GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

Volume 1 - Issue 24

What's in this week's issue?

Week of June 14 - 18, 2021

SPOTLIGHT: Fractures Happen - Bisphosphonates Preventative or an Atypical Femur Fracture Risk?

- Maternal Perinatal Depression and Anxiety May Have Long Term Effects on Children: A Cause for Concern?
- The Cleanup Crew: Does Evinacumab Assist with "Mabbing" Up Excess LDL
- Achilles Tendon Ruptures: Boot Up, Walk Out

Fractures Happen: Bisphosphonates Preventative or an Atypical Fracture Risk?

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Atypical Femur Fracture Risk Versus Fragility Fracture Prevention with Bisphosphonates

Black DM, Geiger EJ, Eastell R, et al. Atypical Femur Fracture Risk Versus Fragility Fracture Prevention with Bisphosphonates. *N Engl J Med.* 2020; 383:743–53.

KEY TAKEAWAY: Occurrence of atypical femur fractures (AFF) increases as the duration of bisphosphonate use increases. AFF occurrence decreases as the time since discontinuation of bisphosphonates increases. Overall clinical fractures prevented by bisphosphonate use outweigh atypical femur fractures incidence.

STUDY DESIGN: Prospective Cohort Study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Bisphosphonate use decreases fracture risk by 40–70%. However significant concern has arisen over bisphosphonates as a cause of atypical femur fractures. Patients and providers question the safety of bisphosphonates. When patients avoid the use of bisphosphonates they lose the benefit of fracture prevention.

PATIENTS: Women ≥50 years

INTERVENTION: Bisphosphonate usage

CONTROL: None

OUTCOME: Atypical fractures and hip fractures

METHODS (BRIEF DESCRIPTION):

- Women >50 years old with osteoporosis were followed for ten years at Kaiser Permanente Southern California.
- The analytical cohort received at least one prescription of a bisphosphonate.
- Atypical femur fractures excluded fractures from any high-energy trauma within the prior 3 days.
- Risk factors: age, ethnicity, glucocorticoid use, height, weight, smoking status
- Duration of bisphosphonate use and exposure updated annually
- Fractures prevented were calculated using a risk/benefit hypothetical cohort modeled from prior studies (Study of Osteoporotic Fractures and national US data)

INTERVENTION (# IN THE GROUP): 196,129

COMPARISON (# IN THE GROUP): N/A

FOLLOW UP PERIOD: January 1, 2007–November 20, 2017

RESULTS:

Primary Outcomes:

- Duration of bisphosphonate usage data demonstrated an increasing trend of AFF per 10,000 person-years:
  - 0.07 at <3 month usage
  - 2.5 at 3–5 years usage
    - 3–5 years of bisphosphonate usage had an increased risk of AFF compared to <3 months of usage (HR 8.9; 95% CI, 2.8–28)
  - 3.1 at >8 years usage
    - >8 years of bisphosphonate usage had an increased risk of AFF compared to <3 months of usage (HR 44; 95% CI, 14–138)
- 65–74 year old women have an increased risk of AFF compared to >80 year olds (HR 2.8; 95% CI, 1.6–4.7)
  - 75–84 year old women have an increased risk of AFF compared to >80 year olds (HR 2.5; 95% CI, 1.5–4.2)
- Asian women are at a higher risk of AFF compared to white women (HR 4.8; 95% CI, 3.6–6.6)
- Those with 3–15 months since bisphosphonate discontinuation had a decreased risk of AFF compared to current users (HR 0.52; 95% CI, 0.37–0.72)

Secondary Outcomes:

- Per 10,000 white women treated with bisphosphonates at 3 years: 2 AFF occurred and 149 fractures were prevented.
- Per 10,000 Asian women treated with bisphosphonates at 3 years: 8 AFF occurred and 91 fractures were prevented.

LIMITATIONS:

- Conflict of interest: program partially funded by Kaiser
- Alendronate used for most of study
- Did not consider morbidity and mortality

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Maternal Perinatal Depression and Anxiety May Have Long Term Effects on Children: A Cause for Concern?

Association between maternal perinatal depression and anxiety and child and adolescent development: a meta-analysis

Rogers A, Obst S, Teague SJ, Rossen L, Spry EA, et al. Association Between Maternal Perinatal Depression and Anxiety and Child and Adolescent Development: A Meta-analysis. *JAMA Pediatr*. 2020; 174(11):1–11.

KEY TAKEAWAY: Perinatal depression and anxiety in mothers is associated with poorer offspring development.

STUDY DESIGN: Systematic review and meta-analysis of observational studies

LEVEL OF EVIDENCE: STEP 3 (downgraded due to study design)

BRIEF BACKGROUND INFORMATION: Perinatal depression and anxiety are common and often undiagnosed and untreated. This study evaluated whether children with mothers who suffered from depression and anxiety during the perinatal period had poorer developmental outcomes from infancy to adolescence.

PATIENTS: Mothers with history of perinatal depression/anxiety and children

INTERVENTION: N/A

CONTROL: N/A

OUTCOMES: Social-emotional, cognitive, language, motor, and adaptability development in offspring from 4 weeks to 18 years

Secondary Outcomes: Stratified results by psychology type, perinatal period, child age at outcome assessment

METHODS (BRIEF DESCRIPTION):

- Study followed PRISMA reporting guidelines.
- Six databases searched: CINAHL Complete, Cochrane Library, Embase, Informit, MEDLINE Complete, and PsycInfo
- Analysis from January 1, 2019 through March 15, 2020.
- 191 articles included in meta-analysis (27,212 assessed, 308 eligible).
- Inclusion criteria: English language articles, human studies, quantitative data, prospective longitudinal design, measured maternal depression/anxiety and child development and investigated the association
- Quality and risk of bias assessed via Cochrane collaboration criteria.
- Data extracted by multiple independent reviewers and Pearson r correlation coefficients calculated.
- Random and fixed effects models used.
- I^2 for heterogeneity assessed.

INTERVENTION (# IN THE GROUP): N/A

COMPARISON (# IN THE GROUP): 195,751 mother-child dyads

FOLLOW UP PERIOD: 4 weeks to 18 years in offspring

RESULTS:

Effect sizes measured using the r correlation coefficient:

- Very small: 0.05
- Small: 0.10
- Medium: 0.20
- Large: 0.30
- Very large: 0.40+

There were mixed results as to whether maternal perinatal depression and anxiety is associated with poorer developmental outcomes in offspring:

- Social-emotional (14 studies, N=36,929; antenatal period, r=0.21; 95% CI, 0.16–0.27; post-natal period, r=0.24; 95% CI, 0.19–0.28)
- Cognitive (3 studies, N=271; antenatal period, r = –0.12; 95% CI, –0.19 to –0.05; postnatal period, r = –0.25; 95% CI, –0.39 to –0.09)
- Language (4 studies, N= 1513; antenatal period, r = –0.11; 95% CI, –0.20 to 0.02; postnatal period, r = –0.22; 95% CI, –0.04 to 0.03)
- Motor (4 studies, N= 1560; antenatal period, r = –0.07; 95% CI, –0.18 to 0.03; r = –0.07; 95% CI, –0.16 to 0.03)
- Adaptive behavior (1 study, N=90; antenatal period, r = –0.26; 95% CI, –0.39 to –0.12)

LIMITATIONS:

- Qualitative review not performed.
- Observational data cannot prove causation or exclude residual confounding.
- Risk of Type I error from multiple comparisons.

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The Cleanup Crew: Does Evinacumab Assist with "Mabbing" Up Excess LDL

Evinacumab for Homozygous Familial Hypercholesterolemia

Raal FJ, Rosenson RS, Reeskamp LF, et al. Evinacumab for Homozygous Familial Hypercholesterolemia. *N Engl J Med*. 2020; 383(8):711–720. doi:10.1056/NEJMoa2004215

KEY TAKEAWAY: When used with baseline lipid lowering therapy, IV evinacumab lowers LDL, non-HDL cholesterol, and apolipoprotein B in patients with familial hypercholesterolemia, despite also resulting in lower HDL.

STUDY DESIGN: Double blind, placebo-controlled, phase 3 trial, conducted at 30 sites in 11 countries

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Patients with homozygous familial hypercholesterolemia have an inability to excrete LDL through the hepatic system due to a loss of function of LDL receptor. Angiopoietin-like 3 (ANGPTL3) is an inhibitory protein which ultimately increases triglyceride and other lipid levels. Patients with loss of function for ANGPTL3 have been noted to have decreases in LDL, triglycerides, and risk of cardiovascular events. Evinacumab is a novel monoclonal antibody which is an inhibitor of ANGPTL3, with anticipated reduction in LDL levels.

PATIENTS: Patients meeting criteria for familial hypercholesterolemia

INTERVENTION: Patients continued baseline lipid lowering therapy (and received 15mg IV infusion of evinacumab at 15mg/kg every four weeks for 24 weeks)

CONTROL: Placebo with baseline lipid lowering therapy

OUTCOMES: Percent change in LDL at 24 weeks

Secondary Outcomes: Percent change in HDL as a safety outcome, reduction in total cholesterol, triglycerides, lipoprotein (a), apolipoprotein B, and apolipoprotein C-III

METHODS (BRIEF DESCRIPTION):

- Patients were diagnosed with familial hypercholesterolemia by either genetic variants in LDL receptor adaptor protein 1, or had homozygous/compound heterozygous variants in the apolipoprotein B or PCSK9 or clinical criteria (untreated total cholesterol of greater than 500 with tendinous/cutaneous xanthomas prior to age 10 or untreated total cholesterol of greater than 250 in both parents).
- Patients were selected if they met criteria for familial hypercholesterolemia, were receiving stable lipid lowering therapy at maximum tolerated dose, were 12 years of age or older, and had LDL levels greater than 70.
- Patients remained on their baseline lipid lowering medications: 94% on statin, 77% on PCSK9 inhibitor, 75% on ezetimibe, 25% on lomitapide, 63% on triple therapy
- Patients who met criteria were randomly assigned to treatment or placebo groups in a 2:1 ratio.
- The treatment group received IV evinacumab 15 mg/kg every 4 weeks while continuing lipid lowering therapy with stratification of randomization based on apheresis or location (Japan).
- Patients were monitored for 24 weeks.

INTERVENTION (# IN THE GROUP): 43

COMPARISON (# IN THE GROUP): 22

FOLLOW UP PERIOD: Trial was conducted for 24 weeks.

RESULTS:

Primary Outcomes:

- IV evinacumab had a greater reduction in LDL than placebo:
    - 47.1% reduction at 24 weeks whereas the placebo group had a 1.9% increase (Mean Difference (MD) –49%; 95% CI, –65 to –33)

Secondary Outcomes:

- Greater decrease of apolipoprotein B with use of evinacumab compared to placebo (mMD –37%; 95% CI, –49 to –25).
- Decrease in total cholesterol seen in patients using evinacumab (MD –48%; 95% CI, –59 to –38).
- Greater decrease in triglycerides in treatment group (MD –50%; 95% CI, –66 to –35).
- Other secondary outcomes were not significant.

LIMITATIONS: The short duration of the study did not allow for assessment of cardiovascular outcomes or long-term safety.

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Achilles Tendon Ruptures: Boot Up, Walk Out

A Randomized Controlled Trial Comparing Traditional Plaster Cast Rehabilitation with Functional Boot Rehabilitation for Acute Achilles Tendon Ruptures

Meampel JF, Clement ND, Duckworth AD, et al. A Randomized Controlled Trial Comparing Traditional Plaster Cast Rehabilitation with Functional Walking Boot Rehabilitation for Acute Achilles Tendon Ruptures. *Am J Sports Med*. 2020; 48(11):2755–2764.

KEY TAKEAWAY: Walking boots are superior to immobilizing casts in initially improving function and pain. At 6 months to 1 year, walking boots are as effective as immobilizing casts in all areas.

STUDY DESIGN: Single-center non-blinded randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Non-operative care of Achilles tendon rupture (ATR) has traditionally been accomplished through fixed cast immobilization. Recent clinical practice has trended toward functional rehabilitation utilizing a walking boot; however, clinical evidence supporting this approach is uncertain.

PATIENTS: Patients with acute ATR 19–59 years old in Edinburg, Scotland

INTERVENTION: 8 weeks walking boot with reduced plantarflexion, followed by physical therapy (PT)

CONTROL: 10 weeks immobilizing cast (first 8 weeks non-weight-bearing) with reduced plantarflexion, followed by PT

OUTCOME: Function

Secondary Outcomes: Function and pain, mean time to return to driving, return to work, dorsiflexion and plantarflexion degrees, calf circumference, ability to complete heel-raise, skin breakdown

METHODS (BRIEF DESCRIPTION):

- Inclusion: 16–60 years old with acute ATR (diagnosed clinically, ultrasound at clinical discretion)
- Exclusion: delayed presentation (>2 weeks), re-rupture, latex allergy
- Control group:
  - 10 weeks below-knee cast with reducing equinus
    - 8 weeks non-weight-bearing
    - 2 weeks weight-bearing
  - Active plantarflexion started at 10 weeks after cast removal
- Intervention process:
  - 8 weeks walking boot with immediate weight-bearing and reducing equinus
  - Physical therapy with active plantarflexion
- Short Musculoskeletal Function Assessment (SMFA) score measured at weeks 0, 4, 6, 8, 10, 26, and ≥52. Lower SMFA score indicates more function through 46 questions with a minimum clinically important difference of 7.
- Secondary Outcome Measurements
  - Achilles Tendon Total Rupture Score (ATRS): Measured at initial visit, then 6 and 12 months. Measures patient-reported functional outcomes. Scores range from 0 to 100, with higher scores indicating less disability.
  - Foot and Ankle Questionnaire (FAQ): at initial visit, then 6 and 12 months. Measures patient-reported functional and pain outcomes through 25 questions.
  - Degree of Ankle Flexion: measured at 10, 26, and 52 weeks, compared to uninjured limb
  - Calf Circumference: measured at 10, 26, and 52 weeks, compared to uninjured limb
  - Heel-Raise Ability: measured at 6, 12 months, and final follow-up

INTERVENTION (# IN THE GROUP): 64

COMPARISON (# IN THE GROUP): 56

FOLLOW UP PERIOD: Median of 393 days

RESULTS:

Primary Outcome:

- Function improved with the walking boot compared to cast at 6 months when measured with SMFA (6.6 vs 11, *P*=.05). This is a statistically significant difference, but less than the minimal clinical important difference for this scale (not addressed by authors).
  - No statistically significant difference at 1 year (2.2 vs 2.9, *P*=.25) or final follow-up (2.2 vs 2.9, *P*=.17)

Secondary Outcomes:

- Function: Improvement at 6 months in the walking boot (72 vs 54, *P*=.01) but no statistically significant difference at 1 year or final follow-up.
- Function and Pain (combined score): Improvement at 6 months in the walking boot group (91 vs 85, *P*=.04) but no statistically significant difference at 1 year or final follow-up.
- Less calf circumference deficit in the walking boot group vs. control at 6 months (5.8% vs 2.8%, *P*<.001) but no statistically significant difference at 1 year or final follow-up.
- Less ankle range of motion deficit between injured and uninjured legs in the walking boot group vs cast group at 10 weeks in plantarflexion (15 vs 6 degrees, *P*<.001) and dorsiflexion (10 vs 5 degrees, *P*=.001). There was no statistically significant difference from 6 months to final follow-up.
- No significant difference in heel-raise, return to driving, and return to work.
- Control group had no skin breakdown, while the 22% of the intervention group had skin breakdown resulting in 2.9% of the intervention group converting to control arm.

LIMITATIONS:

- Outcomes primarily patient-reported
- Medial follow-up 393 days
- Due to low overall risk of re-rupture, study size has inadequate power to evaluate re-rupture rates

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