GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of March 14 - 18, 2022

SPOTLIGHT: Gepants vs Triptans for Acute Migraine: Are They Worth the Headache?

- Does Low Dose Aspirin Actually Prevent Pre-Eclampsia in High-Risk Pregnant Women?
- Extended-Release Versus Immediate Release Metformin: Which One is Best?
- Does Ferric Carboxymaltose Improve Outcomes in Patients with Acute Heart Failure?

Gepants vs Triptans for Acute Migraine: Are They Worth the Headache?

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Comparison of New Pharmacologic Agents with Triptans for Treatment of Migraine: A Systematic Review and Meta-analysis

Yang C, Liang C, Chang C, et al. Comparison of New Pharmacologic Agents with Triptans for Treatment of Migraine. *JAMA Netw Open*. 2021;4(10):e2128544. doi:10.1001/jamanetworkopen.2021.28544

KEY TAKEAWAY: Triptan treatment is superior to gepant, ditan, and dihyroergotamine treatments to reduce pain in adults with acute migraines; however, some triptans have a higher risk of adverse events.

STUDY DESIGN: Meta-analysis of 64 RCTs (N=46,442)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Migraine headaches can be acutely managed with a variety of medications, including triptans. New therapeutic classes, such as serotonin receptor agonists (ditans) and calcitonin gene-related peptide antagonists (gepants), have also been developed, but data on their efficacy and adverse effect profile compared to triptans has been mixed.

PATIENTS: Adults with migraines

INTERVENTION: Ditans, Gepants

CONTROL: Dihydroergotamine, Triptans

OUTCOME: Freedom from pain for two hours after treatment

Secondary Outcomes: Pain relief two hours after treatment, adverse events

METHODS (BRIEF DESCRIPTION):

- A comprehensive literature review of double blinded RCTs comparing monotherapies for acute migraines were completed.
- RCTs were excluded if they only evaluated the same medication given via a different route.
- Studies evaluated adult patients (>18 years old) with acute migraine and taking triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan), ditans (lasmiditan), or gepants (rimegepant, ubrogepant).
- Pain was rated using a four-point global scale (absent, mild, moderate, or severe). Pain freedom was the primary outcome.
- Secondary outcomes were pain relief, defined as absent or mild pain, and any adverse events.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW UP PERIOD: 2 hours post treatment

RESULTS:

Primary Outcome –

- Triptan treatment, especially with eletriptan, was more likely to result in pain freedom at two hours compared to other treatments.
  - Eletriptan 40 mg vs lasmiditan 50 mg: OR 3.4 (95% CI, 2.1–5.4)
  - Eletriptan 40 mg vs rimegepant 75 mg: OR 3.1 (95% CI, 2.2–4.5)
  - Eletriptan 40 mg vs ubrogepant 50 mg: OR 3.1 (95% CI, 2.0–4.6)

Secondary Outcomes –

- Triptan treatment, especially rizatriptan, was more likely to result in pain relief at two hours compared to other treatments.
  - Rizatriptan 10 mg vs lasmiditan 50 mg: OR 3.3 (95% CI, 2.4–4.6)
  - Rizatriptan 10 mg vs rimegepant 75 mg: OR 3.0 (95% CI, 2.3–3.9)
  - Rizatriptan 10 mg vs ubrogepant 50 mg: OR 3.1 (95% CI, 2.4–4.2)
- Rizatriptan, sumatriptan, and zolmitriptan were more likely to cause adverse events compared to cGRP antagonists.
  - Rizatriptan 10 mg vs ubrogepant 50 mg: OR 2.0 (95% CI, 1.1–3.4)
  - Sumatriptan 100 mg vs ubrogepant 50 mg: OR 1.8 (95% CI, 1.1–3.1)
  - Zolmitriptan 2.5 mg vs ubrogepant 50 mg: OR 2.3 (95% CI, 1.4–4.0)
- Ditans had the highest overall risk of causing any adverse event.

LIMITATIONS:

- Selection bias may have been introduced through author disagreements and consensus during study selection.
- No information was provided on the statistical tests employed for determining the odds ratios comparing medication efficacy and adverse effects.

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Does Low Dose Aspirin Actually Prevent Pre-Eclampsia in High-Risk Pregnant Women?

A Randomized Controlled Trial of Low-Dose Aspirin for the Prevention of Pre-Eclampsia in Women at High Risk in China

Lin L, Huai J, Li B, et al. A randomized controlled trial of low-dose aspirin for the prevention of pre-eclampsia in women at high risk in China. *Am J Obstet Gynecol*. 2022;226(2):251.e1-251.e12. doi:10.1016/j.ajog.2021.08.004

KEY TAKEAWAY: Aspirin 100 mg daily, initiated from 12 to 20 weeks gestation until 34 weeks gestation, did not reduce the incidence of pre-eclampsia in high-risk pregnant Chinese women.

STUDY DESIGN: Single blinded RCT

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Low dose aspirin has been promoted to prevent pre-eclampsia in high-risk women. Guidelines for its prophylactic use differs internationally. There is limited evidence from large RCTs on its effects amongst high-risk women and even less evidence regarding Asian women.

PATIENTS: Pregnant Chinese women at high risk for pre-eclampsia

INTERVENTION: 100 mg daily aspirin

CONTROL: No treatment

OUTCOME: Incidence of pre-eclampsia

Secondary Outcomes: Maternal and neonatal outcomes

METHODS (BRIEF DESCRIPTION):

- 1,000 (898 included in study) nulliparous and multiparous Chinese women 18–54 years old from 13 various Chinese hospitals were allocated 1:1 to control or aspirin group.
- Evaluators were not masked to patient group assignment.
- High-risk for pre-eclampsia was defined as having at least one of the following: history of pre-eclampsia, diabetes mellitus I or II, chronic hypertension; or having at least two of the following: advanced maternal age, obesity (pre-pregnancy BMI >28 kg/m^2), nulliparity or family history of pre-eclampsia.
- The intervention group received 100 mg aspirin daily at bedtime started from 12–20 weeks gestation until 34 weeks gestation.
- The control group received no intervention.
- Incidence of pre-eclampsia was defined as hypertension ≥140 mmHg SBP or ≥90 mmHg DBP with proteinuria on two occasions at >20 weeks gestation in women with previously normal blood pressure.
- Maternal outcomes included delivery due to pre-eclampsia 34–37 weeks gestation, gestational hypertension, HELLP syndrome, placental abruption, and postpartum hemorrhage.
- Neonatal outcomes included preterm birth, mortality, abnormalities, SGA, and NICU admission.
- Statistical analysis was performed on an intent-to-treat basis and significant differences were determined by logistical regression analysis.

INTERVENTION (# IN THE GROUP): 464

COMPARISON (# IN THE GROUP): 434

FOLLOW UP PERIOD: None

RESULTS:

- 100 mg of aspirin daily did not reduce the incidence of pre-eclampsia in high-risk pregnant Chinese women (RR 0.99; 95% CI, 0.74–1.3).
- Daily aspirin did not reduce the incidence of maternal or neonatal outcomes.

LIMITATIONS:

- Small sample size with less than 446 participants in each group. This was less than the number needed to power the study.
- Only 100 mg of aspirin was studied, rather than 150 mg, which has been shown to reduce pre-eclampsia in other studies.
- The control group received no treatment instead of placebo.

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Extended Release Versus Immediate Release Metformin: Which One is Best?

Long-Acting Metformin vs Metformin Immediate Release in Patients with Type 2 Diabetes: A Systematic Review

Jixue T, Yang W, Song L, et al. Long-Acting Metformin vs Metformin Immediate Release in Patients with Type 2 Diabetes: A Systematic Review. *Frontiers in Pharmacology.* 2021; 12:1069. doi:10.3389/fphar.669814

KEY TAKEAWAY: There is no difference in efficacy or safety between metformin extended release (XR) and immediate release (IR) formulations.

STUDY DESIGN: Systematic review and meta-analysis

LEVEL OF EVIDENCE: STEP 2 (downgraded due to high risk of bias)

BRIEF BACKGROUND INFORMATION: Metformin has two formulations (IR and XR) but there is limited guidance to which should be used. A comparison between metformin formulations in terms of efficacy, adverse events, compliance, and patient satisfaction can help shape further recommendations.

PATIENTS: Adults with type II diabetes mellitus

INTERVENTION: XR metformin

CONTROL: IR metformin

OUTCOME: Abdominal pain, all-cause mortality, adverse events (AEs), AEs leading to discontinuing medication, gastrointestinal AEs, HbA1c, plasma blood sugar, fasting blood glucose

METHODS (BRIEF DESCRIPTION):

- A systematic review of five RCTs and one observational study in multiple countries in patients who took metformin XR versus metformin IR at the same total daily dose evaluating effectiveness, safety, and patient compliance.
- Patient demographics:
  - Average age: 54 years old
  - 55% male
  - Average BMI: 30 kg/m^2
  - Mean baseline HbA1c: 7.9 mmol/L
  - Mean fasting plasma glucose: 9.0 mmol/L
- Follow up of 12 to 24 weeks and changes from baseline were recorded.

INTERVENTION (# IN THE GROUP): 816

COMPARISON (# IN THE GROUP): 816

FOLLOW UP PERIOD: 12 to 24 weeks

RESULTS:

- Metformin XR had no statistically significant affect compared to metformin IR on:
  - Change in HbA1c (5 trials, N=1,503; Mean Difference (MD) 0.04%; 95% CI, –0.05 to 0.13%)
  - Change in PPBG (2 trials, N=552; MD 0.50 mmol/L; 95% CI, –0.71 to 1.7 mmol/L)
  - Change in FPG (5 trials, N=1,503; MD –0.03 mmol/L; 95% CI, –0.22 to 0.15 mmol/L)
  - Any adverse event (3 trials, N=1,221; RR 1.1; 95% CI, 0.97–1.3)
  - Any adverse event leading to discontinuation (3 trials, N=1,221; RR 1.5; 95% CI, 0.82–2.8)
  - Any gastroenterological (GI) adverse event (4 trials, N=1,573; RR 1.1; 95% CI, 0.93–1.3)
- An observational study showed patient compliance was higher with metformin XR (80%) than with metformin IR (72%).
  - Compliance further increased when Metformin IR was switched to Metformin XR (62% to 81%).

LIMITATIONS:

- Three RCTs had open-label design with high risk of bias.
- Three RCTs had investigated compliance but no quantitative analysis was done because of heterogeneity.
- Compliance results were based on one observational study and no confidence intervals were provided.
- No long-term outcomes were studied.

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Does Ferric Carboxymaltose Improve Outcomes in Patients with Acute Heart Failure?

Ferric Carboxymaltose for Iron Deficiency at Discharge After Acute Heart Failure: A Multicenter, Double-Blind, Randomised, Controlled Trial

Ponikowski P, Kirwan BA, Anker SD, et al. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicenter, double-blinded, randomized, controlled trial. *Lancet.* 2020; 396(10266):1895–1904.

KEY TAKEAWAY: For patients with a left ventricular ejection fraction less than 50% and comorbid iron deficiency who were admitted and treated for an acute heart failure exacerbation, treatment with ferric carboxymaltose prior to hospital discharge did not show a difference in the composite outcome of heart failure hospitalization and cardiovascular death but did reduce the risk of future heart failure hospitalizations.

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

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Iron deficiency with or without anemia is an important and common comorbid condition in patients with congestive heart failure and is associated with worse clinical outcomes. Several studies have found that treatment of iron deficiency with intravenous ferric carboxymaltose in patients with heart failure reduces symptom burden and improves exercise tolerance. Few studies have evaluated the effects of intravenous iron in hospitalized patients after an acute exacerbation of heart failure.

PATIENTS: Adults hospitalized for an acute exacerbation of heart failure and with comorbid iron deficiency

INTERVENTION: Intravenous ferric carboxymaltose

CONTROL: Placebo

OUTCOME: Composite of total hospitalizations for heart failure and cardiovascular death

Secondary Outcome: Composite of cardiovascular hospitalizations/death, heart failure hospitalizations, time to heart failure hospitalization/cardiovascular death, days spent in hospital

METHODS (BRIEF DESCRIPTION):

- Inclusion Criteria: Adult patients hospitalized with acute exacerbation of heart failure with left ventricular ejection fraction <50% and iron deficiency, clinically stabilized ready for discharge.
  - Iron deficiency defined as ferritin <100 µg/L or 100–299 µg/L with transferrin saturation <20%.
- Patients randomly assigned to intravenous ferric carboxymaltose or placebo for 24 weeks or less.
  - Treatment given in four doses. First dose was given before discharge. Second dose was given at week six. Additional doses were given at 12 and 24 weeks in patients who were still iron deficient.
- Medication distribution was completed by unblinded personnel. Participants were given medication in black syringes to blind patients and study personnel.
- Data was analyzed using modified intention-to-treat protocol.

INTERVENTION (# IN THE GROUP): 558

COMPARISON (# IN THE GROUP): 550

FOLLOW UP PERIOD: 52 weeks

RESULTS:

Primary Outcome –

- Ferric carboxymaltose did not affect total heart failure hospitalizations and cardiovascular death compared to placebo (57 vs 73 events per 100 patient-years, respectively; RR 0.79; 95% CI, 0.62–1.0).

Secondary Outcomes –

- Ferric carboxymaltose reduced the number of total heart failure hospitalizations compared to placebo (49% vs 54%, respectively; RR 0.74; 95% CI, 0.58–0.94).
- Ferric carboxymaltose reduced the number of heart failure hospitalizations and death compared to placebo (32% vs 38%, respectively; HR 0.80; 95% CI, 0.66–0.98).
- Ferric carboxymaltose reduced days lost due to heart failure compared to placebo (369 vs 548 days per 100 patient-years, respectively; RR 0.67; 95% CI, 0.47–0.97).
- Treatment did not significantly affect composite of total cardiovascular hospitalizations and death or risk of cardiovascular death.

LIMITATIONS:

- Data analysis used modified intention to treat which increases the potential for bias, though all study participants were accurately accounted for, and authors were forthcoming on reasons for exclusion.
- COVID-19 potentially affected management, follow up, and treatment, though robust data was validated via pre-COVID-19 sensitivity

analysis.

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