GOOD EVIDENCE MATTERS

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# How SMART is SMART? A Review of Asthma Therapy

**Evaluation of Budesonide-Formoterol for Maintenance and Reliever Therapy Among Patients with Poorly Controlled Asthma: A Systematic Review and Meta-Analysis**

Beasley R, Harrison T, Peterson S, et al. Evaluation of Budesonide-Formoterol for Maintenance and Reliever Therapy Among Patients with Poorly Controlled Asthma: A Systematic Review and Meta-analysis. *JAMA Netw Open*. 2022;5(3):e220615. Published 2022 Mar 1. doi:10.1001/jamanetworkopen.2022.0615



**KEY TAKEAWAY:** For patients with poorly controlled asthma, Single Maintenance and Reliever Therapy (SMART) is associated with longer time to first severe asthma exacerbations compared to a step-up approach.

**STUDY DESIGN:** Systemic review and meta-analysis of five randomized clinical trials (RCTs) (N=4,863)

**LEVEL OF EVIDENCE:** STEP 1

**BRIEF BACKGROUND INFORMATION:** Patients with poorly controlled asthma, according to the Global Initiative for Asthma (GINA), have historically been treated with a short-acting beta agonist (SABA) and inhaled corticosteroid (ICS)/long-acting beta agonist (LABA) inhaler regimen. There is a growing body of literature that suggests implementation of single maintenance and reliever therapy to include a single ICS/LABA combination inhaler. This systematic review and meta-analysis aimed to critically appraise current relevant RTCs to determine optimal asthma therapy for otherwise poorly controlled patients.

**PATIENTS:** Patients with poorly controlled asthma

**INTERVENTION:** ICS-LABA

**CONTROL:** ICS-LABA + short-acting beta agonist (SABA)

**PRIMARY OUTCOME:** Time to first severe asthma exacerbation

Secondary Outcome: Number of severe exacerbations, control of asthma, and forced expiratory volume in one second (FEV1)

**METHODS (BRIEF DESCRIPTION):**

- Study databases were searched for RCTs that compared budesonide-formoterol by SMART vs ICS-LABA + SABA.
- Studies that met the following criteria were included in the analysis:
  - Adults or adolescents with asthma
  - Reported baseline data on the GINA step of asthma treatment
  - Reported baseline data on asthma control via the Asthma Control Questionnaire 5-item version (ACQ-5)
  - Reported data on measures of efficacy for severe exacerbations defined by the American Thoracic Society or the European Respiratory society
  - Had at least a 24-week treatment period
  - Received institutional ethics review
  - Had written informed consent provided by all participants
- Poorly controlled asthma was defined as someone having an ACQ-5 score of ≥1.5 at baseline.
- Each patient was classified according to the GINA report 2018.
  - GINA step 3 (low-dose ICS-LABA + SABA reliever)
  - GINA step 4 (medium-dose or high-dose ICS-LABA + SABA reliever)
- Patient data was obtained from each study by independent extraction and were classified as being in the step-up or same-step arm in which patients were randomly assigned (control vs SMART therapy).
  - Step up: Patients stepped up in the GINA treatment hierarchy (i.e., step 3 to step 4).
  - Same step: Patients remained at the same step in the GINA treatment hierarchy compared with the treatment level at enrollment.
- The primary outcome measured the time-to-first severe exacerbation which was defined as deterioration in asthma, leading to treatment with an oral glucocorticoid for at least three days, and/or hospitalization or an emergency department visit. Using a hazards regression model time to treatment could be analyzed.
- The secondary outcomes measured the number of severe exacerbations, control of asthma, and FEV1.
  - Asthma control was measured using the ACQ-5. Scores range from 0–5, with higher scores indicating worse asthma control.

- A negative binomial model with treatment as a fixed factor was used to calculate the number of severe exacerbations.
- Longitudinal data, asthma control questionnaire score, and FEV1 measured at clinical visits (as well as symptom free days, reduced to weekly mean values) were analyzed in a mixed model.

**INTERVENTION (# IN THE GROUP):** 2,077 (SMART)
**COMPARISON (# IN THE GROUP):** 2,786 (GINA)
**FOLLOW-UP PERIOD:** At least 24 weeks

**RESULTS:**

Primary Outcome –

- SMART lengthened the time to first severe asthma exacerbation compared to step up to GINA step 4 (3 studies, n=1,950; hazard ratio [HR] 0.71; 95% CI, 0.52–0.97).
- SMART lengthened the time to first severe asthma exacerbation compared to same GINA step 3 or 4 (5 studies, n=2,913; hazard ratio [HR] 0.70; 95% CI, 0.58–0.85).

Secondary Outcome –

- SMART did not significantly decrease severe exacerbation rate compared to step up to GINA step 4.
- SMART decreased severe exacerbation rate compared to same step GINA step 3 or 4 (risk ratio [RR] 0.60; 95% CI, 0.48–0.74).
- SMART improved asthma symptom control compared to step up to GINA step 4 (difference –0.10; 95% CI, –0.19 to –0.01).
- SMART improved asthma symptom control compared to same step GINA step 3 or 4 (difference –0.12; 95% CI, –0.20 to –0.05).
- SMART did not improve FEV1 volumes compared to step up to GINA step 4.
- SMART improved FEV1 volumes compared to same step GINA step 3 or 4 (47 mL; 95% CI, 15–78).

**LIMITATIONS:**

- The study relied on RCTs using budesonide-formoterol, thus excluding use of other inhaled corticosteroids.
- There are significant conflicts of interest with multiple authors being employees, shareholders, and grant recipients from AstraZeneca, the company that manufactures and sells Symbicort.

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# Getting the Whole Family Involved May Lead to Better Health Outcomes in Childhood Obesity

**Family-Based Behavioral Treatment for Childhood Obesity Implemented in Pediatric Primary Care: A Randomized Clinical Trial**

Epstein LH, Wilfley DE, Kilanowski C, et al. Family-Based Behavioral Treatment for Childhood Obesity Implemented in Pediatric Primary Care: A Randomized Clinical Trial. *JAMA*. 2023;329(22):1947-1956. doi:10.1001/jama.2023.8061



**KEY TAKEAWAY:** Family-based therapy reduces body mass index (BMI) more than standard recommendations not only for enrolled children, but for their family members as well.

**STUDY DESIGN:** Randomized clinical trial

**LEVEL OF EVIDENCE:** STEP 2

**BRIEF BACKGROUND INFORMATION:** Childhood obesity rates continue to rise, and currently family-based therapies are typically only offered through specialty clinics. This study aimed to evaluate the effect of family-based treatment for overweight or obese children and their parents and siblings in pediatric primary care.

**PATIENTS:** Overweight and obese children 6–12 years old

**INTERVENTION:** Family-based behavioral treatment

**CONTROL:** Standard recommendations

**PRIMARY OUTCOME:** Change from baseline to 24 months in the percentage above median BMI in a population matched for age and sex

Secondary Outcome: Changes in above BMI measure for siblings and parents

**METHODS (BRIEF DESCRIPTION):**

- The Primary Care Pediatrics, Learning, Activity, and Nutrition with Families (PLAN) study compared the effectiveness of family-based treatment with usual care for families with a child 6–12 years old with BMI >85th percentile, a parent with a BMI >25, and when available, siblings 2–18 years old with overweight or obesity.
    - Inclusion criteria: No dietary restrictions and living with the participating parent at least 50% of the time.
    - Exclusion criteria: If either child or parent was taking a medication or had a health condition that altered growth or nutritional status, if either had unmanaged psychiatric illness or inability to engage in regular exercise, or if patient planned to have weight loss surgery.
- Families were randomly assigned in a 1:1 ratio to undergo usual care or family-based treatment.
    - Family-based therapies included behavioral techniques to develop healthy eating, physical activity and parenting behaviors within families. Sessions were individual in nature and included monitoring of diet and activity levels, weigh-ins, and goal setting for behavior change. The goal was for families to attend 26 sessions over a 24-month period.
    - The control group followed standard recommendations for childhood obesity by pediatrician guidelines.
- Height and weight measures were collected by study staff at baseline and at six, 12, 18 and 24 months.
- Primary Outcome: Child's change from baseline to 24 months in the percentage above the median BMI in the general population normalized for age and sex.
- Secondary Outcome: Changes in this measure for siblings and in BMI for parents.

**INTERVENTION (# IN THE GROUP):** 226

**COMPARISON (# IN THE GROUP):** 226

**FOLLOW-UP PERIOD:** 24 months

**RESULTS:**

Primary Outcome –

- Family-Based treatment reduced BMI compared to usual care at 24 months (between-group difference –6.2%; 95% CI, –10 to –2.3).

Secondary Outcome –

- Family-based treatment reduced BMI in parents compared to usual care at six months (between-group difference –4.0%; 95% CI, –5.7 to –2.3).
- Family-based treatment reduced BMI in siblings compared to usual care at six months (between-group difference –5.3%; 95% CI, –8.5 to –2.2).
- Differences between the intervention and usual care groups were maintained at 12, 18 and 24 months.

**LIMITATIONS:**

- Intensity of family-based therapy may not be feasible in all primary care settings thus limiting generalizability.
- Sibling participation was not required, limiting results for them and potentially inserting selection bias for families with siblings.
- The percentage of parents lost to follow-up may limit generalizability (119 of 2,083 families assessed for eligibility).
- The COVID-19 pandemic may have had a negative influence on the magnitude of change because it occurred in the middle of the study.

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# An Oldie but a Goodie: Methotrexate, an Effective Treatment for Knee Osteoarthritis

**Pain Reduction with Oral Methotrexate in Knee Osteoarthritis: A Randomized, Placebo-Controlled Clinical Trial**

Kingsbury SR, Tharmanathan P, Keding A, et al. Pain Reduction With Oral Methotrexate in Knee Osteoarthritis: A Randomized, Placebo-Controlled Clinical Trial. *Ann Intern Med*. 2024;177(9):1145-1156. doi:10.7326/M24-0303



**KEY TAKEAWAY:** Weekly oral methotrexate (MTX) minimally decreases knee pain at six months but does not have a significant effect at 12 months in adults with symptomatic knee osteoarthritis (OA).

**STUDY DESIGN:** Multicenter, randomized, double-blind placebo-controlled trial

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

**BRIEF BACKGROUND INFORMATION:** Medication management of OA symptoms have been limited by long term safety concerns of non-steroidal and steroid anti-inflammatory drugs. MTX has long been used in the treatment of rheumatoid arthritis (RA) with demonstrated efficacy and safety. This study examined the use of MTX in reducing pain and stiffness in patients with knee OA.

**PATIENTS:** Patients with confirmed knee OA and knee pain for at least three months

**INTERVENTION:** MTX

**CONTROL:** Placebo

**PRIMARY OUTCOME:** Knee pain

Secondary Outcome: Knee stiffness, physical function

**METHODS (BRIEF DESCRIPTION):**

- Patients >18 years old, who have knee pain occurring on most days for ≥3 months, x-ray evidence of knee OA, severity of pain ≥4 out of 10, and who have inadequate response to current treatment were recruited from primary care and specialty sports medicine clinics were included.
- Patients were randomized 1:1 to either MTX or placebo.
- Patients were started on 10 mg of MTX once a week and titrated every two weeks to a max dose of 25 mg weekly, if they were able to tolerate it without side effects. They continued treatment for 12 months.
- The control group received an oral placebo weekly.
- Both groups received 5 mg of folic acid for six days after the weekly MTX or placebo dose. Both groups continued with usual analgesia.
- The primary outcome measured knee pain at six months using the numeric rating scale (NRS). Scores range from 0–10, with higher scores indicating worse pain.
- The secondary outcomes of stiffness and overall physical function were measured utilizing the following. Higher scores on each of the scales indicate worse symptoms.
    - Knee stiffness was measured using the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) knee stiffness score. Scores range from 0–20.
    - Physical function was measured using the WOMAC physical function score. Scores range from 0–8.
    - Constant pain was measured using the Intermittent and Constant Osteoarthritis Pain (ICOAP) index. Scores range from 0–100.
    - Intermittent pain was measured using the ICOAP index. Scores range from 0–100.
    - Total pain was measured using the ICOAP total pain index. Scores range from 0–100.
    - Worst knee pain in past seven days was measured using the NRS. Scores range from 0–10.
    - Pain in all other joints was measured using the NRS. Scores range from 0–10.

**INTERVENTION (# IN THE GROUP):** 77

**COMPARISON (# IN THE GROUP):** 78

**FOLLOW-UP PERIOD:** Six and 12 months

**RESULTS:**

Primary Outcome –

- MTX improved knee pain compared to placebo after six months (mean difference [MD] 0.79; 95% CI, 0.08–1.51).
- MTX did not significantly affect knee pain compared to placebo after 12 months (MD 0.14; 95% CI, –0.69 to 0.98).

Secondary Outcome –

- MTX decreased knee stiffness compared to placebo at six months (MD 0.60; 95% CI, 0.01–1.2).
- MTX increased knee physical function compared to placebo at six months (MD 5.0; 95% CI, 1.3–8.7).
- MTX improved intermittent pain compared to placebo at six months (MD 13; 95% CI, 5.1–21).
- MTX improved total knee pain compared to placebo at six months (MD 9.5; 95% CI, 2.2–17).
- MTX improved worse knee pain over the last seven days compared to placebo at six months (MD 0.82; 95% CI, 0.05–1.6).
- MTX did not significantly affect constant pain or pain in all other joints compared to placebo at six months.
- MTX did not significantly affect knee stiffness, physical function, constant pain, intermittent pain, total pain, worse knee pain, pain in the past seven days, or pain in all other joints compared to placebo at 12 months.

**LIMITATIONS:**

- This study was limited to enrollees who could tolerate the oral MTX route, even though subcutaneous injection (SQ) has better tolerability.
- Enrolled patients were allowed to enter radiographic evidence up to two years old which may have led to people enrolling with more advanced diseases.
- The small sample size may lead to increased risk of type II error.
- There was relatively short follow-up which made drawing conclusions about long term efficacy and safety difficult.

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# Lowering the SCALE: Liraglutide in Pediatric Obesity

**Liraglutide for Children 6 to <12 Years Old with Obesity - A Randomized Trial**

Fox CK, Barrientos-Pérez M, Bomberg EM, et al. Liraglutide for Children 6 to <12 Years Old with Obesity - A Randomized Trial. *N Engl J Med*. 2025;392(6):555-565. doi:10.1056/NEJMoa2407379



**KEY TAKEAWAY:** Liraglutide with lifestyle interventions reduces body mass index (BMI) compared to matching placebo in pediatric patients six to <12 years old with obesity, providing a pharmaceutical option for pediatric obesity.

**STUDY DESIGN:** Multi-site, double-bind, placebo-controlled randomized controlled trial

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

**BRIEF BACKGROUND INFORMATION:** Childhood obesity serves as a predictor for obesity of adolescence and adulthood and is associated with numerous obesity-related complications. While lifestyle interventions remain first-line therapy for obesity, adjunctive pharmacologic therapy may be needed for treatment. While liraglutide is approved for the treatment of obesity for those ≥12 years old, it is currently not approved for patients <12 years old. Additionally, there are no other pharmaceutical therapies approved for this age group, limiting treatment options for pediatric obesity. This study investigated the efficacy of liraglutide in the treatment of obesity in pediatric populations six to <12 years old.

**PATIENTS:** Children with obesity without type 1 diabetes mellitus and secondary causes of obesity

**INTERVENTION:** Liraglutide

**CONTROL:** Placebo

**PRIMARY OUTCOME:** Change in BMI

Secondary Outcome: Change in weight, reduction of BMI by at least 5%, adverse events

**METHODS (BRIEF DESCRIPTION):**

- Study conducted across 23 sites in nine countries included children six to <12 years old with obesity. Obesity is defined in this study as age-adjusted and sex-adjusted BMI at or above the 95th percentile.
- All participants received lifestyle intervention in addition to liraglutide or matching placebo.
- Liraglutide was initiated at either 0.3 mg or 0.6 mg subcutaneously once daily for one week titrated weekly in increments of 0.6 mg to a maximum daily dose of 3 mg per day or maximally tolerated dose.
- Starting dose was based on starting body weight with the 0.6 mg dose for patients >45 kg.
- Placebo was administered to match those in the liraglutide group.
- The primary outcome measured BMI at eight weeks and 16 weeks, then every 10 weeks until conclusion of trial.
- The following were measured as the secondary outcomes:
  - Body weight was measured weekly through four weeks, then at eight weeks and 16 weeks, with subsequent measurements every 10 weeks until conclusion of trial.
  - Percentage of participants in each group that achieved at least a 5% reduction in BMI was calculated.
  - Adverse events were evaluated during the treatment period, defined as from the first dose of liraglutide or placebo to 14 days after final dose.

**INTERVENTION (# IN THE GROUP):** 56

**COMPARISON (# IN THE GROUP):** 26

**FOLLOW-UP PERIOD:** 56 weeks

**RESULTS:**

Primary Outcome –

- Liraglutide reduced BMI compared to placebo (–5.8% vs 1.6%, respectively; difference –7.4; 95% CI, –12 to –3.2).

Secondary Outcome –

- Liraglutide reduced body weight from baseline compared to placebo (difference –8.4; 95% CI, –13 to –3.3).
- In the liraglutide group, more participants achieved a BMI reduction of at least 5% compared to placebo (46% vs 9%, respectively; adjusted odds ratio [aOR] 6.3; 95% CI, 1.4–29).
- Adverse events were primarily gastrointestinal, with three cases requiring emergency care. No events resulted in hospitalization or sequelae. Treatments for gastrointestinal adverse events included

antiemetic and antinausea therapy, proton-pump inhibitor therapy, and dose reduction or interruption of liraglutide.
- No adverse effects on growth and development were noted, based on changes in height, bone age, and Tanner stages.

**LIMITATIONS:**

- No clear definition of BMI reduction goals for obesity in the pediatric population, limiting clinical significance and applicability of results.
- Limited diversity of participants with 72% of participants being identified as White, reducing generalizability of results.
- The sample size was limited to 82 participants, reducing the external validity of the study.

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# Does Metabolic Syndrome Stand a Chance with the Combination of Exercise and a GLP-1 Receptor Agonist?

**Combination of Exercise and GLP-1 Receptor Agonist Treatment Reduces Severity of Metabolic Syndrome, Abdominal Obesity, and Inflammation: A Randomized Controlled Trial**

Sandsdal RM, Juhl CR, Jensen SBK, et al. Combination of Exercise and GLP-1 Receptor Agonist Treatment Reduces Severity of Metabolic Syndrome, Abdominal Obesity, and Inflammation: A Randomized Controlled Trial. *Cardiovasc Diabetol*. 2023;22(1):41. Published 2023 Feb 25. doi:10.1186/s12933-023-01765-z



**KEY TAKEAWAY:** After one year, the combination of exercise and a glucagon-like peptide receptor agonist (GLP-1 RA) treatment reduces metabolic syndrome severity Z score (MetS-Z), abdominal obesity, and high-sensitivity C-reactive protein (hsCRP) compared to placebo.

**STUDY DESIGN:** Randomized, double-blinded, placebo-controlled trial

**LEVEL OF EVIDENCE:** STEP 3 (downgraded due to study funded by pharmaceutical company, small sample size, and only per-protocol analysis was reported)

**BRIEF BACKGROUND INFORMATION:** GLP-1 RAs are revolutionary medicines that have captured scientific and the general public's attention for their promise in treatment of obesity and improving metabolic syndrome. This study aimed to investigate the effects of adherent exercise, a GLP-1 RAs, or the combination of both, on severity of metabolic syndrome, abdominal obesity, and inflammation following weight loss.

**PATIENTS:** Adults living with obesity (who lost ≥5% of body weight after eight-week low calorie diet run-in period)

**INTERVENTION:** Exercise and placebo, liraglutide and habitual activity, or liraglutide and exercise

**CONTROL:** Placebo and habitual activity

**PRIMARY OUTCOME:** MetS-Z, abdominal obesity measured as android fat, and hsCRP

**METHODS (BRIEF DESCRIPTION):**

- This study included Danish adults 18–65 years old with body mass index (BMI) 32–43 without comorbidities, including diabetes, from 2016–2019.
- Participants completed a restricted diet of 800 kcal/day for eight weeks run-in period.
- Participants who achieved a weight loss of ≥5% were assigned to one of four groups for a year.
- Participants were blinded and randomized 1:1:1:1.
  - The placebo group received volume-matched placebo injections.
  - The exercise group performed either 150 minutes per week of moderate-intensity or 75 minutes per week of vigorous intensity exercise.
  - The liraglutide group received from 0.6 mg per day to a full dose of 3.0 mg per day.
  - The combination group received liraglutide and the exercise protocol.
  - Non-exercise intervention groups were instructed to continue their habitual level of exercise.
- Participants who dropped out after randomization were still included in an intention-to-treat analysis.
- MetS-Z scores are a normally distributed z-score with a mean of zero and a standard deviation of one. The scores show how many standard deviations a given participant's metabolic syndrome scores (waist circumference, high-density lipoprotein-cholesterol levels, triglyceride levels, fasting blood glucose levels and blood pressure measurements) are from the population mean.
- Android fat mass was measured with dual-energy x-ray absorptiometry full-body scans.
- hsCRP was assessed using assay system kits which was sampled from all three visits.
- Outcomes were obtained before the low-calorie diet (8 weeks prior), after the low-calorie diet (week 0—randomization), and at the end of the trial (week 52).
- Continuous variables were summarized as means with standard deviations. Significance testing was performed on the MetS-Z, android fat percentage, and hsCRP outcomes.

**INTERVENTION (# IN THE GROUP):**

- Exercise group: 48 (26 included in analysis)
- Liraglutide group: 49 (36 included in analysis)
- Combination group: 49 (29 included in analysis)

**COMPARISON (# IN THE GROUP):**

- Placebo group: 49 (39 included in analysis)

**FOLLOW-UP PERIOD:** 52 weeks

**RESULTS:**

Primary Outcome –

- Liraglutide only improved MetS-Z compared to placebo (estimated mean difference [MD] –0.37; 95% CI, –0.58 to –1.2).
- Exercise and liraglutide improved MetS-Z compared to placebo (MD –0.48; 95% CI, –0.70 to –0.25).
- Exercise only did not significantly improve MetS-Z compared to placebo (MD –0.11; 95% CI, –0.34 to 0.12).

Secondary Outcome –

- Liraglutide only reduced android fat compared to placebo (MD –2.8% points; 95% CI, –4.8 to –0.8).
- Exercise and liraglutide reduced android fat compared to placebo (MD –6.1% points; 95% CI, –8.2 to –4.0).
- Exercise only reduced android fat compared to placebo (MD –2.6% points; 95% CI, –4.8 to –0.4).
- Liraglutide only or exercise only did not significantly improve hsCRP compared to placebo.
- Exercise and liraglutide improved haCRP compared to placebo (MD –43% points; 95% CI, –66 to –5).

**LIMITATIONS:**

- It was impossible to blind study participants to exercise as an intervention.
- The study had a small sample size.
- Study population was a relatively ethnically homogeneous sample of Danish adults, thus limiting the generalizability of the findings.
- This study was an analysis of the secondary endpoints of another study.
- The study was funded by investigators employed, or on the advisory board of Novo Nordisk.
- Only per-protocol analysis reported, intention-to-treat analysis was only reported in the supplemental material.

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# SGLT-2 Inhibitors: A Tool to Prevent Long-Term Progression of CKD

**Long-Term Effects of Empagliflozin in Patients with Chronic Kidney Disease**

EMPA-KIDNEY Collaborative Group, Herrington WG, Staplin N, et al. Long-Term Effects of Empagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med*. 2025;392(8):777-787. doi:10.1056/NEJMoa2409183



**KEY TAKEAWAY:** Empagliflozin decreases the risk of chronic kidney disease (CKD) progression and cardiovascular (CV) death compared to placebo in patients with CKD.

**STUDY DESIGN:** Double-blind, placebo-controlled randomized controlled trial

**LEVEL OF EVIDENCE:** STEP 3 (downgraded due to significant confounding variables in the post-trial follow-up period)

**BRIEF BACKGROUND INFORMATION:** CKD is one of the most common primary care diagnoses, resulting in significant morbidity and mortality for patients. Empagliflozin was previously studied in the EMPA-Kidney trial (2023) and showed considerable efficacy in reducing the rates of CKD progression and CV death. This study aimed to evaluate the effects of empagliflozin in the EMPA-Kidney trial and two years post-trial observation in participants who had discontinued the medication.

**PATIENTS:** Patients with CKD

**INTERVENTION:** Empagliflozin 10 mg once daily

**CONTROL:** Placebo

**PRIMARY OUTCOME:** CKD progression or CV death

Secondary Outcome: Kidney disease progression, end-stage renal disease (ESRD), composite outcome of death from any cause or ESRD

**METHODS (BRIEF DESCRIPTION):**

- EMPA-Kidney recruited participants from 241 centers across eight countries. Participants were recruited for post-trial from a majority of the original trial centers (77%) in seven of the eight total countries.
- Participants were eligible if they met either of the following conditions: (1) race-adjusted eGFR 20–45 mL/min/1.7m² or (2) eGFR 45–90 mL/min/1.7m² with concurrent proteinuria of at least 200 mg/g and taking a single-agent renin-angiotensin system inhibitor.
- Patients with a history of renal transplant or polycystic kidney disease (PKD) were excluded.
- EMPA-Kidney participants were randomized to receive empagliflozin 10 mg orally once daily or placebo using a minimization process with 10% stochastic element.
- At the end of the two-year trial period, patients could participate in a two-year post-trial observation, in which they were not restricted from receiving SGLT-2 inhibitors, regardless of initial trial allocation.
- The primary outcome of the post-trial was kidney disease progression or CV death, where CKD progression was defined as: (1) 40% decrease in eGFR from baseline at randomization that persisted for at least 30 days, (2) progression to ESRD, (3) persistent eGFR <10, (4) death from renal failure.
- Secondary outcomes included CKD progression alone, ESRD, and the composite outcome of death from any cause or ESRD.

**INTERVENTION (# IN THE GROUP):** 3,304

**COMPARISON (# IN THE GROUP):** 3,305

**FOLLOW-UP PERIOD:** Two years for EMPA-Kidney and two years of post-trial observation (four total years)

**RESULTS:**

Primary Outcome –

- Empagliflozin decreased risk of CKD progression and CV death compared to placebo in all active- and post-trial groups (hazard ratio [HR] 0.79; 95% CI, 0.72–0.87).

Secondary Outcome –

- Empagliflozin decreased risk of kidney disease progression compared to placebo (HR 0.79; 95% CI, 0.72–0.87).
- Empagliflozin decreased the risk of ESRD compared to placebo (HR 0.74; 95% CI, 0.64–0.87).
- Empagliflozin decreased risk of composite outcome of death from any cause or ESRD compared to placebo (HR 0.81; 95% CI, 0.72–0.90).

**LIMITATIONS:**

- Patients in the post-trial were not restricted from taking SGLT-2 inhibitors prescribed by their primary care providers, which introduces potential for confounding.

- Not all sites from the EMPA-Kidney trial were included in the post-trial.
- Only 74% of the original study participants were captured in the follow-up study, and these participants were more likely to have worse renal function.
- Data was collected via medical record review or contacting patients/caregivers/providers to gather information, which can limit accuracy.

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