



GEMs of the Week

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What's in this week's issue?

Week of December 27 - 31, 2021

SPOTLIGHT: Blood Pressure Control - How Low Can You Go?

- Steps Towards Health: More Steps Per Day Can Reduce Mortality
- Dual Therapy Superior to Aspirin Alone in Vascular Patients
- Does Metronidazole Improve Outcomes in Pelvic Inflammatory Disease?

Final Report of a Trial of Intensive versus Standard Blood-Pressure Control

SPRINT Research Group, Lewis CE, Fine LJ, et al. Final Report of a Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med.* 2021; 384(20):1921–1930.

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KEY TAKEAWAY: Intensive treatment of high blood pressure decreases the risk of cardiovascular events and mortality compared to standard treatment in patients with elevated CV risk without diabetes. However, intensive high blood pressure treatment increases adverse events such as syncope, hypotension, and renal failure.

STUDY DESIGN: Multisite, randomized, controlled, open-label trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Treatment of hypertension decreases the risk of adverse CV outcomes, but the optimal target systolic BP is uncertain. In 2007, the National Heart, Lung, and Blood Institute (NHLBI) expert panel hypothesized that a systolic blood-pressure goal of <120 mmHg would decrease adverse clinical events compared to a standard goal of <140 mmHg. Previous trials have evaluated intensive therapy to achieve a BP goal of <140 but none have looked at a specific systolic BP lower than 140.

PATIENTS: Older adults with elevated systolic blood pressure (SBP)

INTERVENTION: Intensive treatment of hypertension

CONTROL: Standard treatment of hypertension

OUTCOME: Composite of acute coronary syndrome (ACS), myocardial infarction, acute decompensated heart failure, stroke, or death from CV causes
Secondary Outcomes: Individual components of the primary outcome and all-cause mortality

METHODS (BRIEF DESCRIPTION):

- Participants were ≥50 years old (mean 68 years old) with a systolic blood pressure of 130–180 mmHg and at least one CV risk factor.
 - CV risk factors: CV disease, 10-year risk of cardiovascular disease ≥15%, chronic kidney disease, or ≥75 years old
 - Exclusion Criteria: diabetes mellitus, previous stroke, dementia

- Participants were assigned randomly to either intensive or standard hypertension treatment.
- Antihypertensive medications were titrated according to specific algorithms to obtain systolic BP of < 120 mm Hg with intensive treatment and 140 mm Hg with standard treatment.
- Follow-up visits and CV outcomes were obtained quarterly via interviews and emergency department or hospital discharge summaries.

INTERVENTION (# IN THE GROUP): 4,678

COMPARISON (# IN THE GROUP): 4,683

FOLLOW UP PERIOD: Mean 3.3 years

RESULTS:

Primary Outcome –

- Intensive treatment decreased the risk for a composite outcome compared to standard treatment (Hazard ratio [HR] 0.73; 95% CI, 0.63–0.86).

Secondary Outcomes –

- Intensive treatment decreased the risk of:
 - Myocardial infarction (HR 0.72; 95% CI, 0.56–0.93)
 - Heart failure (HR 0.63; 95% CI, 0.46–0.86)
 - All-cause mortality (HR 0.75; 95% CI, 0.61–0.92)
- There was no difference between the groups in the following:
 - Strokes (HR 0.89; 95% CI, 0.64–1.2)
 - ACS (HR 1.0; 95% CI, 0.66–1.6)
- The intensive blood pressure treatment group experienced greater adverse events than the control group:
 - Syncope (HR 1.5; 95% CI, 1.2–1.9)
 - Hypotension (HR 1.8; 95% CI, 1.4–2.4)
 - Electrolyte abnormality (HR 1.3; 95% CI, 1.1–1.7)
 - Acute kidney injury/renal failure (HR 1.7; 95% CI, 1.4–2.1).

LIMITATIONS:

- Patients in general practice may be less compliant with medications than persons willing to enlist in a medical trial.
- Patients with diabetes were excluded.
- Rigorous follow up of patients may not be feasible for practicing physicians.

- Only patients with CV risk factors were included so results may not apply to patients without other CV risk factors.

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Steps Towards Health: More Steps Per Day Can Reduce Mortality

Association of Daily Step Count and Step Intensity with Mortality Among US Adults

Saint-Maurice PF, Troiano RP, Bassett DR, et al. Association of Daily Step Count and Step Intensity with Mortality Among US Adults. *JAMA*. 2020; 323(12):1151–1160.

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KEY TAKEAWAY: Higher daily step counts are associated with decreased all-cause mortality. Step intensity is not associated with all-cause mortality.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Results of previous studies comparing daily step count to mortality have not been generalizable. Separately, step intensity has not reliably been demonstrated to correlate definitively with cardiometabolic health.

PATIENTS: Representative sample of adults >40 years old in the United States

INTERVENTION: 2,000 steps/day; 8,000 steps/day; 12,000 steps/day; higher step intensity

CONTROL: 4,000 steps/day; lower step intensity

OUTCOME: All-cause mortality

Secondary Outcomes: Cardiovascular disease (CVD) and cancer mortality

METHODS (BRIEF DESCRIPTION):

- Participant data was obtained from hip accelerometer readings from the National Health and Nutrition Examination Survey (HNANES) from 2003–2004.
- All respondents over age 40 who logged at least one day of accelerometer wear during the survey period were included.
- Step count was calculated as average steps/day. Step counts of approximately 2,000, 8,000, and 12,000 were compared to a 4,000 steps/day reference.
- 3 separate step-intensity measures were used:
 - Number of bouts (continuous walking of >2 minutes)
 - Peak-30 cadence (mean of the 30 highest single-minute step rates per day)
 - Peak-1 cadence (highest single-minute step rate per day)
- Levels of daily steps and intensities were compared against mortality (monitored through 2015).

- Respondent data was adjusted for demographics, race, and health history.

INTERVENTION (# IN THE GROUP): 4,185

COMPARISON (# IN THE GROUP): 655

FOLLOW UP PERIOD: Weighted mean of 10 years

RESULTS:

Primary Outcome –

- More than 4,000 steps/day is associated with lower all-cause mortality.
 - 8,000 vs 4,000 steps/day (HR 0.49; 95% CI, 0.44–0.55)
 - 12,000 vs 4,000 steps/day (HR 0.35; 95% CI, 0.28–0.45)
- Less than 4,000 steps/day is associated with higher all-cause mortality.
 - 2,000 vs 4,000 steps/day (HR 1.5; 95% CI, 1.41–1.62)
- Similar results were found among all age, gender and racial groups represented.
- When adjusted for step count, higher step intensity did not show significant benefit.

Secondary Outcomes –

- 8,000 steps/day compared to 4,000 steps/day decreased the risk of:
 - CVD mortality (HR 0.49; 95% CI, 0.40–0.60)
 - Cancer mortality (HR 0.67; 95% CI, 0.54–0.82)
- Increased step intensity (when adjusted for step count) did not result in significant benefits.

LIMITATIONS:

- Association does not infer causation.
- Confounding factors exist; for instance, a higher step count could be expected from healthier individuals.
- The step-measuring device can misidentify other movement as steps while ignoring swimming, cycling, etc.
- Recorded accelerometer data may be discordant when compared to actual observed steps/minute.
- The collected death certificates may misrepresent cause of death.
- Individuals excluded for missing data significantly differed from the inclusion group.

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Dual Therapy Superior to Aspirin Alone in Vascular Patients

Mortality Benefit of Rivaroxaban Plus Aspirin in Patients with Chronic Coronary or Peripheral Artery Disease

Eikelboom JW, Bhatt DL, Fox KAA, et al. Mortality Benefit of Rivaroxaban Plus Aspirin in Patients with Chronic Coronary or Peripheral Artery Disease. *Journal of the American College of Cardiology*. 2021; 78(1): 14-23. doi:10.1016/j.jacc.2021.04.083
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KEY TAKEAWAY: Combined therapy of rivaroxaban and aspirin (ASA) reduces all cause and cardiovascular mortality in patients with coronary artery disease (CAD) or peripheral artery disease (PAD) as compared to ASA alone.

STUDY DESIGN: Multisite, blinded, randomized control trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: ASA is considered standard secondary prevention in patients with known CAD and PAD, which are major causes of mortality. Previous studies have looked at combination of warfarin and ASA and found increased rate of adverse outcomes without improvement in cardiovascular events. Rivaroxaban is one of the newer anticoagulants that has been used to prevent venous thromboembolism and stroke but use with ASA for secondary prevention has not been examined due to the increased risk of major bleeding.

PATIENTS: Older adults with chronic CAD or PAD

INTERVENTION: Rivaroxaban 2.5 mg BID + ASA 100 mg daily

CONTROL: ASA 100 mg daily

OUTCOME: All-cause mortality, cardiovascular (CV) mortality, and non-CV mortality

METHODS (BRIEF DESCRIPTION):

- Adults with CAD or PAD received ASA and a placebo for 30 days prior to randomization.
- Randomization occurred in a 1:1 ratio.
- Participants were seen at one and six months, followed by six-month intervals with a median follow up of 23 months.
- Study conducted at 602 sites in 33 countries across six continents.
- Trial stopped early (at 1,323 primary events vs 2,200 primary events target) due to clear evidence of benefit.

INTERVENTION (# IN THE GROUP): 9,152

COMPARISON (# IN THE GROUP): 9,126

FOLLOW UP PERIOD: Median of 23 months (range 16–30 months, maximum 47 months)

RESULTS:

- ASA + rivaroxaban reduced all-cause mortality by 18% compared to ASA alone (3.4% vs 4.1%; hazard ratio [HR] 0.82; 95% CI, 0.71–0.96; number needed to treat [NNT]=142).
- ASA + rivaroxaban reduced CV mortality compared to ASA alone (1.7% vs 2.2%; HR 0.78; 95% CI, 0.64–0.96; NNT=200).
- ASA + rivaroxaban does not reduce non-CV mortality compared to ASA alone (1.7% vs 1.9%; HR 0.87; 95% CI, 0.70–1.1).
- The authors note individuals with increased baseline risk of CV events have a higher mortality benefit.

LIMITATIONS:

- Sponsored by Bayer.
- Unknown how chronic modifiable risk factors, such as hypertension or diabetes, were managed.
- Possible misclassification of deaths, as CV deaths are defined as a death without a clear non-CV cause.
- Not clear if all patients were accounted for in the study.

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Does Metronidazole Improve Outcomes in Pelvic Inflammatory Disease?

A Randomized Controlled Trial of Ceftriaxone and Doxycycline, With or Without Metronidazole, for the Treatment of Acute Pelvic Inflammatory Disease

Wiesenfeld HC, Meyn LA, Darville T, Macio IS, Hillier SL. A Randomized Controlled Trial of Ceftriaxone and Doxycycline, With or Without Metronidazole, for the Treatment of Acute Pelvic Inflammatory Disease. *Clin Infect Dis*. 2021; 72(7):1181-1189. doi:10.1093/cid/ciaa101

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KEY TAKEAWAY: In patients with acute Pelvic Inflammatory Disease, addition of metronidazole does not result in changes in symptom improvement or clinical cure but does reduce vaginal microbiota at 30 days.

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

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Pelvic inflammatory disease (PID) is associated with significant cost and pain for affected patients. The current CDC guidelines for treatment are ceftriaxone and doxycycline which have limited anaerobic activity; however, it is postulated that anaerobic pathogens play a significant role in the disease. Prior studies of metronidazole for PID have not used the current standard of care and may underestimate treatment effect.

PATIENTS: Women with acute PID

INTERVENTION: Metronidazole + standard treatment

CONTROL: Standard treatment alone

OUTCOME: Clinical improvement at 3 days

Secondary Outcomes: Clinical cure, pelvic tenderness, and anaerobic organisms at 30 day; adverse events

METHODS (BRIEF DESCRIPTION):

- Women 15–40 years old with criteria for PID were included.
 - Criteria for PID: lower abdominal or pelvic pain and presence of cervical motion tenderness, uterine tenderness, or adnexal tenderness on pelvic exam
 - Exclusion criteria: pregnancy, use of antibiotics in prior seven days, abortion or miscarriage in prior six weeks
- All patients received standard care (ceftriaxone IM 250 mg single dose and doxycycline 100 mg bid) for 14 days.

- Participants were randomized 1:1 to also receive placebo or metronidazole 500 mg bid.
- History and physical examinations (including vaginal and cervical swabs and endometrial aspirates) were performed by trained study clinicians.
 - All clinical assessments and swabs were repeated at 3 days and 30 days.
- A clinical tenderness score was established by grading the severity of pelvic tenderness which was assessed by cervical motion, uterine, and bilateral adnexal tenderness.
- Clinical improvement was defined as any reduction in clinical tenderness score at three days.
- Clinical cure was defined as greater than 70% improvement in clinical tenderness score and absence of fever.

INTERVENTION (# IN THE GROUP): 116

COMPARISON (# IN THE GROUP): 117

FOLLOW UP PERIOD: 30 days

RESULTS:

Primary Outcome –

- Clinical improvement at 3 days did not differ between the metronidazole and placebo groups (92% vs 90%, respectively; $P=.81$).

Secondary Outcomes –

- Clinical cure at 30 days did not differ between the metronidazole and placebo groups (97% vs 90%, respectively; $P=.13$).
- Metronidazole significantly decreased pelvic tenderness at 30 days compared to placebo (9% vs 20%, respectively; $P<.05$).
- Metronidazole significantly decreased anaerobic organisms at 30 days compared to placebo (8% vs 21%, respectively; $P<.05$; relative risk ratio 0.61; number needed to treat=8).
- Adverse events did not differ between the metronidazole group and the placebo group (90% vs 80%, respectively; $P=.07$; number needed to harm=11).

LIMITATIONS:

- Since the clinical cure was similar at 3 days, the significance of decreasing certain organisms in vaginal microbiota is uncertain.

- The study did not investigate whether decreasing these organisms improved fertility or decreased ectopic pregnancies.

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