GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

Volume 2 - Issue 7

FPIN
Family Physicians Inquiries Network

What's in this week's issue?

Week of February 14 - 18, 2022

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Bisphosphonate Therapy Shows Benefit for Osteoporosis Patients with a Life Expectancy >1 Year

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Time to Benefit of Bisphosphonate Therapy for the Prevention of Fractures Among Postmenopausal Women with Osteoporosis

Deardorff W, Cenzer I, Nguyen B, Lee S. Time to Benefit of Bisphosphonate Therapy for the Prevention of Fractures Among Postmenopausal Women with Osteoporosis. *JAMA Internal Medicine*. 2022; 182(1): 33.

KEY TAKEAWAY: Bisphosphonates moderately benefit in preventing nonvertebral fractures in osteoporosis patients with a life expectancy >1 year.

STUDY DESIGN: Meta-analysis of 10 RCTs (N=23,384)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Bisphosphonate therapy is routinely prescribed for patients with osteoporosis who meet criteria for treatment. Little is known about the time to benefit for bisphosphonate therapy to prevent fractures. Knowing time to benefit allows providers to make informed decisions on whether bisphosphonates are warranted in those with a short life expectancy.

PATIENTS: Postmenopausal women with primary osteoporosis

INTERVENTION: Alendronate, Risedronate, or Zoledronic Acid

CONTROL: Placebo

OUTCOME: Time to absolute risk-reduction (ARR) thresholds (0.002, 0.005, 0.010) for the nonvertebral fracture

METHODS (BRIEF DESCRIPTION):

- 10 RCTs were analyzed to calculate the Time to Benefit (TTB) using the Absolute Risk Reduction (ARR) for bisphosphonate therapy in primary osteoporosis patients.
- Studies were excluded if they did not include a placebo, if primary diagnosis was not osteoporosis, or did not include sufficient date to establish a time to fracture.
- 23,384 female participants (>90% of whom were white) with a primary diagnosis of osteoporosis (Z score ≤–2.5) and no prior hip fracture.
- Participants were either treated with Alendronate (dose ranges of 5.0 mg/d to 20 mg/d), Risedronate (dose ranges of 2.5 mg/d to 5.0 mg/d), or Zoledronic Acid (5.0 mg/year) compared with placebo.
- Outcomes were pooled and measured with statistical analysis using Random-effects Weibull survival curves and Markov Chain Monte Carlo methods to calculate the ARR and TTB.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW UP PERIOD: 12–48 months

RESULTS:

- 100 postmenopausal women with osteoporosis treated with bisphosphonates for 12 months (95% CI, 6.3–18 months) will prevent one nonvertebral fracture (ARR=0.010).
- 200 postmenopausal women with osteoporosis treated with a bisphosphonate for 20 months (95% CI, 11–30 months) will prevent one hip fracture (ARR=0.005).
- 200 postmenopausal women with osteoporosis treated with a bisphosphonate for 7.7 months (95% CI, 3.3–12 months) will prevent any clinical fracture.
- 200 postmenopausal women with osteoporosis treated with a bisphosphonate for 12 months (95% CI, 6.4–18 months) will prevent one vertebral fracture (ARR=0.005).

LIMITATIONS:

- Dosage of Alendronate varied from 5.0 mg/d to 20 mg/d in different studies. Different dosage protocols may impact TTB.
- >90% of study participants were white postmenopausal women with no prior hip fracture or secondary cause of osteoporosis, limiting study generalizability to minority populations or those with prior hip fracture.
- Short- and long-term harms of bisphosphonate therapy were not included.

Ryan Allen, MD
Saint Louis University FMRP
Saint Louis, MO

A Review of Anticoagulation Therapy in Critically Ill COVID-19 Patients

Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19

Goligher EC, Bradbury CA, McVerry BJ, et al. Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19. *N Engl J Med*. 2021 Aug 26; 385(9):777–789. doi: 10.1056/NEJMoa2103417. Epub 2021 Aug 4.

KEY TAKEAWAY: COVID-19 patients on therapeutic-dose anticoagulation did not improve in organ support-free days, survival to hospital discharge, or thrombotic events compared to those on prophylactic-dose anticoagulation.

STUDY DESIGN: International, adaptive, multiplatform, randomized, controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: COVID-19 infection can encourage a proinflammatory hypercoagulable state and blood markers of these processes, such as D-dimer, have been utilized as predictive indicators for worsening condition. This phenomenon has led some to hypothesize therapeutic anticoagulation therapy may help limit disease severity and decrease the number of days requiring ICU-level organ support therapies.

PATIENTS: Adults with moderate to severe COVID-19 infection

INTERVENTION: Therapeutic-dose anticoagulation

CONTROL: Prophylactic-dose anticoagulation

OUTCOME: Organ support-free days

Secondary Outcomes: Survival to hospital discharge, major thrombotic events, any thrombotic events, death, major bleeding events

METHODS (BRIEF DESCRIPTION):

- Patients ≥18 years old diagnosed with confirmed moderate to severe COVID-19 infection and admitted to the ICU within 48 hours or to the hospital within 72 hours and not at imminent risk of death or bleeding events.
- Patients were randomly assigned to receive therapeutic-dose anticoagulation with unfractionated or low-molecular-weight heparin or to receive usual-care pharmacologic thromboprophylaxis in an open-label fashion.
- Patients underwent randomization across three sites including 1:1 randomization into therapeutic or prophylactic-dose anticoagulation therapy groups at one site and response-adaptive randomization at the two other sites.
- Therapeutic-dose anticoagulation was administered according to site-specific venous thromboembolism protocol for a total of 14 days, until hospital discharge, or until discontinuation of supplemental oxygen.
- Prophylactic-dose anticoagulation was based on local protocol and included standard low-dose or enhanced intermediate-dose thromboprophylaxis.
- Monthly interim analyses were conducted to monitor for statistical criterion for futility.

INTERVENTION (# IN THE GROUP): 534

COMPARISON (# IN THE GROUP): 564

FOLLOW UP PERIOD: Discharge or day 21 of hospitalization

RESULTS:

Primary Outcome:

- The therapeutic group did not differ in organ support free days compared to the prophylactic group (1 vs 4, respectively; adjusted odds ratio [aOR] 0.83; 85% CI, 0.67–1.0).

Secondary Outcomes ·

- There was no difference in survival to hospital discharge between the therapeutic and prophylactic groups (63% vs 65%, respectively; aOR 0.84; 95% CI, 0.64–1.1).
- Major thrombotic events were consistent between the therapeutic and prophylactic groups (40% vs 41%, respectively; aOR 1.0; 95% CI, 0.79–1.4).
- There was no difference in the incidence of any thrombotic events or death between the therapeutic and prophylactic groups (41% vs 41%, respectively; aOR 1.1; 95% CI, 0.81–1.4).
- The therapeutic and prophylactic groups did not differ in major bleeding events (3.8% vs 2.3%, respectively; aOR 1.5; 95% CI, 0.75–3.0).

LIMITATIONS:

- Open label design may have permitted reporting bias.
- A large percentage of subjects were recruited in the UK where practice guidelines shifted during the trial to treat COVID-19 patients with intermediate dose

thromboprophylaxis including those enrolled in the control group.

Thomas Wickham, DO, MPH
University of Massachusetts Fitchburg FMP
Fitchburg, MA

Efficacy and Safety of the Pfizer COVID-19 Vaccine

Safety and Efficacy of the BNT162b2 mRNA COVID-19 Vaccine

Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA COVID-19 Vaccine. *N Engl J Med.* 2020; 383(27):2603–2615.

KEY TAKEAWAY: Two doses of the Pfizer vaccine confer 95% protection against COVID-19 in those at least 16 years old and is just as safe as other immunizations.

STUDY DESIGN: Multinational, placebo-controlled, observer-blinded, randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: COVID-19 has caused severe respiratory disease especially in those with hypertension and obesity. Due to these risk factors being overwhelmingly common worldwide, there is significant need for immunity. The purpose of this study was to justify the authorization for emergency use of the Pfizer vaccine given these facts.

PATIENTS: Individuals at least 16 years old

INTERVENTION: Pfizer COVID vaccine

CONTROL: Placebo

OUTCOME: Adverse events, efficacy, and safety

METHODS (BRIEF DESCRIPTION):

- Participants were randomly assigned to one of two groups:
  - Two intramuscular doses of BNT162b12 mRNA COVID-19 vaccine 21 days apart
  - Matching saline placebo injections
- Adverse events: Self-reported through an electronic diary for seven days after the initial dose and with continual monitored after second dose.
- Efficacy outcomes: Measured by nucleic acid amplification testing for the virus seven days after the second dose was administered to each group. Positivity was then compared.
- Safety outcomes: Measured by comparing adverse events in the vaccinated group with the placebo group.

INTERVENTION (# IN THE GROUP): 18,556

COMPARISON (# IN THE GROUP): 18,530

FOLLOW UP PERIOD: 2 months

RESULTS:

- The Pfizer vaccine is significantly more effective than placebo (95% efficacy rate; 95% CI, 90–97).
  - 19,965 patients received the vaccine with nine becoming infected.
  - 20,172 received placebo with 169 becoming infected.
- Safety was comparable to other FDA authorized vaccinations.
  - The most common local reaction was mild to moderate pain at the site of injection (65% of intervention group).
  - The most common systemic reaction was generalized fatigue (at least 50% of intervention group).

LIMITATIONS:

- Short follow up interval: long-term data is still being collected and the long-term effects of the vaccine are unknown.
- The study did not involve children less than 16 years old or pregnant women.
- Funding by BioNTech and Pfizer, corporations that will profit from the vaccine.

Aaron P Montgomery, MD
Tripler Army Medical Center FMRP
Tripler AMC, HI

The views expressed in this GEM are the author's and do not reflect the official policy or position of Tripler Army Medical Center, the Department of Defense, or the U.S. Government.

Who You Going to Call? Clot Busters: EVT +/- Alteplase for Stroke

A Randomized Trial of Intravenous Alteplase before Endovascular Treatment for Stroke

LeCouffe NE, Kappelhof M, Treurniet KM, et al. A Randomized Trial of Intravenous Alteplase before Endovascular Treatment for Stroke. *N Engl J Med.* 2021; 385(20):1833-1844.

KEY TAKEAWAY: Endovascular therapy (EVT) alone compared to EVT plus alteplase did not differ in effect on disability, stroke symptoms, lesion volume, and symptomatic intracerebral hemorrhage.

STUDY DESIGN: Investigator-initiated, international, multicenter, prospective, randomized open-label trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Two trials in China found EVT alone was noninferior to alteplase followed by EVT. A study-level meta-analysis of these trials found similar outcomes for the two treatment strategies. This study was designed to determine whether EVT alone would be more effective, or noninferior, as compared with intravenous alteplase followed by EVT.

PATIENTS: European adult patients with acute ischemic anterior circulation stroke eligible for EVT

INTERVENTION: EVT alone

CONTROL: Usual care (IV alteplase prior to EVT)

OUTCOME: Disability at 90 days

Secondary Outcomes: Recanalization, stroke symptoms, size of lesion

Safety Outcomes: Mortality, symptomatic intracerebral hemorrhage

METHODS (BRIEF DESCRIPTION):

- Patients >18 years old from 20 hospitals in France, Netherlands, and Belgium met criteria for acute ischemic stroke due to an intracranial proximal occlusion of anterior circulation.
  - Median age: 71 years old
  - Stroke location identified by imaging in intracranial internal carotid artery, first segment of middle cerebral artery (MCA), or proximal second segment of MCA.
  - Participants were eligible for EVT and IV alteplase if they presented within 4.5 hours of symptom onset to EVT capable center.
  - National Institute of Health Stroke Scale (NIHSS; 0–42 with higher scores indicating greater stroke system impairment) of 2 or more.
- Treatment group received EVT without alteplase.
- The usual care group received IV alteplase 0.9 mg/kg with 10% as a bolus and 90% as a 60-minute infusion and EVT was initiated before completion of alteplase.
- EVT was conducted with Conformite Europeene-approved stent retriever and suction catheters were also used during the study.
- Disability measured using the Rankin scale (0–6 with higher scores indicating greater disability) at 90 days.
- Incidence of recanalization was measured via angiogram at 24 hours.
- Severity of symptoms after stroke was measured via NIHSS score at 5–7 days or discharge.
- Lesion volume measured via imaging at 5–7 days or discharge.
- Safety end points of mortality and symptomatic intracerebral hemorrhage were gathered via interview reports and imaging review at 90 days and 5–7 days or discharge, respectively.

INTERVENTION (# IN THE GROUP): 273

COMPARISON (# IN THE GROUP): 266

FOLLOW UP PERIOD: 90 days

RESULTS:

Primary Outcome –

- EVT alone compared to usual care did not significantly affect disability (3 vs 2, respectively; adjusted odds ratio [aOR] 0.84; 95% CI, 0.62–1.2).

Secondary and Safety Outcomes –

- EVT alone compared to usual care did not significantly affect recanalization, stroke severity, lesion volume, mortality, or symptomatic intracerebral hemorrhage.

LIMITATIONS:

- European population only who presented directly to centers providing EVT were included, limiting generalizability of sample.
- Times from stroke onset to hospital arrival were relatively short, which limits the generalizability of the results.
- Did not include patients who were given alteplase at one hospital and transferred to another hospital for EVT.

- Fewer patients with atrial fibrillation or intracranial atherosclerosis when compared with other study populations.

Alexandra Davis, MD; Janel Kam-Magruder, MD
Alaska Family Medicine Residency
Anchorage, AK