GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

Volume 4 - Issue 5

FPIN
Family Physicians Inquiries Network

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Week of January 29 - February 2, 2024

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Does Cancer Screening Increase Life Expectancy?

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Estimated Lifetime Gained with Cancer Screening Tests: A Meta-Analysis of Randomized Clinical Trials

Bretthauer M, Wieszczy P, Løberg M, et al. Estimated Lifetime Gained With Cancer Screening Tests: A Meta-Analysis of Randomized Clinical Trials. *JAMA Intern Med.* 2023;183(11):1196-1203. doi:10.1001/jamainternmed.2023.3798

KEY TAKEAWAY: Most common cancer screening tests do not extend life expectancy.

STUDY DESIGN: Systematic review and meta-analysis of 18 long-term randomized clinical trials (RCTs) (N=2,111,958)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Cancer screening tests are often promoted as life-saving measures. Screening and early diagnosis have been known to improve cancer outcomes. However, it is not clear what effect cancer screening has on prolonging life.

PATIENTS: Patients eligible for cancer screening

INTERVENTION: Various cancer screenings

CONTROL: No screening

PRIMARY OUTCOME: Lifetime gained based on all-cause mortality data

METHODS (BRIEF DESCRIPTION):

- A comprehensive search for randomized clinical trials and meta-analysis of RCTs that included all-cause mortality and target cancer-specific mortality, compared screening with non-screening. The frequency of screening tests was conducted based on current guidelines and had follow-ups of at least 10 years.
- Screening tests included:
  - Mammography for breast cancer
  - Fecal occult blood test (FOBT), sigmoidoscopy, or colonoscopy for colorectal cancer
  - Prostate specific antigen (PSA) testing for prostate cancer
  - Lung computed tomography (CT) for lung cancer
- Screening tests were based on current guideline recommendations.

INTERVENTION (# IN THE GROUP): 967,602

COMPARISON (# IN THE GROUP): 1,164,081

FOLLOW-UP PERIOD: Median follow-up of

- 10 years for CT, PSA, and colonoscopy
- 13 years for mammography
- 15 years for sigmoidoscopy and FOBT

RESULTS:

Primary Outcome –

- No cancer screening test significantly increased lifetime gain compared to no screening:
  - Sigmoidoscopy (mean gain [MG] 110 days; 95% CI, 0–274 days)
  - Mammography (MG 0 days; 95% CI, –190 to 237 days)
  - Prostate cancer screening (MG 37 days; 95% CI, –37 to 73 days)
  - Colonoscopy (MG 37 days; 95% CI, –146 to 146 days)
  - FOBT screening every year or every other year (MG 0 days; 95% CI, –71 to 71 days)
  - Lung cancer screening (MG 107 days; 95% CI, –286 days to 430 days)
- Cancer screening tests did not decrease the risk of all-cause mortality compared to no screening:
  - Sigmoidoscopy (relative risk [RR] 0.98; 95% CI, 0.95–1.0)
  - Colonoscopy (RR 0.99; 95% CI, 0.96–1.0)
  - FOBT every other year (RR 1.0; 95% CI, 0.99–1.0)
  - FOBT every year (RR 1.0; 95% CI, 0.98–1.0)
  - Mammography (RR 1.0; 95% CI, 0.95–1.0)
  - PSA testing (RR 0.99; 95% CI, 0.98–1.0)
  - CT (RR 0.97; 95% CI, 0.88–1.1)

LIMITATIONS:

- Intention-to-treat analyses may underestimate any associations of cancer screening with longevity.
- Follow-up time may not have been enough in the included trials.
- Larger trials may be needed to identify the association of cancer screening more precisely with longevity.

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Antimuscarinics and Alpha-Blockers: A Pee-rless Partnership?

Role of Antimuscarinics Combined with Alpha-Blockers in the Management of Urinary Storage Symptoms in Patients with Benign Prostatic Hyperplasia: An Updated Systematic Review and Meta-Analysis

Lenfant L, Pinar U, Roupret M, Mozer P, Chartier-Kastler E, Seisen T. Role of Antimuscarinics Combined With Alpha-blockers in the Management of Urinary Storage Symptoms in Patients With Benign Prostatic Hyperplasia: An Updated Systematic Review and Meta-analysis. *J Urol.* 2023;209(2):314-324.
doi:10.1097/JU.0000000000003077

KEY TAKEAWAY: A combination of antimuscarinics and alpha-blockers did not significantly change the management of urinary storage symptoms in men with benign prostatic hyperplasia when compared to using established treatment of alpha-blockers alone.

STUDY DESIGN: Systematic review and meta-analysis of 12 randomized clinical trials (N=4,634)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Benign prostatic hyperplasia (BPH) has a high prevalence in men over 65 years old. Bladder outlet obstruction has been considered the primary cause of urinary storage symptoms in BPH. However, newer data suggests that other bladder-related mechanisms can potentially also contribute to these symptoms. This study aimed to provide an updated recommendation on the utilization of antimuscarinics combined with alpha-blockers to treat urinary storage symptoms in BPH.

PATIENTS: Adult men with BPH

INTERVENTION: Antimuscarinics in combination with alpha-blockers

CONTROL: Alpha-blockers alone or placebo

PRIMARY OUTCOME: Reducing urinary storage symptoms (urgency, frequency)

Secondary Outcome: Toxicity profile and side effects of antimuscarinics

METHODS (BRIEF DESCRIPTION):

- Compared efficacy of antimuscarinics in combination with alpha-blockers vs alpha-blockers or placebo alone in reducing urinary storage symptoms over a 12-week period.
- Inclusion criteria:
  - Men >40 years old with BPH and urinary storage symptoms
  - Daily urgency episodes >1–3
  - Frequency episodes >8
  - Post-void residual (PVR) 50–200 mL
- Urinary storage symptoms were defined as patient-reported symptoms like frequency, urgency, or confirmed by urodynamic studies.
- The primary outcome was evaluated by the efficacy of the addition of antimuscarinics vs alpha-blockers or placebo alone using standardized mean differences (SMDs) in urinary storage symptoms.
- The secondary outcomes were evaluated by the safety of antimuscarinics using SMDs for PVR and risk ratios (RRs) for other adverse effects (acute urinary retention, dry mouth, constipation, and dizziness).

INTERVENTION (# IN THE GROUP): 2,361

COMPARISON (# IN THE GROUP): 2,273

FOLLOW-UP PERIOD: 12 weeks

RESULTS:

Primary Outcome –

- The combination of antimuscarinics and alpha-blockers did not significantly reduce urinary storage symptoms (urgency, frequency) in men with benign prostatic hyperplasia.
  - Urgency (12 trials, N=4,634; SMD –0.23; 95% CI, –0.64 to –0.17)
  - Frequency (12 trials, N=4,634; SMD –0.19; 95% CI, –0.37 to –0.01)

Secondary Outcome –

- The addition of antimuscarinics caused unfavorable side effects:
  - Increased post-void residual (SMD 0.26; 95% CI, 0.13–0.39)
  - Acute urinary retention (RR 3.3; 95% CI, 1.4–7.9)
  - Dry mouth (RR 3.1; 95% CI, 1.7–5.6)
  - Constipation (RR 3.5; 95% CI, 2.23–5.5)
  - Dizziness (RR 1.02; 95% CI, 0.22–4.7)
- There was an increased risk of treatment interruption due to side effects of antimuscarinics (RR 1.7; 95% CI, 1.3–2.4).

LIMITATIONS:

- The placebo group tracked voiding habits in a daily diary and therefore could not be considered a “no treatment group”.
- The studies were concluded after 12 weeks. Hence, there is unclear evidence of efficacy or persistence of adverse effects of antimuscarinics beyond this period.
- There were no identifiable predictive factors to determine the efficacy of antimuscarinics in patients with BPH. In other post hoc studies, baseline PSA or serum PSA levels were used.
- Some of the included studies did not measure specific improvements in urgency or frequency as main outcomes, which could lead to bias.
- There was variability in the inclusion and exclusion criteria across studies, leading to variance in the reported severity of baseline symptoms potentially affecting the mean reduction in the primary outcome.

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Use of Selective Aldosterone Synthase Inhibitor, Baxdrostat, for Treatment-Resistant Hypertension

Phase 2 Trial of Baxdrostat for Treatment-Resistant Hypertension

Freeman MW, Halvorsen YD, Marshall W, et al. Phase 2 Trial of Baxdrostat for Treatment-Resistant Hypertension. *N Engl J Med.* 2023;388(5):395-405. doi:10.1056/NEJMoa2213169

KEY TAKEAWAY: Baxdrostat significantly reduces blood pressure (BP) and has an acceptable safety profile in patients with treatment-resistant hypertension.

STUDY DESIGN: Randomized, double-blind, placebo-controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Approximately 10% of people with hypertension in the United States have treatment-resistant hypertension. Increased aldosterone is hypothesized as a cause for some of these cases. Spironolactone addresses this by blocking mineralocorticoid receptors but is associated with adverse effects. Previous attempts at aldosterone synthase inhibition have led to undesired decreases in serum cortisol levels. Baxdrostat is the first aldosterone synthase inhibitor with high selectivity as demonstrated in a phase one trial, making it a promising potential intervention for patients with treatment-resistant hypertension.

PATIENTS: Adults with treatment-resistant hypertension

INTERVENTION: Baxdrostat

CONTROL: Placebo

PRIMARY OUTCOME: Systolic BP

Secondary Outcome: Diastolic BP

METHODS (BRIEF DESCRIPTION):

- The trial was conducted primarily at community-based practices in the U.S.
- The study population consisted of White (70%), Black (28%), Hispanic (43%), and Asian (2%) participants.
- Inclusion criteria:
  - Adult male or female patients ≥18 years old.
  - On a stable regimen of ≥3 antihypertensive agents at the time of screening, one of which is a diuretic.
  - Mean seated BP ≥130/80 mmHg.
- Exclusion criteria:
  - Mean seated systolic BP ≥180 mmHg or diastolic BP ≥110 mmHg.
  - Estimated glomerular filtration rate (GFR) <45 ml/minute/1.73 m2 of body surface area.
  - Uncontrolled diabetes
- Patients were divided into the following treatment groups for medication taken once daily by mouth (PO):
  - Baxdrostat 0.5 mg
  - Baxdrostat 1 mg
  - Baxdrostat 2 mg
  - Placebo
- BP was measured while the participant was seated at approximately the same time of day and in the same arm each time.
  - No morning medications were given before blood pressure measurement.
  - The difference in the mean seated systolic BP from baseline to the end of the 12-week treatment period was measured for the primary outcome.
  - The secondary outcome was measured by the mean seated difference in diastolic BP.

INTERVENTION (# IN THE GROUP): 205

COMPARISON (# IN THE GROUP): 69

FOLLOW-UP PERIOD: 12 weeks

RESULTS:

Primary Outcome –

- Baxdrostat 2 mg significantly reduced systolic BP compared to placebo (−20±2.1 mmHg vs –9.4 mmHg, respectively; mean difference [MD] –11 mmHg; 95% CI, –16 to –5.5).
- Baxdrostat 1 mg significantly reduced systolic BP compared to placebo (−18±2.0 mmHg vs –9.4 mmHg, respectively; MD –8.1 mmHg; 95% CI, –14 to –2.8).
- Baxdrostat 0.5 mg reduced systolic blood pressure but not significantly compared to placebo (−12±1.9 mmHg vs –9.4 mmHg, respectively)

Secondary Outcome –

- Baxdrostat 2 mg significantly reduced diastolic blood pressure compared to placebo (–14±1.3 mmHg; MD –5.2mmHg; 95% CI, –8.7 to –1.6).

LIMITATIONS:

- The trial was stopped early because the independent data monitoring committee found that the trial had met predetermined criteria for overwhelming efficacy.
- The risks and benefits of aldosterone synthase inhibition greater than 12 weeks were not evaluated.
- Aldosterone synthase inhibition with alternative antihypertensive agents was not studied. Baxdrostat was not compared to other antihypertensives in this study.
- Patients with GFR <45 were excluded and therefore not potential efficacy of Baxdrostat was not evaluated in this population.
- Patients with adherence of <75% to medication were excluded and therefore potential efficacy of Baxdrostat was not evaluated in this population.

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To Ablate or Not Ablate: The End-Stage Heart Failure Debate

Catheter Ablation in End-Stage Heart Failure with Atrial Fibrillation

Sohns C, Fox H, Marrouche NF, et al. Catheter Ablation in End-Stage Heart Failure with Atrial Fibrillation. *N Engl J Med.* 2023;389(15):1380-1389. doi:10.1056/NEJMoa2306037

KEY TAKEAWAY: Catheter ablation therapy in combination with medical therapy prevents significantly more deaths than medical therapy alone in adults with end-stage heart failure (ESHF).

STUDY DESIGN: Single-site, open-label randomized trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to non-blinded study)

BRIEF BACKGROUND INFORMATION: Studies of catheter ablation in patients with heart failure with symptomatic atrial fibrillation found a lower rate of death and symptomatic heart failure. This study investigates the effect of catheter ablation on patients with ESHF in regard to morbidity and mortality.

PATIENTS: Adults eligible for heart transplant or left ventricular assist device (LVAD)

INTERVENTION: Catheter ablation and medical therapy

CONTROL: Medical therapy

PRIMARY OUTCOME: Composite score of death, LVAD placement, and heart transplantation

Secondary Outcome: Individual occurrence of death from any cause, LVAD, urgent heart transplantation, and atrial fibrillation occurrence

METHODS (BRIEF DESCRIPTION):

- Adult patients were recruited from a heart transplant referral center in Germany with end-stage heart failure and symptomatic atrial fibrillation.
- Inclusion criteria were New York Heart Association functional classification class two or higher, left ventricular ejection fraction of ≤35%, and impaired functional capacity via six minute walk test.
- Exclusion criteria included prior catheter ablation, <12 months life expectancy, and contraindications to anticoagulation.
- Participants had a mean age of 62 years old in the ablation group and 65 years old in the medical therapy group.
    - 88% of participants identified as men in the ablation group vs 74% in the medical therapy group.
- The treatment group underwent standard ablation in conjunction with direct current cardioversion at the time of the procedure and antiarrhythmic medications were stopped.
- Both groups received medical therapy based on current guidelines.
- The primary endpoint was the composite score of death, implantation of LVAD, or urgent heart transplantation.
    - Follow-up occurred every three months for the first year then annually with an echocardiogram, device interrogation, and physician symptom assessment interview at each visit.
- Secondary endpoints were individual scores for death from cardiovascular causes, LVAD, heart transplant placement, and atrial fibrillation burden or occurrence.

INTERVENTION (# IN THE GROUP): 97

COMPARISON (# IN THE GROUP): 97

FOLLOW-UP PERIOD: Median duration of 18 months

RESULTS:

Primary Outcome –

- The ablation group had a lower risk of the composite outcome of death, LVAD placement, and heart transplant as compared to the medical therapy group (hazard ratio [HR] 0.24; 95% CI, 0.11–0.52, NNT=5).

Secondary Outcome –

- Individual occurrence of death from any cause, LVAD, and atrial fibrillation occurrence were lower in the ablation group compared to medical therapy alone.
    - Death from any cause (HR 0.29; 95% CI, 0.12–0.72)
    - LVAD (HR 0.09; 95% CI, 0.01-0.70)
    - Atrial fibrillation burden at 12 months (mean between-group difference 23 percentage points; 95% CI, 13–33).
- There was no statistically significant decrease in urgent heart transplants in the ablation group compared to the medical therapy group.

LIMITATIONS:

- Death was measured due to cardiovascular death, to which they were already predisposed and may skew results.
- The medical therapy group was older which may be possibly biased towards worse outcomes.
- The number of patients in the study was limited.
- The trial was stopped early.
- The study had a high crossover rate with 16 patients from medical therapy also receiving ablation.

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Nothing to Sneeze At: An Update on Amoxicillin-Clavulanate vs Amoxicillin for Pediatric Acute Sinusitis

Treatment Failure and Adverse Events After Amoxicillin-Clavulanate vs Amoxicillin for Pediatric Acute Sinusitis

Savage TJ, Kronman MP, Sreedhara SK, Lee SB, Oduol T, Huybrechts KF. Treatment Failure and Adverse Events After Amoxicillin-Clavulanate vs Amoxicillin for Pediatric Acute Sinusitis. *JAMA*. 2023;330(11):1064-1073. doi:10.1001/jama.2023.15503

KEY TAKEAWAY: Overall, there is no significant difference in acute sinusitis treatment failure between amoxicillin-clavulanate and amoxicillin in pediatric patients. However, amoxicillin-clavulanate has significantly fewer treatment failures than amoxicillin in patients 12–17 years old. There is a significantly higher risk of overall adverse events (gastrointestinal symptoms, yeast infections) with amoxicillin-clavulanate treatment compared to amoxicillin treatment.

STUDY DESIGN: Cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Acute sinusitis is a well-known and common reason why antibiotics are prescribed for pediatric patients in the outpatient setting. However, there is a lack of consensus over whether amoxicillin-clavulanate or amoxicillin is the optimal initial treatment. There is also a need for updated information on the efficacy and safety of these treatments.

PATIENTS: Pediatric patients with acute sinusitis

INTERVENTION: Amoxicillin-clavulanate

CONTROL: Amoxicillin

PRIMARY OUTCOME: Treatment failure

Secondary Outcome: Adverse events

METHODS (BRIEF DESCRIPTION):

- Nationwide data was obtained from the MarketScan Commercial Claims and Encounters Database.
- Demographics:
  - 51% female
  - Patients 0–17 years old (50% 12–17 years old)
- Inclusion criteria:
  - An outpatient encounter with the International Classification of Disease (ICD)-10 code for acute sinusitis and a same-day amoxicillin-clavulanate or amoxicillin prescription.
  - At least 365 days of continuous insurance enrollment.
- Exclusion criteria:
  - Chronic sinus disease diagnosis.
  - A same-day diagnosis of an additional infectious disease.
  - An oral antibiotic prescription or acute sinusitis diagnosis within the previous 30 days.
- Treatment failure was defined by any new antibiotic prescription, ER visit, or inpatient admission within 14 days of initial prescription for acute sinusitis or a complication from acute sinusitis.
- Adverse events included gastrointestinal symptoms, yeast infections, skin reactions, hypersensitivity reactions, *Clostridiodes difficile (C. difficile)* infections, or acute kidney injury (AKI).
- Follow-up period timeframe was determined based on pre-existing data that the most common treatment window for either amoxicillin-clavulanate or amoxicillin prescriptions was 10 days.

INTERVENTION (# IN THE GROUP): 99,471

COMPARISON (# IN THE GROUP): 99,471

FOLLOW-UP PERIOD: 14 days

RESULTS:

Primary Outcome –

- No significant difference in overall treatment failure between patients receiving amoxicillin-clavulanate and amoxicillin (relative risk [RR] 0.98; 95% CI, 0.92–1.1).
- In the subgroup of patients 12–17 years old, amoxicillin-clavulanate had significantly fewer treatment failures compared to amoxicillin (RR 0.87; 95% CI, 0.79–0.95).

Secondary Outcome –

- Significantly higher risk of gastrointestinal symptoms (RR 1.2; 95% CI, 1.1–1.3) and yeast infections (RR 1.3; 95% CI, 1.2–1.5) with amoxicillin-clavulanate treatment compared to amoxicillin treatment.
- There were no significant differences in skin reactions, hypersensitivity reactions, *C. difficile* infections, or AKI between the two medications.

LIMITATIONS:

- The study cohort was commercially insured.

- The lack of demographic data reported in the study limited generalizability.
- The study did not evaluate medication adherence.
- Weight-based dosing and microbiologic data were not obtained.

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