GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of November 28 - December 2, 2022

SPOTLIGHT: You're Kidding Me - SGLT2i Use in Type 2 Diabetes Pediatric and Adolescent Patients

- Can GLP-1RA, DPP4, and SGLT2i Improve Outcomes for Patients with CVD?
- What's the "Gab" on Nausea in Pregnancy? Using Gabapentin to Treat Hyperemesis Gravidarum
- Twin Pregnancy and Short Cervix: Does Pessary Use Play a Role?

You're Kidding Me: SGLT2i Use in Type 2 Diabetes Pediatric and Adolescent Patients

Efficacy and Safety of Dapagliflozin in Children and Young Adults with Type 2 Diabetes: A Prospective, Multicentre, Randomised, Parallel Group, Phase 3 Study

Tamborlane WV, Laffel LM, Shehadeh N, et al. Efficacy and safety of dapagliflozin in children and young adults with type 2 diabetes: a prospective, multicentre, randomised, parallel group, phase 3 study. *Lancet Diabetes Endocrinol*. 2022;10(5):341-350. doi:10.1016/S2213-8587(22)00052-3

KEY TAKEAWAY: Dapagliflozin may lower A1c with no additional safety risks compared to placebo in patients 10–24 years old with type 2 diabetes.

STUDY DESIGN: Phase three prospective, multicenter, placebo-controlled, double-blind, randomized, parallel group study

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: There is an increasing number of pediatric and adolescent patients diagnosed with Type 2 Diabetes Mellitus (T2DM), but FDA-approved treatment options are limited to metformin, insulin, and injectable liraglutide or exenatide. An additional oral agent without risks of hypoglycemia is thought to improve adherence and A1c without increasing adverse events in this patient population. Dapagliflozin is approved in Europe for T2DM patients at least 10 years old, and this trial analyzed efficacy and safety of SGLT2i use in these patients.

PATIENTS: Patients with type 2 diabetes 10–24 years old

INTERVENTION: Dapagliflozin added to baseline treatment (metformin, insulin, or both)

CONTROL: Placebo

PRIMARY OUTCOME: A1c

Secondary Outcomes: Fasting blood glucose (FBG), discontinuation, A1c <7%, adverse events, hypoglycemia, liver function, vital signs (BMI and blood pressure), CBC (Hct, Hgb, leukocytes, and platelets), growth and maturation markers, bone biomarkers

METHODS (BRIEF DESCRIPTION):

- Patients 10–24 years old with T2DM from 30 sites in North America, Latin America, and Europe were randomly assigned to the treatment of dapagliflozin or placebo.
- Inclusion criteria included children with A1c levels of 6.5 to 11%; FBG ≤ 225 mg/dL; and being on a stable dose of metformin, insulin, or both for eight weeks or more between June 22, 2016 and March 15, 2019.
- Exclusion criteria included a T1DM diagnosis, DKA up to six months prior to study screening, treatment with medications other than insulin or metformin prior to screening, pregnancy, renal dysfunction, and volume depletion.
- The study involved continuing their baseline regimen during the four-week placebo lead-in, 24 weeks of double-blind dapagliflozin vs. placebo, and 28 week open-label safety extension where all patients were given dapagliflozin.
- Of the 72 patients randomized, 34 in the dapagliflozin group and 26 in the placebo group were included in the per-protocol analysis.
- The primary outcome was assessed by unstructured covariance matrix in both the intention-to-treat (ITT) and per-protocol (PP) populations to determine efficacy in patients who were adherent to the medication.
- Safety outcomes included hypoglycemia requiring glycemic rescue and adverse events leading to permanent discontinuation.

INTERVENTION (# IN THE GROUP): 39

COMPARISON (# IN THE GROUP): 33

FOLLOW UP PERIOD: 56 weeks

RESULTS:

Primary Outcomes –

- ITT analysis: Dapagliflozin did not decrease A1C more than placebo (mean difference [MD]; –0.75%; 95% CI, –1.7 to 0.15).
- PP analysis of adherent participants: Dapagliflozin decreased A1C more than placebo (MD –1.1%; 95% CI, –2.0 to –0.26).
- A1c reduction from baseline based on sex and background medication was not statistically significant.

Secondary outcomes (ITT analyses) –

- Dapagliflozin did not statistically change FBG, discontinuations, adverse events, hypoglycemia, achievement of A1c <7%, liver function, CBC, BMI, blood pressure, or bone biomarkers.

LIMITATIONS:

- The study population was too small to extrapolate statistically significant findings of secondary outcomes.

- More patients in the dapagliflozin group were on insulin compared to the placebo group.
- Recruited patients from North and Latin America and Europe, other races/ethnicities/nationalities were underrepresented.
- Difficult to assess weight or blood pressure changes in this population due to puberty and rapid growth changes.
- 28 week open-label period focused on safety with no data shared on A1c changes or glucose levels.
- No additional analysis on efficacy for participants switched from placebo to dapagliflozin.
- Unable to extrapolate findings for patients who are non-adherent, as shown in the ITT analysis vs. the per-protocol analysis.

Samantha Korsak, PharmD, BCPS
Providence St. Peter Hospital FMRP
Olympia, WA

Can GLP-1RA, DPP4, and SGLT2i Improve Outcomes for Patients with CVD?

Dipeptidyl Peptidase-4 Inhibitors, Glucagon-Like Peptide 1 Receptor Agonists and Sodium-Glucose Co-Transporter-2 Inhibitors for People with Cardiovascular Disease: A Network Meta-Analysis

Kanie T, Mizuno A, Takaoka Y, et al. Dipeptidyl peptidase-4 inhibitors, glucagon-like peptide 1 receptor agonists and sodium-glucose co-transporter-2 inhibitors for people with cardiovascular disease: a network meta-analysis. *Cochrane Database Syst Rev*. 2021 Oct 25;10(10):CD013650. doi: 10.1002/14651858.CD013650.pub2.

KEY TAKEAWAY: GLP-1RA and SGLT2i reduce mortality in patients with cardiovascular disease.

STUDY DESIGN: Meta-analysis of 20 RCTs (N=129,465)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Though GLP-1RA, DPP4i, and SGLT2i are utilized for the treatment of diabetes, there has been a growing volume of evidence that points toward their benefit for treating patients with known cardiovascular disease including stroke, myocardial infarction, and heart failure. Additionally, there are questions about safety outcomes such as incidences of hypoglycemia, renal failure, pancreatitis, and bone fracture.

PATIENTS: Adults with CVD or HF, with or without type 2 diabetes

INTERVENTION: GLP-1RA, DPP4i, and SGLT2i as add-on therapy to usual care

CONTROL: Placebo

PRIMARY OUTCOME: CVD mortality, fatal and non-fatal MI, fatal and non-fatal stroke

Secondary Outcomes: All-cause mortality, hospitalization for HF, safety outcomes (renal functioning, pancreatitis, hypoglycemia, bone fractures)

METHODS (BRIEF DESCRIPTION):

- Patients had established atherosclerotic cardiovascular disease (CVD) or heart failure (HF), with or without type 2 diabetes (DM2).
- The studies groups consisted of either treatment with GLP-1RA, DPP4i, and/or SGLT2i vs placebo.
- The data then underwent a systematic review with pairwise and network meta-analysis by pooling studies.
- Majority of studies were low risk of bias with high level of certainty.

INTERVENTION (# IN THE GROUP): 64,729

- DPP4i: 26,271
- GLP-1RA: 23,208
- SGLT2i: 15,030

COMPARISON (# IN THE GROUP): 59,587

FOLLOW UP PERIOD: 0.5–3.8 years

RESULTS:

Primary Outcomes –

- SGLT2i and GLP-1RA reduced CVD mortality compared to placebo:
  - DPP4i: OR 1.0 (95% CI, 0.91–1.1)
  - GLP-1RA: OR 0.87 (95% CI, 0.79–0.95)
  - SGLT2i: OR 0.82 (95% CI, 0.70–0.95)
- None reduced fatal and non-fatal MI compared to placebo:
  - DPP4i: OR 0.97 (95% CI, 0.88–1.1)
  - GLP-1RA: OR 0.89 (95% CI, 0.78–1.9)
  - SGLT2i: OR 0.97 (95% CI, 0.84–1.1)
- GLP-1RA reduced fatal and non-fatal stroke compared to placebo:
  - DPP4i: OR 1.0 (95% CI, 0.87–1.1)
  - GLP-1RA: OR 0.87 (95% CI, 0.77–0.98)
  - SGLT2i: OR 1.1 (95% CI, 0.92–1.4)

Secondary Outcomes –

- SGLT2i and GLP-1RA reduced all-cause mortality compared to placebo:
  - DPP4i: OR 1.0 (95% CI, 0.96–1.1)
  - GLP-1RA: OR 0.88 (95% CI, 0.82–0.95)
  - SGLT2i: OR 0.84 (95% CI, 0.74–0.96)
- SGLT2i and GLP-1RA reduced hospitalization for HF compared to placebo:
  - DPP4i: OR 0.99 (95% CI, 0.80–1.2)
  - GLP-1RA: OR 0.95 (95% CI, 0.85–1.1)
  - SGLT2i: OR 0.65 (95% CI, 0.59–0.71)
- DPP4i increases the risk of pancreatitis compared to placebo:
  - DPP4i: OR 1.6 (95% CI, 1.1–2.4)
  - GLP-1RA: OR 0.96 (95% CI, 0.68–1.4)
  - SGLT2i: OR 0.85 (95% CI, 0.39–1.9)
- GLP-1RA and SGLT2i reduce the risk of worsening renal function compared to placebo:
  - DPP4i: OR 1.1 (95% CI, 0.88–1.3)
  - GLP-1RA: OR 0.61 (95% CI, 0.44–0.84)
  - SGLT2i: OR 0.59 (95% CI, 0.43–0.82)
- No increase in the risk of bone fracture or hypoglycemia compared to placebo.

LIMITATIONS:

- Further studies are needed to evaluate the CVD benefit in exclusively non-diabetic patients to ascertain if there is a specific mechanism for CVD treatment or if the benefit is secondary to blood sugar control.

Matthew Blazon Yee, DO
PIH Downey
Downey, CA

What's the "Gab" on Nausea in Pregnancy? Using Gabapentin to Treat Hyperemesis Gravidarum

Effect of Gabapentin on Hyperemesis Gravidarum: A Double-Blind, Randomized Controlled Trial

Guttuso T Jr, Messing S, Tu X, et al. Effect of gabapentin on hyperemesis gravidarum: a double-blind, randomized controlled trial. *Am J Obstet Gynecol MFM*. 2021;3(1):100273. doi:10.1016/j.ajogmf.2020.100273

KEY TAKEAWAY: Gabapentin may be more effective than standard therapy in managing outpatient hyperemesis in pregnancy.

STUDY DESIGN: Double-blind, multicenter RCT

LEVEL OF EVIDENCE: STEP 3 (downgraded due to mid-study protocol changes and inadequate power)

BRIEF BACKGROUND INFORMATION: Hyperemesis gravidarum (HG) is one of the leading causes of hospitalization in pregnancy and can result in adverse maternal and fetal outcomes. There is a need for an effective outpatient medication to treat HG, and gabapentin has been used to treat nausea and vomiting in several clinical scenarios outside of pregnancy.

PATIENTS: Pregnant adults with hyperemesis gravidarum

INTERVENTION: Oral gabapentin (up to 2400 mg/d)

CONTROL: Oral ondansetron (up to 32 mg/day) or metoclopramide (up to 60 mg/day)

PRIMARY OUTCOME: Nausea and emesis

Secondary Outcomes: Nausea, vomit and retch, oral nutrition, quality of life, satisfaction, consideration of pregnancy termination

METHODS (BRIEF DESCRIPTION):

- Inclusion criteria: >18 years old with singleton pregnancy <16 weeks GA who had received at least one administration of IV fluids for nausea and vomiting of pregnancy (NVP), failed at least one outpatient antiemetic, and had evidence of ketonuria, hypokalemia, or >5% weight loss from pre-pregnancy.
- Participants were blinded and randomized to oral gabapentin (up to 2400 mg/d) or standard of care – either oral ondansetron (up to 32 mg/d) or oral metoclopramide (up to 60 mg/d). Metoclopramide replaced ondansetron mid-study due to concerns for potential fetal harms of ondansetron.
- The double-blind study phase was reduced from 14 to seven days mid-study to improve retention.
- Motherisk-PUQE was used as a validated scale to measure pregnancy-unique nausea and emesis.
- Secondary outcomes measured with Nausea and Vomiting of Pregnancy Quality of Life (NVPQOL) questionnaire as well as two investigator-developed questionnaires for daily oral nutrition and termination consideration questionnaire.

INTERVENTION (# IN THE GROUP): 12

COMPARISON (# IN THE GROUP): 9

FOLLOW UP PERIOD: Seven days

RESULTS:

Primary Outcome –

- Gabapentin resulted in superior reduction in pregnancy-unique nausea and emesis compared to standard of care at five to seven days (–6.9 difference; *P*=.01).

Secondary Outcomes –

- Gabapentin significantly improved the following compared to standard care:
  - Oral nutrition (3.9 difference; *P*=.01)
  - Satisfaction of treatment score (1.6 difference; *P*=.03)
  - Nausea (–2.8 difference; *P*=.005)
  - Vomit/retch (–4.5 difference; *P*=.005)

LIMITATIONS:

- The study was significantly underpowered due to loss of funding and high attrition rate.
- There were two major protocol changes during the study (metoclopramide replacing ondansetron as standard of care and reduction of the double-blind phase from 14 to seven days).
- The oral nutrition score was investigator-developed.

Bryana Williams, MD, MPH
Duke University Department of Family Medicine
Durham, NC

Twin Pregnancy and Short Cervix: Does Pessary Use Play a Role?

Arabin Pessary to Prevent Adverse Perinatal Outcomes in Twin Pregnancies with a Short Cervix: A Multicenter Randomized Controlled Trial (PESSARONE)

Groussolles M, Winer N, Sentilhes L, et al. Arabin pessary to prevent adverse perinatal outcomes in twin pregnancies with a short cervix: a multicenter randomized controlled trial (PESSARONE). *Am J Obstet Gynecol*. 2022;227(2):271.e1-271.e13. doi:10.1016/j.ajog.2022.01.038

KEY TAKEAWAY: Pessary use does not significantly prevent preterm birth and subsequent neonatal complications in twin gestation pregnancies with a short cervix present.

STUDY DESIGN: Multicenter, open label, randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Multiple gestations are becoming more common due to several factors in our society, including assistive fertility methods and increasing birthing parent age. Multiple gestations are associated with increased risk of preterm delivery and complications. Progesterone therapy and cervical cerclage are current methods used in the management of multiple gestations and short cervix. This research investigates the use of another modality for the management and improvement of outcomes.

PATIENTS: Pregnant persons with twin gestations and shortened cervix

INTERVENTION: Arabin pessary

CONTROL: Standard of care

PRIMARY OUTCOME: Adverse neonatal outcomes

Secondary Outcomes: Change in preterm birth rates, time for delivery following pessary placement, or significant pessary side effects

METHODS (BRIEF DESCRIPTION):

- Pregnant persons with twin pregnancies at 16 weeks and 0/7 days to 24 weeks and 0/7 days gestation with shortened cervix (<35 mm) were included.
- Participants were randomized into one of two treatment arms. This randomization was not revealed to the healthcare providers that enrolled patients in the study. Patients and healthcare providers were not blinded to type of treatment.
    - Control group: Standard of care of without Arabin pessary use.
    - Treatment group: Standard of care with Arabin pessary (65x25x32 mm) placement with plan for removal at 36 weeks and 0/7-day gestation for asymptomatic patients.
- Pessaries were placed by obstetricians in an outpatient clinical setting.
- Use of vaginal progesterone or cervical cerclage for management were not part of treatment protocol.
- Neonatal complications in this study included bronchopulmonary dysplasia, periventricular leukomalacia, sepsis (with positive culture), interventricular hemorrhage (grade three to four), retinopathy of prematurity (that needed treatment) and necrotizing enterocolitis (grade two or more).
    - Complications were measured until discharge from the inpatient setting and neonatal death upon 28 days following the infant being at term.
- Patient outcomes were measured via hospital charts following birth and up to 28 days post term gestational age.

INTERVENTION (# IN THE GROUP): 157

COMPARISON (# IN THE GROUP): 158

FOLLOW UP PERIOD: 28 days following the term date of infant

RESULTS:

Primary Outcome –

- There was no significant difference in adverse neonatal outcomes between Arabin pessary use compared to standard of care (risk ratio 0.69; 95% CI, 0.39–1.2).

Secondary Outcomes –

- There was no difference between preterm birth rates in test and control groups, time for delivery following pessary placement, or significant pessary side effects.

LIMITATIONS:

- Some sites experienced small sample sizes.
- Lack of data for primary outcomes in small group of participants, approximately 10% (majority due to lack of paternal consent) which could decrease the power of the study.
- The patient population excluded pregnant patients with medical conditions such as diabetes, hypertension, and chronic kidney disease, among others.

Jasmine McKissick, MD, MPH
Texas AM Family Medicine Residency Program
Bryan-College Station, TX