GOOD EVIDENCE MATTERS

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# Dialing Down the Opioids: Investigating System, Clinic, and Provider-Level Interventions

**Strategies to Deimplement Opioid Prescribing in Primary Care: A Cluster Randomized Clinical Trial**

Quanbeck A, Robinson J, Jacobson N, et al. Strategies to Deimplement Opioid Prescribing in Primary Care: A Cluster Randomized Clinical Trial. *JAMA Netw Open*. 2024;7(10):e2438325. Published 2024 Oct 1. doi:10.1001/jamanetworkopen.2024.38325



**KEY TAKEAWAY:** The most intensive de-implementation strategies that included systemic, clinic, and prescriber level interventions reduces daily mean morphine milligram equivalent (MME) dose prescription compared to the least intensive strategy. The small decrease in MME is statistically significant but not clinically meaningful.

**STUDY DESIGN:** Cluster randomized clinical trial

**LEVEL OF EVIDENCE:** STEP 2

**BRIEF BACKGROUND INFORMATION:** The Center for Disease Control (CDC) guidelines recommend reducing opioid prescribing for chronic pain. A 2020 systematic review of de-implementation interventions that engage patients within patient-clinician interactions led to significant reductions in low-value care. The study aimed to address strategies for de-implementation at the system, clinic, and prescriber level to support reductions in opioid prescribing.

**PATIENTS:** Adults receiving primary care in rural and metropolitan areas in clinics who have been prescribed opioids within the past 12 months

**INTERVENTION:** De-implementation education strategies at the system level, clinic level, and prescriber level

**CONTROL:** Group only receiving system level intervention (EMAF) only

**PRIMARY OUTCOME:** Prescribers mean MME daily dose change per patient receiving opioids calculated over three-months

**METHODS (BRIEF DESCRIPTION):**

- 32 primary care clinics from two US health care systems between February 2020 and March 2022 containing 8,978 patients and 268 clinicians.
- Inclusion criteria:
  - Clinics offering non-pediatric primary care, internal medicine, or family medicine
  - Did not receive intervention prior to study
  - Did not prohibit opioid therapy
  - Had <80% of patients prescribed opioids with treatment agreements
  - Had >10% of patients prescribed opioids receiving doses above the MME of 90 mg/d.
- Exclusion criteria: Patients with cancer diagnosis or in hospice.
- Interventions
  - Educational meetings with audit and feedback (EMAF): Six quarterly meetings with initial in-person meetings followed by synchronous online recordings. Each clinic received monthly feedback reports on metrics.
  - Practice facilitation (PF): External change agents working with clinic implementation teams to introduce system engineering tools. Six monthly meetings and four quarterly meetings via videoconferencing. Implemented at month three for half the clinics.
  - Prescriber peer consulting (PCC): Physician trained external change agents providing four quarterly video conferencing sessions with prescribers to address patient challenges. Implemented at month nine for half the clinics.
- Patients were screened for depression using PHQ-2 and pain level using PEG-3

**INTERVENTION (# IN THE GROUP):**

- EMAF: 2,427 (7 clinics)
- EMAF + PCC: 2,021 (8 clinics)
- EMAF + PF: 2,486 (8 clinics)
- EMAF + PF + PCC: 2,044 (8 clinics)

**COMPARISON (# IN THE GROUP):** 2,427

**FOLLOW-UP PERIOD:** 21 months

**RESULTS:**

Primary Outcome –

- EMAF + PF + PPC significantly decreased mean prescribing MME dose compared to EMAF alone (−2.4 mg/d; 95% CI, −4.3 to −0.5).

**LIMITATIONS:**

- Study was conducted in two health systems serving relatively rural, mostly white populations, limiting generalizability of the study's findings.

- Clinics voluntarily participated, indicating that there may be more motivated leadership and readiness for change than those that did not participate
- COVID-19 interrupted the study, diverting clinical focus away from opioid prescribing.
- Blinding investigators or participants to group assignment was infeasible.

***Bianca Ji, MD***
*Advocate Illinois Masonic FMRP*
*Chicago, IL*

# Shielding Newborns Before Their First Breath: Prenatal RSV Protection Through Maternal Vaccination

**Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants**

Kampmann B, Madhi SA, Munjal I, et al. Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants. *N Engl J Med*. 2023;388(16):1451-1464. doi:10.1056/NEJMoa2216480



**KEY TAKEAWAY:** For infants born from uncomplicated pregnancies, administration of respiratory syncytial virus (RSV) prefusion F (preF) protein-based vaccine during pregnancy is effective in decreasing incidence of and hospitalization from severe medically attended RSV-associated lower respiratory tract illness (MA-LRTI).

**STUDY DESIGN:** Double-blind randomized controlled trial

**LEVEL OF EVIDENCE:** STEP 2

**BRIEF BACKGROUND INFORMATION:** RSV-associated respiratory illness is a significant cause of disease and hospitalization amongst newborns and infants. This study examined whether RSVpreF vaccination during pregnancy could reduce the incidence or severity of lower respiratory tract illness in the first few months of life.

**PATIENTS:** Infants born from uncomplicated, full-term, and low risk pregnancies

**INTERVENTION:** RSVpreF vaccine

**CONTROL:** Placebo

**PRIMARY OUTCOME:** Severe MA-LRTI and MA-LRTI associated with RSV

Secondary Outcome: MA-LRTI and hospitalization associated with RSV, and MA-LRTI due to any cause that happened within 360 days after birth

**METHODS (BRIEF DESCRIPTION):**

- Healthy women with uncomplicated singleton pregnancy were recruited from 18 countries (from highest to lowest enrollment): United States, South Africa, Argentina, Japan, Taiwan, Spain, the Gambia, Netherlands, Chile, Finland, New Zealand, Philippines, Mexico, Brazil, Denmark, Canada, Australia, and Republic of Korea.
- Median age and median gestation at injection were 29 years old and 31 weeks, respectively. 51% of the infant participants were male. 94% were born at term (37 to <42 weeks).
- Participants in the intervention group received one dose of intramuscular injection of 120 microgram bivalent RSVpreF vaccine between 24- and 36-weeks' gestation.
- Participants were blindly assigned in a 1:1 ratio to receive the RSVpreF vaccine or placebo.
- The RSVpreF vaccine and placebo were manufactured by the study sponsor, Pfizer.
- Primary outcome was measured using nasal swabs for reverse transcription polymerase chain reaction (RT-PCR assays), obtained at any MA-LRTI visit. Swabs were also taken weekly for the first six months of age. Swabs were either positive or negative.
- RSV associated hospitalization was measured using RT-PCR assay showing RSV during hospitalization for 360 days after birth.
- LRTI from any cause were measured using nasal swabs for RT-PCR assays at any MA-LRTI visit.
- Vaccine efficacy (VE) was computed as (1 – RR) x 100, where RR is the relative risk of the variable of interest based on comparing the incidence in the vaccine group with the placebo group.
- The VE was considered a success if the lower boundary of the confidence interval (CI) for the VE of the primary and secondary outcome was greater than 20% and 0%, respectively.

**INTERVENTION (# IN THE GROUP):** 3,570

**COMPARISON (# IN THE GROUP):** 3,558

**FOLLOW-UP PERIOD:** Up to 360 days

**RESULTS:**

Primary Outcome –

- RSVpreF vaccine was effective in decreasing the incidence of severe RSV-MA-LRTI in infants compared to placebo.
  - 90 days after birth (6 vs 33 cases, respectively; vaccine efficacy [VE] 82%; 96% CI, 41–96)
  - 120 days after birth (12 vs 46 cases, respectively; VE 74%; 98% CI, 46–89)
  - 150 days after birth (16 vs 55 cases, respectively; VE 71%; 98% CI, 45–86)
  - 180 days after birth (19 vs 62 cases, respectively; VE 69%; 98% CI, 44–84)

- RSVpreF vaccine was effective in decreasing the incidence of RSV-MA-LRTI in infants compared to placebo.
    - 120 days after birth (35 vs 81 cases, respectively; VE 57%; 98% CI, 31–74)
    - 150 days after birth (47 vs 99 cases, respectively; VE 53%; 98% CI, 29–69)
    - 180 days after birth (57 vs 117 cases; respectively; VE 51%; 98% CI, 29–67)

Secondary Outcome –

- RSVpreF vaccine was effective in decreasing the incidence of RSV-MA-LRTI in infants compared to placebo beyond 180 days after birth.
    - 210 days after birth (70 vs 127 cases, respectively; VE 45%; 99% CI, 18–64)
    - 240 days after birth (76 vs 133 cases, respectively; VE 43%; 99% CI, 16–62)
    - 270 days after birth (82 vs 137 cases, respectively; VE 40%; 99% CI, 13–59)
    - 360 days after birth (92 vs 156 cases, respectively; VE 41%; 99% CI, 16–59)
- The vaccine group had fewer cases of hospitalization compared to the placebo group within:
    - 90 days after birth (10 vs 31 cases, respectively; VE 68%; 99% CI, 16–90)
    - 120 days after birth (15 vs 37 cases, respectively; VE 60%; 99% CI, 8.3–84)
    - 150 days after birth (17 vs 39 cases, respectively; VE 56%; 99% CI, 5.2–82)
    - 180 days after birth (19 vs 44 cases, respectively; VE 57%; 99% CI, 10–81)
- The vaccine did not protect against MA-LRTI from any cause within 90 days after birth.

**LIMITATIONS:**

- Participants with high-risk pregnancies such as preterm birth, multiple pregnancy, or previous infant with congenital anomaly were excluded.
- Limited data from low-income countries limit the generalizability of the findings.
- The trial was underpowered to examine differences in vaccine efficacy according to RSV antigen subtype.
- Because at least one co-author was affiliated with Pfizer, the study's sponsor, the findings should be interpreted with caution regarding potential sponsorship bias.

***Stephen Burraston, DO***
*Womack Army Medical Center FMR*
*Fort Bragg, NC*

*The views expressed herein are those of the author and do not necessarily reflect the official policy of the Department of the Army, Defense Health Agency, Department of Defense, or the U.S. Government.*

# For Better or for Worse: Do Statins Improve Outcomes in Decompensated Cirrhosis?

**Simvastatin and Rifaximin in Decompensated Cirrhosis: A Randomized Clinical Trial**

Pose E, Jiménez C, Zaccherini G, et al. Simvastatin and Rifaximin in Decompensated Cirrhosis: A Randomized Clinical Trial. *JAMA*. 2025;333(10):864-874. doi:10.1001/jama.2024.27441



**KEY TAKEAWAY:** For patients with decompensated cirrhosis, adding simvastatin + rifaximin to standard therapy does not reduce the incidence of developing acute-on-chronic liver failure (ACLF) compared to placebo.

**STUDY DESIGN:** Multicenter, double-blind randomized control trial

**LEVEL OF EVIDENCE:** STEP 2

**BRIEF BACKGROUND INFORMATION:** ACLF is a leading cause of death in patients with cirrhosis. Statins are commonly prescribed in the primary care setting and may offer improvement in this patient population through their anti-inflammatory effects. They also reduce portal pressure in patients with cirrhosis and increase survival. Rifaximin, an antibiotic, is also used in this patient population to modulate the gut microbiome and reduce the recurrence of hepatic encephalopathy. This study aimed to determine whether the combination of these drugs, in addition to standard therapy, decreases the incidence of ACLF in patients with decompensated cirrhosis.

**PATIENTS:** Adults with decompensated cirrhosis

**INTERVENTION:** Simvastatin + rifaximin

**CONTROL:** Placebo

**PRIMARY OUTCOME:** Incidence of ACLF

Secondary Outcome: Transplant or death, ACLF severity, composite of complications of cirrhosis, changes in liver function tests (LFTs), model for end-stage liver disease (MELD) score

**METHODS (BRIEF DESCRIPTION):**

- Patients ≥18 years old with decompensated cirrhosis recruited from 14 European hospitals, including Child-Pugh Class B or C.
- Patients with severe liver impairment (including patients with ACLF at enrollment), hepatocellular carcinoma, severe extra-hepatic comorbidities, those already on or indicated to be on rifaximin or a statin, and those with increased risk of adverse events with these medications or were excluded.
- Patients were randomized 1:1 to simvastatin 20 mg + rifaximin 1,200 mg daily + standard care or identical placebo + standard care.
- Patients followed for 12 months, with follow up visits at one, three, six, nine and 12 months
- The primary outcome measured the incidence of ACLF.
- The following were measured as the secondary outcomes:
  - Transplant or death
  - ACLF severity
  - Composite of complications of cirrhosis, which included ascites, hepatic encephalopathy, variceal bleeding, acute kidney injury (AKI), and infection.
  - Changes in LFTs, including bilirubin, creatinine, INR, albumin, and C-reactive protein
  - MELD score measures liver dysfunction using three lab values: Bilirubin, creatinine, and INR levels. Scores range from 6–40, with higher scores indicating worse severity.
  - Lab values assessed with mixed models
  - Other events measured similarly to primary outcome
- Transplant or death outcomes measured without competing risk strategy.
- Results reported from the intention-to-treat population.

**INTERVENTION (# IN THE GROUP):** 117

**COMPARISON (# IN THE GROUP):** 120

**FOLLOW-UP PERIOD:** 12 months

**RESULTS:**

Primary Outcome –

- There was no significant difference in the incidence of ACLF between simvastatin + rifaximin compared to placebo (hazard ratio [HR] 1.2; 95% CI, 0.65–2.3).

Secondary Outcome –

- There was no significant difference in transplant or death, ACLF severity, composite of complications of cirrhosis, changes in LFTs except for albumin, or MELD scores for simvastatin + rifaximin compared to placebo.

- Simvastatin + rifaximin increased albumin compared to placebo (mean difference [MD] –0.18; 95% CI, –0.32 to –0.04).

**LIMITATIONS:**

- Alcohol related cirrhosis was overrepresented in this study population, compared with other cirrhosis etiologies. Intervention may be effective in other groups.
- Patients included in the study had more severe disease.
- Women were underrepresented, and the population was racially homogenous with >90% White patients.
- Simvastatin dose was relatively low at 20 mg per day. Although the decrease in LDL was significant in the treatment group, a higher dose may be more effective for ACLF.

***Spring Davis, MD***
*Northeast Georgia Medical Center FMRP*
*Gainesville, GA*

# The Power of Partnership: LDL-C Control with Ezetimibe + Atorvastatin Combination Therapy

**LDL-C Goal Attainment with Fixed-Dose Ezetimibe and Atorvastatin vs High-Dose Atorvastatin in Chinese Patients: Subgroup Analysis of a Randomized Trial**

Qian J, Zhang X, Chen J, et al. LDL-C Goal Attainment with Fixed-Dose Ezetimibe and Atorvastatin Versus High-Dose Atorvastatin in Chinese Patients: Subgroup Analysis of a Randomized Trial. *Adv Ther*. 2026;43(3):1187-1198. doi:10.1007/s12325-025-03429-8



**KEY TAKEAWAY:** Fixed-dose ezetimibe/atorvastatin (EZ/AS) significantly improved low-density lipoprotein cholesterol (LDL-C) goal attainment compared to higher-dose atorvastatin monotherapy at 12 weeks in Chinese adults with hypercholesterolemia at very-high-risk for atherosclerotic cardiovascular disease (ASCVD) regardless of age.

**STUDY DESIGN:** Phase III randomized, double-blind, active-controlled trial with post-hoc subgroup analysis

**LEVEL OF EVIDENCE:** STEP 2

**BRIEF BACKGROUND INFORMATION:** Elevated LDL-C is strongly associated with ASCVD through plaque formation. Given this well-established causal relationship, LDL-C remains a primary target for both primary and secondary prevention of cardiovascular disease through guideline-directed LDL-C goals. This study evaluated the efficacy of a fixed-dose combination of EZ and AS compared with higher-dose atorvastatin monotherapy for lowering LDL-C, followed by post-hoc subgroup analysis.

**PATIENTS:** Chinese adults with uncontrolled hypercholesterolemia

**INTERVENTION:** Fixed-dose ES/AS combination therapy

**CONTROL:** AS monotherapy

**PRIMARY OUTCOME:** LDL-C goal attainment at six and 12 weeks with subgroup analysis of ASCVD risk, age, and sex

Secondary Outcome: LDL-C reduction ≥30%, ≥50%, and non-HDL-C goal attainment at week 12

**METHODS (BRIEF DESCRIPTION):**

- Chinese adults with uncontrolled hypercholesterolemia after a five-week statin run-in.
  - Only patients who failed to meet LDL-C goals after the run-in were eligible for the study.
- Patients were stratified and randomized into one of two cohorts:
  - Cohort A (with run-in of AS 10 mg):
    - Intervention group: EZ 10 mg/AS 10 mg FDC
    - Control group: AS 20 mg
  - Cohort B (with run-in of AS 20 mg):
    - Intervention group: EZ 10 mg/AS 20 mg FDC
    - Control group: AS 40 mg
  - All treatments were given once daily for 12 weeks.
- The primary outcome was LDL-C goal attainment at weeks six and 12. LDL-C goals were taken from the 2016 Chinese dyslipidemia guidelines:
  - Low/medium risk: <130 mg/dL
  - High risk: <100 mg/dL
  - Very high risk: <70 mg/dL
- The secondary outcomes were:
  - Non-HDL-C goal attainment, which reflects atherogenic lipoprotein burden, including LDL, VLDL, IDL, lipoprotein(a), and chylomicron remnants.
    - Non-HDL-C goals were also taken from 2016 Chinese dyslipidemia guidelines.
  - Achievement of >30% LDL-C reduction
  - Achievement of >50% LDL-C reduction
- This study performed a post-hoc subgroup analysis to investigate LDL-C and non-HDL-C goal attainment on FDC vs statin monotherapy for the following subgroups:
  - ASCVD risk (low/medium, high, very high)
  - Age <65 years old vs ≥65 years old
  - Sex (male/female)

**INTERVENTION (# IN THE GROUP):**

- Cohort A: 88
- Cohort B: 137

**COMPARISON (# IN THE GROUP):**

- Cohort A: 89
- Cohort B: 140

**FOLLOW-UP PERIOD:** 12 weeks

**RESULTS:**

Primary Outcome –

- Across both cohorts, fixed-dose EZ and AS were associated with significantly higher LDL-C goal attainment compared to AS monotherapy.

- Cohort A (63% vs 35%; *p*=.0009)
- Cohort B (68% vs 31%; *p*<.0001)

- Most participants (89%) were classified as very-high-risk for ASCVD.
- Sample sizes for low/medium and high-risk subgroups were too small to provide statistically significant results.
- Among very-high-risk patients, EZ/AS significantly outperformed AS monotherapy in both primary and secondary outcomes.
- Very-high-risk LDL-C goal attainment at week 12
  - Cohort A (62% vs 34%; risk difference [RD] 28%; 95% CI, 11–46)
  - Cohort B (69% vs 30%; RD 40%; 95% CI, 28–52)
- Very-high-risk LDL-C reduction >30%
  - Cohort A (42% vs 5.1%; RD 36%; 95% CI, 23–50)
  - Cohort B (40% vs 6.3%; RD 34%; 95% CI, 22–46)
- Very-high-risk non-HDL-C goal attainment
  - Cohort A (70% vs 32%; RD 38%; 95% CI, 21–55)
  - Cohort B (76% vs 45%; RD 31%; 95% CI, 18–43)
- FDC improved LDL-C goal attainment in both age groups with no evidence of decreased response in adults <65 years old.
  - Cohort A (59% vs 36%; RD 23%; 95% CI, 1.6–44)
  - Cohort B (67% vs 30%; RD 37%; 95% CI, 22–52)
- ≥65 years old
  - Cohort A (68% vs 33%; RD 34%; 95% CI, 11–58)
  - Cohort B (69% vs 33%; RD 35%; 95% CI, 16–55)
- Males and females both had improved LDL-C goal attainment with FDC therapy; however, statistical significance was observed only in males in cohort B and females in cohort A.
  - Male:
    - Cohort A (62% vs 45%; RD 17%; 95% CI, –4.5 to 38)
    - Cohort B (72% vs 32%; RD 40%; 95% CI, 26–54)
  - Female:
    - Cohort A (64% vs 20%; RD 44%; 95% CI, 23–66)
    - Cohort B (54% vs 30%; RD 24%; 95% CI, 0.0–49)

Secondary Outcome –

- LDL-C reduction of at least 30% favored FDC in both cohorts and was statistically significant.
  - Cohort A (45% vs 6.5%; *p*<.0001)
  - Cohort B (40% vs 6.9%; *p*<.0001)
- LDL-C reduction of at least 50% was statistically insignificant in both cohorts.
- Non-HDL-C goal attainment and achievement of at least 30% LDL-C favored FDC in both cohorts and was statistically significant.
  - Cohort A (69% vs 38%; *p*=.0002)
  - Cohort B (75% vs 46%; *p*<.0001)

**LIMITATIONS:**

- Subgroup analyses were post-hoc exploratory endpoints and were not powered for these comparisons, nor protected by randomization. Once the randomized groups were subdivided post-hoc, baseline imbalances may have emerged, and the small sample sizes (especially in the low/medium, high-risk, and sex-specific subgroups) resulted in wide confidence intervals and no significant estimates. Therefore, post-hoc findings cannot establish causality.
- Follow-up period was limited to 12 weeks, preventing assessment of long-term lipid control or clinical outcomes
- Generalizability is limited for several reasons. The study applied Chinese dyslipidemia guidelines, the China-PAR risk model, and non-HDL-C targets that differ from U.S. ACC/AHA recommendations (though the 2026 update has reintroduced non-HDL-C goals). Additionally, the exclusively Chinese study population may differ in genetics and lifestyle factors, further limiting external applicability.

***Corey Pendergraft, MD***
*Washington State University FMRP*
*Pullman, WA*

# Inject and Freeze, or Just Inject? Treatment Options for Common Warts

**Efficacy of Cryotherapy Combined with Intralesional Purified Protein Derivative (PPD) vs Intralesional PPD Monotherapy in the Treatment of Multiple Common Warts**

Awad SM, Gomaa AS, Hassan HA, Tawfik YM. Efficacy of Cryotherapy Combined with Intralesional Purified Protein Derivative (PPD) Versus Intralesional PPD Monotherapy in the Treatment of Multiple Common Warts. *J Cutan Med Surg*. 2023;27(2):117-125. doi:10.1177/12034754231152224



**KEY TAKEAWAY:** Combining cryotherapy with intralesional purified protein derivative (PPD) injection immunotherapy does not provide a greater percentage reduction in size and number of warts compared to intralesional PPD alone.

**STUDY DESIGN:** Prospective randomized clinical trial

**LEVEL OF EVIDENCE:** STEP 3 (downgraded due to low sample size and limited power)

**BRIEF BACKGROUND INFORMATION:** Common warts are often difficult to treat for many patients. In recent years, many new treatment modalities have been investigated and are becoming more integrated into clinical practice, providing more treatment options for this condition. This study aimed to determine the efficacy and safety of intralesional PPD injection immunotherapy alone compared to intralesional PPD injection immunotherapy plus cryotherapy as treatment options for common warts.

**PATIENTS:** Men and women ≥18 years old

**INTERVENTION:** Cryotherapy and intralesional injection of PPD immunotherapy

**CONTROL:** Intralesional injection of PPD immunotherapy alone

**PRIMARY OUTCOME:** Reduction in the size and number of warts

Secondary Outcome: Patient satisfaction following completion of treatment, number of sessions needed for treatment completion, adverse effects

**METHODS (BRIEF DESCRIPTION):**

- Patients ≥18 years old with >3 common warts who attended an outpatient clinic in Egypt from August 2020 to February 2021 were included.
- Patients were excluded if they were pregnant or lactating, were immunocompromised, had an acute febrile illness, had received treatment for their warts within the preceding two months, or had conditions such as Raynaud's phenomenon, chilblains, or other conditions exacerbated by exposure to cold.
- Patients were all tested with subdermal injection of PPD to confirm immunity prior to the study. The dose of PPD injected during the study was determined based on mm of induration seen with this initial PPD injection.
  - 5–9 mm induration: 0.3 mL PPD
  - 10–15 mm induration: 0.2 mL PPD
  - >15 mm induration: 0.1 mL PPD
- Baseline data were collected and recorded regarding size, location, and standardized measurements of each wart, and photographs of existing lesions were taken.
- Patients were randomly assigned to one of two groups:
  - Patients who were treated with intralesional PPD immunotherapy in addition to cryotherapy (intervention group).
  - Patients who were treated with intralesional PPD immunotherapy alone (control group).
- Intervention group protocol: All lesions present were treated with liquid nitrogen cryotherapy with one freezing cycle. Lesions were sprayed from 1 cm away with 1–2 mm margin for 10–20 seconds. Then, PPD was injected into the largest wart using the same standardized technique and equipment.
- Control group protocol: PPD was injected into the largest wart using standardized technique and equipment.
- For both groups, this process was repeated every two weeks for a maximum of four treatment sessions or until complete resolution of warts.
- Photographs and measurements were collected for each wart every two weeks, at the end of the four sessions, and two months after.
- Primary outcome: Percentage reduction in the size or number of warts as clinical response:

- No or minimal response: <25% decrease in size/number of warts.
- Moderate response: 25–75% decrease in size/number of warts.
- Near complete response: 76–99% decrease in size/number of warts.
- Complete response: 100% decrease in size/number of warts.

- The primary outcome was compared within and across groups.
- Number of sessions needed for complete resolution of lesions was recorded.
- Secondary outcomes were measured as follows:
  - Patient satisfaction was measured using a Likert scale: Very satisfied, satisfied, slightly satisfied, and unsatisfied
  - Number of sessions needed for complete resolution of lesions was recorded as one, two, three, or four.
  - Adverse effects following each treatment included pain, erythema, edema, hypopigmentation, blistering, and recurrence of lesions.

**INTERVENTION (# IN THE GROUP):** 25

**COMPARISON (# IN THE GROUP):** 25

**FOLLOW-UP PERIOD:** Two months

**RESULTS:**

Primary Outcome –

- Both groups demonstrated a significant reduction in the size and number of warts after completion of treatment ($p$<.001).
- Combining cryotherapy with intralesional PPD immunotherapy led to 44% complete clearance of lesions compared to only PPD immunotherapy, which led to 48% complete clearance of lesions, but this was not statistically significant ($P$=.39).

Secondary Outcome –

- Combining cryotherapy with intralesional PPD immunotherapy led to complete resolution of lesions in 2–3 sessions in 60% compared to 22% with resolution of lesions in 2–3 sessions in the control group ($p$=.002).
- Combining cryotherapy with intralesional PPD immunotherapy led to near complete/complete response in patients with larger mean induration at 16 mm compared to minimal to moderate response in patients with smaller mean induration at 11 mm ($p$=.02).
- PPD immunotherapy alone led to near complete/complete response in patients with larger mean induration at 14 mm compared to minimal to moderate response in patients with smaller mean induration at 8.5 mm ($p$=.02).
- Combining cryotherapy with intralesional PPD immunotherapy led to hypopigmentation in 56% compared to PPD immunotherapy alone, which led to hypopigmentation in 8% ($p$<.001).
- Combining cryotherapy with intralesional PPD immunotherapy led to blistering in 80% compared to PPD immunotherapy alone, which led to blistering in 4% ($p$<.001).
- Combining cryotherapy with intralesional PPD immunotherapy led to recurrence of warts within two months in 0% compared to PPD immunotherapy alone, which led to recurrence of warts within two months in 20% ($p$=.049).
- Combining cryotherapy with intralesional PPD immunotherapy did not lead to a significant difference in patient satisfaction, pain, erythema, or edema compared to PPD immunotherapy alone.

**LIMITATIONS:**

- The study had a small sample size, thus limiting statistical power.
- The study focused on a relatively homogeneous population, thus limiting the generalizability of the results.
- The study had a brief follow-up period, thus limiting the ability to assess long-term response to treatment or recurrence.
- The study had a control group for intralesional PPD immunotherapy but did not have a control group for cryotherapy alone, thus allowing for potentially confounding variables.

***Jacob D. Smith, MD***
*Spokane Family Medicine Residency*
*Spokane, WA*

# Does Sitting Time Reduction Improve Health in Older Adults?

**Sitting Time Reduction and Blood Pressure in Older Adults: A Randomized Clinical Trial**

Rosenberg DE, Zhu W, Greenwood-Hickman MA, et al. Sitting Time Reduction and Blood Pressure in Older Adults: A Randomized Clinical Trial. *JAMA Netw Open*. 2024;7(3):e243234. Published 2024 Mar 4. doi:10.1001/jamanetworkopen.2024.3234



**KEY TAKEAWAY:** Reducing sitting time could be a practical strategy for lowering systolic blood pressure (SBP) in older patients.

**STUDY DESIGN:** Parallel group randomized control trial conducted primarily remotely

**LEVEL OF EVIDENCE:** STEP 3 (downgraded due to open-label study design and disease-oriented outcomes)

**BRIEF BACKGROUND INFORMATION:** Moderate to vigorous activity has been shown to improve mental and physical health. Hypertension (HTN) is highly prevalent in older adults. Short-term experimental studies have shown that reduction in sitting times leads to reduced blood pressure (BP), especially in those with HTN. Older adults spend a significant amount of time sitting, therefore, finding modifiable risk factors such as the reduction of sitting time is crucial to help reduce BPs in older adults.

**PATIENTS:** Adults with high sitting time and body mass index (BMI)

**INTERVENTION:** Sitting reduction intervention

**CONTROL:** General healthy lifestyle

**PRIMARY OUTCOME:** Sitting time, SBP, and diastolic blood pressure (DBP)

Secondary Outcome: Weight, BMI, waist circumference, adverse events

**METHODS (BRIEF DESCRIPTION):**

- Patients age 60–89 years old were recruited from a large healthcare system in Washington to assess a sitting time reduction intervention.
- Included participants reported >6 hours of daily sitting, had a BMI of 30–50 kg/m$^2$, and the ability to walk one block.
- Patients were excluded if they received palliative or hospice care and had dementia or serious mental health disorders.
- The mean age was 69 years old, most were women (66%), baseline total sitting time (mean sitting time 652 minutes per day), baseline SBP 136 mmHg and DBP was 80 mmHg.
- The sitting reduction intervention received 10 health coaching sessions (over 6 months) that included identification of sitting reduction goals, a standing desk and fitness tracker to prompt breaks in sitting.
- Comparison group received 10 coaching sessions prompting general healthy lifestyle goals.
- Sitting time reduction was measured at baseline, three months, six months using accelerometers.
- SBP and DBP were measured at baseline and six months pre-COVID pandemic by assessors then during the pandemic by participant self-measurement with instruction by telephone.
- Weight and height and were self-reported by the participants using a calibrated digital scale (Seca and Etekcity).
- Waist circumference self-measured by participants with coaching by telephone.
- Adverse events were reported during coaching telephone encounters.

**INTERVENTION (# IN THE GROUP):** 140

**COMPARISON (# IN THE GROUP):** 143

**FOLLOW-UP PERIOD:** Six months

**RESULTS:**

Primary Outcome –

- Patients in the sitting reduction intervention group had greater reductions in sitting time compared to the control group at three months (difference in adjusted mean change –31 min/day; 95% CI, –49 to –14).
- Patients in the sitting reduction intervention group had greater reductions in SBP compared to the control group at six months (difference in adjusted mean change –3.5 mmHg; 95% CI, –6.7 to –0.28).
- Patients in the sitting reduction intervention group had greater reductions in sitting time compared to the control group at six months (difference in adjusted mean change –32 min/day; 95% CI, –53 to –11).

- Patients in the sitting reduction intervention group had no significant reduction in DBP compared to the control group at six months.

Secondary Outcome –

- There were no statistically significant changes in secondary outcomes for weight, BMI, and waist circumference at six months in the intervention group compared to the control group.
- There were 87 adverse events reported in the intervention group as compared to 57 adverse events reported in the control group, with 35 musculoskeletal events in the intervention group and 19 in the control group. There were six serious events in the intervention and control group, respectively that were unrelated to the study.

**LIMITATIONS:**

- The study took place during the COVID pandemic causing interruptions during the enrollment period and early discontinuation (study initially planned to last 12 months).
- Because of social distancing measures during the COVID-19 pandemic, primary and coprimary measures were self-measured and reported by participants.
- There was underrepresentation of Asian and Hispanic/Latino population.
- There was a potential Hawthorne effect in the intervention group as they are more likely to change behaviors when wearing the accelerometer.
- There is a potential underestimation of blood pressure reduction effects due to inclusion of normotensive individuals.

***Christian Negron Rolon, MD***
*Alaska FMRP*
*Anchorage, AK*

# Beta-Blockers: Benefit or Bust? Beta-Blocker Treatment After MI

**Beta-Blockers After Myocardial Infarction Without Reduced Ejection Fraction** Ibanez B, Latini R, Rossello X, et al. Beta-Blockers after Myocardial Infarction without Reduced Ejection Fraction. *N Engl J Med*. 2025;393(19):1889-1900. doi:10.1056/NEJMoa2504735



**KEY TAKEAWAY:** Beta blockers do not reduce the incidence of death from any cause, reinfarction, or hospitalization for heart failure (HF) after invasive care for myocardial infarction (MI) in patients with a left ventricular ejection fraction (LVEF) ≥40%.

**STUDY DESIGN:** Open-label randomized controlled trial (RCT)

**LEVEL OF EVIDENCE:** STEP 3 (downgraded due to lack of regulation in type of beta-blocker medication used and lack of blinding)

**BRIEF BACKGROUND INFORMATION:** Beta-blockers have been a cornerstone of post–MI care, which is supported by early trials showing significant mortality reduction. However, these studies predated modern therapies, raising uncertainty about their benefit in patients with preserved or mildly reduced ejection fraction (EF). Recent observational data and meta-analyses have yielded conflicting results, prompting re-investigation through randomized trials after modern therapies in the hospital.

**PATIENTS:** Patients with type 1 or 2 MI treated with coronary angiography during hospitalization and without reduced ejection fraction (EF ≥40%)

**INTERVENTION:** Beta blocker therapy (treatment team choice of drug and dose)

**CONTROL:** No beta blocker therapy

**PRIMARY OUTCOME:** Composite of death from any cause, reinfarction, or hospitalization for HF

Secondary Outcome: Individual components of primary outcome, cardiac death, ventricular arrhythmias, resuscitated cardiac arrest

**METHODS (BRIEF DESCRIPTION):**

- The RCT was conducted in Spain and Italy and included patients ≥18 years old with recent MI who required invasive care during initial hospitalization with a LVEF >40% before discharge.
- Patients were excluded if they had a history of HF (including Killip class ≥II during index hospitalization), contraindication to beta-blockers, or indication for beta-blockers unrelated to MI.
- Patients were randomized 1:1 using a secure web-based system.
- Patients randomized to beta-blocker had therapy initiated at discharge or within 14 days. Type and dose were determined by the treating physician. Six different beta-blocker categories were used.
  - Atenolol: 26
  - Bisoprolol: 3,549
  - Carvedilol: 128
  - Metoprolol: 309
  - Nebivolol: 114
  - Unspecified beta blocker: 5
- Both groups received standard post-MI care.
- Follow-up was completed at three, 15, 36, and 48 months via phone interviews, medical record review, and national registries.
- The primary outcome measured the composite of death from any cause, reinfarction, or hospitalization for HF.
- The secondary outcomes measured the individual components of the primary outcome, in addition to cardiac death, ventricular arrhythmias, and resuscitated cardiac arrest.

**INTERVENTION (# IN THE GROUP):** 4,207

**COMPARISON (# IN THE GROUP):** 4,231

**FOLLOW-UP PERIOD:** Median 3.7 years

**RESULTS:**

Primary Outcome –

- There was no difference in the composite outcome for beta-blockers compared to no beta-blockers (hazard ratio [HR] 1.0; 95% CI, 0.89–1.2).

Secondary Outcome –

- There was no statistically significant difference in any secondary outcomes for beta blockers compared to no beta blockers.

**LIMITATIONS:**

- The choice of beta-blocker type and dosage was not regulated and was left to the prescriber, leading to inconsistent treatments in the intervention patient population. This potentially introduces many confounding variables related to treatment inconsistency.

- All parties were aware of the treatment medications and dosages being used, potentially introducing some bias components for data analysis.
- The characteristics of the patients at baseline did not account for ethnicity, potentially introducing confounding variables related to genetics in the patient population.
- Patients continued existing additional medication therapies, which may account for some confounding variables that may have affected outcomes. It is worth noting, however, that per Table 1, the cardiac medications used in each group were similar, which may mitigate some potential confounders.

***Noah Chun MD***
***Erica Luke DO***
*University of Iowa Hospitals and Clinics*
*Sioux City, IA*

# Patients Can "ACT" Now to Improve Fibromyalgia Symptoms

**Self-Guided Digital Behavioral Therapy Versus Active Control for Fibromyalgia (PROSPER-FM): A Phase 3, Multicenter, Randomized Controlled Trial**

Gendreau RM, McCracken LM, Williams DA, et al. Self-Guided Digital Behavioral Therapy Versus Active Control for Fibromyalgia (PROSPER-FM): A Phase 3, Multicenter, Randomized Controlled Trial. *Lancet*. 2024;404(10450):364-374. doi:10.1016/S0140-6736(24)00909-7



**KEY TAKEAWAY:** Digitally delivered and self-guided acceptance and commitment therapy (ACT) significantly improves self-reported global symptoms compared to symptom-tracking in people with fibromyalgia.

**STUDY DESIGN:** Randomized controlled trial

**LEVEL OF EVIDENCE:** STEP 3 (downgraded due to lack of true blinding, uncertain if the primary outcome met the minimal clinically important difference [MCID])

**BRIEF BACKGROUND INFORMATION:** Fibromyalgia affects approximately 6% of the population and causes chronic pain, fatigue, sleep disturbance, and mood symptoms. Management is multimodal, often combining pharmacologic and nonpharmacologic therapies, including ACT. However, access is limited by the ability to find therapists, reimbursement, and centers providing these services. Digital ACT offers an accessible alternative with potential to improve outcomes. This study aims to evaluate the efficacy of a self-guided digital ACT intervention compared with an active control in improving fibromyalgia symptoms.

**PATIENTS:** Adults with fibromyalgia

**INTERVENTION:** An app delivering ACT

**CONTROL:** Symptom tracking tool and fibromyalgia health education

**PRIMARY OUTCOME:** Response rate on Patient Global Impression of Change (PGIC)

Secondary Outcome: Pain, sleep, fatigue, depression, impairment

**METHODS (BRIEF DESCRIPTION):**

- Adults ≥18 years old with a diagnosis of fibromyalgia, access to a smartphone, and ability to engage with a digital app were included.
- Participants were largely non-Hispanic White; predominantly female (93%), and the mean age was 50 years. Most participants had moderate to severe symptoms based on standardized symptom scores.
- Unstable medical or psychiatric conditions or inability to participate with the digital app excluded participants.
- A 12-week, self-guided digital ACT program delivered via the Stanza app on a smartphone that consists of daily interactive lessons and exercises targeting psychological flexibility, pain coping and behavior change.
- After adhering to a four-day app-based screening, participants were randomized to a self-guided digital ACT program or an active control symptom-tracking app.
- Patients with fibromyalgia continued stable medications and non-pharmacologic therapies.
- PGIC, a validated seven-point Likert scale, measured overall benefits from treatment, where higher scores indicated greater perceived improvement.
- The Revised Fibromyalgia Impact Questionnaire (FIQ-R) assessed functional impairment. Scores range from 0–10, where lower scores indicate a better outcome. Lower scores also indicated improvement in weekly pain intensity, pain interference, and sleep interference.
- Fatigue, sleep disturbance, depression, and psychological flexibility used other validated scales such as Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue, PROMIS Sleep disturbance, Inflexibility in Pain Scale (PIPS), Committed Action Questionnaire (CAQ-8), and Beck Depression Inventory II (BDI-II).

**INTERVENTION (# IN THE GROUP):** 140

**COMPARISON (# IN THE GROUP):** 135

**FOLLOW-UP PERIOD:** 12 weeks

**RESULTS:**

Primary Outcome –

- Digital ACT improved symptoms (minimally improved or better) at week 12 compared to symptom tracking (99 vs 30, respectively; between-group difference 48%; 95% CI, 38–59).

Secondary Outcome –

- Digital ACT reduced functional impairment from fibromyalgia compared to symptom tracking (–10 vs

–2.2, respectively; between-group difference –8.0; 95% CI, –0.98 to –5.1).

- Digital ACT improved pain intensity compared to symptom tracking (–1.1 vs –0.4, respectively; between-group difference –0.7; 95% CI, –1.1 to –0.28).
- Digital ACT reduced fatigue and sleep disturbance compared to symptom tracking.
    - Fatigue (–4.2 vs –1.0, respectively; between-group difference –3.2; 95% CI, –4.7 to –1.7)
    - Sleep disturbance (–2.7 vs –0.7, respectively; between-group difference –2.0; 95% CI, –3.4 to –0.66)
- The digital app for ACT reduced depressive symptoms compared to symptom tracking (–3.6 vs –0.1, respectively; between-group difference –3.5; 95% CI, –5.0 to –2.0).

**LIMITATIONS:**

- The study lacked true blinding.
- There was limited generalizability as participants included mostly non-Hispanic, White women.
- The intervention required smartphone access which could limit accessibility.
- The results relied on self-reported outcomes susceptible to expectancy bias and similarly did not include objective outcome measures.

***Crystal Bruce, MD***
*Spokane Teaching Health Center*
*Spokane, WA*