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Challenges in the Communication of Results from Randomized Clinical Trials

2026 Annual Meeting of the Society for Clinical Trials

Phoenix, Arizona

May 18, 2026

Patient Reported Outcomes (PROs)

Research

JAMA | Original Investigation

Telehealth and Online Cognitive Behavioral Therapy–Based Treatments for High-Impact Chronic Pain
A Randomized Clinical Trial

Lynn L. DeBar, PhD, MPH; Meghan Mayhew, MPH; Robert D. Wellman, MS; Benjamin H. Balderson, PhD; John F. Dickerson, PhD, MPH; Charles R. Elder, MD, MPH; Morgan Justice, MA; Francis J. Keefe, PhD; Carmit K. McMullen, PhD, MPH; Ashli A. Owen-Smith, PhD, SM; Christine Rini, PhD; Michael Von Korff, ScD; Stephen Waring, DVM, PhD; Anusha Yarava, PharmD, MPH; Ziling Shen, ScM; Richard E. Thompson, PhD; Amy E. Clark, MS; T. Charles Casper, PhD, MStat; Andrea J. Cook, PhD

IMPORTANCE Cognitive behavioral therapy (CBT) skills training interventions are recommended first-line nonpharmacologic treatment for chronic pain, yet they are not widely accessible.

OBJECTIVE To examine effectiveness of remote, scalable CBT-based chronic pain (CBT-CP) treatments (telehealth and self-completed online) for individuals with high-impact chronic pain, compared with usual care.

DESIGN, SETTING, AND PARTICIPANTS This comparative effectiveness, 3-group, phase 3 randomized clinical trial enrolled 2331 eligible patients with high-impact chronic musculoskeletal pain from 4 geographically diverse health care systems in the US from January 2021 through February 2023. Follow-up concluded in April 2024.

INTERVENTIONS Participants were randomized 1:1:1 to 1 of 2 remote, 8-session, CBT-based skills training treatments: health coach–led via telephone/videoconferencing (health coach; n = 778) or online self-completed program (painTRAINER; n = 776); or to usual care plus a resource guide (n = 777).

MAIN OUTCOMES AND MEASURES The primary outcome was attaining or exceeding the minimal clinically important difference (MCID) in pain severity score (≥30% decrease; score range, 0-10) on the 11-item Brief Pain Inventory–Short Form from baseline to 3 months; 6 and 12 months from baseline were secondary time points. Secondary outcomes at 3, 6, and 12 months included pain intensity, pain-related interference, PROMIS (Patient-Reported Outcomes Measurement Information System) social role and physical functioning; and patient global impression of change.

Supplemental content

CME Quiz at jamacmelookup.com

JAMA Network Open

Original Investigation | Complementary and Alternative Medicine

Acupuncture for Chronic Low Back Pain in Older Adults
A Randomized Clinical Trial

Lynn L. DeBar, PhD, MPH; Robert D. Wellman, MS; Morgan Justice, PhD; Andrew L. Avins, MD; Matthew Beyrouty, MPA; Carolyn M. Eng, PhD; Patricia M. Herman, PhD, ND; Arya Nielsen, PhD; Alice Pressman, PhD; Katie L. Stone, PhD, MA; Raymond Y. Teets, MD; Andrea J. Cook, PhD

Abstract

IMPORTANCE The study was carried out to inform Medicare acupuncture coverage decisions addressing the gap in evidence on acupuncture effectiveness, specifically for older adults with chronic low back pain (CLBP).

OBJECTIVE To determine the effectiveness of standard acupuncture (SA) or SA plus maintenance (enhanced acupuncture [EA]) to improve CLBP-related disability relative to usual medical care (UMC) at 3, 6, and 12 months after randomization.

DESIGN, SETTING, AND PARTICIPANTS This multisite, 3-arm, parallel-group randomized clinical trial of older adults with CLBP collected data from 4 US health care systems in 3 geographic areas and compared SA and EA treatment with UMC only. Study enrollment was conducted from August 12, 2021, to October 27, 2022; follow-up concluded on November 7, 2023.

INTERVENTIONS Both SA (8-15 treatment sessions over 12 weeks plus UMC) and EA (SA plus 4-6 maintenance sessions during the next 12 weeks) were provided by experienced, community-based licensed acupuncturists. Participants were randomized 1:1:1 to the 3 groups.

MAIN OUTCOMES AND MEASURES The primary outcome was CLBP-related disability measured by a baseline-to-6-month change in the Roland-Morris Disability Questionnaire (RMDQ) score. Secondary outcomes included pain intensity and the percentage of participants with clinically meaningful (≥30%) improvements.

Key Points

Question Is acupuncture needling (both a standard acupuncture course and additional maintenance sessions) an effective treatment for older adults with chronic low back pain (CLBP)?

Findings In this randomized clinical trial that included 800 older adults with CLBP, acupuncture needling (both a standard course and additional maintenance sessions) improved pain-related disability with CLBP at 6 months and 12 months, with no statistically discernible benefit of additional maintenance sessions.

Meaning These findings suggest that acupuncture needling is an effective and safe treatment option for older adults with CLBP.

Visual Abstract

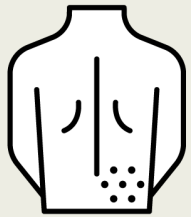
Patient Reported Outcomes (PROs)

JAMA Network Open

RCT: Acupuncture for Chronic Low Back Pain in Older Adults

POPULATION

305 Men, 495 Women

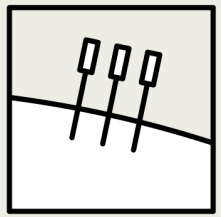


Older adults (aged ≥65 y) with chronic low back pain

Mean age: 73.6 y

INTERVENTION

800 Individuals randomized



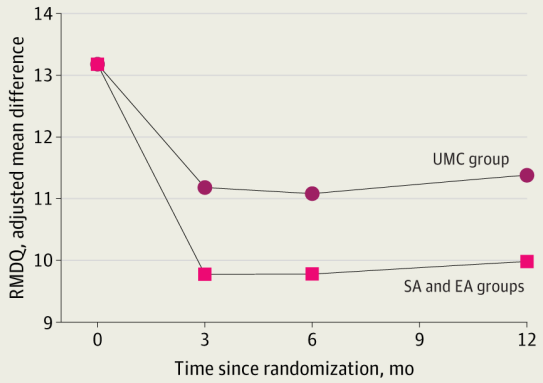
266 Usual medical care (UMC)
Access to all covered pain-related services available from participating health care systems

265 Standard acupuncture (SA)
Between 8 and 15 acupuncture needling sessions over 12 wk + UC

269 Standard plus enhanced acupuncture (EA)
SA plus ≤6 maintenance acupuncture needling sessions during next 12 wk

FINDINGS

RMDQ score changes were significantly better in the SA and EA groups compared with the UMC group; benefits persisted at 12 mo



Adjusted mean difference:
SA vs UMC: −1.0 (95% CI, −1.9 to −0.1)
EA vs UMC: −1.5 (95% CI, −2.5 to −0.6)

SETTINGS / LOCATIONS

4 Health systems in the US

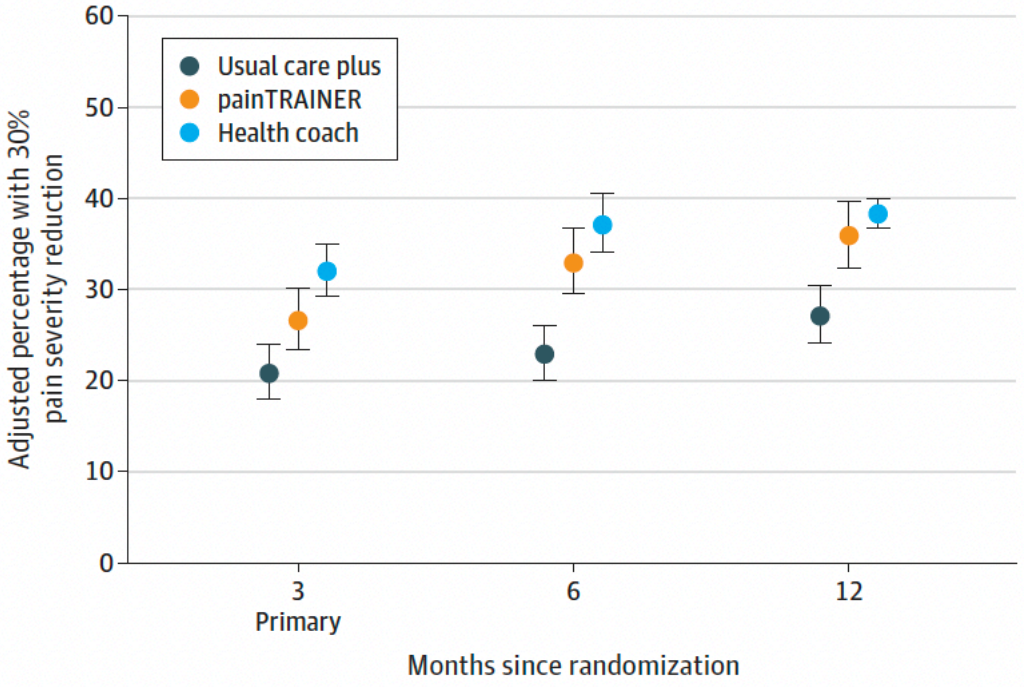
PRIMARY OUTCOME

Back pain-related disability measured by change in Roland Morris Disability Questionnaire (RMDQ) score at 6 mo; scores ranged from 0 to 24, with higher scores (≥18) indicating greater disability

DeBar LL, Wellman RD, Justice M, et al. Acupuncture for chronic low back pain in older adults: a randomized clinical trial. *JAMA Netw Open*. 2025;8(9):e2531348. doi:10.1001/jamanetworkopen.2025.31348

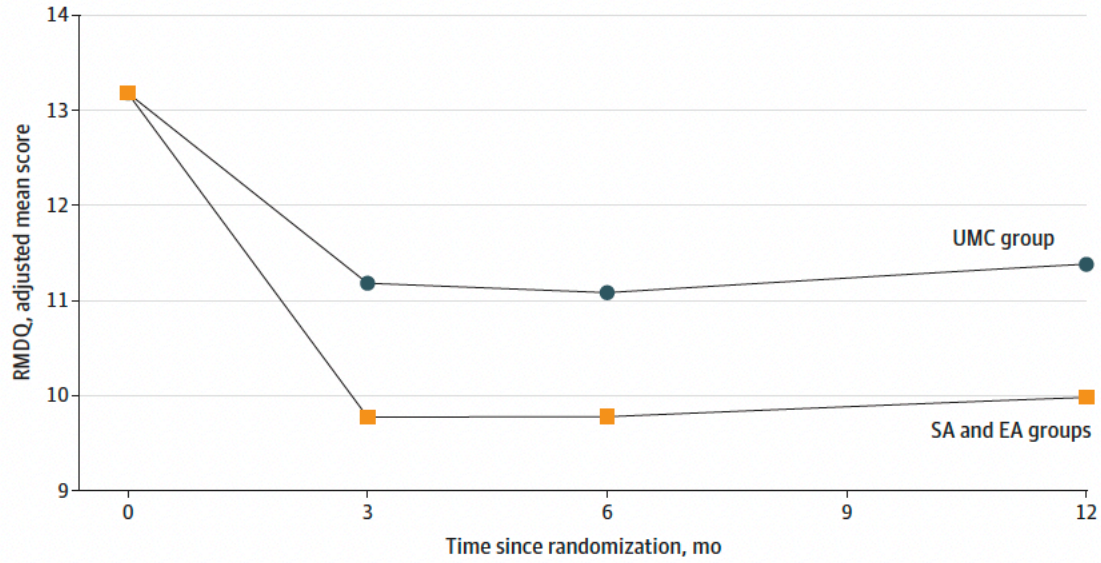
Patient Reported Outcomes (PROs)

Figure 2. Adjusted Percentage With 30% or Greater Reduction in Pain Severity (Primary Outcome)



DeBar et al. (2025) JAMA – n=2331

Figure 2. Functional Disability: Acupuncture vs Usual Medical Care (UMC)



JAMA Network Open. 2025;8(9):e2531348. doi:10.1001/jamanetworkopen.2025.31348

DeBar et al. (2025) JNO – n=800

Patient Reported Outcomes (PROs)

CLINICAL

Q: Primary outcome is a validated scale (feels, functions) – is it more clinically interpretable to analyze as a responder outcome (30% improvement from baseline), or as the underlying scale with comparison of group means?

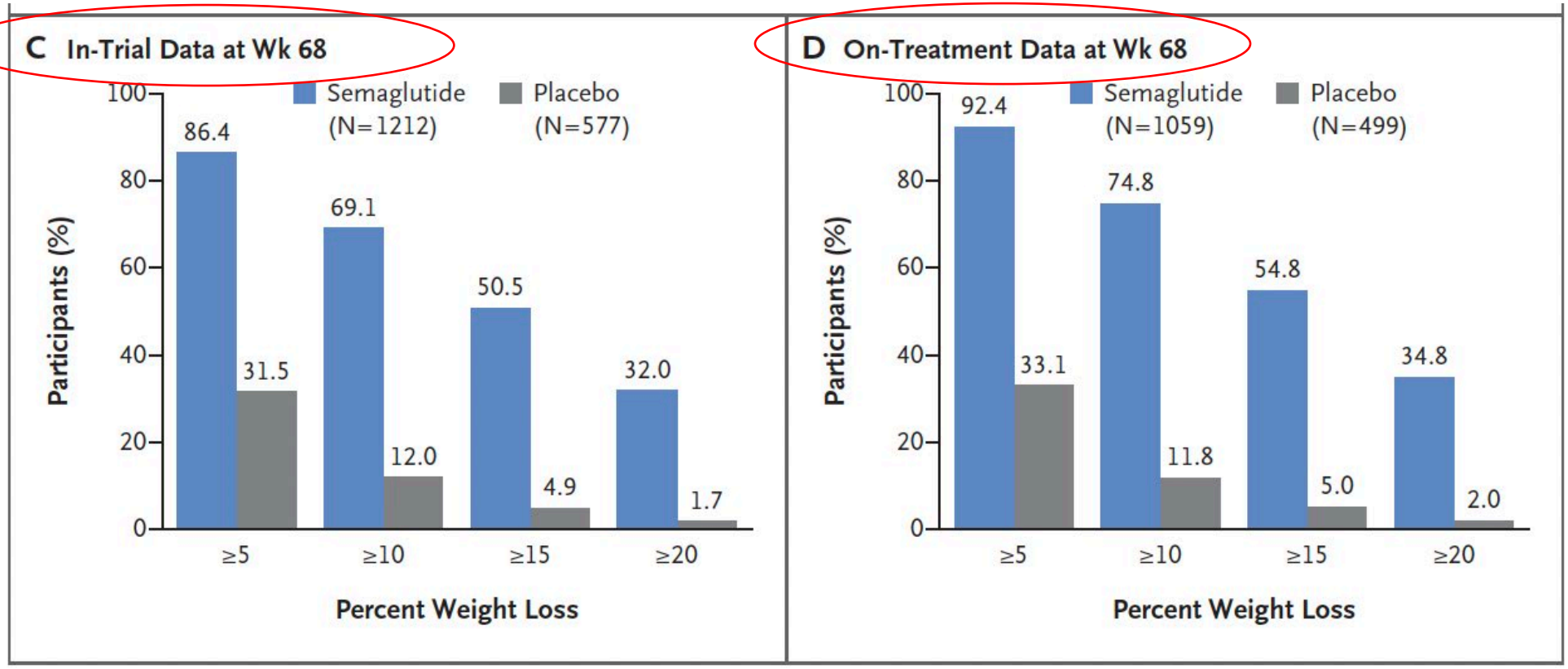
Q: How to interpret meaningfulness of group mean differences? Should we pre-specify this as a criterion?

Q: How concerning is the use of a PRO with an unblinded intervention?

STATISTICAL

Q: What are the key statistical issues that interact with the clinical considerations?

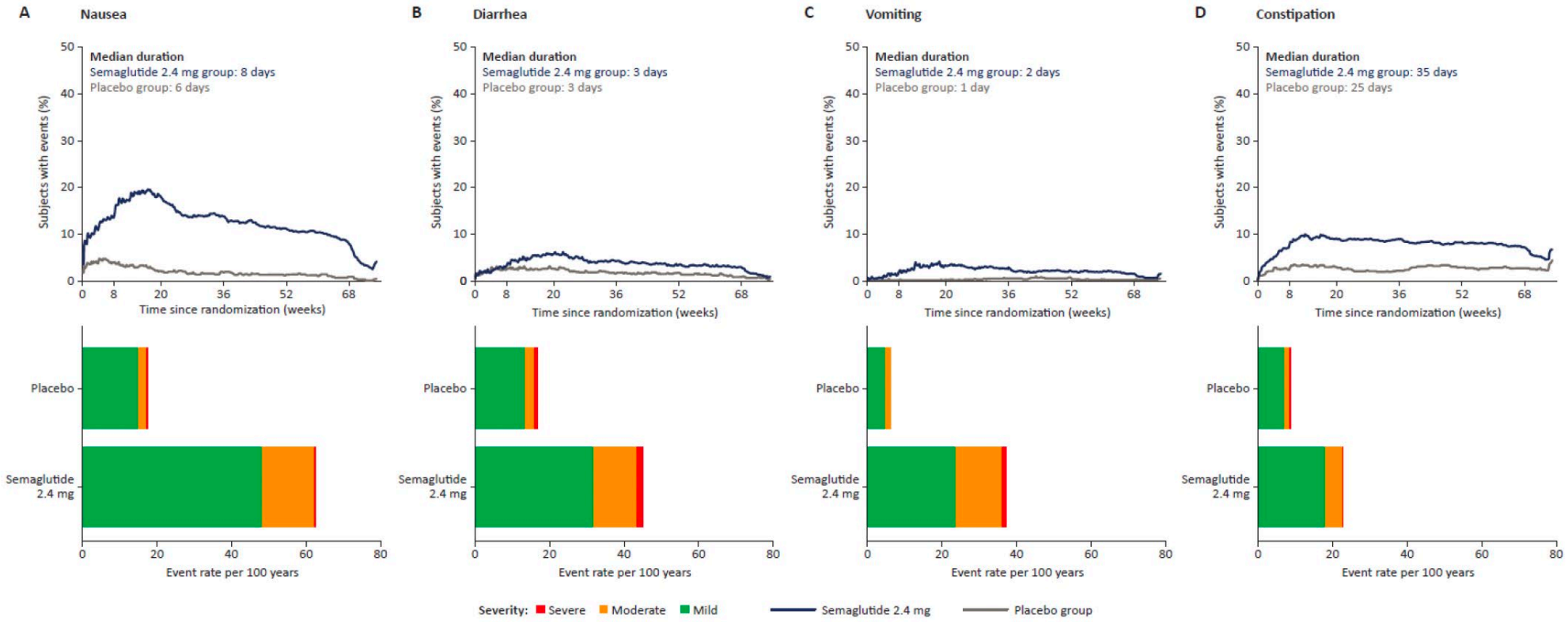
Estimands with Intercurrent Events



Wilding et al. (2021) *NEJM* -- supplement

Estimands with Intercurrent Events

Figure S8. Prevalence and Duration of Gastrointestinal Events by Severity



Estimands with Intercurrent Events

Table 1 Intercurrent events in weight management clinical trials, their potential impact on body weight, and interpretation of results.

Intercurrent event	Impact on body weight	Implications for the placebo-adjusted treatment effect	Interpretation of treatment effect when weight measurements are included/excluded in analysis	
			Included in analysis	Exclude from analysis
Discontinuation of investigational drug due to intolerability	• Weight regain may occur if the treatment had initially resulted in weight loss	Reduced	• Reflects how adherence to any treatment is likely to vary between patients • Represents a situation in which people don't respond to, or are unsatisfied with, their treatment and try other medications • Represents a broad population in which different intercurrent events would be likely to occur • May be of interest to policy-makers	• Represents a hypothetical situation in which all participants tolerated and adhered to treatment, or switched to another approved medication • Provides the closest estimate of the true pharmacological effect of the drug but relies on assumptions that are not always achievable in practice
Switching to another approved weight loss medication due to lack of efficacy	• More weight loss could be observed for an individual in the placebo arm than if they had only received placebo	Reduced		
	• For a poor-responder receiving the investigational drug, better weight loss could be achieved with another approved weight loss medication	Increased		

Wharton et al. (2021) *International Journal of Obesity*

Estimands with Intercurrent Events

Analysis and imputation methods to address the treatment policy and trial product estimands for the primary and confirmatory secondary endpoints in the statistical testing hierarchy.

Objective	Endpoint	Test order	Endpoint type	Estimand	Statistical model	Imputation approach	Missing results at week 68, n (%)
Primary endpoints							
Primary	% weight change	1	Continuous	Treatment policy*	ANCOVA	RD-MI	Placebo: 78 (11.9) Semaglutide: 94 (7.2)
				Trial product†	MMRM	-	Placebo: 212 (32.4) Semaglutide: 356 (27.3)
Primary	5% responders	2	Binary	Treatment policy*	LR	RD-MI	Placebo: 78 (11.9) Semaglutide: 94 (7.2)
				Trial product†	LR	MMRM	Placebo: 212 (32.4) Semaglutide: 356 (27.3)

Note:

- Real missing data = 7.2% in semaglutide
- Created missing data = +20.1% in semaglutide (27.3% total)

Estimands with Intercurrent Events

CLINICAL

Q: Are the different estimands (and associated estimators) clearly understood by our readers? Should these have “equal billing” in the presentation?

Q: Do we have the right labels for these estimands?

Q: Could hypothetical adherence-based estimands be misinterpreted as clinical endorsement for adherence as an (unrealistic) expectation?

STATISTICAL

Q: How well do we communicate the implicit assumptions that underly handling of discontinuation / missingness?

JAMA | Original Investigation

Metformin Plus Insulin for Preexisting Diabetes or Gestational Diabetes in Early Pregnancy

The MOMPOD Randomized Clinical Trial

Kim A. Boggess, MD; Arielle Valint, MS; Jerrie S. Refuerzo, MD; Noelia Zork, MD; Ashley N. Battarbee, MD, MSCR; Kacey Eichelberger, MD; Gladys A. Ramos, MD; Gayle Olson, MD; Celeste Durnwald, MD; Mark B. Landon, MD; Kjersti M. Aagaard, MD, PhD; Kedra Wallace, PhD; Christina Scifres, MD; Todd Rosen, MD; Wadia Mulla, MD; Amy Valent, DO; Sherri Longo, MD; Laura Young, MD, PhD; M. Alison Marquis, MStat; Sonia Thomas, DrPH; Ashley Britt, MS; Diane Berry, PhD

IMPORTANCE Insulin is recommended for pregnant persons with preexisting type 2 diabetes or diabetes diagnosed early in pregnancy. The addition of metformin to insulin may improve neonatal outcomes.

OBJECTIVE To estimate the effect of metformin added to insulin for preexisting type 2 or diabetes diagnosed early in pregnancy on a composite adverse neonatal outcome.

DESIGN, SETTING, AND PARTICIPANTS This randomized clinical trial in 17 US centers enrolled pregnant adults aged 18 to 45 years with preexisting type 2 diabetes or diabetes diagnosed prior to 23 weeks' gestation between April 2019 and November 2021. Each participant was treated with insulin and was assigned to add either metformin or placebo. Follow-up was completed in May 2022.

INTERVENTION Metformin 1000 mg or placebo orally twice per day from enrollment (11 weeks -<23 weeks) through delivery.

MAIN OUTCOME AND MEASURES The primary outcome was a composite of neonatal complications including perinatal death, preterm birth, large or small for gestational age, and hyperbilirubinemia requiring phototherapy. Prespecified secondary outcomes included maternal hypoglycemia and neonatal fat mass at birth, and prespecified subgroup analyses by maternal body mass index less than 30 vs 30 or greater and those with preexisting vs diabetes early in pregnancy.

RESULTS Of the 831 participants randomized, 794 took at least 1 dose of the study agent and were included in the primary analysis (397 in the placebo group and 397 in the metformin group). Participants' mean (SD) age was 32.9 (5.6) years; 234 (29%) were Black, and 412 (52%) were Hispanic. The composite adverse neonatal outcome occurred in 280 (71%) of the metformin group and in 292 (74%) of the placebo group (adjusted odds ratio, 0.86 [95% CI 0.63-1.19]). The most commonly occurring events in the primary outcome in both groups were preterm birth, neonatal hypoglycemia, and delivery of a large-for-gestational-age infant. The study was halted at 75% accrual for futility in detecting a significant difference in the primary outcome. Prespecified secondary outcomes and subgroup analyses were similar between groups. Of individual components of the composite adverse neonatal outcome, metformin-exposed neonates had lower odds to be large for gestational age (adjusted odds ratio, 0.63 [95% CI, 0.46-0.86]) when compared with the placebo group.

CONCLUSIONS AND RELEVANCE Using metformin plus insulin to treat preexisting type 2 or gestational diabetes diagnosed early in pregnancy did not reduce a composite neonatal adverse outcome. The effect of reduction in odds of a large-for-gestational-age infant observed after adding metformin to insulin warrants further investigation.

Visual Abstract
Editorial page 2167
Supplemental content

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CONCLUSIONS AND RELEVANCE Using metformin plus insulin to treat preexisting type 2 or gestational diabetes diagnosed early in pregnancy did not reduce a composite neonatal adverse outcome. The effect of reduction in odds of a large-for-gestational-age infant observed after adding metformin to insulin warrants further investigation.

JAMA®

QUESTION Does metformin plus insulin for the treatment of preexisting type 2 diabetes or diabetes identified early in pregnancy reduce the risk of adverse neonatal outcomes?

CONCLUSION Metformin plus insulin to treat preexisting type 2 or gestational diabetes diagnosed early in pregnancy did not reduce a composite neonatal adverse outcome; reduced odds of a large-for-gestational-age infant observed after this treatment warrants further study.

POPULATION

831 Women

Pregnant adults aged 18-45 years with preexisting type 2 or gestational diabetes identified at <23 wk

Mean age: **32.9** years

LOCATIONS

17 Centers in the US

INTERVENTION

831 Patients randomized
794 Patients analyzed

415
Metformin
Metformin 1000 mg orally twice daily + insulin from enrollment until delivery

416
Placebo
Placebo orally twice daily + insulin from enrollment until delivery

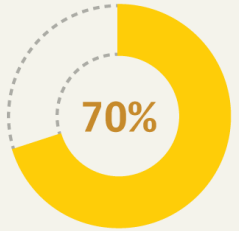
PRIMARY OUTCOME

A composite of neonatal complications (perinatal death, preterm birth, large or small for gestational age, or hyperbilirubinemia requiring phototherapy)

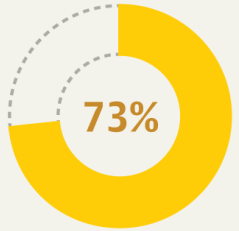
FINDINGS

Adverse neonatal outcomes

Metformin
278 of 397 patients



Placebo
290 of 397 patients



Metformin + insulin did not reduce a composite neonatal adverse outcome:

Adjusted odds ratio, 0.86
(95% CI, 0.63 to 1.19)

Unadjusted absolute difference, −3.95
(95% CI, −11.49 to 3.99)

Boggess KA, Valint A, Refuerzo JS, et al. Metformin plus insulin for preeexisting diabetes or gestational diabetes in early pregnancy: the MOMPOD randomized clinical trial. *JAMA*. Published December 12, 2023. doi:10.1001/jama.2023.22949

Table 2. Primary Composite Neonatal Outcome and Components

	Metformin plus insulin (n = 397)[a]	Insulin plus placebo (n = 397)[a]	Unadjusted absolute difference (95% CI)	Adjusted odds ratio (95% CI)[b]
Composite primary outcome[c]	280 (71)	292 (74)	−3.95 (−11.49 to 3.99)	0.86 (0.63 to 1.19)
Live births[d]	386 (97)	384 (97)		
Fetal and neonatal death	11 (3)	13 (3)	−4.30 (−24.54 to 15.95)	0.83 (0.36 to 1.89)
Miscarriage <20 wk	7 (2)	4 (1)		
Stillbirth ≥20 wk	3 (1)	7 (2)		
Neonatal death <28 d	1 (<1)	2 (1)		
Preterm birth <37 wk	130 (34)	143 (37)	−3.89 (−11.27 to 3.49)	0.86 (0.64 to 1.16)
Neonatal hypoglycemia	152 (39)	162 (42)	−2.91 (−10.09 to 4.28)	0.89 (0.67 to 1.19)
Birth trauma	16 (4)	16 (4)	−0.14 (−17.83 to 17.56)	1.02 (0.50 to 2.07)
Umbilical artery pH <7.05	9 (2)	9 (2)		
Shoulder dystocia	7 (2)	7 (2)		
Hyperbilirubinemia requiring phototherapy	87 (23)	92 (24)	−1.99 (−10.35 to 6.37)	0.93 (0.66 to 1.30)
Large for gestational age (>90th percentile)	100 (26)	137 (36)	−11.46 (−19.04 to −3.88)	0.63 (0.46 to 0.86)
Small for gestational age (<10th percentile)	30 (8)	26 (7)	3.71 (−9.86 to 17.28)	1.17 (0.68 to 2.02)
Low birth weight (<2500 g)	81 (21)	73 (19)	3.08 (−5.73 to 11.90)	1.14 (0.80 to 1.63)

[a] Eleven participants in the metformin plus insulin group and 15 in the insulin plus placebo group had missing data, and as prespecified in the statistical analysis plan, are assumed to have the composite primary outcome.

[b] Adjusted by study site, timing of diabetes diagnosis (pregestational vs diagnosed early in pregnancy), gestational age at randomizations stratified at 18 weeks, and baseline maternal body mass index as a continuous variable.

[c] Preterm birth before 37 weeks' gestation, neonatal hypoglycemia, birth trauma, hyperbilirubinemia, large for gestational age, small for gestational age, and low birth weight odds ratios are reported for live births (observed and assumed) and are adjusted for all baseline characteristics noted in Table 1, except study site as some sites had too few events.

[d] Percent values for the following categories: preterm birth, neonatal hypoglycemia, birth trauma, umbilical artery pH, shoulder dystocia, hyperbilirubinemia requiring phototherapy, large for gestational age, small for gestational age, and low birth weight are calculated from live birth denominators.

Early Stopping for Futility

INTERPRETATION

Q: Is a trial stopped for futility as definitively negative as a trial with a negative result after full enrollment?

Q: How do we interpret and communicate a nominally significant secondary comparison after a negative overall trial result?

Futility in Clinical Trials

Barbara Wendelberger, PhD; Roger J. Lewis, MD, PhD

The primary objectives of a confirmatory clinical trial, namely a clinical trial conducted with the intention of changing clinical practice or obtaining regulatory approval, are typically to demonstrate and quantify the benefit of a treatment in a specific population of patients. Occasionally, accumulating evidence makes it clear that an ongoing clinical trial is unlikely to meet its original goals. When this occurs, the trial may be stopped early for futility. Futility may result from lack of evidence supporting the desired benefit, from evidence of harm, or from practical issues that make successful completion unlikely.[1]

Pérez de la Ossa et al[2] reported the results of RACECAT, a cluster randomized clinical trial evaluating the optimal transport strategy to a hospital for patients in nonurban areas with suspected ischemic stroke due to large vessel occlusion. The trial compared the effect of directly transporting patients to a thrombectomy-capable center (experimental strategy) vs transporting them to the closest local stroke center (control strategy). The primary end point was disability at 90 days, measured by the modified Rankin Scale (mRS). The trial design used prespecified statistical stopping rules for both efficacy and futility[3] and included 2 interim analyses in which results were reviewed at planned time points during the trial, and a final analysis. The RACECAT trial was terminated for futility after the second interim analysis following a recommendation from the data and safety monitoring board (DSMB) to halt enrollment because a prespecified binding futility rule had been met.[2] The rule suggested that the apparent lack of efficacy of direct transport to a thrombectomy-capable center was not likely to be reversed by completing the clinical trial.

rules give the DSMB flexibility in recommending study continuation. As an alternative to objective criteria, investigators may describe more informal stopping guidelines, eg, providing general considerations regarding the balance of patient benefit, risk, and scientific value to be appli
stopped, instead of provic
are stopped for statistical
ered negative, while trials
considered inconclusive.

Futility stopping rules
ticipants and society by re
or harmful intervention wi
sary or in more participan
larly binding futility rules
trial design's operating ch
positive result (ie, type I e
(ie, type II error), and the e
to complete the trial relati
The risk of a type I error is
stopped for futility cannot
the accumulation of additi
error—failing to detect a true benefit—may be slightly increased because a trial that would have been positive if completed has a small chance of being stopped early for futility due to early accumulating data that are anomalously discouraging. The expected number of participants is often slightly reduced relative to the number that would be required if there were no futility stopping rule. A conservative approach should be taken when calculating operating characteristics for a trial with a nonbinding futility rule.

A conservative approach should be taken when calculating operating characteristics for a trial with a nonbinding futility rule. The type I error rate should be determined assuming the futility stopping rule will not be followed, because type I error will be higher without the futility stopping rule. Conversely, the trial's statistical power should be determined assuming that the futility stopping rule will be followed, since there will be lower power with the futility stopping rule.

JAMA | Original Investigation

Apixaban to Prevent Recurrence After Cryptogenic Stroke in Patients With Atrial Cardiopathy

The ARCADIA Randomized Clinical Trial

Hooman Kamel, MD; W. T. Longstreth Jr, MD; David L. Tirschwell, MD; Richard A. Kronmal, PhD; Randolph S. Marshall, MD; Joseph P. Broderick, MD; Rebeca Aragón García, BS; Pamela Plummer, MSN; Noor Sabagha, RPH; Qi Pauls, MS; Christy Cassarly, PhD; Catherine R. Dillon, MS; Marco R. Di Tullio, MD; Eldad A. Hod, MD; Elsayed Z. Soliman, MD; David J. Gladstone, MD; Jeff S. Healey, MD; Mukul Sharma, MD; Seemant Chaturvedi, MD; L. Scott Janis, PhD; Balaji Krishnaiah, MD; Fadi Nahab, MD; Scott E. Kasner, MD; Robert J. Stanton, MD; Dawn O. Kleindorfer, MD; Matthew Starr, MD; Toni R. Winder, MD; Wayne M. Clark, MD; Benjamin R. Miller, MD; Mitchell S. V. Elkind, MD; for the ARCADIA Investigators

IMPORTANCE Atrial cardiopathy is associated with stroke in the absence of clinically apparent atrial fibrillation. It is unknown whether anticoagulation, which has proven benefit in atrial fibrillation, prevents stroke in patients with atrial cardiopathy and no atrial fibrillation.

OBJECTIVE To compare anticoagulation vs antiplatelet therapy for secondary stroke prevention in patients with cryptogenic stroke and evidence of atrial cardiopathy.

DESIGN, SETTING, AND PARTICIPANTS Multicenter, double-blind, phase 3 randomized clinical trial of 1015 participants with cryptogenic stroke and evidence of atrial cardiopathy, defined as P-wave terminal force greater than 5000 μV × ms in electrocardiogram lead V_1, serum N-terminal pro-B-type natriuretic peptide level greater than 250 pg/mL, or left atrial diameter index of 3 cm/m^2 or greater on echocardiogram. Participants had no evidence of atrial fibrillation at the time of randomization. Enrollment and follow-up occurred from February 1, 2018, through February 28, 2023, at 185 sites in the National Institutes of Health StrokeNet and the Canadian Stroke Consortium.

INTERVENTIONS Apixaban, 5 mg or 2.5 mg, twice daily (n = 507) vs aspirin, 81 mg, once daily (n = 508).

MAIN OUTCOMES AND MEASURES The primary efficacy outcome in a time-to-event analysis was recurrent stroke. All participants, including those diagnosed with atrial fibrillation after randomization, were analyzed according to the groups to which they were randomized. The primary safety outcomes were symptomatic intracranial hemorrhage and other major hemorrhage.

RESULTS With 1015 of the target 1100 participants enrolled and mean follow-up of 1.8 years, the trial was stopped for futility after a planned interim analysis. The mean (SD) age of participants was 68.0 (11.0) years, 54.3% were female, and 87.5% completed the full duration of follow-up. Recurrent stroke occurred in 40 patients in the apixaban group (annualized rate, 4.4%) and 40 patients in the aspirin group (annualized rate, 4.4%) (hazard ratio, 1.00 [95% CI, 0.64-1.55]). Symptomatic intracranial hemorrhage occurred in 0 patients taking apixaban and 7 patients taking aspirin (annualized rate, 1.1%). Other major hemorrhages occurred in 5 patients taking apixaban (annualized rate, 0.7%) and 5 patients taking aspirin (annualized rate, 0.8%) (hazard ratio, 1.02 [95% CI, 0.29-3.52]).

CONCLUSIONS AND RELEVANCE In patients with cryptogenic stroke and evidence of atrial cardiopathy without atrial fibrillation, apixaban did not significantly reduce recurrent stroke risk compared with aspirin.

Visual Abstract
Editorial page 564
Supplemental content
CME Quiz at jamacmelookup.com

INTERVENTIONS Apixaban, 5 mg or 2.5 mg, twice daily (n = 507) vs aspirin, 81 mg, once daily (n = 508).

MAIN OUTCOMES AND MEASURES The primary efficacy outcome in a time-to-event analysis was recurrent stroke. All participants, including those diagnosed with atrial fibrillation after randomization, were analyzed according to the groups to which they were randomized. The primary safety outcomes were symptomatic intracranial hemorrhage and other major hemorrhage.

RESULTS With 1015 of the target 1100 participants enrolled and mean follow-up of 1.8 years, the trial was stopped for futility after a planned interim analysis. The mean (SD) age of participants was 68.0 (11.0) years, 54.3% were female, and 87.5% completed the full duration of follow-up. Recurrent stroke occurred in 40 patients in the apixaban group (annualized rate, 4.4%) and 40 patients in the aspirin group (annualized rate, 4.4%) (hazard ratio, 1.00 [95% CI, 0.64-1.55]). Symptomatic intracranial hemorrhage occurred in 0 patients taking apixaban and 7 patients taking aspirin (annualized rate, 1.1%). Other major hemorrhages occurred in 5 patients taking apixaban (annualized rate, 0.7%) and 5 patients taking aspirin (annualized rate, 0.8%) (hazard ratio, 1.02 [95% CI, 0.29-3.52]).

CONCLUSIONS AND RELEVANCE In patients with cryptogenic stroke and evidence of atrial cardiopathy without atrial fibrillation, apixaban did not significantly reduce recurrent stroke risk compared with aspirin.

Author Affiliations: Author

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QUESTION Is anticoagulation superior to antiplatelet therapy for prevention of recurrent stroke in patients with cryptogenic stroke and evidence of atrial cardiopathy?

CONCLUSION This randomized trial found that in patients with cryptogenic stroke and evidence of atrial cardiopathy without atrial fibrillation, apixaban did not significantly reduce recurrent stroke risk compared with aspirin.

POPULATION

551 Women
464 Men

Adults ≥45 years with cryptogenic stroke and evidence of atrial cardiopathy

Mean age: **68** years

LOCATIONS

185
Sites in the US and Canada

INTERVENTION

1015 Patients randomized

507
Apixaban
Oral dose of apixaban, 5 mg or 2.5 mg, twice daily
+ aspirin placebo

508
Aspirin
Oral dose of aspirin, 81 mg, once daily
+ apixaban placebo

PRIMARY OUTCOME

Recurrent stroke of any type

FINDINGS

Recurrent stroke

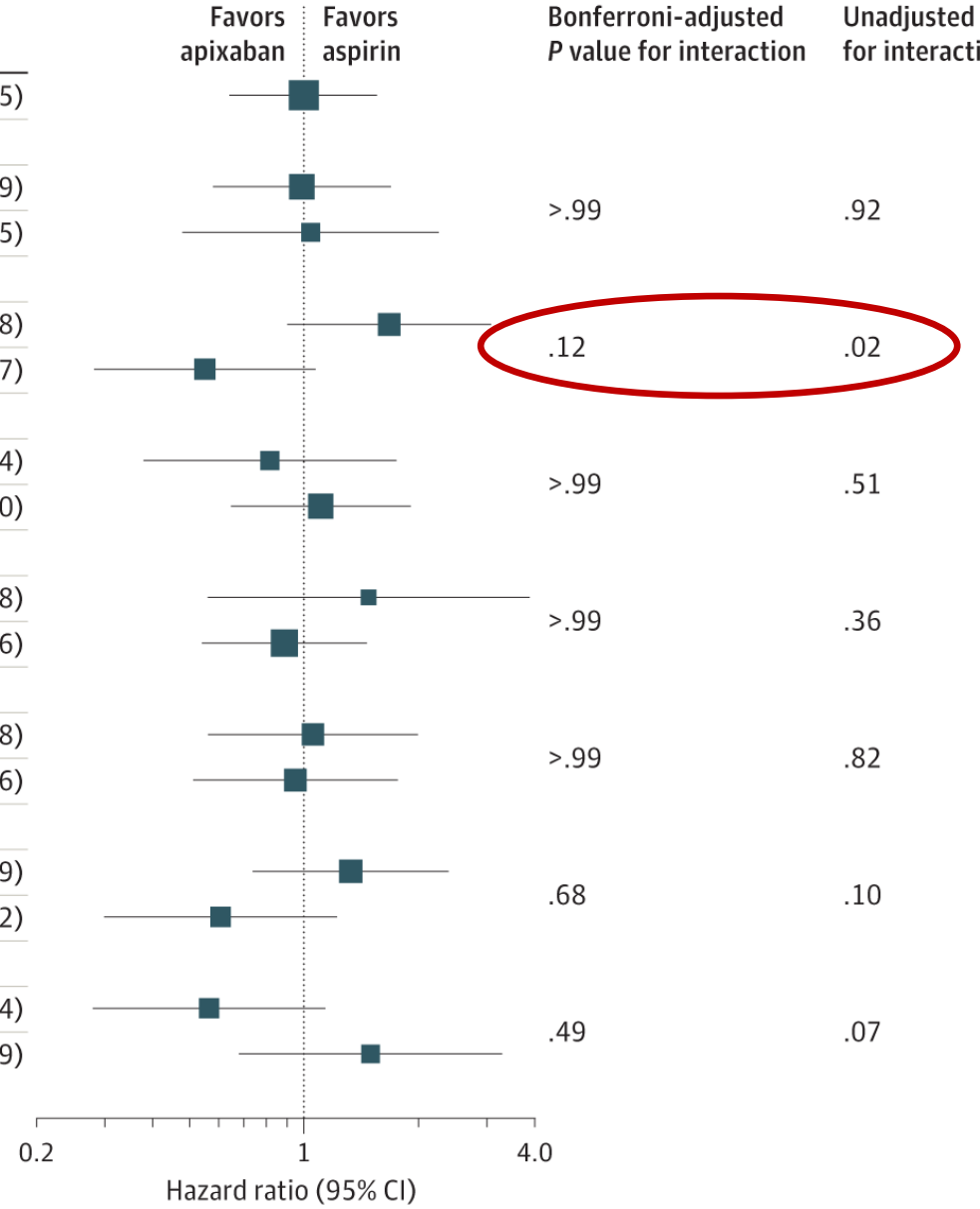
Apixaban
Annualized rate, 4.4%
(40 of 507 patients)

Aspirin
Annualized rate, 4.4%
(40 of 508 patients)

Apixaban did not significantly reduce recurrent stroke risk vs aspirin:
Hazard ratio, 1.00
(95% CI, 0.64 to 1.55)

Kamel H, Longstreth WT Jr, Tirschwell DL, et al; ARCADIA Investigators. Apixaban to prevent recurrence after cryptogenic stroke in patients with atrial cardiopathy: the ARCADIA randomized clinical trial. *JAMA*. Published online February 7, 2024. doi:10.1001/jama.2023.27188

Subgroup	Group, No. of events/ participants (%)		Hazard ratio (95% CI)	Bonferroni-adjusted *P* value for interaction	Unadjusted *P* value for interaction
	Apixaban	Aspirin			
All patients	40/507 (7.9)	40/508 (7.9)	1.00 (0.64-1.55)		
Age, y					
<75	27/359 (7.5)	27/365 (7.4)	0.99 (0.58-1.69)	>.99	.92
≥75	13/148 (8.8)	13/143 (9.1)	1.04 (0.48-2.25)		
Sex					
Female	26/272 (9.6)	17/279 (6.1)	1.67 (0.91-3.08)	.12	.02
Male	14/235 (6.0)	23/229 (10.0)	0.55 (0.28-1.07)		
Race and ethnicity					
Asian, Black, Hispanic, or other	12/152 (7.9)	15/151 (9.9)	0.82 (0.38-1.74)	>.99	.51
Non-Hispanic White	28/348 (8.1)	25/347 (7.2)	1.11 (0.65-1.90)		
Weight, kg					
<70	10/121 (8.3)	7/117 (6.0)	1.48 (0.56-3.88)	>.99	.36
≥70	30/386 (7.8)	33/389 (8.5)	0.89 (0.54-1.46)		
NT-proBNP level, pg/mL					
Below median (<303)	21/266 (7.9)	18/233 (7.7)	1.06 (0.56-1.98)	>.99	.82
Above median (≥303)	19/236 (8.1)	22/263 (8.4)	0.95 (0.51-1.76)		
$PTFV_1$, μV × ms					
Below median (<5200)	25/230 (10.9)	20/244 (8.2)	1.32 (0.74-2.39)	.68	.10
Above median (≥5200)	13/271 (4.8)	20/259 (7.7)	0.61 (0.30-1.22)		
Left atrial diameter index, cm/m^2					
Below median (<1.8)	12/194 (6.2)	23/215 (10.7)	0.57 (0.28-1.14)	.49	.07
Above median (≥1.8)	16/212 (7.6)	10/197 (5.1)	1.49 (0.68-3.29)		



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Research

JAMA | Original Investigation

A Vaping Cessation Text Message Program for Adolescent E-Cigarette Users
A Randomized Clinical Trial

Amanda L. Graham, PhD; Sarah Cha, MSPH; Megan A. Jacobs, MPH; Michael S. Amato, PhD; Anna L. Funsten, MSN; Giselle Edwards, MHS; George D. Papandonatos, PhD

IMPORTANCE E-cigarettes are the most commonly used tobacco product among adolescents. Despite known harms of nicotine exposure among teens, there are no empirically tested vaping cessation interventions.

OBJECTIVE To compare the effectiveness of a text message program for nicotine vaping cessation among adolescents with assessment-only control.

DESIGN, SETTING, AND PARTICIPANTS A parallel, 2-group, double-blind, individually randomized clinical trial with follow-ups at 1 and 7 months after randomization was conducted from October 1, 2021, to October 18, 2023. Participants were recruited via social media ads; the intervention was delivered via text message; and assessments were completed online or by telephone. Eligible individuals were US residents aged 13 to 17 years who reported past 30-day e-cigarette use, were interested in quitting within 30 days, and owned a mobile phone with an active text message plan. To optimize study retention, all participants received monthly assessments via text message about e-cigarette use.

INTERVENTIONS Assessment-only controls (n = 744) received only study retention text messages. Intervention participants (n = 759) also received an automated, interactive text message program for vaping cessation that delivers cognitive and behavioral coping skills training and social support.

MAIN OUTCOMES AND MEASURES The primary outcome was self-reported 30-day point-prevalence abstinence from vaping at 7 months analyzed as intention-to-treat, with missingness coded as vaping.

Research

JAMA | Original Investigation

Letermovir vs Valganciclovir for Prophylaxis of Cytomegalovirus in High-Risk Kidney Transplant Recipients
A Randomized Clinical Trial

Ajit P. Limaye, MD; Klemens Budde, MD; Atul Humar, MD, MSc; Flavio Vincenti, MD; Dirk R. J. Kuypers, MD, PhD; Robert P. Carroll, BM, BCh, DM; Nicole Stauffer, BS; Yoshihiko Murata, MD, PhD; Julie M. Strizki, PhD; Valerie L. Teal, MS; Christopher L. Gilbert, BS; Barbara A. Haber, MD

IMPORTANCE Valganciclovir for 200 days is standard care for cytomegalovirus (CMV) prophylaxis in high-risk CMV-seronegative kidney transplant recipients who receive an organ from a CMV-seropositive donor, but its use is limited by myelosuppression.

OBJECTIVE To compare the efficacy and safety of letermovir with valganciclovir for prevention of CMV disease in CMV-seronegative kidney transplant recipients who receive an organ from a CMV-seropositive donor.

DESIGN, SETTING, AND PARTICIPANTS Randomized, double-masked, double-dummy, noninferiority, phase 3 trial in adult CMV-seronegative kidney transplant recipients who received an organ from a CMV-seropositive donor at 94 participating sites between May 2018 and April 2021 (final follow-up in April 2022).

INTERVENTIONS Participants were randomized in a 1:1 ratio (stratified by receipt of lymphocyte-depleting induction immunosuppression) to receive letermovir, 480 mg, orally daily (with acyclovir) or valganciclovir, 900 mg, orally daily (adjusted for kidney function) for up to 200 days after transplant, with matching placebos.

MAIN OUTCOMES AND MEASURES The primary outcome was CMV disease, confirmed by an independent masked adjudication committee, through posttransplant week 52 (prespecified noninferiority margin, 10%). CMV disease through week 28 and time to onset of CMV disease through week 52 were secondary outcomes. Exploratory outcomes included quantifiable CMV DNAemia and resistance. The rate of leukopenia or neutropenia through week 28 was a prespecified safety outcome.

Visual Abstract
Editorial page 27
Multimedia
Supplemental content

Incomplete Data

JAMA

QUESTION Is a tailored, interactive text message program for vaping cessation effective in promoting abstinence from e-cigarettes among adolescents?

CONCLUSION A tailored, interactive text message intervention increased self-reported vaping cessation rates among adolescents recruited via social media channels.

POPULATION

755 Females
628 Males
110 Nonbinary or other

US adolescents with past 30-day e-cigarette use interested in quitting within 30 days

Mean age: **16.4** years

LOCATIONS

1 Text message program from nonprofit organization in the US

INTERVENTION

1681 Participants randomized
1503 Participants analyzed

759
Text message intervention
Tailored, interactive vaping cessation text messages and study retention text messages

744
Assessment-only control
Study retention text messages only

PRIMARY OUTCOME

Self-reported 30-day point-prevalence abstinence from vaping at 7 months

FINDINGS

Point-prevalence abstinence

Text message intervention	Assessment-only control
37.8% (95% CI, 34.4%-41.3%)	**28.0%** (95% CI, 24.9%-31.3%)

Between-group difference was statistically significant:

9.9% (95% CI, 5.1%-14.5%)

Relative risk, **1.35** (95% CI, 1.17-1.57); *P*<.001

Graham AL, Cha S, Jacobs MA, et al. A vaping cessation text message program for adolescent e-cigarette users: a randomized clinical trial. *JAMA*. Published August 7, 2024. doi:10.1001/jama.2024.11057

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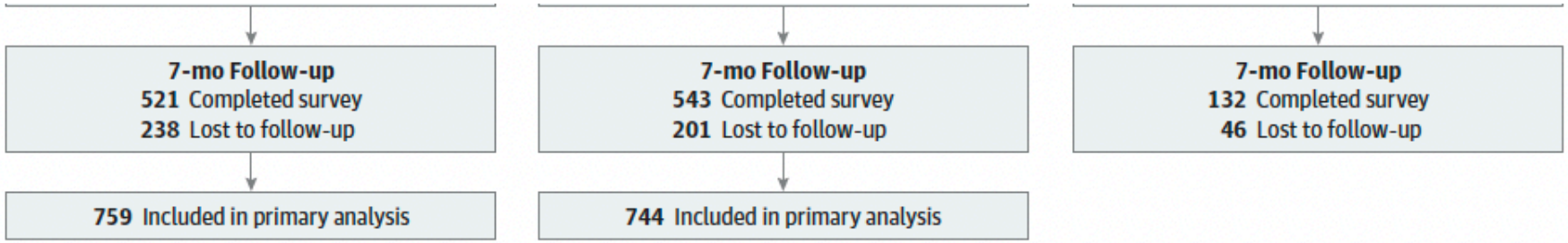

Figure depicts 2 main trial groups (This is Quitting, assessment-only control; total sample n = 1503) and a third group (waitlist control), which was included to provide context for assessment-only control. Recruitment to waitlist control was stopped early due to budget constraints.

Table 2. Vaping Cessation Outcomes at 7 Months[a]

Outcome variable (point-prevalence abstinence)	% (95% CI)					
	Intervention (n = 759)	Assessment-only control (n = 744)	Rate difference (95% CI)	Relative risk (95% CI)	Odds ratio (95% CI)	*P* value
30 d	37.8 (34.4-41.3)	28.0 (24.9-31.3)	9.9 (5.1-14.5)	1.35 (1.17-1.57)	1.57 (1.26-1.95)	<.001
Repeated	17.3 (14.7-20.1)	8.2 (6.4-10.4)	9.1 (5.7-12.4)	2.10 (1.58-2.80)	2.34 (1.69-3.22)	<.001

[a] Missing outcomes were counted as vaping.

238/759=31% 201/744=27% Supplement: MI as sensitivity

Incomplete Data

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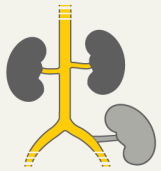
QUESTION Is letermovir noninferior to valganciclovir prophylaxis for cytomegalovirus (CMV) disease prevention in high-risk adult CMV-seronegative kidney transplant recipients who receive an organ from a CMV-seropositive donor?

CONCLUSION Letermovir was noninferior to valganciclovir for prophylaxis of CMV disease over 52 weeks among adult CMV-seronegative recipients who received an organ from a CMV-seropositive donor.

POPULATION



422 Men
167 Women

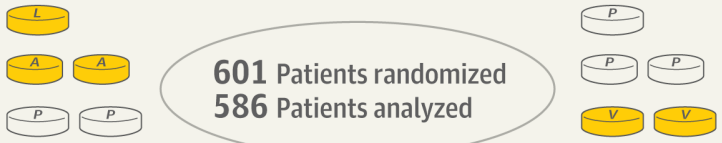
Adult CMV-seronegative kidney transplant recipients receiving an organ from a CMV-seropositive donor

Mean age: 50 years

LOCATIONS

94
Hospitals worldwide

INTERVENTION



301
Letermovir
480 mg of letermovir orally daily, 400 mg of acyclovir twice daily, and a valganciclovir placebo

300
Valganciclovir
900 mg of valganciclovir orally daily with letermovir and acyclovir placebos

PRIMARY OUTCOME

CMV disease through 52 weeks after transplant

FINDINGS

Patients with committee-confirmed CMV through week 52

Letermovir
10.4% (30 of 289 patients)

Valganciclovir
11.8% (35 of 297 patients)

Letermovir was noninferior to valganciclovir:
Stratum-adjusted difference, −1.4%
(95% CI, −6.5% to 3.8%)

Limaye AP, Budde K, Humar A, et al. Letermovir vs valganciclovir for prophylaxis of cytomegalovirus in high-risk kidney transplant recipients: a randomized clinical trial. *JAMA*. Published online June 6, 2023. doi:10.1001/jama.2023.9106

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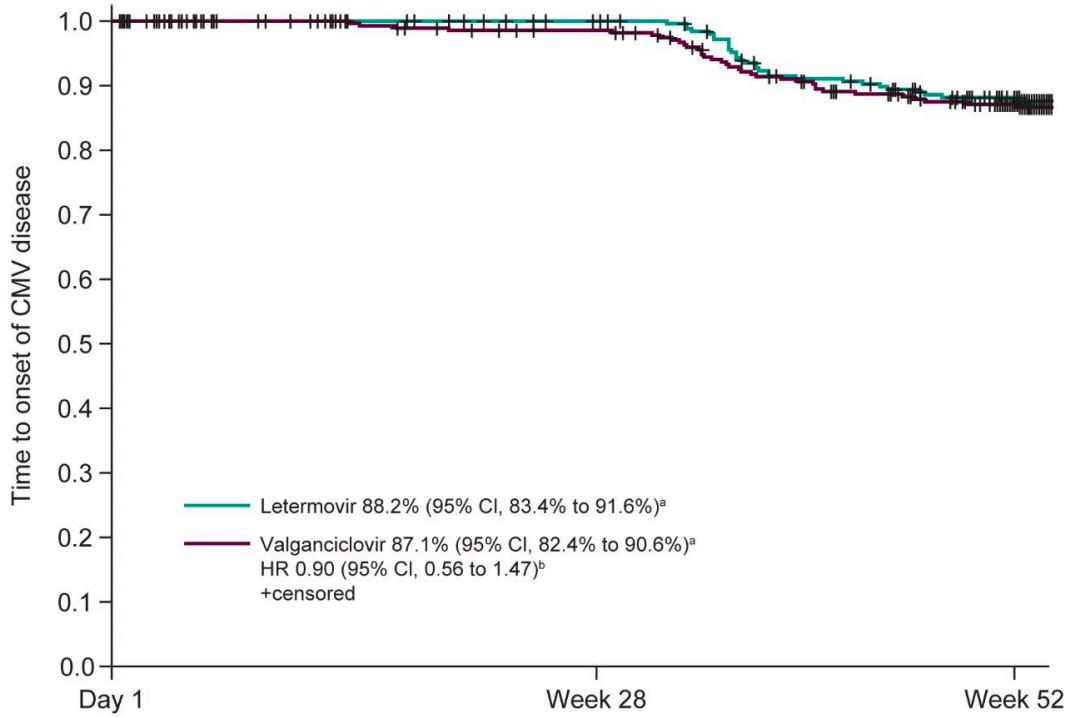
eFigure 4. Time to Onset of CMV Disease Through Week 52 in the Full Analysis Set



No. of participants at risk			
Letermovir	289	252	196
Valganciclovir	297	268	191
No. of events			
Letermovir	0	29	1
Valganciclovir	4	30	1

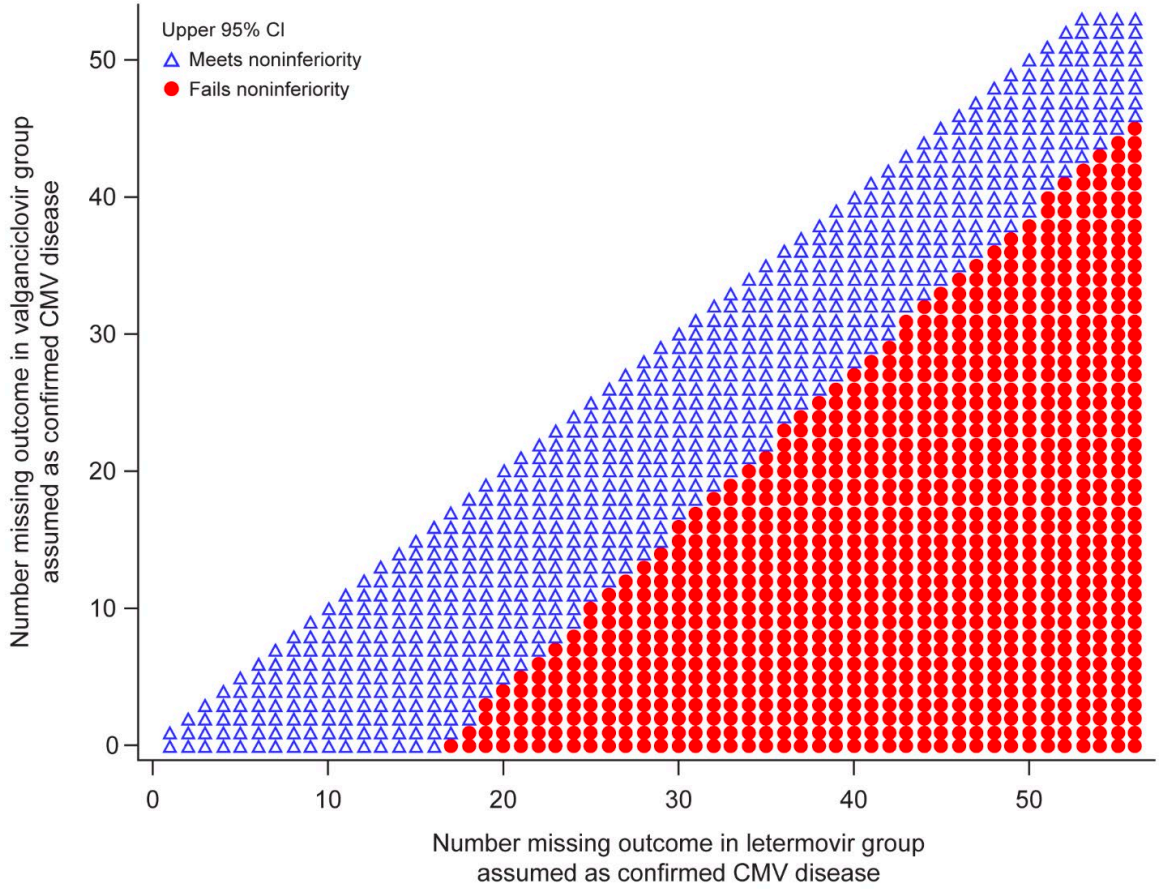
Primary NI analysis based on 30 vs 35 confirmed – but:

L: 56 incomplete counted as 0

V: 53 incomplete counted as 0

Incomplete Data

eFigure 3. Tipping Point Analysis



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CLINICAL

Q: Conventions in certain domains dictate conservative strategies for handling missing outcomes – are these clinically appropriate or understood by the reader? Are these norms movable?

Q: We expect presentation of pre-specified primary analyses – are these ultimately viewed by our readers as “endorsed” even when sensitivity analyses are invited / required?

STATISTICAL

Q: Use of contemporary methods to address missing data?

Q: Are sensitivity analyses sufficient for communication of uncertainty?

JAMA | Original Investigation

CNM-Au8 in Amyotrophic Lateral Sclerosis
The HEALEY ALS Platform Trial

Writing Committee for the HEALEY ALS Platform Trial

IMPORTANCE Bioenergetic failure has been proposed as a driver of amyotrophic lateral sclerosis (ALS). CNM-Au8 is a suspension of gold nanocrystals that catalyzes the conversion of nicotinamide adenine dinucleotide hydride into NAD^+, resulting in an increase of cellular adenosine triphosphate production.

OBJECTIVE To determine the effects of (

DESIGN, SETTING, AND PARTICIPANTS CN
Platform Trial, a phase 2/3, multicenter,
was conducted at 54 sites in the US fro
2022). A total of 161 participants with A
regimen-specific placebo (n = 41). Data
participants in other regimens were co

INTERVENTIONS Eligible participants we
60 mg daily (n = 61), CNM-Au8 30 mg da

MAIN OUTCOMES AND MEASURES The p
through week 24 in ALS disease severity
function (based on the Revised Amyotr
survival, which provided an estimate of
disease rate ratio (DRR), with a DRR of l
end points included a Combined Assess
rate of decline in slow vital capacity (pe
assisted ventilation.

RESULTS Among 161 participants who were randomized within the CNM-Au8 regimen (mean age, 58.4 years; 61 [37.9%] female), 145 (90%) completed the trial. In the primary analysis comparing the combined CNM-Au8 dosage groups vs the combined placebo groups, the primary end point (DRR, 0.97 [95% credible interval, 0.783-1.175]; posterior probability of DRR <1, 0.65) and the 3 secondary end points suggested no benefit or harm of CNM-Au8. In the active (n = 120) vs placebo (n = 163) groups, the most common adverse events were diarrhea (23 [19%] vs 12 [7%]), nausea (17 [14.2%] vs 14 [8.6%]), fatigue (12 [10.8%] vs 30 [18.4%]), and muscular weakness (24 [20%] vs 45 [27.6%]).

CONCLUSIONS AND RELEVANCE No benefit of CNM-Au8 on ALS disease progression was observed at 24 weeks.

DESIGN, SETTING, AND PARTICIPANTS CNM-Au8 was tested as a regimen of the HEALEY ALS Platform Trial, a phase 2/3, multicenter, randomized, double-blind platform trial. The study was conducted at 54 sites in the US from July 2020 to March 2022 (final follow-up, March 17,
ceive CNM-Au8 (n = 120) or
ndomized placebo

tio to receive CNM-Au8
lacebo (n = 41) for 24 weeks.

was change from baseline
shared parameter model of
nctional Rating Scale) and
ession measured by the
ment benefit. Secondary
vival using a joint-rank test,
rate of decline in slow vital capacity (percent predicted), and survival free of permanent assisted ventilation.

RESULTS Among 161 participants who were randomized within the CNM-Au8 regimen (mean age, 58.4 years; 61 [37.9%] female), 145 (90%) completed the trial. In the primary analysis comparing the combined CNM-Au8 dosage groups vs the combined placebo groups, the primary end point (DRR, 0.97 [95% credible interval, 0.783-1.175]; posterior probability of DRR <1, 0.65) and the 3 secondary end points suggested no benefit or harm of CNM-Au8. In the active (n = 120) vs placebo (n = 163) groups, the most common adverse events were diarrhea (23 [19%] vs 12 [7%]), nausea (17 [14.2%] vs 14 [8.6%]), fatigue (12 [10.8%] vs 30 [18.4%]), and muscular weakness (24 [20%] vs 45 [27.6%]).

CONCLUSIONS AND RELEVANCE No benefit of CNM-Au8 on ALS disease progression was observed at 24 weeks.

JAMA®

QUESTION What is the effect of CNM-Au8, an oral suspension of catalytically active gold particles, on disease progression of amyotrophic lateral sclerosis (ALS) over 24 weeks?

CONCLUSION Over 24 weeks, no significant benefit of CNM-Au8 was observed on ALS disease progression.

POPULATION

186 Men
98 Women

Adults with a diagnosis of ALS defined by the revised El Escorial criteria

Mean age: 58 years

LOCATIONS

54 Northeast ALS Consortium centers in the US

INTERVENTION

CNM-Au8 group
Received CNM-Au8 60 mg or 30 mg daily for 24 weeks

Shared placebo group
Received matching placebo for 24 weeks (including 123 patients from other regimens)

PRIMARY OUTCOME

Change from baseline through week 24 in ALS disease severity measured by Revised ALS Functional Rating Scale (ALSFRS-R) score and survival measured by disease rate ratio (DRR)

FINDINGS

Monthly change in ALSFRS-R score

CNM-Au8 group	−1.00 (95% CrI, −1.153 to −0.858) Mortality event rate, 0.006
Shared placebo group	−1.03 (95% CrI, −1.176 to −0.892) Mortality event rate, 0.007

There was no significant difference between groups:

Disease rate ratio, 0.97
(95% CrI, 0.783 to 1.175)

Writing Committee for the HEALEY ALS Platform Trial. CNM-Au8 in amyotrophic lateral sclerosis: results from the HEALEY ALS platform trial. *JAMA*. Published online February 17, 2025. doi:10.1001/jama.2024.27643