GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

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SPOTLIGHT: Abbreviated DAPT Therapy for PCI in High-Risk Bleeding Populations

Abbreviated DAPT Therapy for PCI in High-Risk Bleeding Populations

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Dual Antiplatelet Therapy after PCI in Patients at High Bleeding Risk

Valgimigli M, Frigoli E, Heg D, et al. Dual Antiplatelet Therapy after PCI in Patients at High Bleeding Risk. *N Engl J Med*. 2021; 385(18):1643–1655. doi:10.1056/NEJMoa2108749

KEY TAKEAWAY: In patients at high-risk for bleeding after receiving a drug-eluting stent, a shortened course of one month of dual antiplatelet therapy (DAPT) was noninferior to a standard minimum three-month course and resulted in fewer adverse clinical events.

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

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: It is well documented that drug-eluting stents are superior to metal stents in patients with a high-risk of bleeding. However, the question regarding the course of DAPT after the implantation of a drug-eluting stent in patients with high bleeding risk has not yet been established. It is suspected that an abbreviated antiplatelet regimen may be of benefit to those at high-risk of bleeding compared to longer treatment durations currently recommended.

PATIENTS: Those with high-risk of bleeding after primary coronary intervention with drug-eluting stent

INTERVENTION: One month of DAPT

CONTROL: Standard DAPT for three months if on oral anticoagulant and six months otherwise

OUTCOME: Net adverse clinical events, cardiac/cerebral events, bleeding

Secondary Outcomes: Death, stroke or TIA, bleeding events

METHODS (BRIEF DESCRIPTION):

- Inclusion Criteria:
  - Acute or chronic CAD and had undergone PCI with a biodegradable-polymer sirolimus-eluding stent (Ultimaster, Terumo)
  - Had no additional revascularization procedures planned
  - Free from adverse cardiovascular events within the first month of the PCI
- Central randomization 1:1 at 30–44 days post procedure (median 34 days) to stop DAPT (continuing monotherapy) or continue DAPT for a minimum of three to six months (median 193 days).
- The intervention group was evaluated for noninferiority compared to the control group regarding net adverse clinical events, major cardiac/cerebral events, and major or nonmajor clinically relevant bleeding.

INTERVENTION (# IN THE GROUP): 2,204

COMPARISON (# IN THE GROUP): 2,230

FOLLOW UP PERIOD: 335 days

RESULTS:

Primary Outcomes –

- One month of DAPT was noninferior to continuing for three to six months for the following outcomes:
  - Net adverse clinical events: 7.5 vs 7.7% (HR 0.97; 95% CI, 0.78–1.2)
  - Major adverse cardiac/cerebral events: 6.1% vs 5.9% (HR 1.0; 95% CI, 0.8–1.3)
- One month of DAPT was superior to control for reducing major or nonmajor clinically relevant bleeding (6.4% vs 9.2%; HR 0.68; 95% CI, 0.55–0.85).

Secondary Outcomes –

- One month of DAPT was noninferior to control for the outcome of death from CV and non-CV causes (3.3% vs 3.6%; HR 0.92; 95% CI, 0.67–1.3).
- One month of DAPT was superior to control for the following outcomes:
  - Stroke or TIA: 0.8% vs 1.4% (HR 0.53; 95% CI, 0.25–0.95)
  - Bleeding events (all BARC types): 8.7% vs 13% (HR 0.64; 95% CI, 0.53–0.77)

LIMITATIONS:

- Only 4% of the patients who underwent screening (representing approximately 22% of the patients who were eligible for the trial) were enrolled, raising the possibility of selection bias.
- Treatments were open label rather than blinded.
- The duration of the dual antiplatelet therapy varied in the standard-therapy group (median 193 days, interquartile range 102–366).
- The type of single antiplatelet therapy used was not consistent in the abbreviated-therapy group (clopidogrel was used in 54%).
- The results may not apply to patients who are at a lower bleeding risk or those who receive other stent types (i.e., non-sirolimus-eluting stents).

Jared Darlian, DO, DrPH, MBA
Eastern Maine Medical Center FMRP
Bangor, ME

Does Zinc Prevent or Treat Acute Viral Respiratory Tract Infections?

Zinc for the Prevention or Treatment of Acute Viral Respiratory Tract Infections in Adults: A Rapid Systematic Review and Meta-Analysis of Randomised Controlled Trials

Hunter J, Arentz S, Goldenberg J, et al. Zinc for the prevention or treatment of acute viral respiratory tract infections in adults: a rapid systematic review and meta-analysis of randomised controlled trials. *BMJ Open*. 2021; 11(11):e047474. Published 2021 Nov 2. doi:10.1136/bmjopen-2020-047474

KEY TAKEAWAY: The use of zinc may prevent respiratory tract infections (RTI) as well as shorten the duration and severity of illness without causing serious adverse effects.

STUDY DESIGN: Systematic review and meta-analysis of 28 RCTs (N=5,446)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: It is known that zinc plays a role in immunity, tissue response to hypoxia, and inflammation during viral RTIs. It is not clear whether zinc prevents or treats acute viral RTIs including COVID-19. Zinc supplementation has increased globally during the pandemic; however, the evidence for use is lacking.

PATIENTS: Adults with clinical symptoms of viral RTI, confirmed viral RTI, or with increased risk of developing an RTI

INTERVENTION: Zinc products

CONTROL: Placebo and active comparison groups (e.g. quinine lozenge, naphazoline nasal spray)

OUTCOME: RTI incidence, symptoms, and adverse effects

METHODS (BRIEF DESCRIPTION):

- Authors used key words such as COVID, SARS, MERS, lower/upper respiratory infection, bronchitis, or common cold and zinc and excluded trials if non-viral infections (bacterial) or zinc deficiencies were present.
- Interventions varied by study:
  - Prevention (4 RCTs): Daily oral zinc 15 mg or 45 mg (elemental) for 7 to 12 months; topical nasal zinc 0.92–2.6 mg daily
  - Treatment (17 RCTs): Zinc sublingual (SL) lozenge 80–276 mg if symptomatic on day three or seven; topical nasal zinc 0.9–2.6 mg daily for the duration of symptoms
- 19 RCTs were conducted in the US and subjects were mostly younger than 65 years old, had a mean age of 37 years old, and were generally healthy.

INTERVENTION (# IN THE GROUP):

- Prevention: 1,899
- Treatment: 1,126

COMPARISON (# IN THE GROUP):

- Prevention: 1,887
- Treatment: 815

FOLLOW UP PERIOD:

- Prevention: 7 days to 12 months
- Treatment: Varied (3–10 days commonly reported)

RESULTS:

- Zinc decreased the relative risk of developing mild/moderate RTI symptoms by 32% compared to placebo and active controls (incidence rate ratios (IRR) 0.68; 95% CI, 0.58–0.80).
  - Intranasal and oral Zinc prevented 5 RTIs per 100 person–months (95% CI, 1–8; NNT=20; moderate-certainty).
  - When subjects were inoculated with rhinovirus, SL zinc did not prevent infection (RR 0.96; 95% CI, 0.77–1.2; moderate-certainty).
- SL and intranasal zinc resulted in earlier symptom resolution (2 days; 95% CI, 0.61–3.5; very low certainty).
  - The placebo and active control groups had 19 more people per 100 with symptoms at day 7 compared to the zinc treatment groups (95% CI, 2 to 38; NNT=5; low certainty).
- Zinc reduced day three severity of symptoms by a standardized mean difference of –1.2 points (95% CI, -0.66 to –1.7; low-certainty).
- The zinc groups had more non-serious side effects (RR 1.4; 95% CI, 1.2–1.7; NNH=7; moderate-certainty).
- There were no differences involving illness duration and serious adverse events.

LIMITATIONS:

- Rapid review methods included single reviewers and protocol changes.
- Omission of COVID-19 trials still pending at the time of publication.
- Lack of comparative efficacy and effectiveness of the many products of zinc and doses.
- Many RCTs were industry funding or partial support.

Joshua Byrd, MD
SIU Quincy FMR
Quincy, IL

Are You in a Rut Because of Your Gut?

Prebiotics and Probiotics for Depression and Anxiety: A Systematic Review and Meta-analysis of Controlled Clinical Trials

Citation Liu RT, Walsh RFL, Sheehan AE. Prebiotics and probiotics for depression and anxiety: A systematic review and meta-analysis of controlled clinical trials. *Neurosci Biobehav Rev.* 2019; 102:13–23. doi:10.1016/j.neubiorev.2019.03.023

KEY TAKEAWAY: Probiotics may alleviate some symptoms of anxiety and depression. Prebiotics were not found to have a significant impact on either.

STUDY DESIGN: Meta-analysis of 34 RCTs (N=3,160)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Depression and anxiety are the two most common mental health disorders, impacting over 25% of the population. With growing interest in gut microbiome and how it impacts overall health, there is great potential in developing novel therapeutic modalities that could treat anxiety and depression by altering the gut flora.

PATIENTS: Adults with anxiety or depression

INTERVENTION: Prebiotics or probiotics

CONTROL: Placebo

OUTCOME: Depression and anxiety

METHODS (BRIEF DESCRIPTION):

- Comprehensive literature review of RCTs involving effects of prebiotics or probiotics on depression or anxiety.
- Inclusion criteria were studies in which patients were only treated with prebiotics or probiotics and depression and anxiety were separately analyzed as outcomes.
- Outcomes were measured by clinician rating or self-reporting.
- Age as a categorical variable was excluded, but mean age per study ranged from 20 to 72 years old.
- Prebiotics were administered for a range of four hours to four weeks.
- Probiotics were administered for a range of eight days to 45 weeks.

INTERVENTION (# IN THE GROUP): 3,160

COMPARISON (# IN THE GROUP): Not available

FOLLOW UP PERIOD: Four to 45 weeks

RESULTS:

- Probiotics improved symptoms of depression compared to placebo (23 trials, N=2,802; SDM –0.24; 95% CI, –0.36 to –0.12).
- Probiotics improved symptoms of anxiety compared to placebo (22 trials, N=2,527; SDM –0.10; 95% CI, –0.19 to –0.01).
- Prebiotics did not influence symptoms of depression or anxiety compared to placebo.

LIMITATIONS:

- There were relatively few studies included in the prebiotic analysis; therefore, these findings are preliminary and demand further investigation with a larger number of trials.
- The results have limited generalizability due to most studies evaluating healthy individuals with low levels of disease and no studies included patients with clinically relevant anxiety symptoms.
- It was difficult to determine a causal relationship between probiotics and anxiety/depression, as studies included those with chronic conditions such as IBS.

Natalie Jewett, MD & Austin Klint, MD
Cahaba - UAB Family Medicine Residency
Birmingham, AL

The Benefits of Chlorthalidone in Advanced CKD

Chlorthalidone for Hypertension in Advanced Chronic Kidney Disease

Agarwal R, Sinha AD, Cramer AE, et al. Chlorthalidone for Hypertension in Advanced Chronic Kidney Disease. *N Engl J Med*. 2021; 385(27):2507–2519. doi:10.1056/NEJMoa2110730

KEY TAKEAWAY: Chlorthalidone therapy reduces blood pressure and the degree of albuminuria, which may indicate the potential of providing cardiovascular and kidney protection in patients with chronic kidney disease (CKD). Hypokalemia, hyperglycemia, and reversible increases in serum creatinine were seen in the chlorthalidone group.

STUDY DESIGN: Double blind, randomized control trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Previous research on chlorthalidone for hypertension has not assessed patients with stage 4 CKD or in African American patients resulting in unknown safety and efficacy in these populations. This chlorthalidone trial sought to uncover renoprotective and cardioprotective benefits in these underrepresented communities.

PATIENTS: Adults with stage 4 CKD and hypertension (HTN)

INTERVENTION: Chlorthalidone (12.5–50 mg)

CONTROL: Placebo

OUTCOME: Blood Pressure

Secondary Outcomes: Urinary albumin-to-creatinine ratio, N-terminal pro-B-type natriuretic peptide (NT-proBNP), adverse events

METHODS (BRIEF DESCRIPTION):

- Patients with stage 4 CKD and uncontrolled HTN were required to be receiving an angiotensin-converting enzyme (ACE) inhibitor or beta blocker at the time of randomization.
  - Uncontrolled HTN: Systolic blood pressure (SBP) >130 mmHg or diastolic blood pressure (DBP) >80 mmHg
  - 121 had diabetes; 96 were on loop diuretics.
  - Exclusion criteria: SBP >160 mmHg, DBP >100 mmHg, stroke, myocardial infarction, heart failure resulting in hospitalization, or thiazide diuretic
  - 40% of participants identified as Black.
- Patients were randomly assigned in a 1:1 ratio to either chlorthalidone or placebo.
  - Initial dose of chlorthalidone was 12.5 mg daily and dosage was increased every four weeks if needed, for a total of 12 weeks (max dose of 50 mg/day).
  - Placebo comparison was blinded, and placebo capsules were manufactured to look and taste identical to chlorthalidone group.
  - Randomization was stratified according to previous use of loop diuretics.
- Blood pressure was confirmed by a 24-hour blood pressure monitor.

INTERVENTION (# IN THE GROUP): 81

COMPARISON (# IN THE GROUP): 79

FOLLOW UP PERIOD: 14 weeks

RESULTS:

Primary Outcomes –

- Chlorthalidone therapy improved blood pressure control at 12 weeks compared to the placebo group.
  - 24-hour systolic blood pressure (SBP) mean difference (MD) –11 mmHg (95% CI, –15 to –6.4)
  - 24-hour diastolic blood pressure (DBP) MD –3.9 mmHg (95% CI, –6.3 to –1.5)

Secondary Outcomes –

- Chlorthalidone decreased urinary albumin/creatinine ratios by 50% from baseline (95% CI, –60 to –37).
- Chlorthalidone decreased NT-proBNP levels more than placebo (MD –21%; 95% CI, –35 to –4).
- Chlorthalidone was more likely to cause hypokalemia, increases in serum creatinine levels, hyperglycemia, hyperuricemia, and dizziness than placebo.

Adverse Events–

- Hospitalizations occurred in eight patients in the chlorthalidone group and 11 in the placebo group (no statistical analysis).
  - One death in the chlorthalidone group from cardiac arrest.

LIMITATIONS:

- Small trial with an underrepresentation of women (22%), Asians (2%), and Hispanics (1%).
- Relatively short study duration

John Renzi, MD
Southern Illinois University Quincy FMR
Quincy, IL

Halting Hypoglycemic Hospitalizations: Optimizing Glycemic Control for Patients in Nursing Homes

Comparative Safety of Dipeptidyl Peptidase-4 Inhibitors and Sulfonylureas Among Frail Older Adults

Zullo AR, Smith RJ, Gutman R, et al. Comparative safety of dipeptidyl peptidase-4 inhibitors and sulfonylureas among frail older adults. *J Am Geriatr Soc*. 2021;69(10): 2923–2930.

KEY TAKEAWAY: Amongst older adults in nursing homes, dipeptidyl peptidase-4 inhibitors (DPP4I) are associated with less risk of severe hypoglycemia compared to sulfonylurea (SU) medications.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: There is currently limited data to support the safety and efficacy of glucose-lowering medications in elderly individuals in nursing homes. Severe hypoglycemia amongst frail individuals is associated with increased morbidity and mortality. Thus, it is important to identify medications that optimally treat hyperglycemia without causing severe hypoglycemia amongst elderly individuals in nursing homes.

PATIENTS: Nursing home patients with diabetes

INTERVENTION: DPP4I medications

CONTROL: SU medications

OUTCOME: Severe hypoglycemia requiring hospital-level interventions

Secondary Outcomes: Cardiovascular incidents, heart failure, death

METHODS (BRIEF DESCRIPTION):

- Participants were identified from a study cohort using propensity score matching and included individuals 65 years old or older residing in nursing homes.
  - Patients were enrolled January 1, 2008 – September 30, 2010.
  - Patients were included if they were prescribed either DPP4I or SU for glycemic control.
  - Exclusion Criteria: Medicare disenrollment, hospice, cancer, paralysis, or missing data
  - Cohorts were established for those prescribed DPP4I versus SU.
- Characteristics were identified that might influence the likelihood of DPP4I versus SU prescription or would likely provoke an outcome.
  - A logistics model was used to find probable confounding variables based on these characteristics.
- Statistical calculations done with Cox proportional hazard regression models.
- Stability analyses performed to test intervention result validity.

INTERVENTION (# IN THE GROUP): 1,008

COMPARISON (# IN THE GROUP): 1,008

FOLLOW UP PERIOD: One year, end of Medicare enrollment, or death

RESULTS:

- DPP4I resulted in fewer hypoglycemic events requiring hospital-level care in elderly nursing home patients (HR 0.57; 95% CI, 0.34–0.94; NNT=5).
- There were no differences in risk of death, cardiovascular events, heart failure, and hyperglycemia.

LIMITATIONS:

- There were potential confounding factors because of the observational nature of the study.
- Hyperglycemic and hypoglycemic events may have been under- or over-reported based on the capabilities of the nursing homes included in the study.

Courtney S Isaacs, DO, MHA
University of Wyoming FMRP
Casper, WY

Sacubitril/Valsartan in HFpEF: Any Clinical Benefit?

Effect of Sacubitril/Valsartan vs Standard Medical Therapies on Plasma NT-proBNP Concentration and Submaximal Exercise Capacity in Patients with Heart Failure and Preserved Ejection Fraction: The PARALLAX Randomized Clinical Trial

Pieske B, Wachter R, Shah SJ, et al. Effect of Sacubitril/Valsartan vs Standard Medical Therapies on Plasma NT-proBNP Concentration and Submaximal Exercise Capacity in Patients with Heart Failure and Preserved Ejection Fraction: The PARALLAX Randomized Clinical Trial. *JAMA*. 2021; 326(19):1919–1929. doi:10.1001/jama.2021.18463

KEY TAKEAWAY: Sacubitril/valsartan was shown to be more effective at lowering N-terminal pro-brain natriuretic peptide (NT-proBNP) levels in patients with heart failure with preserved ejection fraction (HFpEF). However, sacubitril/valsartan did not affect exercise tolerance, quality of life, or functional capacity compared to background therapy.

STUDY DESIGN: Multisite, randomized, double-blind, parallel group clinical trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: In prior studies, sacubitril/valsartan had greater reductions in NTpro-BNP compared to valsartan alone. Lower levels of NTpro-BNP were associated with less heart failure hospitalizations and cardiovascular (CV) deaths. However, the effects of sacubitril/valsartan on exercise tolerance and quality of life have not been fully evaluated.

PATIENTS: Adults >45 years old with HFpEF

INTERVENTION: Sacubitril/valsartan

CONTROL: Prior background medication (ACEI, ARB, or placebo)

OUTCOME: NT-proBNP levels and exercise tolerance

Secondary Outcomes: Quality of life and functional capacity

METHODS (BRIEF DESCRIPTION):

- Patients were 45 years old or older (mean 72 years old) with heart failure with mildly reduced ejection fraction (HFmrEF) or HFpEF (EF >40% with evidence of structural heart disease) and left atrial enlargement or left ventricular hypertrophy.
- Additional inclusion criteria:
  - Elevated NTpro-BNP levels (>220 if in sinus rhythm and >600 if in atrial fibrillation or atrial flutter)
  - KCCQ-CSS score <75 (KCCQ-CSS is scaled 0-100 higher scores indicating better quality of life)
  - NYHA class II-IV (NYHA is scaled I-IV with higher scores indicating worse functional capacity)
- Patients with acute coronary syndrome or acute decompensated heart failure were included.
- For 24 weeks, treatment group received sacubitril/valsartan 97 mg / 103 mg orally twice a day.
- The comparison group received background therapy if already taking an ACEI or ARB for hypertension (enalapril 10 mg or valsartan 160 mg) or placebo.
- NTpro-BNP levels were measured at 12 weeks.
- Exercise tolerance was measured via six-minute walk test at 12 weeks.
- Quality of life was measured via KCCQ-CSS scores with a minimal clinically important difference of five-points at 24 weeks.
- Functional capacity was measured via NYHA class with a change in one class level being of clinical significance at 24 weeks.

INTERVENTION (# IN THE GROUP): 1,281

COMPARISON (# IN THE GROUP): 1,285

FOLLOW UP PERIOD: 24 weeks

RESULTS:

Primary Outcomes –

- At 12 weeks, sacubitril/valsartan reduced NT-proBNP levels compared to the background therapy group (adjusted geometric mean ratio of 0.84; 95% CI, 0.80–0.88).
- At 12 weeks, sacubitril/valsartan showed no significant difference in six-minute walk test compared to the background therapy group (adjusted mean difference −2.5 m; 95% CI, −8.5 to 3.5 m).

Secondary Outcomes –

- There was no statistically significant change in quality of life or functional capacity between the two groups at 24 weeks.

LIMITATIONS:

- This was a relatively short study (only 24 weeks). While the NTpro-BNP values responded very quickly to treatment, it is possible that patients require a longer period of heart remodeling before seeing any clinical benefits in measures such as the six-minute walk test, quality of life, and functional capacity.

- Obesity has been shown to alter NTpro-BNP levels; however, mean BMI in this study was 30 and anyone with a BMI >40 was excluded.

Jaime Oswald, MD
Providence Alaska Family Medicine Residency
Anchorage, Alaska