GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of June 28 - July 2, 2021

SPOTLIGHT: The "Not so Sweet" Side Effects of SGLT2 Inhibitors

- Accuracy of Blood Pressure Cuff Measurement
- Shorter or Longer Mag: Which Works Better to Prevent Eclampsia?

The "Not so Sweet" Side Effects of SGLT2 Inhibitors

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Comparative safety of the sodium glucose co-transporter 2 (SGLT2) inhibitors: a systematic review and meta-analysis

Donnan JR, Grandy CA, Chibrikov E, et al. Comparative safety of the sodium glucose co-transporter 2 (SGLT2) inhibitors: a systematic review and meta-analysis. *BMJ Open*. 2019; 9:e022577. doi:10.1136/bmjopen-2018-022577

KEY TAKEAWAY: SGLT2 inhibitors do not pose an increased risk for acute kidney injury (AKI), diabetic ketoacidosis (DKA), urinary tract infections (UTI), or fractures. However, dapagliflozin increases the risk for UTIs.

STUDY DESIGN: Systematic review and meta-analysis of 112 RCTs

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: The safety of SGLT2 inhibitor use has been brought into question in regard to their potential risk for AKIs, DKA, UTIs, bone fractures, and lower limb amputation. However, recent studies have shown a significant benefit in the use of SGLT2 inhibitors for populations with existing cardiovascular and kidney disease. Therefore, further investigation is needed to evaluate the safety warnings initially associated with this drug class.

PATIENTS: ≥18 years old with type 2 diabetes

INTERVENTION: SGLT2 inhibitors

CONTROL: Placebo or other active diabetes treatment

OUTCOMES: AKIs, DKA, bone fractures, lower limb amputations

METHODS (BRIEF DESCRIPTION):

- Participants: Patients 18 years or older with a diagnosis of type 2 diabetes
- Participants were randomized into two groups:
  - SGLT2 inhibitors: canagliflozin, dapagliflozin, empagliflozin, ipragliflozin
  - Placebo, metformin, incretin agent, sulfonylurea, pioglitazone, and within-class comparisons
- Dosing and duration of treatment were not specifically defined.

INTERVENTION (# IN THE GROUP): 6,862–26,195 (depending on the outcome)

COMPARISON (# IN THE GROUP): 3,787–13,126 (depending on the outcome)

FOLLOW UP PERIOD: 6 months – 4 years

RESULTS:

- SGLT2 inhibitors decrease the incidence of AKIs compared to placebo (11 RCTs, N=10,651; RR 0.59; 95% CI, 0.39–0.89)
- SGLT2 inhibitors increase the risk for lower limb amputation compared to placebo (1 RCT, N=187; RR 1.9; 95% CI, 1.4–2.8)
- Dapagliflozin increases the risk of UTIs compared to placebo (30 RCTs, N=11,286; RR 1.2; 95% CI, 1.0–1.4)
- There was no difference between SGLT2 inhibitors and placebo in the following outcomes:
  - Diabetic ketoacidosis (26 RCTs, N=14,753; RR 0.66; 95% CI, 0.30–1.5)
  - Urinary tract infections (88 RCTs, N=39,321; RR 1.0; 95% CI, 0.95–1.1)
  - Bone fractures (47 RCTs, N=29,590; RR 0.87; 95% CI, 0.69–1.1)
- There was no difference between SGLT2 inhibitors and other active medications in the following areas:
  - Urinary tract infections (22 RCTs, N=15,013; RR 1.1; 95% CI, 1.0–1.3)
  - Bone fractures:
    - Compared to metformin (6 RCTs, N=2,830; RR 0.69; 95% CI, 0.19–2.5)
    - Compared to sulfonylureas (3 RCTs, N= 5,134; RR 1.2; 95% CI, 0.66–2.0)
    - Compared to incretins (3 RCTs, N=2,989; RR 1.4; 95% CI, 0.31–6.2)
  - Lower limb amputations (2 RCTs, N=2,730; RR 1.1; 95% CI, 0.81–1.3)

LIMITATIONS:

- Benefits of SGLT2 inhibitors were not analyzed.
- Some of the adverse effects occurred infrequently and therefore could be a result of reporting bias.
- The occurrence of complicated vs uncomplicated UTIs were not evaluated.

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Accuracy of Blood Pressure Cuff Measurement

Accuracy of Cuff-Measured Blood Pressure: Systematic Review and Meta-analysis

Picone DS, Schultz MG, Otahal P, et al. Accuracy of cuff-measured blood pressure: Systematic reviews and meta-analysis. *J Am Coll Cardiol*. 2017; 70(5):572–586.

KEY TAKEAWAY: Cuff brachial blood pressure (BP) methods provide inaccurate measurements of intra-arterial brachial BP. There is a need to develop other methods of measuring blood pressure that will accurately reflect intra-arterial brachial and aortic blood pressure.

STUDY DESIGN: 3 Meta-Analyes of 74 studies including cross-sectional and prospective studies

LEVEL OF EVIDENCE: STEP 2, downgraded due to significant heterogeneity.

BRIEF BACKGROUND INFORMATION: Blood pressure is the most common metric used to classify hypertension and determine the approach to the management of elevated blood pressure. Effective management of hypertension depends mainly on the accurate measurement of blood pressure. However, there are growing concerns about the accuracy of cuff BP including whether cuff BP measures intra-arterial brachial BP or aortic BP accurately.

PATIENTS: Overweight adults

INTERVENTION: Cuff BP measure/intra-arterial BP

CONTROL: Intra-arterial BP/aortic valve pressure

OUTCOMES: BP measurement accuracy; hypertension classification accuracy

METHODS (BRIEF DESCRIPTION):

- PRISMA guidelines used to conduct the systematic review and meta-analyses.
- Three separate meta-analyses performed totaling in 74 studies and 3,073 participants
- Patients: BMI >26, middle to older age, majority men, presenting with indications for coronary artery catheterizations
- Intra-arterial BP was assessed and the different measurement techniques were compared at the same period of time
- Comparisons:
  - Cuff brachial BP vs intra-arterial brachial BP
  - Intra-arterial brachial BP vs aortic valve pressure

INTERVENTION (# IN THE GROUP): 3,073

COMPARISON (# IN THE GROUP): 3,073

FOLLOW UP PERIOD: No follow up

RESULTS:

- Cuff blood pressure measurements underestimated systolic blood pressure compared to intra-arterial brachial systolic blood pressure measurements (22 studies, N=735; Mean Difference [MD] –5.7 mmHg; 95% CI, –8.0 to –3.5).
- Cuff blood pressure measurements overestimated diastolic blood pressure compared to intra-arterial brachial diastolic blood pressure measurements (22 studies, N=735; MD 5.5 mmHg; 95% CI, 3.5 to 7.5 mmHg).
- Intra-arterial brachial blood pressure overestimated systolic blood pressure compared to aortic valve pressure (39 studies, N=1,823; MD 8.0 mmHg; 95% CI, 5.9 to 10.1 mmHg).
- Intra-arterial brachial blood pressure underestimated diastolic blood pressure compared to aortic valve pressure (39 studies, N=1,823; MD 1.0 mmHg; 95% CI, –2.0 to –0.1)
- Hypertension classification based on JNC 7 (normal, pre-HTN, HTN stage 1, HTN stage 2) using cuff measured blood pressure compared to intra-arterial brachial blood pressure was:
  - 60% accurate classifying normal BP
  - 50% accurate classifying pre-hypertension
  - 53% accurate classifying HTN stage 1
  - 80% accurate classifying HTN stage 2

LIMITATIONS:

- The authors reported significant heterogeneity among studies in the analyses of systolic BP, diastolic BP, and pulse pressure possibly due to variations in BP protocols (I^2>86%; *P*<.0001).
- Study sample included patients with certain characteristics (more overweight, middle to older age men who typically presented to the healthcare setting with indications for coronary artery catheterizations) and therefore the findings may not be generalizable to the healthy or general population.

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Shorter or Longer Mag: Which Works Better to Prevent Eclampsia?

Shortened postpartum magnesium sulfate treatment vs traditional 24h for severe pre-eclampsia: a systematic review and meta-analysis of randomized trials

Yifu P, Lei Y, Yujin G, Xingwang Z, Shaoming L. Shortened postpartum magnesium sulfate treatment vs traditional 24h for severe preeclampsia: a systematic review and meta-analysis of randomized trials. *Hypertens Pregnancy*. 2020; 39 (2): 1860195. Doi: 10.1080/10641955.2020.

KEY TAKEAWAY: Use of shortened postpartum magnesium sulfate did not show any significant difference in prevention of eclampsia in comparison to prolonged 24-hour treatment.
STUDY DESIGN: Meta-analysis of 7 RCTs
LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Patients with severe pre-eclampsia are at an increased risk for developing eclampsia, especially in the immediate postpartum setting. Magnesium sulfate is the drug of choice for prevention of eclampsia in severe pre-eclamptic patients, despite its side-effects.

PATIENTS: Postpartum women with severe preeclampsia
INTERVENTION: Shortened duration magnesium sulfate
CONTROL: Traditional 24-hour magnesium sulfate
OUTCOME: Eclampsia
Secondary: Total complications, ambulation, duration of magnesium sulfate, mode of delivery, hospital stay, flushing

METHODS (BRIEF DESCRIPTION):

- Inclusion criteria: postpartum patients with severe pre-eclampsia from developing countries
- Shortened duration of magnesium sulfate (6 hour or ≤12 hours) compared to traditional 24 hours for eclampsia prevention.
  - No information on dosage, frequency, or route provided.
- Cochrane risk of bias tool was used for blinding participants, outcome data, and produce random sequence generation for RCT quality evaluation.

INTERVENTION (# IN THE GROUP): 572
COMPARISON (# IN THE GROUP): 552

FOLLOW UP PERIOD: From spontaneous vaginal or cesarean delivery through 3 to 12 days postpartum

RESULTS:

- Shorter duration magnesium sulfate did not significantly affect the risk of eclampsia compared to traditional 24-hour treatment (7 trials, N = 1,124; Risk difference (RD) 0.0; 95% CI, -0.01 to 0.01)
- Shorter duration magnesium sulfate did not significantly affect the risk of eclampsia compared to traditional 24-hour treatment (7 trials, N=1,124; RD 0.0; 95% CI, -0.01 to 0.01)
- Shorter duration magnesium sulfate compared to traditional 24-hour treatment did not significantly affect total complications, ambulation, duration of magnesium sulfate, mode of delivery, and hospital stay.

LIMITATIONS:

- Not universally applicable as these RCTs were conducted in developing countries.
- The RCTs included a small number of participants.
- Rare occurrences of eclampsia limited the statistical power of the study.
- Limited information on long term outcomes.

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