GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

Volume 3 - Issue 50

FPIN
Family Physicians Inquiries Network

What's in this week's issue?

Week of December 11 - 15, 2023

SPOTLIGHT: How Many Steps Does It Take to Get to a Longer Life?

- Sodium-Glucose Cotransporter-2 Inhibitors: The Elixir for Recurrent Gout Flares?
- Orforglipron Use for Obesity
- Transmasculine Gender Affirmation: Is Surgical Efficiency Worth the Risk?

How Many Steps Does It Take to Get to a Longer Life?

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Daily Steps and All-Cause Mortality: A Meta-Analysis of 15 International Cohorts

Paluch AE, Bajpai S, Bassett DR, et al. Daily steps and all-cause mortality: a meta-analysis of 15 international cohorts. *Lancet Public Health*. 2022;7(3):e219-e228. doi:10.1016/S2468-2667(21)00302-9

KEY TAKEAWAY: Taking more steps per day is associated with a progressively lower risk of all-cause mortality.

STUDY DESIGN: Meta-analysis of 15 observational studies and one systematic review (N=47,471)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Although 10,000 steps per day are widely promoted as having health benefits, there is little evidence to support this recommendation. This article demonstrates the association between the number of steps per day with all-cause mortality.

PATIENTS: Ambulatory adults

INTERVENTION: Higher quartiles of steps per day

CONTROL: Lower quartiles of steps per day

PRIMARY OUTCOME: All-cause mortality

METHODS (BRIEF DESCRIPTION):

- Eligibility criteria included longitudinal design, participants ≥18 years old, non-patient populations, and the study reported an association between daily step counts and mortality.
- In each study, participants wore a step-counting device for at least one week, steps per day were averaged, and then participants were followed up for death from any cause. The step rate was also analyzed when data was available.
- The Steps for Health Collaborative standardized protocol was used to process participant-level data.
- Step volume was categorized into quartiles and associations with all-cause mortality were examined and referenced against the lowest quartile using Cox proportional hazards regression. Investigators of participating studies completed models for each study's overall sample by age group and sex.
- Median steps per day were calculated by quartile from each study's medians.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Median 7.1 years (2.7–13 years)

RESULTS:

Primary Outcome –

- Taking more steps per day was associated with progressively lower mortality risk, with the risk plateauing for adults ≥60 years old at 6,000–8,000 steps per day (HR 0.43; 95% CI, 0.34–0.53).
- For younger adults <60 years old, mortality risk reduction was associated with 8,000–10,000 steps per day (HR 0.60; 95% CI, 0.44–0.83).
- Compared with the lowest quartile, the adjusted hazard ratio for all-cause mortality was:
  - Quartile 2 (aHR 0.60; 95% CI, 0.51–0.71)
  - Quartile 3 (aHR 0.55; 95% CI, 0.49–0.62)
  - Quartile 4 (aHR 0.47; 95% CI, 0.39–0.57)
- Association between step counts and mortality was stronger in the six studies with fewer than six years of follow-up (HR 0.32; 95% CI, 0.25–0.41) than among the nine studies with six years of follow-up or more (HR 0.57; 95% CI, 0.49–0.66) when comparing the lowest and highest quartile.
- Step rate did not have a significant impact on mortality when controlled for the total step count.
- There was no significant difference in mortality reduction between females and males.

LIMITATIONS:

- The data was derived from observational studies which are at higher risk for bias and confounding variables.
- Steps were measured at a single time point and did not account for changes in steps per day over time.
- All included studies were in high-income countries and participants were volunteers primarily among White populations, restricting the generalizability of the findings.
- Device type, wear location, walking speed, and duration can affect the accuracy of step estimates.
- Further studies may be indicated for the impact of step rate on mortality.

Tyson Oswald, DO
University of Wyoming Family Practice-Casper
Casper, WY

Sodium-Glucose Cotransporter-2 Inhibitors: The Elixir for Recurrent Gout Flares?

Comparative Effectiveness of Sodium-Glucose Cotransporter-2 Inhibitors for Recurrent Gout Flares and Gout Primary Emergency Department Visits and Hospitalizations: A General Population Cohort Study

McCormick N, Yokose C, Wei J, et al. Comparative Effectiveness of Sodium-Glucose Cotransporter-2 Inhibitors for Recurrent Gout Flares and Gout-Primary Emergency Department Visits and Hospitalizations: A General Population Cohort Study. *Ann Intern Med.* 2023;176(8):1067-1080. doi:10.7326/M23-0724

KEY TAKEAWAY: Sodium-glucose cotransporter-2 inhibitors (SGLT2i) initiation leads to a 34% lower rate of recurrent gout flare in patients with gout and type 2 diabetes compared with dipeptidyl peptidase 4 inhibitors (DPP-4is), and this outcome is consistent across demographic subgroups.

STUDY DESIGN: Propensity score matched (PSM), new-user cohort study

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Patients with gout and diabetes are increasingly experiencing recurrent gout flares. This has led to more emergency department visits, hospitalizations, opioid use, and transient CV risk.
This study considers the impact of SGLT2is, known to decrease serum urate levels, and DPP-4is, a second-line glucose-lowering agent, in preventing recurrent gout flares.

PATIENTS: Patients with gout and type 2 diabetes

INTERVENTION: SGLT2is

CONTROL: DPP-4is

PRIMARY OUTCOME: Gout flare

METHODS (BRIEF DESCRIPTION):

- A general population study was conducted on adults with one year of continuous healthcare enrollment within British Columbia, Canada, who were first dispensed SGLT2is and DPP-4is between January 1, 2014–June 30, 2022.
- Demographic characteristics:
  - Patients had a mean age of 66 years old, 71% were male.
  - They had at least one International Classification of Diseases (ICD) code for both gout and type 2 diabetes.
  - Patients were excluded if they did not have both diabetes and gout diagnoses, were under 18 years old, or had prior SGLT2i/DPP-4i use.
  - The mean duration of diabetes was 12.8 years, and gout was 11.5 years.
  - SGLT2is includes empagliflozin, canagliflozin, and dapagliflozin at standard dosages.
  - DPP-4i included linagliptin, sitagliptin, and saxagliptin at standard dosages.
- Recurrent gout flare counts among all patients were noted before and after propensity score matching (PSM).
- Gout flare was defined as an emergency department visit or hospitalization with a primary diagnosis of gout or an outpatient visit with an ICD code of gout and at least one treatment (colchicine, corticosteroids, or NSAIDs).

INTERVENTION (# IN THE GROUP):

- SGLT2is: 8,318 (before PSM)
- SGLT2is: 4,075 (after PSM)

COMPARISON (# IN THE GROUP):

- DPP-4is: 6,749 (before PSM)
- DPP-4is: 4,075 (after PSM)

FOLLOW-UP PERIOD: 8.5 years

RESULTS:

Primary Outcome –

- SGLT2i reduced flare rates more than DPP-4i (rate difference [RD] –27 per 1,000 person-years; 95% CI, –36 to –19).
- SGLT2i reduced flares requiring an ED visit or hospitalization more than DPP-4i (RD –3.4 per 1,000 person-years; 95% CI, –5.8 to –0.9).
- SGLT2i reduced the cumulative incidence of the first recurrent flare compared to DPP-4i (RD –14 per 1,000 person-years; 95% CI, –22 to –6.8).

LIMITATIONS:

- Flare counts may be underestimated as flares not requiring medical attention were not recorded.
- Neither serum urate nor hemoglobin A1c levels were accessible to measure treatment impact on these measures.

Obiageli Esotu, RN, NP, MD
Southern Illinois University-Quincy
Quincy, IL

Orforglipron Use for Obesity

Daily Oral GLP-1 Receptor Agonist Orforglipron for Adults with Obesity

Wharton S, Blevins T, Connery L, et al. Daily Oral GLP-1 Receptor Agonist Orforglipron for Adults with Obesity. *N Engl J Med.* 2023;389(10):877-888. doi:10.1056/NEJMoa2302392

KEY TAKEAWAY: Daily use of oral orforglipron results in weight reduction in those who are obese without diabetes.

STUDY DESIGN: Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Injectable GLP-1 receptor agonists have become more widely used to decrease weight and have shown long-term efficacy in managing weight. Injections are a barrier for some patients. Oral medications of GLP-1 have only been approved for treating type 2 diabetes not for weight management.

PATIENTS: Overweight or obese adults without diabetes

INTERVENTION: Orforglipron

CONTROL: Placebo

PRIMARY OUTCOME: Percent change in body weight after 26 weeks

Secondary Outcome: Percent change in body weight after 36 weeks

METHODS (BRIEF DESCRIPTION):

- The study population included participants of which 59% were women and 91% were white, with a mean age of 54.2 years old, a mean body weight of 108.7 kg, and a mean BMI of 37.9.
- They were adults without diabetes who were either obese or overweight with at least one weight-related condition (hypertension, dyslipidemia, cardiovascular disease, obstructive sleep apnea).
- They were randomly assigned to receive an oral capsule of orforglipron or placebo daily in the morning.
- The intervention group was subdivided into cohorts receiving orforglipron maximum doses of 12 mg, 24 mg, 36 mg, and 45 mg daily.
- The dose-escalation phase was up to 16 weeks depending on dose cohort.

INTERVENTION (# IN THE GROUP):

- 12 mg: 50
- 24 mg: 53
- 36 mg: 58
- 45 mg: 61

COMPARISON (# IN THE GROUP): 50

FOLLOW-UP PERIOD: 40 weeks

RESULTS:

Primary Outcome –

- The percent change in body weight at week 26 from baseline shows a decrease in weight of all participants:
  - 12 mg: –8.6% (95% CI, –10% to –6.9%)
  - 24 mg: –11% (95% CI, –13% to –10%)
  - 36 mg: –12% (95% CI, –14% to –11%)
  - 45 mg: –13% (95% CI, –14% to –11%)
  - Placebo: –2.0% (95% CI, –3.6% to –0.4%)

Secondary Outcome –

- The percent change in body weight at week 36 from baseline shows a decrease in weight of all participants:
  - 12 mg: –9.4% (95% CI, –12% to –7.4%)
  - 24 mg: –13% (95% CI, –15% to –11%)
  - 36 mg: –14% (95% CI, –15.3% to –11.6%)
  - 45 mg: –15% (95% CI, –17% to –13%)
  - Placebo: –2.3% (95% CI, –4.3% to –0.4%)

LIMITATIONS:

- A relatively small number of participants were in each cohort with a mostly homogenous trial population.
- Gastrointestinal events occurred frequently due to the different dose-escalation regimens.

Pooja Nair, MD
Southern Illinois University-Quincy
Quincy, IL

Transmasculine Gender Affirmation: Is Surgical Efficiency Worth the Risk?

Combining Total Laparoscopic Hysterectomy and Bilateral Salpingo-Oophorectomy with Subcutaneous Mastectomy in Trans Men: The Effect on Safety Outcomes

Elfering L, van de Grift TC, Bouman MB, et al. Combining total laparoscopic hysterectomy and bilateral salpingo-oophorectomy with subcutaneous mastectomy in trans men: The effect on safety outcomes. *Int J Transgend Health.* 2020;21(2):138-146. Published 2020 Apr 25. doi:10.1080/26895269.2020.1751014

KEY TAKEAWAY: Combining mastectomy with total laparoscopic hysterectomy and bilateral salpingo-oophorectomy (TLH+/-BSO) in trans men leads to significantly higher hematoma and reoperation rates.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Masculinizing mastectomy is the most requested gender-affirming surgery in trans men and often the first procedure they will undergo. Many gender-affirming surgeons offer trans men the option of combining masculinizing mastectomy and TLH+/-BSO in a single surgical session. Four studies with small sample sizes have reviewed these outcomes in trans men and have concluded that the combined procedure is safe, feasible, time-saving, cost-saving, and valuable.

PATIENTS: Trans men undergoing masculinizing mastectomy

INTERVENTION: Combined mastectomy and TLH+/-BSO

CONTROL: Mastectomy only (separate encounter for TLH+/-BSO)

PRIMARY OUTCOME: Hematoma formation and reoperation

METHODS (BRIEF DESCRIPTION):

- The authors performed a retrospective chart review of all adult trans men who underwent a masculinizing mastectomy in the Amsterdam UMC and the Slotervaart Medical Center from July 2012–December 2017.
  - These participants were retrospectively identified from hospital registries. People seeking transmasculine gender affirmation surgeries whose chart did not identify them as trans men were not included in this analysis.
- Participant data:
  - Participants had a BMI range of 18–35 (median 25.16).
  - The median age of participants was 25 years old.
  - 23.8% of participants smoked.
  - 94% of participants were on testosterone therapy.
- Surgical techniques:
  - 58.1% of participants had infra-mammary skin resection with full thickness free nipple graft.
  - 37.9% had a concentric circular mastectomy.
  - 4.0% had a mastectomy without skin resection.
- The order of procedures in the combined group was determined by logistics such as surgeon availability.
- Postoperative mastectomy regimen:
  - Continue wound drainage until 24-hour fluid production was below 30 cc and six weeks of chest compression with avoidance of heavy activity.
- Postoperative hysterectomy regimen:
  - No major physical activity for six weeks.

INTERVENTION (# IN THE GROUP): 212

- TLH+/-BSO first: 152
- Mastectomy first: 60

COMPARISON (# IN THE GROUP): 268

FOLLOW-UP PERIOD:

- Mastectomy: First follow up in 5–7 days for bandage renewal of free nipple graft, second follow up in 2–3 weeks, third follow up in three months.
- Hysterectomy: Six-week follow-up.

RESULTS:

Primary Outcome –

- Combined surgery was associated with significantly more postoperative chest hematomas compared to separate operations when controlling for surgical technique, testosterone treatment, and smoking (OR 2.72; 95% CI, 1.48–4.89).
- Combined surgery was associated with significantly more reoperations compared to separate operations when controlling for surgical technique,

testosterone treatment, and smoking (OR 2.39; 95% CI, 1.17–4.90).

LIMITATIONS:

- Only trans men were eligible for the study, other people who may desire transmasculine surgical affirmation were not included.
- Only patient BMI of 18–35 was included, so this data may not be applicable to individuals with obesity.

Justine Monthony-Eaton, DO
Health Alliance Fitchburg FMR
Fitchburg, MA