GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of March 29 - April 2, 2021

SPOTLIGHT: Is Ticagrelor better taken alone?

- Induction of labor apparently not associated with postpartum hemorrhage
- Does opioid detoxification work in pregnant women?
- Can Empagliflozin improve cardiovascular related mortality in patients with and without diabetes?
- Beyond the CPAP: Improving the care of OSA patients

Antiplatelet Therapy after Stent Placement: Is Ticagrelor better taken alone?

Effect of Ticagrelor Monotherapy vs Ticagrelor with Aspirin on Major Bleeding and Cardiovascular Events in Patients with Acute Coronary Syndrome: The TICO Randomized Clinical Trial

Kim BK, Hong SJ, Cho YH, et al. Effect of Ticagrelor Monotherapy vs Ticagrelor with Aspirin on Major Bleeding and Cardiovascular Events in Patients with Acute Coronary Syndrome. *JAMA*. 2020; 323(23):2407–16.

KEY TAKEAWAY: In patients with acute coronary syndrome (ACS) requiring percutaneous coronary intervention (PCI) with drug eluting stent placement, a statistically significant but modest reduction in combined major bleeding and adverse cardiovascular events was noted with those taking ticagrelor alone compared to those taking dual antiplatelet therapy 3–12 months after stent placement. However, the study took place in South Korea and may not apply to other areas.

STUDY DESIGN: Multisite, investigator initiated, unblinded randomized trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Dual antiplatelet therapy (DAPT) of aspirin with a P2Y12 inhibitor for 12 months is the standard of care for patients with drug eluting stent placement after treatment of ACS. However, DAPT can lead to adverse bleeding and cardiovascular events, whereas antiplatelet monotherapy could be given post-stenting.

PATIENTS: Patients who have received drug-eluting stent placement after PCI for ACS

INTERVENTION: DAPT with aspirin and ticagrelor for 3 months after PCI, followed by ticagrelor monotherapy for an additional 9 months

CONTROL: Aspirin/ticagrelor DAPT for 12 months after stent placement

OUTCOME: Overall rate of adverse events (composite of major bleeding and cardiac and cerebrovascular events) Secondary: Major/minor bleeding or cardiac/cerebrovascular events

METHODS (BRIEF DESCRIPTION):

- Patients (mean age 61, mean BMI 24.9, 79% male in intervention group and 80% male in control group) from 38 centers in South Korea who had undergone placement of ultrathin bioresorbable polymer sirolimus-eluting stents for ACS (STEMI, NSTEMI, & unstable angina)
- Random assignment after stent placement:
  - Daily combined 180 mg ticagrelor and 100 mg aspirin therapy for 3 months followed by 180 mg daily ticagrelor for 9 months
  - Daily 100 mg aspirin and 180 mg ticagrelor therapy for all 12 months
- Both groups were monitored for:
  - Major bleeding events: intracranial hemorrhage, drop of 5g/dL hemoglobin, or bleeding causing death within 7 days
  - Adverse cardiovascular events: stent thrombosis, MI, stroke, target-vessel revascularization, and patient death

INTERVENTION (# IN THE GROUP): 1527
COMPARISON (# IN THE GROUP): 1527

FOLLOW UP PERIOD: 12 months

RESULTS:

- Less composite adverse events occurred in the intervention group vs control group (59 events vs 89 events; HR 0.66; 95% CI, 0.48–0.92)
- Less major bleeding events in the intervention group vs control group (25 events vs 45 events; HR 0.56; 95% CI, 0.34–0.91)
- No statistically significant difference in adverse cardiovascular events/acute myocardial infarction between groups (HR 0.69; 95% CI, 0.45–1.1)

LIMITATIONS:

- Results may be underpowered as individuals with a high bleeding risk were excluded.
- Drug adherence not monitored.
- Only patients of Korean Ethnicity were involved in this study.
- Open-label rather than placebo controlled.

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Induction of labor apparently not associated with postpartum hemorrhage

Induction of labor and postpartum blood loss

Brun R, Spoerri E, Schaffer L, Zimmermann R, Haslinger C. Induction of labor and postpartum blood loss. *BMC Pregnancy Childbirth*. 2019; 19(1):265

KEY TAKEAWAY: Induction of labor (IOL) was not more likely than spontaneous labor (SOL) to be associated with postpartum hemorrhage (PPH).

STUDY DESIGN: Secondary sub-analysis of a primary prospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Previous studies have found conflicting results regarding the association of IOL with PPH. However, most studies were not designed to directly determine the effect of IOL on PPH. In addition, no study to date has assessed the relationship between IOL and linear measurements of postpartum blood loss.

PATIENTS: Pregnant women with singleton gestation greater than 36 weeks with anticipated vaginal delivery and cephalic presentation without a known coagulation disorder or placenta previa

INTERVENTION: Induction of labor (indication not specified)

CONTROL: Women giving birth via spontaneous labor

OUTCOME: Primary outcomes: incidence of PPH; change in hemoglobin (Hb) after delivery; change in Hb ≥ 3 g/dL. Secondary outcomes: mode of delivery; length of hospital stay; need for surgical management of PPH; neonatal outcomes

METHODS (BRIEF DESCRIPTION):

- IOL was accomplished with misoprostol (52.4%), oxytocin (36.3%), or misoprostol followed by oxytocin (11.3%)
- Vaginal bleeding after delivery was assessed by the investigators using a combination of qualitative and quantitative measures
- PPH was defined as ≥ 500 mL after vaginal delivery and ≥ 1000 mL after cesarean delivery
- Blood loss was measured until 24 hours after delivery
- Hb was measured before delivery and 24 to 48 hours postpartum
- A multivariate linear regression analysis was performed to assess the impact of potential confounding variables

INTERVENTION (# IN THE GROUP): 380

COMPARISON (# IN THE GROUP): 585

FOLLOW UP PERIOD: 24-48 hours after delivery

RESULTS:

- The incidence of PPH was not significantly different between the IOL group and the SOL group (24.7% vs 21.2%; P=.20)
- Decline in Hb was less in the IOL group compared to the SOL group (1.3g/dL vs 1.63 g/dL; P<.01)
- The incidence of change in Hb ≥ 3.0 g/dL was not significantly different between the IOL group and the SOL group (12.9% vs 13.8%; P=.67)

Rates of operative vaginal delivery, unplanned C-section, length of hospital stay and adverse neonatal outcomes were not statistically different between groups

LIMITATIONS:

- The results may not be generalizable to all settings as the study population was located in Germany
- Calculation of the sample size necessary to detect a statistically significant difference between groups was not performed
- The study did not analyze results for women undergoing IOL for medical vs. elective reasons
- Non-blinded, non-randomized study (potential for assessment bias and unmeasured confounders)

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Does opioid detoxification work in pregnant women?

Opioid detoxification in pregnancy: systematic review and meta-analysis of perinatal outcomes

Wang M, Kuper S, Sims B, et al. Opioid detoxification in pregnancy: systematic review and meta-analysis of perinatal outcomes. *American Journal of Perinatology*. 2019; 35:581–87.

KEY TAKEAWAY: Opioid detoxification, compared to MAT, led to a statistically significant increase in maternal relapse without decreasing the risk for preterm birth or neonatal abstinence syndrome.

STUDY DESIGN: Meta-analysis of three retrospective cohort studies

LEVEL OF EVIDENCE: STEP 4

BRIEF BACKGROUND INFORMATION: Opiate use during pregnancy is associated with receiving less prenatal care and a higher risk of prenatal complications including preterm birth and neonatal abstinence syndrome (NAS). The current recommended treatment for opiate use during pregnancy is medication assisted therapy (MAT). Further investigation is required to determine if opioid detoxification or MAT is superior to decrease preterm birth rates, NAS, and maternal relapse.

PATIENTS: Pregnant women with opiate use disorder
INTERVENTION: Medication assisted treatment
CONTROL: Opioid detoxification
OUTCOME: Maternal relapse, NAS, or preterm birth

METHODS (BRIEF DESCRIPTION):

- Three studies were identified representing combinations of inpatient and outpatient interventions for pregnant women on medication assisted treatment versus tapers with buprenorphine or methadone.
- Inclusion Criteria:
  - Comparing MAT versus detoxification therapy in pregnant women with opioid dependence
  - Report on at least one related outcome including maternal abstinence at time of delivery, preterm birth, neonatal abstinence syndrome, or still birth
- Exclusion Criteria:
  - Two studies excluded patients with concurrent alcohol or benzodiazepine use
  - One study excluded women <18 years of age or >41 years of age
  - One study excluded women <6 weeks gestational age or >30 weeks of gestation
  - Two studies excluded multigestational pregnancies
- Dosage of MAT was not specified in studies
- Protocol for opioid detoxification varied with tapers from 3–7 days in length and starting doses of 30–60 mg of methadone which were subsequently tapered
- Intervention combinations:
  - Outpatient MAT with methadone (N=78) versus inpatient detoxification (N=22)
  - Outpatient MAT with buprenorphine or methadone (N=17) versus outpatient detoxification with methadone (N=8)
  - Outpatient MAT with methadone (N=80) versus outpatient detoxification with methadone (N=95)
- Authors used random effects model to calculate a pooled relative risk. An I^2 test was used to assess heterogeneity among the studies.

INTERVENTION (# IN THE GROUP): 139
COMPARISON (# IN THE GROUP): 175

FOLLOW UP PERIOD: ≥6 weeks gestational age through delivery

RESULTS:

- Opioid detoxification vs MAT:
  - Statistically significant increase in the risk of maternal relapse (RR 1.91; 95% CI, 1.1–3.2)
  - No significant difference in the risk of NAS (RR 0.99; 95% CI, 0.10–1.6)
  - No significant difference in the risk of preterm birth (RR 0.39; 95% CI, 0.10–1.6)

LIMITATIONS:

- Small subset of data with low power
- No blinding or placebo measures with significant cross-over from maternal detoxification to MAT
- Confounders: variations in NAS definitions, inpatient vs outpatient settings, different support systems, unclear gestational age, and different medications used

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Can Empagliflozin improve cardiovascular related mortality in patients with and without diabetes?

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

Packer M, Anker S, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *The New England Journal of Medicine.* 2020; 383 (1413–1424).

KEY TAKEAWAY: Patients with Heart failure (HF) with reduced ejection fraction (EF) receiving guideline directed HF therapy + Empagliflozin have decreased rates of cardiovascular death and hospitalization for heart failure in both patients with and without diabetes.
STUDY DESIGN: Double Blind, Randomized Control Trial
LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Previously Dapagliflozin has demonstrated mortality benefits for patients without diabetes, but the effects in both diabetics and non-diabetics, including patients with markedly reduced EF and increased levels of natriuretic peptides, has not previously been studied.

PATIENTS: Patients ≥18 years old with class II, III, or IV HF and an ejection fraction ≤40%
INTERVENTION: Empagliflozin (10mg once daily) in addition to standard heart failure therapy
CONTROL: Placebo in addition to standard heart failure therapy
OUTCOME: Rate of hospitalizations for HF; cardiovascular death
Secondary: the rate of decline in the estimated GFR; total first and recurrent numbers of hospitalizations for HF

METHODS (BRIEF DESCRIPTION):

- Double blind randomly assignment:
  - Oral empagliflozin 10mg daily + recommended heart failure therapy
  - Placebo + recommended heart failure therapy
- Participant Demographics:
  - Median age of the treatment group was 67 and 66.5 years of age in the placebo group
  - 77% of the treatment group and 76% of the of the placebo group were male
  - 71% of the treatment group and 70% of the placebo group were white
  - 50% of participants in each group had diabetes
  - The trial was performed in 20 countries at 520 centers

INTERVENTION (# IN THE GROUP): 1863
COMPARISON (# IN THE GROUP): 1867

FOLLOW UP PERIOD: Median duration of 16 months

RESULTS:
All results were consistent for both patients with and without diabetes.
Primary Outcomes:

- Empagliflozin decreased the rate of hospitalizations for HF (HR 0.69, 95% CI, 0.59–0.81)
- Empagliflozin decreased mortality from cardiovascular causes (HR 0.92, 95% CI, 0.75–1.12)

Secondary Outcomes:

- Empagliflozin decreased the total number of hospitalizations for HF (HR 0.70; 95% CI, 0.58–0.85)
- Empagliflozin led to a slower rate of decline in GFR (HR 1.73, 95% CI 1.10–2.37)

LIMITATIONS:

- Patients with heart failure with preserved EF or class I heart failure patients with reduced ejection fraction were not included in the study
- Conflict of interest: study performed by companies that commercialize diabetes medications
- Long-term effects were not studied.
- Cannot be applied to typical heart failure patients, as participants were ≥65 years old, 77% male, 71% white, and only 0.5% were in NYHA class IV.

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Beyond the CPAP: Improving the care of OSA patients

Cardiometabolic Benefits of a Weight-Loss Mediterranean Diet/Lifestyle Intervention in Patients with Obstructive Sleep Apnea

Georgoulis M, Yiannakouris N, Kechribari I, et al. Cardiometabolic Benefits of a Weight-Loss Mediterranean Diet/Lifestyle Intervention in Patients with Obstructive Sleep Apnea: The "MIMOSA" Randomized Clinical Trial. *Nutrients*. 2020;12(6):1570. Published 2020 May 28. doi:10.3390/nu12061570.

KEY TAKEAWAY: Standard care with CPAP prescription, in combination with a weight-loss Mediterranean diet/lifestyle intervention, leads to significant cardiometabolic benefits and reduction in metabolic syndrome compared to standard care alone.

STUDY DESIGN: 12-month, single-center, single-blind, parallel-group (1:1), randomized, controlled, superiority clinical trial

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Continuous positive airway pressure (CPAP) is the first-line treatment for obstructive sleep apnea (OSA), but its effects on cardiometabolic measures for patients with OSA is not well understood and more analysis is needed. The Mediterranean diet is recommended by the American Heart Association to help prevent heart disease and stroke by reducing cardiometabolic risk factors such as diabetes, obesity, hyperlipidemia, and hypertension.

PATIENTS: Patients with moderate-to-severe OSA prescribed CPAP

INTERVENTION: Designated to a Mediterranean diet group (MDG) or a Mediterranean lifestyle group (MLG)

CONTROL: Standard of care group (SCG)

OUTCOME: Prevalence of metabolic syndrome and secondary cardiometabolic outcomes.

METHODS (BRIEF DESCRIPTION):

- 187 overweight or obese Greek adult participants who had moderate or severe OSA were followed for 6 months.
- The standard care group received brief written advice on a healthy diet and lifestyle and had no other interventions for the duration of the six months. All patients were prescribed and using CPAP.
- Participants in both the Mediterranean diet group and the Mediterranean lifestyle group participated in seven counseling sessions throughout the six month intervention. The goals for both groups during this time were a 5–10% weight loss and an increase in the level of adherence to the Mediterranean diet.
- Both pre- and post- intervention (at the end of six months) participants were evaluated in terms of cardiometabolic indices, lifestyle habits, and anthropometric parameters (body weight, height, and waist circumference).
- The cardiometabolic profile was assessed via pre- and post- intervention measurements.

INTERVENTION (# IN THE GROUP): 62 patients designated to a Mediterranean diet group (MDG) and 60 patients designated to a Mediterranean lifestyle group (MLG)

COMPARISON (# IN THE GROUP): 65 patients designated to a standard care group (SCG)

FOLLOW UP PERIOD: The trial lasted 12 months and each participant was involved in the trial for a total of 6 months

RESULTS:

Primary Outcome:

- The relative risk of metabolic syndrome (MS) was significantly decreased in both the Mediterranean diet group (RR 0.58, 95% CI: 0.34–0.99) and Mediterranean lifestyle group (RR 0.30; 95% CI: 0.17–0.52).
- The Mediterranean lifestyle group had a lower relative risk for metabolic syndrome vs. the Mediterranean diet group (RR 0.52; 95% CI: 0.30–0.89).

Secondary Outcomes:

- The Mediterranean lifestyle group saw a significant improvement in metabolic profile endpoints vs the standard of care group (MD – Mean Difference):
  - Insulin levels, pmol/L (MD -51.8; 95% CI: -74.8 to -28.8),
  - HDL Cholesterol, mmol/L (MD 0.15; 95% CI: 0.09 to 0.21)
  - Triglycerides, mmol/L (MD -0.49; 95% CI: -0.76 to -0.21).

- The Mediterranean diet group saw a significant improvement in metabolic profile endpoints vs. the standard of care group:
  - Diastolic Blood Pressure, mmHg (MD -9.52; 95% CI -13.4 to -5.63).
  - Body weight, kg (MD -8.96; 95% CI -12.6 to -6.33)
  - BMI, kg/m2 (MD -3.07; 95% CI -3.93 to -2.22)
  - Waist Circumference, cm (MD -5.51; 95% CI -8.50 to -2.51).

LIMITATIONS:

- A single-center trial with mostly male and obese study population
- Use and counseling on importance of the CPAP was not included in the study and likely contributed to participants' low adherence to the treatment.
- CPAP use was extracted by participants from the device reports and misreporting bias is not accounted for
- There were no groups in which CPAP therapy was not implemented both with and without dietary and lifestyle interventions.

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