GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

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Does Empagliflozin Sweeten the Outcomes After Acute MI?

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Empagliflozin After Acute Myocardial Infarction

Butler J, Jones WS, Udell JA, et al. Empagliflozin after Acute Myocardial Infarction. *N Engl J Med*. 2024;390(16):1455-1466. doi:10.1056/NEJMoa2314051

KEY TAKEAWAY: Empagliflozin initiated after acute myocardial infarction (MI), compared to placebo, does not decrease the risk of hospitalization for heart failure (HF) or death from any cause among adults at risk for HF.

STUDY DESIGN: International, event-driven, double-blind, randomized, placebo-controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION Empagliflozin is known to have cardiovascular benefits in patients with heart failure, type 2 diabetes mellitus (T2DM), and chronic kidney disease (CKD). However, its benefit in preventing HF in the post-MI setting is unknown. Previous studies of empagliflozin after MI were not designed to assess clinical outcomes or were limited by small overall event numbers in the trial period.

PATIENTS: Patients hospitalized after acute MI and at risk for HF

INTERVENTION: Empagliflozin

CONTROL: Placebo

PRIMARY OUTCOME: Composite endpoint of first hospitalization for HF or death from any cause

Secondary Outcome: Total number of hospitalizations for HF, cardiovascular events, MI, or other conditions, and death from any cause

METHODS (BRIEF DESCRIPTION):

- Patients were ≥18 years old, comprised 75% men, 84% White, and 66% from the Europe region, who had been hospitalized for acute MI.
- The included patients had:
  - A newly developed left ventricular ejection fraction (LVEF) <45% or clinical congestion requiring treatment while hospitalized.
  - At least one factor known to be related to HF hospitalization (≥65 years old; LVEF <35%; previous MI; atrial fibrillation or diabetes; CKD; elevated natriuretic peptide or uric acid; elevated pulmonary artery pressure; multi-vessel coronary artery disease; peripheral arterial disease; or lack of revascularization).
- Patients with previous HF and taking or planning to take SGLT2 inhibitors were excluded from the study.
- Patients were randomized in a 1:1 ratio to treatment (empagliflozin 10 mg daily dose) or placebo.
- Enrollment and initiation of treatment happened within 14 days after admission with a median of five days.
- The primary outcome was a first hospitalization for HF or death from any cause measured in a time-to-first-event analysis.
- Secondary outcomes were the total number of hospitalizations for HF, cardiovascular events, MI, or other conditions, and death from any cause.
- Outcomes were assessed via telehealth at two weeks, in-person at six months, and then telehealth every six months until the completion of the trial.

INTERVENTION (# IN THE GROUP): 3,260

COMPARISON (# IN THE GROUP): 3,262

FOLLOW-UP PERIOD: Median 18 months

RESULTS:

Primary Outcome –

- There was no statistically significant difference for empagliflozin compared to placebo for first hospitalization for heart failure or all-cause mortality (8.2% vs 9.1%, respectively; hazard ratiov[HR] 0.9; 95% CI, 0.8–1.1).

Secondary Outcome –

- The secondary endpoints between empagliflozin and placebo were not statistically significant for the total number of hospitalizations or deaths from any cause for HF, cardiovascular events, MI, and hospitalization for any cause.

LIMITATIONS:

- Non-heart failure mechanisms of cardiovascular death in the post-MI period (stent thrombosis, reinfarction, arrhythmias) may have contributed to the similarity of the mortality endpoint between groups.
- The length of the trial was extended due to a lower-than-expected primary outcome event rate based on blinded trial data.
- The trial was conducted during COVID-19 which impacted hospitalization rates.

- Two participating centers were affected by war.
- Measured outcomes did not capture outpatient heart failure encounters.
- Women, older adults, and racial and ethnic minorities were underrepresented.

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The views expressed herein are those of the author and do not necessarily reflect the official policy of the Department of the Army, Defense Health Agency, Department of Defense, or the US Government.

Combination Buprenorphine + Naloxone: Is It Safe in Pregnancy?

Comparative Safety of In-Utero Exposure to Buprenorphine Combined with Naloxone vs Buprenorphine Alone

Straub L, Bateman BT, Hernández-Díaz S, et al. Comparative Safety of In Utero Exposure to Buprenorphine Combined With Naloxone vs Buprenorphine Alone. *JAMA*. 2024;332(10):805-816. doi:10.1001/jama.2024.11501

KEY TAKEAWAY: Pregnancies exposed to a combination of buprenorphine + naloxone result in either similar or more favorable perinatal outcomes compared to pregnancies exposed to buprenorphine alone for opioid-use disorder (OUD) in pregnancy.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: OUD in pregnancy has become more common in the US, with estimates from 2017 suggesting that 8.2 per 1,000 pregnancies are affected. Recently, there has been an increase in treating OUD during pregnancy with buprenorphine in place of methadone. Buprenorphine + naloxone is commonly prescribed for OUDs outside of pregnancy; however, its use during pregnancy is not well-studied.

PATIENTS: Medicaid-insured pregnant individuals with OUD

INTERVENTION: Buprenorphine + naloxone

CONTROL: Buprenorphine alone

PRIMARY OUTCOME: Major congenital malformations, low birth weight, neonatal abstinence syndrome, neonatal intensive care unit (NICU) admission, preterm birth, respiratory symptoms, small for gestational age, cesarean delivery, maternal morbidity

METHODS (BRIEF DESCRIPTION):

- Pregnant individuals 12–55 years old with their liveborn infants selected from the Medicaid Analytic eXtract/Transformed Medicaid Statistical Information System Analytic Files (MAX/TAF) from 2000–2018 were included and assessed for eligibility.
- Eligible individuals were divided into two groups:
  - Exposed to buprenorphine + naloxone
  - Exposed to buprenorphine alone
- Exposure was based on prescription fills during the first trimester of pregnancy.
- Individuals were excluded if they were exposed to teratogenic medications, methadone, or the other treatment arm during the first trimester or 90 days before the last menstrual period.
- Outcomes were measured by comparing congenital malformations, birth weight, NICU admissions, neonatal abstinence syndrome, preterm birth, respiratory symptoms, cesarean section rates, and severe maternal morbidity recorded in maternal records within 30 days after delivery.
- Outcomes were expressed in terms of relative risk for buprenorphine + naloxone (treatment group) vs buprenorphine alone (control group).

INTERVENTION (# IN THE GROUP):

- Malformations: 3,438
- Neonatal abstinence syndrome: 1,071
- Other outcomes: 3,369

COMPARISON (# IN THE GROUP):

- Malformations: 1,947
- Neonatal abstinence syndrome: 4,454
- Other outcomes: 5,326

FOLLOW-UP PERIOD: Throughout their pregnancies and postpartum period

RESULTS:

Primary Outcome –

- Buprenorphine + naloxone had fewer occurrences of neonatal abstinence syndrome compared to buprenorphine (relative risk [RR] 0.67; 95% CI, 0.62–0.73).
- Buprenorphine + naloxone had fewer NICU admissions compared to buprenorphine (RR 0.88; 95% CI, 0.82–0.93).
- Buprenorphine + naloxone had fewer infants born small for gestational age compared to buprenorphine (RR 0.81; 95% CI, 0.71–0.91).
- Buprenorphine + naloxone resulted in no statistical difference in occurrences of low birth weight, preterm birth, respiratory symptoms in infants, cesarean delivery, severe maternal morbidity, or congenital malformations, including cardiac malformations compared to buprenorphine.

LIMITATIONS:

- Exposure to the medication was defined by prescription fills, which does not necessarily equate to actual use of the medication.
- The study, however, required the presence of multiple dispensing to increase the likelihood that a medication fill resulted in taking the medication as prescribed.
- Additional limitations include incomplete data regarding alcohol, tobacco, other drug use, and the severity of OUD.

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Making the Cut: Voluntary Male Circumcision to Decrease HIV?

Efficacy of Voluntary Medical Male Circumcision to Prevent HIV Infection Among Men Who Have Sex with Men: A Randomized Controlled Trial

Gao Y, Zhan Y, Sun Y, et al. Efficacy of Voluntary Medical Male Circumcision to Prevent HIV Infection Among Men Who Have Sex With Men: A Randomized Controlled Trial. *Ann Intern Med*. 2024;177(6):719-728. doi:10.7326/M23-3317

KEY TAKEAWAY: Voluntary medical male circumcision (VMMC) may be an effective strategy for lowering human immunodeficiency virus (HIV) infection among men who have sex with men (MSM).

STUDY DESIGN: Randomized controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to a limited follow-up period of 12 months and the limited incidence of the primary outcome)

BRIEF BACKGROUND INFORMATION: MSM has the highest incidence of HIV infection. While VMMC has been shown to decrease the risk of HIV infection rates in men who have sex with women, there have been no prior studies on the MSM population. This study aimed to identify if VMMC reduces the risk of HIV infection in MSM.

PATIENTS: MSM

INTERVENTION: Immediate male circumcision

CONTROL: Delayed medical male circumcision for 12 months

PRIMARY OUTCOME: HIV seroconversion

Secondary Outcome: Sexually transmitted infection (STI) incidence, impact on sexual behavior

METHODS (BRIEF DESCRIPTION):

- This study was conducted in Mainland China over 12 months in eight geographically different cities with subjects recruited both online and through in-person outreach from MSM community organizations, dermatology hospital departments, and local government Centers for Disease Control (CDC).
- Patients 18–49 years old, uncircumcised, HIV-negative men who practice penetrative anal intercourse amongst ≥2 male sexual partners over the past six months were included in the study.
- Patients were randomized to either:
    - Immediate medical male circumcision (intervention): Circumcision was initiated within three months of randomization
    - Delayed medical male circumcision (control): Circumcision was delayed for 12 months
- The 12-month follow-up period began six weeks post-procedure or at the time of the first sexual encounter (whichever was first).
- After the 12-month follow-up period, members in the control group were encouraged to have a voluntary circumcision as well.
- The primary outcome of HIV seroconversion was tested at three, six, nine, and 12-month follow-ups, and the primary outcome was a positive result at any point during the 12-month evaluation.
- The following were measured as the secondary outcomes of the study:
    - Other STI infections including syphilis, human papillomavirus (HPV), and herpes simplex virus 2 (HSV-2) were tested at six and 12-month follow-ups.
    - Sexual risk behaviors were self-reported and evaluated at six and 12 months.

INTERVENTION (# IN THE GROUP): 120

COMPARISON (# IN THE GROUP): 123

FOLLOW-UP PERIOD: 12 months

RESULTS:

Primary Outcome –

- Immediate medical male circumcision significantly reduced the 12-month incidence of HIV seroconversion compared to delayed medical male circumcision (hazard ratio [HR] 0.09; 95% CI, 0.00–0.81; NNT=25).

Secondary Outcome –

- There was no statistically significant difference in STI incidence and sexual risk behaviors between immediate medical male circumcision and delayed medical male circumcision.

LIMITATIONS:

- Only five HIV seroconversions occurred during the study; this small outcome event rate, even with a statistically significant difference, may indicate a less clinically significant effect.

- Limited follow-up of only 12 months for the study could have resulted in underestimating the true long-term effects of this intervention
- HIV Pre-Exposure Prophylaxis (PrEP) use was excluded from the study, which could have significantly impacted HIV seroconversion. Given PrEP is becoming more commonplace, future studies could incorporate it into their design.

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Early vs Late DOAC in Stroke with Atrial Fibrillation

Early vs Late Anticoagulation in Minor, Moderate, and Major Ischemic Stroke with Atrial Fibrillation: Post Hoc Analysis of the ELAN Randomized Clinical Trial

Goeldlin MB, Hakim A, Branca M, et al. Early vs Late Anticoagulation in Minor, Moderate, and Major Ischemic Stroke With Atrial Fibrillation: Post Hoc Analysis of the ELAN Randomized Clinical Trial. *JAMA Neurol*. 2024;81(7):693-702. doi:10.1001/jamaneurol.2024.1450

KEY TAKEAWAY: In patients with minor, moderate, and major ischemic stroke and atrial fibrillation there is no difference in recurrent stroke or bleeding between early vs late direct oral anticoagulation (DOAC) initiation.

STUDY DESIGN: Randomized controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to the unblinded study design and posthoc analysis)

BRIEF BACKGROUND INFORMATION: Studies on initiation of direct oral anticoagulant (DOAC) after stroke demonstrate a risk of hemorrhagic conversation. Larger infarcts are thought to have a further increased risk of bleeding and hemorrhage. This study investigated early vs late DOAC stratified by minor, moderate, and major stroke size.

PATIENTS: Adults with ischemic stroke

INTERVENTION: Early DOAC initiation

CONTROL: Late DOAC initiation

PRIMARY OUTCOME: Composite outcome of recurrent stroke, bleeding, or death within 30 days

Secondary Outcome: Composite outcome of stroke and bleeding within 90 days

METHODS (BRIEF DESCRIPTION):

- Investigators conducted a post-hoc analysis of the previously published randomized ELAN trial which examined early or late anticoagulant initiation for patients with ischemic stroke and underlying atrial fibrillation.
- Patients >18 years old were recruited from 103 stroke units in Europe, the Middle East, and Asia all had acute ischemic stroke as defined by MRI or neurologic deficit and had atrial fibrillation.
- Patients were excluded if they had contraindications to DOAC, illicit drug and alcohol usage, severe comorbidities, or life expectancy <6 months.
- Participants had a mean age of 77 years old, 44% were women, the mean CHA2D2SVASc score was 5.0, and a majority of received either intravenous thrombolysis or mechanical thrombectomy.
- A minor stroke was defined as <1.5 cm in the posterior and anterior territory, a moderate stroke was defined as >1.5 cm in the anterior territory but not involving the entire middle or anterior cerebral artery territory, and a major stroke involved the entire anterior or middle cerebral artery territory or >1.5 cm in the posterior territory.
- The treatment group received early DOAC initiation which was within 48 hours for patients with minor or moderate stroke and 6–7 days for patients with major stroke.
- The comparator group received late DOAC initiation with timing based on grading (minor at 3–4 days, moderate at 6–7 days, or major at 12–14 days) of ischemic stroke.
- The primary outcome was recurrent ischemic stroke, symptomatic intracranial hemorrhage, extracranial bleeding, systemic embolism, or vascular death within 30 days of the initial event measured via telephone interview and validated by record review.
- The secondary outcome was measured via the above but within 90 days of the initial event.

INTERVENTION (# IN THE GROUP): 978

- Minor: 376
- Moderate: 397
- Major: 227

COMPARISON (# IN THE GROUP): 984

- Minor: 368
- Moderate: 396
- Major: 235

FOLLOW-UP PERIOD: 90 days

RESULTS:

Primary Outcome –

- Early and late DOAC initiation had a similar risk of stroke, hemorrhage, and death for all stroke types:
  - Minor (2.7% vs 3.0%, respectively; unadjusted odds ratio [uOR] 0.89; 95% CI, 0.38–2.1)
  - Moderate (2.8% vs 3.6%, respectively; uOR 0.80; 95% CI, 0.35–1.7)

- Major (3.7% vs 7.0%, respectively; OR 0.52; 95% CI, 0.21–1.2)

Secondary Outcome –

- Early and late DOAC had a similar risk of stroke, hemorrhage, and death at 90 days for all stroke types.
- In the fully adjusted analysis, the risk of stroke, hemorrhage, and death was similar for all stroke types when comparing early vs late DOAC initiation.

LIMITATIONS:

- This study was a secondary analysis, not the primary purpose of the original study.
- The event rate in the trial population was low resulting in a lack of power to detect differences.
- The time at which anticoagulants were initiated was determined by infarct size and can lend itself to bias.
- Initiating a DOAC earlier than one week in a major stroke may not be ethical to test in a clinical trial.

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Self-Administered Acupressure Improves Osteoarthritis-Related Knee Pain

Self-Administered Acupressure for Probable Knee Osteoarthritis in Middle-Aged and Older Adults: A Randomized Clinical Trial

Yeung WF, Chen SC, Cheung DST, et al. Self-Administered Acupressure for Probable Knee Osteoarthritis in Middle-Aged and Older Adults: A Randomized Clinical Trial. *JAMA Netw Open*. 2024;7(4):e245830. Published 2024 Apr 1. doi:10.1001/jamanetworkopen.2024.5830

KEY TAKEAWAY: Self-administered acupressure is an effective means of decreasing osteoarthritis (OA) related knee pain in middle-aged and older adults.

STUDY DESIGN: Single-site, randomized controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to lack of blinding)

BRIEF BACKGROUND INFORMATION: Studies on OA indicate that acupressure may have some benefit in the perception of OA pain. The effect of acupressure is beneficial in pain but is unknown regarding other functional measures. This study investigated the outcomes related to self-administered acupressure compared to knee health education.

PATIENTS: Adults with knee OA

INTERVENTION: Self-administered acupuncture (SAA) + education

CONTROL: Education alone

PRIMARY OUTCOME: Knee-related pain

Secondary Outcome: Pain, stiffness, physical function

METHODS (BRIEF DESCRIPTION):

- Patients ≥50 years old who met the criteria for OA were recruited through posters at Hong Kong Polytechnic University, community centers, and social media.
- Patients were included if they had ≥3 months of moderate or worse pain and any three of the following: Morning stiffness, crepitus in motion, bone tenderness, bone enlargement, and no palpable joint warmth.
- Patients with rheumatic disease, BMI >30, and those with previous acupuncture or steroid injections in the last six months, a previous knee replacement, certain medical diagnoses (e.g., alcohol/drug abuse, bleeding disorders, cognitive impairment), or pregnancy were excluded from the study.
- The mean age of participants was 67 years old, the average BMI was 24, 78% were women, and 70% had other health problems besides knee OA.
- The SAA group was trained on proper SAA technique and given knee health education (KHE), then instructed to perform the SAA twice daily in addition to the other knee health activities and keep a logbook of their daily participation.
- The KHE-only group received the same KHE education and was instructed to perform the KHE activities and log their participation as well.
- The primary outcome was measured with the Numerical Rating Scale (NRS) for pain. Scores range from 0–10, with 10 being the most severe pain imaginable at four, eight, and 12 weeks.
- The secondary outcomes were measured using:
  - The Western Ontario and McMaster University Osteoarthritis Index (WOMAC). Scores range from 0–96 with higher scores indicating greater severity.
  - The Short Form 6 Dimensions (SF-6D) which includes six domains of quality of life. Scores range from 0–1, with a score of one indicating perfect health.
  - The Timed Up and Go (TUG) is defined as the duration the patient takes to accomplish standing, walking, turning, and returning to sit at four, six, and 12 weeks.
- Effect sizes (d) were calculated to quantify the magnitude of benefit defined as:
  - Small=0.2
  - Medium=0.5
  - Large=0.8

INTERVENTION (# IN THE GROUP): 157

COMPARISON (# IN THE GROUP): 157

FOLLOW-UP PERIOD: 12 weeks

RESULTS:

Primary Outcome –

- SAA resulted in decreased pain compared to the KHE-only group.
  - Four weeks (mean difference [MD] –0.59; 95% CI, −0.96 to −0.21; d=0.35)
  - Eight weeks (MD –0.67; 95% CI, −1.1 to −0.25; d=0.35)

    - 12 weeks (MD –0.54; 95% CI, −0.97 to −0.10; d=0.27)

Secondary Outcome –

- Participants treated with SAA showed similar outcomes for decreasing pain, stiffness, and physical function compared to the KHE-only group as measured by WOMAC scores.
- Participants treated with SAA showed similar function as compared to KHE at weeks four and eight and a slightly increased improvement in function compared to the KHE-only group at week 12 as measured by the SF-6 (MD 0.03; 95% CI, 0.003–0.01; d=0.24).
- Participants treated with SAA showed improvement in TUG at week eight compared to the KHE-only group (MD –0.46 seconds; 95% CI, −0.88 to −0.05; d=0.25).
    - There was no difference with TUG in the SAA compared to the KHE-only group at four and 12 weeks.

LIMITATIONS:

- The study lacked a sham acupressure group.
- The follow-up period was limited to 12 weeks and lacked an objective measurement for swelling.
- The population was fairly homogenous and thus results may not be completely generalizable.
- The magnitude of the effect for SAA was small and may not be clinically meaningful.

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