GOOD EVIDENCE MATTERS

GEMs of the Week

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SGLT2i Wins the MACE Race

Sodium-Glucose Cotransporter-2 Inhibitors and Major Adverse Cardiovascular Outcomes: A SMART-C Collaborative Meta-Analysis

Patel SM, Kang YM, Im K, et al. Sodium-Glucose Cotransporter-2 Inhibitors and Major Adverse Cardiovascular Outcomes: A SMART-C Collaborative Meta-Analysis. Circulation. 2024;149(23):1789-1801. doi:10.1161/CIRCULATIONAHA.124.069568

KEY TAKEAWAY: Sodium-glucose cotransporter-2 inhibitors (SGLT2is) reduce the risk of major adverse cardiovascular events (MACE) by 9% in patients with diabetes at high-risk for atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), or chronic kidney disease (CKD).

STUDY DESIGN: Meta-analysis of 11 phase 3, randomized, placebo-controlled double-blind studies. (N=78,607)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: SGLT2i therapy has been shown to improve HF and kidney-related adverse outcomes in a diverse patient population irrespective of diabetes status. However, the effects of SGLT2is on MACE are ambiguous. This data aimed to provide guidance on selection of SGLT2is among a broad range of cardiovascular-kidney-metabolic disease patients in primary care practice.

PATIENTS: Diabetic patients at high-risk for ASCVD, patients with established HF or CKD

INTERVENTION: SGLT2is

CONTROL: Placebo

PRIMARY OUTCOME: Composite of MACE

Secondary Outcome: MACE sub-components

METHODS (BRIEF DESCRIPTION):

- A literature search was conducted on PubMed for articles published between January 1, 2012, and December 28, 2023, featuring phase 3 placebo-controlled, double-blind, randomized trials of SGLT2i therapy with at least 1,000 participants each in the study and control groups, and median follow-up of at least six months.
- Two authors independently reviewed the eligible trials and completed a risk of bias assessment.
- Trials with combination SGLT1/2i therapy were excluded from the study.
- Baseline characteristics such as age, sex, race, medical history (established ASCVD, diabetes, MI, HF, estimated glomerular filtration rate [eGFR]), eGFR range, and urine albumin-creatinine ratios (UACR) were compared across the three study groups.
- Participants were 62–72 years old. 34% were female and 74% were White. Patients with diabetes constituted 80%, HF 36% and CKD 37% of the study population.
- Intervention groups in each trial received treatment with Canagliflozin, Dapagliflozin, Empagliflozin, or Ertugliflozin.
- Comparator groups received treatment with placebo.
- The primary outcome assessed the composite of MACE.
- The secondary outcome measured assessed the MACE sub-components defined as cardiovascular death, fatal and nonfatal events for MI and stroke

INTERVENTION (# IN THE GROUP): 42,585

COMPARISON (# IN THE GROUP): 36,022

FOLLOW-UP PERIOD:

- Patients with diabetes at high risk for ASCVD: 2.4–4.2 years
- Patients with HF: 1.3–2.2 years
- Patients with CKD: 2.0–2.6 years

RESULTS:

Primary Outcome –

- SGLT2is decreased the rate of MACE compared to placebo (11 trials, n=78,607; hazard ratio [HR] 0.91; 95% CI, 0.87–0.96; I^2=0%).

Secondary Outcome –

- SGLT2is decreased the risk of cardiovascular death compared to placebo (11 trials, n=78,607; HR 0.86; 95% CI, 0.81–0.92; I^2=0%).
- The reduction in cardiovascular death was primarily due to a reduction in:
  - HF death (11 trials, n=78,607; HR 0.68; 95% CI, 0.46–1.0; I^2=79%)
  - Sudden cardiac death (11 trials, n=78,607; HR 0.86; 95% CI, 0.78–0.95; I^2=0%)

- SGLT2is had no significant effect on rates of MI or stroke compared to placebo.

LIMITATIONS:

- Results are affected by variations in the eligibility criteria, follow-up duration, and subgroup definitions across trials.
- The small number of studies for each drug offers limited data for comparing different members of the class.
- Inclusion criteria may not permit result generalization to all patients.
- Heterogeneity of treatment effect among subgroups should be understood as hypothetical and inconclusive evidence considering the multiple outcomes and subgroups tested.

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Smooth as a Baby: Preventing Pediatric Eczema with Emollients

Emollients to Prevent Pediatric Eczema: A Randomized Clinical Trial

Simpson EL, Michaels LC, Ramsey K, et al. Emollients to Prevent Pediatric Eczema: A Randomized Clinical Trial. *JAMA Dermatol*. Published online July 23, 2025. doi:10.1001/jamadermatol.2025.2357

KEY TAKEAWAY: Full-body emollient application started within the first two months of life reduced the risk of atopic dermatitis (AD) development, especially in those without a family history of atopy or with a dog in the household.

STUDY DESIGN: Multicenter, parallel-group, single-blinded randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Pediatric atopic dermatitis (AD) creates a considerable health care burden in US primary care clinics. There is conflicting evidence on interventions for the skin barrier on preventing AD, with those studies performed on high-risk populations not generalizable to primary care clinics.

PATIENTS: 1,247 parent-infant dyads from 25 primary care clinics in four US states

INTERVENTION: Daily full-body emollient application starting by age nine weeks

CONTROL: Infrequent or intermittent emollient use for dry skin if needed

PRIMARY OUTCOME: Physician-diagnosed AD recorded in the patient's medical record by age 24 months
Secondary Outcome: Skin infections, food allergies, disease severity

METHODS (BRIEF DESCRIPTION):

- Parent-infant dyads at well child clinic visits were recruited for this study.
- Infants 0–8 weeks old were included in the study.
- Infants with a prior diagnosis of AD, <25 weeks gestation, birth weight <1,000g, diagnosed immunodeficiency syndrome, or a sibling in the study were excluded.
- Participants were randomly assigned by 1:1 allocation ratio by history of AD in a first-degree family member to daily full-body emollient use vs no use.
- Infants in the intervention group received a full-body application of an emollient chosen by their parents from five options, mailed to their home every six months.
- Infants in the control group got emollients intermittently for dry skin as deemed necessary by the parents.
- The primary outcome was the cumulative incidence of AD by age 24 months recorded in the health care record by a credentialed health care clinician.
- Participants were risk stratified based on history of atopy in a parent or sibling and presence of cats or dogs in the household.
- Secondary outcomes were measured using the following:
    - Incidence of skin infections, hay fever/allergic rhinitis, asthma, wheeze, food allergy testing, adverse events secondary to skin products, and serious adverse events were collected via health record review at the end of the follow up period.
    - Information on emollient use frequency in both groups, alternate AD definitions, reported food allergy diagnosis, adverse skin care-related or serious events were collected via quarterly and annual surveys.
    - Participants who reported a clinician-diagnosis of AD or met Children's Eczema Questionnaire criteria completed the Patient-Oriented Eczema Measure (POEM) and the Infant Dermatology Quality of Life (IDQoL).

INTERVENTION (# IN THE GROUP): 614

COMPARISON (# IN THE GROUP): 633

FOLLOW-UP PERIOD: 24 months

RESULTS:

Primary Outcome –

- At 24 months, daily moisturizer use reduced the incidence of AD compared to the control group (36% vs 43%, respectively; relative risk [RR] 0.84; 95% CI, 0.73–0.97).

- Among children without family history of atopy, the cumulative incidence was significantly reduced in the moisturizer group compared to the control group (33% vs 43%, respectively; risk difference [RD] –10%; 95% CI, –18 to –2.2).
- Families with dog ownership benefited significantly from daily moisturizer use (RD –14; 95% CI, –23 to –4.6) compared to those without any pets (RD 0.3; 95% CI, –9.6 to 10).

Secondary Outcome –

- Rates of skin infections and food allergy reports were not significantly different between groups.
- Disease severity was not clinically different between groups.

LIMITATIONS:

- Emollients were provided free of charge for this study, but daily full-body moisturizer may be cost-prohibitive for some families.
- Participants were allowed to swap and choose between emollients, and the study was not powered to reveal differences in AD incidence by emollient type (ceramide vs non-ceramide containing).
- The incidence of AD in this trial was much higher (36% in intervention group and 43% in the control group) than the expected incidence (24%) based on literature review which could artificially elevate the treatment effect.

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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 Army, Defense Health Agency, Department of Defense, or the U.S. Government.

The Weight Loss Showdown: Tirzepatide vs Semaglutide

Tirzepatide as Compared with Semaglutide for the Treatment of Obesity

Aronne LJ, Horn DB, le Roux CW, et al. Tirzepatide as Compared with Semaglutide for the Treatment of Obesity. *N Engl J Med*. 2025;393(1):26-36. doi:10.1056/NEJMoa2416394

KEY TAKEAWAY: Tirzepatide is a more effective treatment for weight loss compared to semaglutide in patients with obesity but without type 2 diabetes mellitus (T2DM).

STUDY DESIGN: Multisite, open label, randomized controlled

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Obesity negatively affects health by increasing the risk of serious chronic diseases such as T2DM. Both tirzepatide, a glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist, and semaglutide, a (GLP-1) receptor agonist, have been shown to be effective for weight loss. The effectiveness of tirzepatide versus semaglutide for weight loss in adults with obesity but without T2DM is unknown.

PATIENTS: Adults with obesity without T2DM

INTERVENTION: Tirzepatide

CONTROL: Semaglutide

PRIMARY OUTCOME: Change in body weight from baseline to week 72

Secondary Outcome: Weight loss of at least 10%, 15%, 20%, and 25%; change in waist circumference

METHODS (BRIEF DESCRIPTION):

- Adults with obesity (65% women, 76% White, mean age 45 years old, mean body weight 113 kg, mean body mass index [BMI] 39) were recruited from 32 sites in the United States and Puerto Rico.
- Individuals ≥18 years old, BMI ≥30 or BMI ≥27 with at least one obesity-related complication such as hypertension (HTN), dyslipidemia, obstructive sleep apnea (OSA), or cardiovascular disease (CVD), and had failed weight loss through dietary changes were included in the study.
- Individuals with a diabetes diagnosis, previous or planned surgery for obesity, weight loss medication within 90 days of screening or >5 kg of body weight change within 90 days prior to screening were excluded from the study.
- Participants were randomly assigned 1:1 to tirzepatide or semaglutide treatment.
  - Tirzepatide was started at 2.5 mg per week and increased by 2.5 mg every four weeks to a maximum tolerated dose of 10 mg or 15 mg.
  - Semaglutide was started at 0.25 mg per week and increased every four weeks to a maximum tolerated dose of 1.7 mg or 2.4 mg.
- All participants were counseled on nutrition and physical activity.

INTERVENTION (# IN THE GROUP): 374

COMPARISON (# IN THE GROUP): 376

FOLLOW-UP PERIOD: 72 weeks

RESULTS:

Primary Outcome –

- Tirzepatide had significantly larger weight reduction compared to semaglutide (–20% vs –14%, respectively; treatment difference –6.5%; 95% CI, –8.1 to –4.9).

Secondary Outcome –

- Tirzepatide treatment was 1.3, 1.6, 1.8. and 2.0 times more likely than semaglutide to show at least 10%, 15%, 20%, and 25% weight reduction from baseline, respectfully.
- Tirzepatide treatment resulted in significantly greater reduction in waist circumference compared to semaglutide (–18 cm vs –13 cm, respectively; treatment difference –5.4 cm; 95% CI, –7.1 to –3.6).

LIMITATIONS:

- This study was not blinded.
- Tirzepatide is manufactured by Eli Lilly, the study sponsor

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