GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of February 13 - 17, 2023

SPOTLIGHT: Patterns of Physical Activity - How Do They Influence Mortality?

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Patterns of Physical Activity: How Do They Influence Mortality?

Association of the "Weekend Warrior" and Other Leisure-Time Physical Activity Patterns with All-Cause and Cause-Specific Mortality: A Nationwide Cohort Study

dos Santos M, Ferrari G, Lee DH, et al. Association of the "Weekend Warrior" and Other Leisure-time Physical Activity Patterns with All-Cause and Cause-Specific Mortality: A Nationwide Cohort Study. *JAMA Internal Med*. 2022; 182(8):840–848.

KEY TAKEAWAY: Performing the WHO recommended level of exercise weekly may be beneficial whether achieved in ≥3 sessions weekly ('regularly active') or only 1–2 sessions weekly ('weekend warrior').

STUDY DESIGN: Prospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: The World Health Organization (WHO) recommends that adults perform at least 150 minutes of moderate exercise or at least 75 minutes of vigorous exercise weekly. It is unknown if obtaining these goals in ≥3 sessions weekly versus 1–2 sessions weekly provides the same benefits in all-cause, cardiovascular (CVD), or cancer mortality.

PATIENTS: Adults 18–84 years old

INTERVENTION: Achieving WHO recommended levels of physical activity in 1–2 or ≥3 sessions weekly

CONTROL: Inactivity

PRIMARY OUTCOME: All-cause mortality

Secondary Outcome: CVD and cancer mortality

METHODS (BRIEF DESCRIPTION):

- Adults 18–84 years old from US National Health Interview Survey (NHIS) were randomly selected.
- Participants were excluded if diagnosed with cancer, COPD, heart disease, stroke, or if unable to perform moderate or vigorous physical activity.
- Participants were classified as active or inactive based on responses to a questionnaire.
- The active group was then divided into groups based on whether they performed exercise in ≥3 sessions weekly (regularly active) or 1–2 sessions weekly (Weekend Warrior).
- Mortality outcomes were collected from National Death Index.

INTERVENTION (# IN THE GROUP):

- Weekend Warriors: 9,992
- Regularly active: 150,906

COMPARISON (# IN THE GROUP): 190,080

FOLLOW-UP PERIOD: Median 10.4 years

RESULTS:

Primary Outcome –

- The regularly active group compared to the inactive group had significant benefits in:
  - All-cause mortality (hazard ratio [HR] 0.85; 95% CI, 0.83–0.88)
  - CVD mortality (HR 0.77; 95% CI, 0.71–0.84)
  - Cancer mortality (HR 0.88; 95% CI, 0.83–0.94)
- The Weekend Warrior group did not significantly differ from the inactive group:
  - All-cause mortality (HR 0.92; 95% CI, 0.83–1.02)
  - CVD mortality (HR 0.87; 95 %CI, 0.66–1.1)
  - Cancer mortality (HR 0.94; 95% CI, 0.77–1.1)
- The Weekend Warrior group did not significantly differ from the regularly active group:
  - All-cause mortality (HR 1.1; 95% CI, 0.97–1.2)
  - CVD mortality (HR 1.1; 95% CI, 0.85–1.5)
  - Cancer mortality (HR 1.1; 95% CI, 0.85–1.3)

LIMITATIONS:

- The questionnaire was utilized to ascertain the level of physical activity.
- Exclusions as above were not included in the analysis. Many of these exclusions are prevalent in the general patient population (heart disease, stroke, etc.).
- Diet was not adjusted for as a potential confounding factor.
- The Weekend Warrior group had a small number of deaths overall.
- The study did not include deaths after December 31, 2015.
- The definition of physical activity was narrow and did not include those that exercised but did not meet the study threshold.

Breanne Hunley, DO
UAMS Southwest FMRP
Texarkana, AR

Does Physical Activity as a Child Prevent Cardiovascular Health Conditions Later in Life?

Association of Cardiorespiratory Fitness Levels During Youth with Health Risk Later in Life: A Systematic Review and Meta-Analysis

García-Hermoso A, Ramírez-Vélez R, García-Alonso Y, Alonso-Martínez AM, Izquierdo M. Association of Cardiorespiratory Fitness Levels During Youth With Health Risk Later in Life: A Systematic Review and Meta-analysis. *JAMA Pediatr*. 2020;174(10):952–960. doi:10.1001/jamapediatrics.2020.2400

KEY TAKEAWAY: Cardiorespiratory fitness (CRF) early in life may be associated with lower body mass index (BMI) and may improve cardiometabolic health parameters later in life.

STUDY DESIGN: Systematic review and meta-analysis of prospective cohort studies

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: The leading cause of death in the US is cardiovascular disease. Health measures to prevent cardiovascular disease are often not implemented until adulthood. This meta-analysis examines the association between targeting increased CRF early in life and cardiometabolic health parameters later in life.

PATIENTS: Healthy children 3–18 years old

INTERVENTION: Increased CRF

CONTROL: Decreased CRF

PRIMARY OUTCOME: Adiposity measurements and cardiometabolic parameters

METHODS (BRIEF DESCRIPTION):

- Prospective cohort studies obtained from MEDLINE, Embase, and SPORTDiscus electronic databases.
- Inclusion criteria for studies:
  - CRF was measured using a validation test (field or laboratory test).
  - CRF was assessed at baseline and/ or any change from baseline during the follow-up period.
  - Healthy children between 3–18 years old
  - Prospective cohort studies with follow-up of at least one year
- 37,563 participants were included in the final analysis.
- Outcomes that were measured or compared: adiposity measurements (BMI, waist circumference, skinfold thickness, body fat percentage) and cardiometabolic parameters (lipid panel, fasting glucose, fasting insulin, blood pressure).
- Bias risk of studies was assessed using the Newcastle-Ottawa Scale.
- Analyses were conducted using random effects models and Comprehensive Meta-analysis, version 2.2 (Biostat).
- Estimates were converted to correlations coefficient (r). r values of 0.10 or less are considered weak effects, r values of 0.10 to 0.36 are considered moderate effects, and r values of 0.37 are considered large effects.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Range of one year to 27 years

RESULTS:

Primary Outcome –

- A weak moderate association was found between CRF at baseline and BMI (r = –0.11; 95% CI, –0.18 to –0.04; I^2=59).
- For the various cardiometabolic parameters studied, a weak-moderate relationship with CRF at baseline was found.
  - Total cholesterol level (r = –0.12; 95% CI, –0.19 to –0.05; I^2=76)
  - Fasting glucose (r = –0.02; 95% CI, –0.07 to 0.02; I^2=0)
  - Systolic BP (r = –0.02; 95% CI, –0.08 to 0.04; I^2=75)

LIMITATIONS:

- The studies had varying measures they used as health parameters thereby increasing the heterogeneity of the results.
- In defining CRF, the authors focused on assessing based on oxygen consumption. This oxygen consumption was reported in ratio to body fat in all but three studies.

Oluwatobiloba Adenuga, MD
Indiana University School of Medicine (Arnett) Program
Lafayette, IN

Endometriosis is Associated with Early Natural Menopause

Association Between Laparoscopically Confirmed Endometriosis and Risk of Early Natural Menopause

Thombre Kulkarni M, Shafrir A, Farland LV, et al. Association between laparoscopically confirmed endometriosis and risk of early natural menopause. *JAMA Network Open*. 2022;5(1). doi:10.1001/jamanetworkopen.2021.44391

KEY TAKEAWAY: Women with laparoscopically confirmed endometriosis are at 50% greater risk for early natural menopause (ENM) after accounting for demographic, behavioral, and reproductive factors. An even greater risk is observed in women who are nulliparous or in those who have never used oral contraceptives.

STUDY DESIGN: Population-based cohort study (prospective time to event analysis)

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: ENM (menopause before 45 years of age) and endometriosis (which affects 10% of women) have similar risk factors and are both associated with cardiovascular disease and early death. Endometriosis and endometriomas have been associated with a decreased ovarian reserve and increased ovary age respectively, while ENM is associated with a shortened reproductive window. More research was needed to investigate the association between endometriosis and the risk for ENM.

PATIENTS: Premenopausal women

INTERVENTION: Laparoscopically confirmed endometriosis

CONTROL: No diagnosis of endometriosis

PRIMARY OUTCOME: Incidence of ENM

Secondary Outcome: Effect of body mass index, cigarette smoking, oral contraceptive use, parity, and infertility attributed to ovulatory disorder on the incidence of ENM in those with endometriosis

METHODS (BRIEF DESCRIPTION):

- This study used survey data from the Nurse's Health Study II which included female registered nurses 25–42 years old.
    - Participants provided information on mental and physical health. The study used data from 1989 to 2015.
- Inclusion criteria: Premenopausal with no previous history of cancer, hysterectomy, or oophorectomy
- Participants without surgically confirmed endometriosis were excluded from the endometriosis group.
- Menopause was defined as amenorrhea for 12 months and for three consecutive questionnaires. Questionees reported cessation secondary to surgery, radiotherapy, chemotherapy, or natural.
- Questionnaires included data on weight, cigarette smoking status, oral contraception use and duration, parity, lactation duration, and history of infertility.
- Participants contributed person-months to the cohort until one of the following occurred: (1) menopause; (2) 45 years old; (3) hysterectomy; (4) oophorectomy; (5) cancer diagnosis; (6) death; (7) loss to follow up; (8) the end of follow up (May 2017).
- The Cox proportional hazards regression model was used for the association of ENM and endometriosis.
- Likelihood ratios were calculated for the effects of smoking status, OC use, parity, and infertility history to account for cofounders.

INTERVENTION (# IN THE GROUP): 3,921

COMPARISON (# IN THE GROUP): 102,712

FOLLOW-UP PERIOD: 1,508,462 person-years

RESULTS:

Primary Outcome –

- Women with surgically confirmed endometriosis had a 50% greater risk of early menopause compared with women without endometriosis (HR 1.5; 95% CI, 1.3–1.7).

Secondary Outcome –

- The risk of early menopause in women with endometriosis increased for those with no prior oral contraceptive use (HR 2.0; 95% CI, 1.3–3.1 never vs HR 1.2; 95% CI, 1.0–1.4 ever).
- Nulliparous women with endometriosis also were at increased risk for ENM (HR 1.5; 95% CI, 1.2–1.9 nulliparous vs HR 1.1; 95% CI, 0.94–1.4 parous).
- There was no difference in the association between endometriosis and early menopause when

accounting for BMI, smoking status, or history of infertility due to ovarian cause.

LIMITATIONS:

- All participants in the study were registered nurses and the race/ethnicity of the study was homogeneous (approximately 96% White), limiting generalizability.
- Censoring can cause selection bias.
- Self-reported data can lead to exposure misclassification.
- Low incidence of early menopause presented some limitations with estimating and the need for large sample sizes and long follow-up duration.

Abigail Calkins, DO
Family Medicine of Southwest Washington PeaceHealth
Vancouver, WA

A Flood of New Information: Does Fluid Restriction for the Treatment of Septic Shock for Patients in the ICU Increase Mortality?

Restriction of Intravenous Fluid in ICU Patients with Septic Shock

Meyhoff TS, Hjortrup PB, Wetterslev J, et al. Restriction of Intravenous Fluid in ICU Patients with Septic Shock. *N Engl J Med*. 2022;386(26):2459-2470. doi:10.1056/NEJMoa2202707

KEY TAKEAWAY: Fluid restriction in patients in the ICU with septic shock does not increase the risk of mortality at 90 days.

STUDY DESIGN: International, stratified, open-table, randomized clinical trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Current guidelines for treating septic shock in the ICU recommend an initial fixed volume of fluid equaling 30 mL/kg. However, the level of certainty for this treatment is low and there is no current recommendation concerning fluid restriction in patients who still show signs of hypo perfusion after initial resuscitation efforts have been made.

PATIENTS: ICU patients in septic shock

INTERVENTION: Restriction of fluids

CONTROL: Standard fluids

PRIMARY OUTCOME: Mortality

Secondary Outcome: Serious adverse events

METHODS (BRIEF DESCRIPTION):

- Adults with the diagnosis of septic shock and being treated in the ICU were included.
- Septic shock was defined as all of the following:
  - Suspected or confirmed infection
  - Plasma lactate level ≥2 mmol per liter
  - Use of vasopressor or inotropic
  - Received ≥1 liter of IV fluids in 24 hours
- Patients were randomized into two treatment groups:
  - Restrictive fluid therapy (mean 3,414 after 90 days)
  - Standard fluid therapy (mean 5,275 after 90 days)
- Primary outcome was death within 90 days.
- Mortality data were retrieved from patient records or administrative registries.
- Secondary outcome was serious adverse events which included cerebral, cardiac, intestinal, or limb ischemic events or new acute kidney injury.

INTERVENTION (# IN THE GROUP): 755

COMPARISON (# IN THE GROUP): 776

FOLLOW-UP PERIOD: 90 days

RESULTS:

Primary Outcome –

- There was no difference in mortality at 90 days between restrictive and standard fluid therapy (adjusted relative risk [ARR] 1.0; 95% CI, 0.89–1.1).

Secondary Outcome –

- There was no difference in the occurrence of serious adverse events between restrictive and standard fluid therapy (ARR 0.95; 95% CI, 0.77–1.2).

LIMITATIONS:

- Patients, doctors, and researchers were aware of patient assignment.
- Some patients did receive fluid before randomization.
- Most patients received more fluid than required per protocol.
- The study did not consider some of the co-interventions patients received.

Alexis House, DO
UAMS FMR, Southwest Regional Program
Texarkana, AR

Platelet-Rich Plasma: Taking a Stab at Knee Osteoarthritis

The Effectiveness of Leucocyte-Poor Platelet-Rich Plasma Injections on Symptomatic Early Osteoarthritis of the Knee: The PEAK Randomized Controlled Trial

Lewis E, Merghani K, Robertson I, et al. The effectiveness of leucocyte-poor platelet-rich plasma injections on symptomatic early osteoarthritis of the knee: the PEAK randomized controlled trial. *Bone Joint J*. 2022;104-B(6):663-671. doi:10.1302/0301-620X.104B6.BJJ-2021-1109.R2

KEY TAKEAWAY: Single and serial platelet-rich plasma (PRP) injections are not superior to normal saline.

STUDY DESIGN: Single-blinded, parallel-group, randomized controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to small sample size)

BRIEF BACKGROUND INFORMATION: Knee osteoarthritis is a common disease leading to disability and decreased quality of life. Despite its ubiquitous nature, treatments are still lacking in notable efficacy regarding stabilization or reversal of disease process. Platelet-rich plasma is a popular alternative to corticosteroid injections although with conflicting findings in past studies.

PATIENTS: Patients with early evidence of knee osteoarthritis

INTERVENTION: PRP injection(s)

CONTROL: Placebo

PRIMARY OUTCOME: Pain and function

Secondary Outcome: Likelihood of recommending the injection to others

METHODS (BRIEF DESCRIPTION):

- Adults with early evidence of knee osteoarthritis with Kellgren-Lawrence scale 0–2 radiographic evidence to support the diagnosis.
- Patients were excluded for systemic illness, previous open knee surgeries, and coagulopathies.
- Patients were randomized to placebo, single PRP injection, or serial PRP injections.
- Patients then received injections at one-week intervals for a total of three injections.
- Venous puncture was performed on all patients to blind patients, who were then blindfolded for each injection.
- Primary outcomes of pain and function identified with a Knee injury and Osteoarthritis Outcome Score (KOOS) and EuroQol five-dimension five-level index (EQ-5D-5L).
- KOOS scored 0-100, with a higher score meaning less pain and 0 being the worst pain possible.
- EQ-5D-5L indexed with scores –0.281 to 1, with lower numbers representing worse pain.
- Secondary outcomes were whether the patient would recommend treatment to others using a Likert scale (–2 to 2), patient subjective assessment of injection using a Likert scale (–2 to 2) and pain assessed by visual analogue scale (1–10), with 10 being the worst pain imaginable.
- Outcomes were measured at baseline, week six, week 12, six months, and 12 months.

INTERVENTION (# IN THE GROUP):

- One PRP + two placebo injections: 47
- Three PRP injections: 27

COMPARISON (# IN THE GROUP): 28

FOLLOW-UP PERIOD: 12 months

RESULTS:

Primary Outcome –

- Using the KOOS score, only the placebo and single PRP injections showed a significant improvement in pain.
  - Six weeks: 8.5 (95% CI, 3.2–14) vs 7.3 (95% CI, 3.2–11), respectively
  - 12 months: 7.9 (95% CI, 2.6–13) vs 10 (95% CI, 6.1–14), respectively
- Using the KOOS score, between single PRP and Multiple PRP injections, there was no statistically significant improvement in pain at any of the weeks.
- Using the ED-5D-5L score, only the placebo injection showed a significant improvement in pain at 12 weeks compared to single or multiple PRP injections (0.076; 95% CI, 0.019–0.13).
- Using the ED-5D-5L score, only the single PRP injection showed a significant improvement in pain at six weeks compared to placebo or multiple PRP injections (0.057; 95% CI, 0.012–0.10).
- Using the ED-5D-5L score, between single PRP and multiple PRP injections, there was no difference in pain improvement at any of the time intervals.

Secondary Outcome –

- Using the VAS score, there was no significant difference in patient perception of whether the injections (PRP or placebo) helped.
- Using the VAS score, there was no significant difference in whether a patient would recommend the injections (PRP or placebo).

LIMITATIONS:

- Patient selection was limited to early stages of osteoarthritis and thus limited ability to analyze the effect of PRP injection in moderate/advanced stages of osteoarthritis.
- The wide confidence intervals suggest study would need 400 to 550 patients to show a minimally important clinical difference.

Nelson Shreve, MD
Primary Care Sports Medicine Fellow/Travis AFB
Travis AFB, CA

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Repurposing Metformin, Ivermectin, and Fluvoxamine for COVID-19 Treatment?

Randomized Trial of Metformin, Ivermectin, and Fluvoxamine for COVID-19

Bramante CT, Huling JD, Tignanelli CJ, et al. Randomized Trial of Metformin, Ivermectin, and Fluvoxamine for Covid-19. *N Engl J Med*. 2022;387(7):599-610. doi:10.1056/NEJMoa2201662

KEY TAKEAWAY: Metformin, ivermectin, or fluvoxamine do not prevent hypoxemia, ED visits, hospitalizations, or death in patients with non-hospitalized COVID-19 at 14 days.

STUDY DESIGN: Multicenter, double-blind, randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Metformin, ivermectin, and fluvoxamine have either shown anti-inflammatory actions or in vitro activity against COVID-19. Prior to this study, no randomized control trials tested whether these medications prevented the severe progression of COVID-19.

PATIENTS: Non-hospitalized adults with COVID-19

INTERVENTION: Metformin, fluvoxamine, ivermectin, and/or placebo

CONTROL: Placebo only

PRIMARY OUTCOME: Composite of COVID-19-related hypoxemia, emergency department (ED) trips, hospitalizations, and death

Secondary Outcome: Correlation between each medication and ED visits, hospitalizations, and/or death

METHODS (BRIEF DESCRIPTION):

- Inclusion criteria included adult patients that had confirmed proof of COVID-19 infection within three days of randomization with a BMI consistent with being overweight or obese and the onset of symptoms within seven days of randomization.
  - 1,305 patients were analyzed with completed data (median age 46 years old, 56% female, median BMI 30), with 333 patients experiencing the primary endpoint (25.5%).
- A 2-by-3 factorial design was utilized. Six groups of patients received a different combination of therapies, including metformin plus fluvoxamine, metformin plus ivermectin, metformin plus placebo, placebo plus fluvoxamine, placebo plus ivermectin, and placebo plus placebo.
  - The groups who received metformin were given 1500 mg per day for 14 days.
  - Those who received ivermectin were given a dose of 390 to 470 micrograms/kg/day for three days.
  - Those receiving fluvoxamine were given a dose of 50 mg twice daily for 14 days.
- All patients received two different types of pills, including the placebo groups, to maintain blinding.
- Medications were delivered to the patients at their homes.
- Primary and secondary endpoints were then assessed at the end of day 14. Primary endpoints included a reduction in COVID-19-related hypoxemia ($O_2 \leq 93\%$), emergency department trips, hospitalizations, and death. Secondary endpoints included daily symptom severity and drug discontinuation.

INTERVENTION (# IN THE GROUP):

- Metformin + placebo: 663
- Metformin + ivermectin: 410
- Metformin + fluvoxamine: 334

COMPARISON (# IN THE GROUP):

- Placebo: 660
- Placebo + ivermectin: 410
- Placebo + fluvoxamine: 327

FOLLOW-UP PERIOD: 14 days

RESULTS:

Primary Outcome –

- All three medications did not affect the primary composite outcome compared to the placebo:
  - Metformin: Odds ratio (OR) 0.84; 95% CI, 0.66–1.1
  - Ivermectin: OR 1.1; 95% CI, 0.76–1.5
  - Fluvoxamine: OR 0.94; 95% CI, 0.66–1.4

Secondary Outcome –

- Metformin reduced the risk of ED visits, hospitalizations, and/or death (adjusted OR 0.58; 95% CI, 0.35–0.94).
  - Ivermectin and fluvoxamine did not significantly affect the risk of ED visits, hospitalizations, and/or death.

LIMITATIONS:

- The study results cannot be expanded to adults younger than 30 years old, older than 85 years old, or with a normal BMI.
- The study included fewer Latino Americans and African Americans compared to the national population.
- The primary endpoint of hypoxemia was likely nonsystematic due to the differing accuracy of home pulse oximeters, and there was some moderate amount of concern for recall bias in patients who reported hypoxemia without written documentation.

Ethan Ledbetter, MD
Cabarrus Family Medicine
Cabarrus, NC

Screening for Atrial Fibrillation: Does It Work?

Clinical Outcomes in Systematic Screening for Atrial Fibrillation (STROKESTOP): A Multicentre, Parallel Group, Unmasked, Randomised Controlled Trial

Svennberg E, Friberg L, Frykman V, Al-Khalili F, Engdahl J, Rosenqvist M. Clinical outcomes in systematic screening for atrial fibrillation (STROKESTOP): a multicentre, parallel group, unmasked, randomised controlled trial. *Lancet*. 2021;398(10310):1498-1506. doi:10.1016/S0140-6736(21)01637-8

KEY TAKEAWAY: Screening for atrial fibrillation does not reduce the risk of experiencing at least one of the following: ischemic or hemorrhagic stroke, systemic embolism, bleeding resulting in hospitalization, and all-cause mortality.

STUDY DESIGN: Unmasked randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Atrial fibrillation is a major cause of stroke and increases mortality and morbidity in patients. Oral anticoagulants aid in decreasing mortality and morbidity, particularly due to a reduction in stroke events. Early diagnosis may allow for treatment, preventing negative endpoints such as stroke. There is confusion in recommendations for screening worldwide.

PATIENTS: 75- to 76-year-old patients

INTERVENTION: Screening for atrial fibrillation

CONTROL: No screening

PRIMARY OUTCOME: Combined endpoint of ischemic or hemorrhagic stroke, systemic embolism, bleeding leading to hospitalization, and all-cause mortality

Secondary Outcome: Individual components of the composite outcome

METHODS (BRIEF DESCRIPTION):

- All living individuals 75 to 76 years old from Holland and Stockholm, Sweden were eligible without exclusion criteria.
- They were randomly assigned to screening or non-screening groups.
  - The screening group received up to three invitations to screen.
  - The control group received no invitations.
- Both groups were followed for at least five years.
- The invited group was separated into those who participated in a screening and those who opted out of screening despite being invited.
- Endpoints, anticoagulation during follow-up, and comorbidities/socioeconomic conditions were obtained through civic identification linkage to Swedish registers.
- The diagnosis of atrial fibrillation was made if at least one episode of irregular rhythm without p-waves for 30 seconds, or two or more of 10 to 29 seconds.
- If detected, participants would follow with cardiology and start anticoagulation if not contraindicated.

INTERVENTION (# IN THE GROUP): 13,979

COMPARISON (# IN THE GROUP): 13,996

FOLLOW-UP PERIOD: At least 5.6 years

RESULTS:

Primary Outcome –

- Screening did not reduce the risk of the composite endpoint compared to no screening (HR 0.96; 95% CI, 0.92–1.0; number needed to screen=91).

Secondary Outcome –

- Screening had no difference on ischemic stroke events, hemorrhagic stroke events, systemic embolism, hospitalization for major bleeding, or all-cause mortality events per 100 years.
- The proportion of participants who had atrial fibrillation and were on anticoagulation was greater in the participant group versus the non-participant group (66% versus 60%, *P*=.0052).
  - However, they approached similar percentages over seven years and the difference diminished.
- The proportion of those using anticoagulants was not significantly different between intervention and control groups.

LIMITATIONS:

- All those with atrial fibrillation, including paroxysmal, were included. Patients with paroxysmal atrial fibrillation may have a lower risk of stroke than permanent atrial fibrillation.
- When comparing participants to control for analyses, non-participants were excluded. These

non-participants had a substantially greater risk than the participant group.

- Participants were only screened for a short period of time. This could lead to the underdiagnosis of atrial fibrillation.
- Results may not be generalizable to other populations outside of Sweden.
- No masking or blinding of the trial.
- The study enrolled participants who already had atrial fibrillation and who were also taking anticoagulants.

Justin Harris, DO
Samaritan Family Medicine Residency
Corvallis, OR