GEMs of the Week

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Bempedoic Acid, A Potential Alternative to Statins

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients

Nissen SE, Lincoff AM, Brennan D, et al. Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients. *N Engl J Med.* 2023;388(15):1353-1364. doi:10.1056/NEJMoa2215024

KEY TAKEAWAY: Bempedoic acid reduces major adverse cardiovascular events (MACE) in participants unable to tolerate statins.

STUDY DESIGN: Randomized control trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Current guidelines recommend statins for patients at high risk for MACE. A significant number of patients are unable to tolerate stains exposing them to increased risk for MACE. Bempedoic acid could be a beneficial alternative for statin-intolerant individuals.

PATIENTS: Statin-intolerant individuals

INTERVENTION: Bempedoic acid

CONTROL: Placebo

PRIMARY OUTCOME: Prevention of MACE

Secondary Outcome: Myocardial infarction, stroke, coronary revascularization, cardiovascular mortality, all-cause mortality

METHODS (BRIEF DESCRIPTION):

- Inclusion criteria: Adults 18–85 years old (mean age of 65.5 years old) who reported intolerance to statins and had a prior cardiovascular event or were at high risk for a cardiovascular event.
- High risk was defined as having one of the following:
  - 10-year Reynolds risk score >30% or a SCORE risk score >7.5%
  - Coronary artery calcium score >400 Agatston units
  - Patients with type 1 or type 2 diabetes, age >65 years old (women) or >60 years old (men).
- Patients received bempedoic acid 180 mg daily or a matching placebo.
  - Patients were permitted to remain on low-dose statins, ezetimibe, niacin, bile acid resins, fibrates, or proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors during the trial.
- Outcomes included the occurrence of a composite of four major cardiovascular events (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization) during a median follow-up of 40.6 months.

INTERVENTION (# IN THE GROUP): 2,100

COMPARISON (# IN THE GROUP): 2,106

FOLLOW-UP PERIOD: Median 40.6 months

RESULTS:

Primary Outcome –

- Bempedoic acid reduced the occurrence of MACE compared to placebo (hazard ratio [HR] 0.87; 95% CI, 0.79–0.96).

Secondary Outcome –

- Bempedoic acid reduced the following compared to placebo:
  - Fatal or nonfatal myocardial infarction (HR 0.77; 95% CI, 0.66–0.91)
  - Coronary revascularization (HR 0.81; 95% CI, 0.72–0.92)
- Bempedoic acid did not reduce fatal or nonfatal stroke, death from cardiovascular causes, or death from any cause compared to placebo.

LIMITATIONS:

- The sample size was a fraction of the total enrolled population thus the number of events was smaller causing a wider confidence interval.
- Including patients who reported inability to tolerate statins resulted in a high mean baseline LDL-C level and populations with lower pretreated LDL-C levels were not studied.
- The trial was sponsored by a pharmaceutical company.
- Patients taking other lipid-lowering medications were also included in the trial.
- Statin intolerance was self-reported.

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Are Oral Anticoagulants as Effective as Heparin for Recurrent VTE?

Direct Oral Anticoagulants vs Low Molecular Weight Heparin and Recurrent VTE in Patients with Cancer: A Randomized Clinical Trial

Schrag D, Uno H, Rosovsky R, et al. Direct Oral Anticoagulants vs Low-Molecular-Weight Heparin and Recurrent VTE in Patients with Cancer: A Randomized Clinical Trial. *JAMA*. 2023;329(22):1924-1933. doi:10.1001/jama.2023.7843

KEY TAKEAWAY: Direct oral anticoagulants (DOACs) were non-inferior to low molecular weight heparin (LMWH) for preventing venous thromboembolism (VTE) among adults with cancer over six months.

STUDY DESIGN: Randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: From 2012–2015, four DOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) were approved for the treatment of VTE based on randomized clinical trials. These results showed similar efficacy and safety to warfarin in patients with atrial fibrillation who underwent orthopedic surgery however, patients who had cancer were excluded from these studies. The efficacy and safety of DOACs in cancer patients with VTEs is undetermined.

PATIENTS: Patients with known cancer diagnosis

INTERVENTION: DOAC

CONTROL: LMWH

PRIMARY OUTCOME: Incidence of VTE

METHODS (BRIEF DESCRIPTION):

- The RCT was conducted at 67 oncology practices.
- 671 patients were enrolled who had cancer including any invasive solid tumor, lymphoma, multiple myeloma, or chronic lymphocytic leukemia.
- Patients who also had a new clinical or radiological diagnosis of VTE were also included.
- The study used noninferiority criteria for anticoagulation comparing DOAC vs LMWH.
- Criteria was based on the upper limit of the one-sided 95% confidence interval.
- The difference of a DOAC relative to LMWH should be less than 3%.

INTERVENTION (# IN THE GROUP): 335

COMPARISON (# IN THE GROUP): 336

FOLLOW-UP PERIOD: Six months

RESULTS:

Primary Outcome –

- Rates of recurrent VTE were 8.8% in the LMWH group and 6.1% in the DOAC group (difference 2.7%; 1-sided 95% CI, –100% to 0.7%) consistent with the prespecified noninferiority criterion.

LIMITATIONS:

- Physicians and participants were not blinded.
- Some patients were treated with different therapy before randomization.
- The study was unable to distinguish VTE as the cause of death in patients with advanced cancer.
- There was poor representation of Asian and Black individuals as well as Hispanic ethnicity.
- Detailed medication adherence diaries were not obtained.
- There was a lower adherence to LMWH relative to DOAC.
- The study was unable to perform superiority testing.
- The anti-clot treatment scale may not be sufficiently sensitive to detect differences in the burden of treatment between groups.

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Ticagrelor, Not a Hammer for Sickle Crisis

Ticagrelor vs Placebo for the Reduction of Vaso-Occlusive Crises in Pediatric Sickle Cell Disease: The HESTIA3 Study

Heeney MM, Abboud MR, Githanga J, et al. Ticagrelor vs placebo for the reduction of vaso-occlusive crises in pediatric sickle cell disease: the HESTIA3 study. *Blood*. 2022;140(13):1470-1481. doi:10.1182/blood.2021014095

KEY TAKEAWAY: Ticagrelor does not reduce vaso-occlusive crisis in pediatric patients with sickle cell disease.

STUDY DESIGN: Double-blinded, randomized, parallel-group placebo control phase three study

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Pediatric patients with sickle cell disease often have composite painful crises due to vaso-occlusion. The study aims to use ticagrelor, a P2Y12 inhibitor, as an antiplatelet commonly used in ACS to reduce the number of vaso-occlusive crises and ACS.

PATIENTS: Sickle cell disease

INTERVENTION: Ticagrelor

CONTROL: Placebo

PRIMARY OUTCOME: Painful crises

METHODS (BRIEF DESCRIPTION):

- The study involved 193 randomized patients from 54 different centers.
- Pediatric patients were included:
  - Ages 2–17 years old
  - Homozygous sickle cell anemia or sickle beta-zero thalassemia
  - At least two vaso-occlusive crises in the past 12 months
  - On a stable hydroxyurea regimen adjusted for weight and maintained for more than three months, with a minimum weight greater than 12 kg.
- Patients in the study were randomly assigned to either the treatment group receiving weight-based ticagrelor (15 mg/30 mg/45 mg) or a matching placebo.
- Acute chest syndrome (ACS) was described as an illness characterized by fever, respiratory infection, and radiographic evidence of pulmonary infiltrate.
- Vaso-occlusive crises were defined as events lasting greater than two hours and requiring opioid or NSAID administration either in a medical setting or at home.
- Blood samples were collected at various time points to measure plasma levels of ticagrelor and its active metabolite using chromatography/mass spectrometry.
  - The lower limit of detection was set at 1 ng/ml for ticagrelor and 2.5 ng/ml for its metabolite AR-C124910XX.
- These crises were monitored and recorded by either the patients themselves or trained caregivers using handheld electronic devices.
  - The assessment was based on the revised faces pain scale and the face, legs, activity, cry, consolability (FLACC) scale, which were adapted to the patient's age and language.

INTERVENTION (# IN THE GROUP): 101

COMPARISON (# IN THE GROUP): 92

FOLLOW-UP PERIOD: 297 days

RESULTS:

Primary Outcome –

- Ticagrelor increased the estimated yearly incidence rate of vaso-occlusive crises compared to placebo (rate 2.7; 95% CI, 2.2–3.5).
- There was no difference in painful crisis between ticagrelor and placebo (ratio of 1.0; 95% CI, 0.7–1.5).
- There were no clinically significant changes in the episodes of acute coronary syndrome (ACS) between ticagrelor to placebo (incidence RR 0.76; 95% CI, 0.17–3.30).

Secondary Outcome –

- No differences were observed in the number and duration of painful crises between the groups.
- There was no reduction in the number of ACS episodes with the ticagrelor group compared to the placebo group.
- There was no reduction in the incidence of vaso-occlusion requiring hospitalization or emergency room visits in the ticagrelor group.

LIMITATIONS:

- Small sample size

- Exclusion criteria of NSAID use in SCD patients limited population selection.

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D-Mannose for Preventing and Treating Urinary Tract Infections

D-Mannose for Preventing and Treating Urinary Tract Infections

Cooper TE, Teng C, Howell M, Teixeira-Pinto A, Jaure A, Wong G. D-mannose for preventing and treating urinary tract infections. *Cochrane Database Syst Rev.* 2022;8(8):CD013608. Published 2022 Aug 30. doi:10.1002/14651858.CD013608.pub2

KEY TAKEAWAY: There is uncertainty about the efficacy and harms of D-mannose in treating or preventing urinary tract infections (UTIs).

STUDY DESIGN: Systematic review of seven randomized control trials (N=719)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to high risk of bias across all studies, small sample size, and limited data)

BRIEF BACKGROUND INFORMATION: One of the most common infections in adults globally is UTIs, typically treated with antibiotics. D-mannose is an alternative often used in the treatment and prevention of UTIs, however, very little information is available about its benefits or harms.

PATIENTS: Adults seeking treatment or prophylaxis of UTI

INTERVENTION: D-mannose

CONTROL: Pharmacological treatments (antibiotics or prebiotics), non-pharmacological treatments, placebo, no treatment

PRIMARY OUTCOME: Incidence of symptomatic and bacteriuria-confirmed UTI, pain

METHODS (BRIEF DESCRIPTION):

- Adults of any sex and age, in any setting in the general population were included in the study.
  - The health status of the participants included acute cystitis, multiple sclerosis, acute symptomatic UTI, and undergoing urological procedures.
- Studies were selected from Italy, Croatia, Russia, and Spain.
- Treatment arms included D-mannose administered for prophylaxis or treatment of symptomatic or asymptomatic UTI.
  - All routes of administration (such as oral tablets and liquids) duration, dosage, and frequency were included.
  - Some studies compared D-mannose to placebo, antibiotics, vitamins/herbal supplements, other non-pharmacological treatments, and no treatment.
  - Combination therapy with D-mannose plus cranberry or vitamins was also studied.
- Outcomes were measured in the following ways:
  - Urine analysis and culture
  - Pain was assessed using a visual analog scale (VAS) of 0–10 where 0 indicates no pain.
  - Symptoms were assessed using symptom diaries and a 12-question questionnaire to evaluate female symptoms over the last four weeks and their impact on the patient's quality of life (ICIQ-FLUTS).
    - It is scored 0–48 with higher scores indicating greater impact of individual symptoms for the patient.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Varied from no follow-up to 12 months

RESULTS:

Primary Outcome –

- D-mannose reduced the number of symptomatic and bacteriuria-confirmed UTIs (1 study, 205 participants; RR 0.24; 95% CI, 0.15–0.39).
- Participants taking D-mannose prophylaxis experienced a longer symptom-free period than those receiving nitrofurantoin and those not receiving prophylaxis (1 study, 308 participants; *P*=.12; no numerical results reported for this figure).
- Symptom-free periods:
  - D-mannose group (103 participants): 43 days
  - Nitrofurantoin group (103 participants): 24 days
  - Control/no treatment group (102 participants): 28 days
- There was no difference between D-mannose and nitrofurantoin on symptomatic and bacteriuria-confirmed UTIs (1 study, 206 participants; RR 0.71; 95% CI, 0.39–1.3).

- The participants in the D-mannose group and nitrofurantoin group had a significantly lower risk of recurrent cystitis episodes during prophylactic therapy compared to patients in the non-prophylaxis group. This outcome was assessed in one study.
    - Prophylaxis group (RR 0.239; 95% CI, 0.146–0.392)
    - No treatment group (RR 0.335; 95% CI, 0.222–0.506)
- Mean pain on the VAS scale was (mean ± SD) 1.2 ± 1.1 for the D-mannose treatment group and 1.3 ± 0.9 for the no-treatment group.
- There was no significant difference in pain scores between the two groups (1 study, 40 participants; RR –0.10; 95% CI, –0.72 to 0.52).

LIMITATIONS:

- The included studies had a small sample size and insufficient power.
- Most studies assessed the efficacy and harms of D-mannose in females only.
- There was a high risk of bias across all studies.
- Outcomes and how they were measured varied greatly by scale, unit, time, and point definitions across studies.
- Definitions of UTI varied across studies.
- Very few of the primary and secondary outcomes were assessed.

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