMITATIONS:

- Small sample size limits generalizability.
- Single-center study conducted in Italy
- Short follow-up period without post-intervention monitoring
- Dietary intake and lifestyle factors were not strictly controlled.
- Industry funding introduces potential risk of bias.

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