GEMs
GOOD EVIDENCE MATTERS

# GEMs of the Week

Volume 3 - Issue 4

FPIN
Family Physicians Inquiries Network

## What's in this week's issue?

**Week of January 23 - 27, 2023**

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# Can SGLT2i's Also Prevent Cardiovascular and Renal Outcomes?

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SPOTLIGHT

**SGLT2 Inhibitors for Primary and Secondary Prevention of Cardiovascular and Renal Outcomes in Type 2 Diabetes: A Systematic Review and Meta-Analysis of Cardiovascular Outcome Trials**

Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials [published correction appears in *Lancet*. 2019 Jan 5;393(10166):30]. *Lancet*. 2019;393(10166):31-39. doi:10.1016/S0140-6736(18)32590-X



KEY TAKEAWAY: SGLT2i's have moderate benefit on major atherosclerotic adverse cardiovascular events that are confined to patients with established cardiovascular illness. However, SGLT2i's lead to decreased hospitalizations for heart failure and evolution of renal disease irrespective of existing atherosclerosis or history of heart failure.

STUDY DESIGN: Systematic review and meta-analysis (3 RCTs; N=34,322)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: The magnitude of the effect of SGLT2is on cardiovascular outcomes in patients with existing cardiovascular disease (CVD) is known. However, this study looked to see if SGLT2i's can be used in primary and secondary prevention of cardiovascular and renal outcomes in patients with type two diabetes.

PATIENTS: Patients with type 2 diabetes

INTERVENTION: SGLT2i

CONTROL: Placebo

PRIMARY OUTCOME: Cardiovascular death, hospitalization for heart failure, hospitalization for renal disease

Secondary Outcomes: Major adverse cardiovascular events (myocardial infarction, stroke, or cardiovascular death), progression of renal disease

METHODS (BRIEF DESCRIPTION):

- Data from three identified trials of 34,322 patients with type 2 diabetes was stratified by baseline presence of atherosclerotic cardiovascular disease, heart failure, and degree of baseline renal function.
- The patients in the study were on average 64 years old and 35% were women.
- The treatment group received SGTL2i's, such as empagliflozin, canagliflozin, and dapagliflozin.
- The control group received a placebo.
- Results were stratified by baseline atherosclerotic cardiovascular disease, heart failure, and renal function.
- Efficacy outcomes included major adverse effects, cardiovascular death, hospitalization for heart failure, and worsening of renal function.

INTERVENTION (# IN THE GROUP): 19,064

COMPARISON (# IN THE GROUP): 15,258

FOLLOW UP PERIOD: 2.4–4.2 years

RESULTS:

Primary Outcomes –

- SGLT2i's reduce the risk of cardiovascular death or hospitalization for heart failure by 23% in those with or without a history of heart failure (HR 0.77; 95% CI, 0.71–0.84).
- SGLT2i's reduce the risk of hospitalizations for renal disease advancement compared to placebo by 45% irrespective of existing cardiovascular disease or heart failure (HR 0.55; 95% CI, 0.48–0.64).

Secondary Outcomes –

- SGLT2i's reduce major adverse cardiovascular events by 11% only in patients with a history of atherosclerotic cardiovascular disease (HR 0.86; 95% CI, 0.80–0.93).
- SGLT2i's do not reduce major adverse cardiovascular events in patients without atherosclerotic disease (HR 1.0; 95% CI, 0.87–1.2).
- The benefit of SGLT2i varied with baseline kidney function. There was less of a reduction for the advancement of renal disease if severe kidney disease was baseline.

LIMITATIONS:

- Study-level data was combined instead of individual participant data.
- The exact inclusion criteria and definitions of endpoints varied among the included trials.
- Standard presence of established atherosclerotic cardiovascular disease and heart failure was investigator-reported in all trials. Therefore, patients could have had undiagnosed cardiovascular disease and heart failure at baseline.

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# Could Early Food Intervention Prevent Food Allergy in Infants?

**Early Food Intervention and Skin Emollients to Prevent Food Allergy in Young Children (PreventADALL): A Factorial, Multicentre, Cluster-Randomised Trial**

Skjerven HO, Lie A, Vettukattil R, et al. Early food intervention and skin emollients to prevent food allergy in young children (PreventADALL): a factorial, multicentre, cluster-randomised trial. *Lancet*. 2022;399(10344):2398-2411. doi:10.1016/S0140-6736(22)00687-0



KEY TAKEAWAY: Exposure to common food allergens at three months old results in reduced risk of food allergies at 36 months old.

STUDY DESIGN: 2x2 factorial, cluster-randomized trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Current trials reporting exposure of allergenic foods at four to six months of life have established benefit. There is limited evidence showing how interventions before the age of four months affect allergy development. This study uniquely combines food allergy and emollients with early exposure at three months old to prevent allergies.

PATIENTS: Healthy newborns

INTERVENTION: Skin, food, or combined intervention

CONTROL: Usual care

PRIMARY OUTCOME: Incidence of any food allergy at 36 months

Secondary Outcome: Allergy specific to peanut, cow's milk, wheat, or egg

METHODS (BRIEF DESCRIPTION):

- Newborns were at least 35 weeks gestation and born of mothers enrolled in the PreventADALL study between December 9, 2014 and October 31, 2016.
- All pregnant women were included at their 18-week ultrasound at three sites.
- Patients were excluded if the pregnancy contained more than two fetuses, there was a language barrier, plans to move, or severe maternal, fetal, or neonatal disease.
- Newborns were randomized by computer generation into one of four groups that were predetermined before the study began.
- Food intervention group: Between the ages of 12 and 16 weeks, foods were added one at a time in one-week intervals (peanut butter, cow's milk, wheat porridge, and scrambled eggs).
- Skin intervention group: At two weeks to eight months old for at least four days per week five-to-10-minute baths were given with solely the provided emulsified oil and cream spread over the face after the bath.
- Control group: No instructions were provided except to follow the advice of their healthcare provider and health guidelines until they were six months old.
- Follow up visits occurred at three, six, 12, 24, and 36 months of newborn age.
- Electronic diaries were collected weekly up to 26 weeks and electronic questionnaires were collected every three months during the first year of life and twice per year after.
- Outcomes were measured in groups (food allergy, probable food allergy, no food allergy, and unclear).
    - Primary outcomes were met when they fit into the food allergy and probable food allergy categories.
    - Secondary outcomes were indicated by allergy to peanuts, cow's milk, wheat, or egg.

INTERVENTION (# IN THE GROUP):

- Skin interventions: 575
- Food interventions: 642
- Combined interventions: 583

COMPARISON (# IN THE GROUP): 597

FOLLOW UP PERIOD: Three years

RESULTS:

Primary Outcome –

- The food intervention reduced the risk of food allergy compared to non-food interventions (risk difference [RD] –1.6%; 95% CI, –2.7 to –0.5; NNT=63).

Secondary Outcomes –

- 3.9% of the control group and 1.5% of food intervention groups had peanut allergy at 36 months (no p-values reported).
- 0.5% of the control group and 0.17% of food intervention groups had milk allergy (no p-values reported).
- 1.2% of the control group and 0.8% of food intervention groups had egg allergy (no p-values reported).

LIMITATIONS:

- Participants and caregivers were not blinded to their assignment.
- Only a third of participants assigned to the combined intervention group adhered to the protocol.

- Low doses of allergenic food may have been suboptimal to prevent allergy.

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# Let's See: Making Pilocarpine More Tolerable

**Safety and Efficacy of AGN-190684 in Individuals with Presbyopia: The GEMINI 1 Phase 3 Randomized Clinical Trial**

Waring GO, Price FW, Wirta D etal. Safety and Efficacy of AGN-190584 in Individuals with Presbyopia: The GEMINI 1 Phase 3 Randomized Clinical Trial. *JAMA Ophthalmol*. 2022 Apr 1;140(4):363-371. doi: 10.1001/jamaophthalmol.2022.0059.



KEY TAKEAWAY: At three- and six-hours there is improvement in vision using pilocarpine with vehicle, but there is no difference at eight hours.

STUDY DESIGN: Multi-site, randomized, double-blind trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Studies show pilocarpine hydrochloride (at 1.5% or less) improves near vision and tolerability in patients with presbyopia. This study combines pilocarpine 1.25% with a pH equilibrating vehicle to see if this would further improve tolerability.

PATIENTS: Adults with presbyopia

INTERVENTION: 1.25% pilocarpine with vehicle

CONTROL: Vehicle

PRIMARY OUTCOME: Sight improvement at three hours

Secondary Outcomes: Sight improvement at six and eight hours, adverse events

METHODS (BRIEF DESCRIPTION):

- Patients 40 to 55 years old with presbyopia were enrolled from 36 sites in the United States.
  - The mean age was 49.6 years old.
  - Participants had presbyopia (complaints of poor near vision impacting daily activities and willingness to wear mono-focal correction).
- Inclusion Criteria: Photopic high contrast corrected distance visual acuity 20/25 or better, mesopic high contrast distance corrected near visual acuity (DCNVA) of 20/40–20/100, photopic near visual acuity corrected to 20/40 or better bilaterally
- Patients with severe dry eye disease, intraocular surgery (except laser-assisted in-situ keratomileusis and keratectomy), and history of glaucoma were excluded.
- For 30 days, the treatment group received pilocarpine with pH equilibrating vehicle once daily with one drop to each eye bilaterally.
- The comparison group received the vehicle without pilocarpine.
- The primary outcome was the proportion of participants with three or more lines of improvement in DCNVA three hours after treatment on day 30.
- The secondary outcomes were the proportion of participants with three or more lines of improvement in DCNVA at six and eight hours after treatment on day 30.
- Adverse events and other potential side effects, including intraocular pressure, were assessed at pre-specified intervals on day 30.

INTERVENTION (# IN THE GROUP): 163

COMPARISON (# IN THE GROUP): 160

FOLLOW UP PERIOD: 30 days

RESULTS:

Primary Outcome –

- Pilocarpine with vehicle improved sight compared to vehicle alone at day 30 hour three (31% versus 8.1% respectively; between group difference 23%; 95% CI, 14%–31%).

Secondary Outcomes –

- Pilocarpine with vehicle improved sight compared to vehicle alone at day 30 hour six (18% and 8.8% respectively; between group difference 9.7%; 95% CI, 2.3%–17%).
- Pilocarpine with vehicle did not significantly change sight at 8 hours compared to vehicle alone at day 30.
- Safety outcome of headache occurred in 14% of patients receiving pilocarpine with vehicle and 9.4% of patients receiving just vehicle.

LIMITATIONS:

- Participant sight was tested in the daytime excluding evening hours with less light.
- The study was limited to once daily dosing.
- This study was funded by a drug manufacturer.
- Results were not broken down by severity of vision impairment.
- Majority of the participants were identified as White.
- The study did not address possible differences between those who wear corrective lenses and those who do not.

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# Peer Coaching Can Improve Diabetes Self-Management in Low-Income Veteran Black Men

**Peer Coaching to Improve Diabetes Self-Management Among Low-Income Black Veteran Men: A Mixed Methods Assessment of Enrollment and Engagement**

Turner CD, Lindsay R, Heisler M. Peer Coaching to Improve Diabetes Self-Management Among Low-Income Black Veteran Men: A Mixed Methods Assessment of Enrollment and Engagement. Ann Fam Med. 2021;19(6):532-539. doi:10.1370/afm.2742



KEY TAKEAWAY: Black diabetic men with higher A1C levels and poor self-perceived benefit were more likely to enroll in peer-to-peer coaching.

STUDY DESIGN: Single site unblinded randomized control trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Black men have higher rates of type 2 diabetes mellitus and are at a higher risk of diabetes-related complications, when compared to non-Hispanic White men. There is limited research on how to best address this health disparity among Black men. Peer support interventions have previously shown effectiveness in improving diabetes outcomes.

PATIENTS: Veteran diabetic males

INTERVENTION: Peer health coaching program with e-health tool

CONTROL: Peer health coaching program without e-health tool

PRIMARY OUTCOME: Characteristics of those who chose to engage

Secondary Outcomes: HbA1c levels, themes related to engaging

METHODS (BRIEF DESCRIPTION):

- A two-arm randomized control trial was conducted at John Dingell VA Medical Center.
- Patients were invited to enroll if their HbA1C was >7.9 in those less than 70 years old and >8.4% in those >70 years old.
- Patients were enrolled in a six-month peer coaching program. Those enrolling and declining enrollment were surveyed on scales of self-reported health status, diabetes self-management ability, satisfaction with healthcare, and ease of establishing social relationships.
- Patients that were enrolled were also surveyed on medication adherence and exercise, diabetes distress, decision conflict.
- At the end of six months the enrolled patients were evaluated on how supportive their coach was of their autonomy using the Health Care Climate Questionnaire. Scores ranged from 1–100, with higher scores representing higher perceived autonomy.
- Patients were randomized to an interactive e-health tool, the intervention, or no e-health tool, the control.
- Those enrolling and not enrolling were asked to share their demographic data and complete a pre-enrollment questionnaire.
- After six months of coaching, those in the intervention group completed a post enrollment questionnaire and focus interviews were conducted.

INTERVENTION (# IN THE GROUP): 146

COMPARISON (# IN THE GROUP): 144

FOLLOW UP PERIOD: Six months

RESULTS:

Primary Outcomes –

- There were no statistically significant differences in baseline characteristics of those who did and did not engage.
- Peer coaches rated with greater autonomy supportiveness were more likely to have engaged participants than those who did not (mean scale score 85 vs 71, $P<.001$).

Secondary Outcomes –

- Engaging in peer coaching did not reduce HbA1C compared to those who did not engage (change coefficient 0.10, $P=.71$).
- Qualitative analysis revealed themes that related to engaging in the peer coaching program.
  - Themes: peer coach who was encouraging, supportive, authentic, accountable, and consistent with shared experiences providing helpful tips and self-management information with an intentional focus on improving self-management behaviors

LIMITATIONS:

- Only 40% of those in the control group agreed to answer a survey.
- The study was conducted in a single health system.
- The population of the study was predominantly older men, limiting generalizability.

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