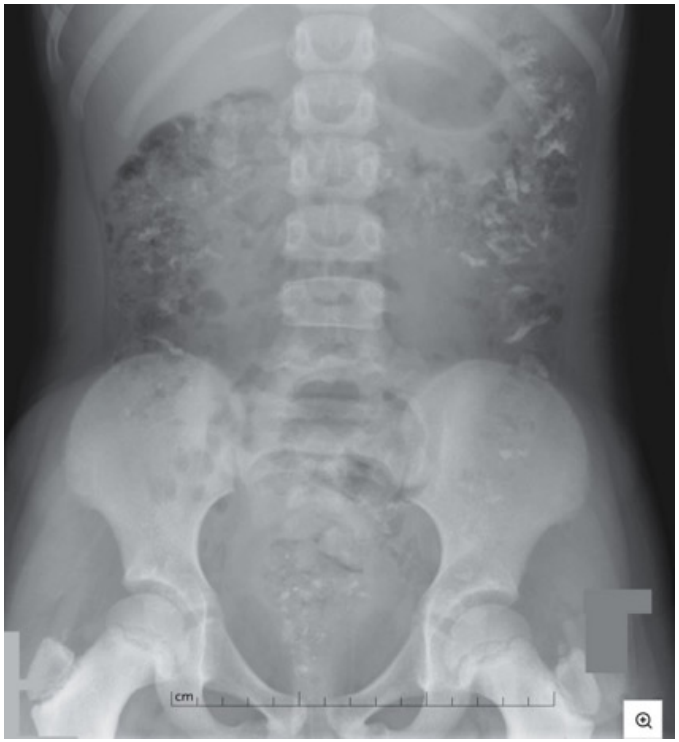
https://www.mdc-berlin.de/de/veroeffentlichungstypen/clinical-journal-club

Als gemeinsame Einrichtung von MDC und Charité fördert das Experimental and Clinical Research Center die Zusammenarbeit zwischen Grundlagenwissenschaftlern und klinischen Forschern. Hier werden neue Ansätze für Diagnose, Prävention und Therapie von Herz-Kreislauf- und Stoffwechselerkrankungen, Krebs sowie neurologischen Erkrankungen entwickelt und zeitnah am Patienten eingesetzt. Sie sind eingeladen, uns beizutreten. Bewerben Sie sich!

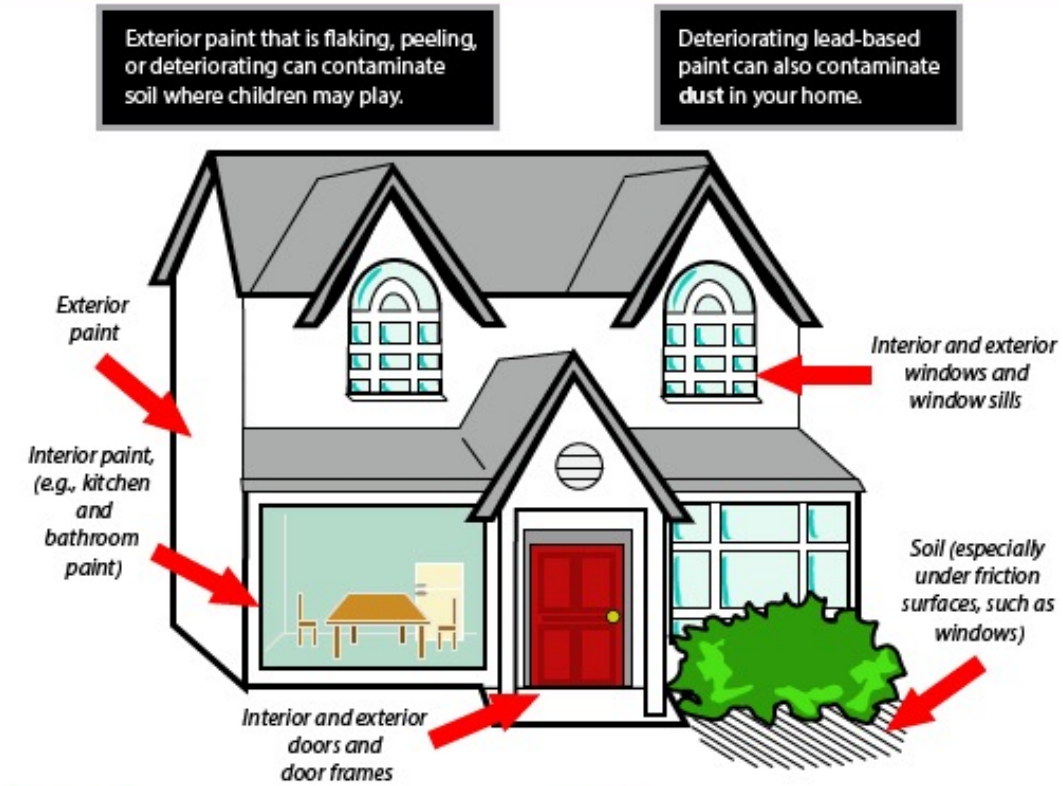


A 7-year-old girl was referred to the emergency department for evaluation of abnormal blood work. Her family had recently made an immigration journey to the United States. Physical examination was notable for dental caries, mild conjunctival pallor, and no signs of neurodevelopmental delay. Laboratory studies showed a hemoglobin level of 10.5 g per deciliter (reference range, 11.3 to 14.6), a mean corpuscular volume of 64.4 fl (reference range, 77.8 to 86.5), and a ferritin level of 8 ng per milliliter (reference range, 10 to 320). An abdominal radiograph showed intraluminal radiodensities throughout the colon. Which of the following diagnoses best explains the patient's laboratory and radiographic abnormalities?

Bismuth poisoning
Copper deficiency
Lead poisoning
Inflammatory bowel disease
Thalassemia

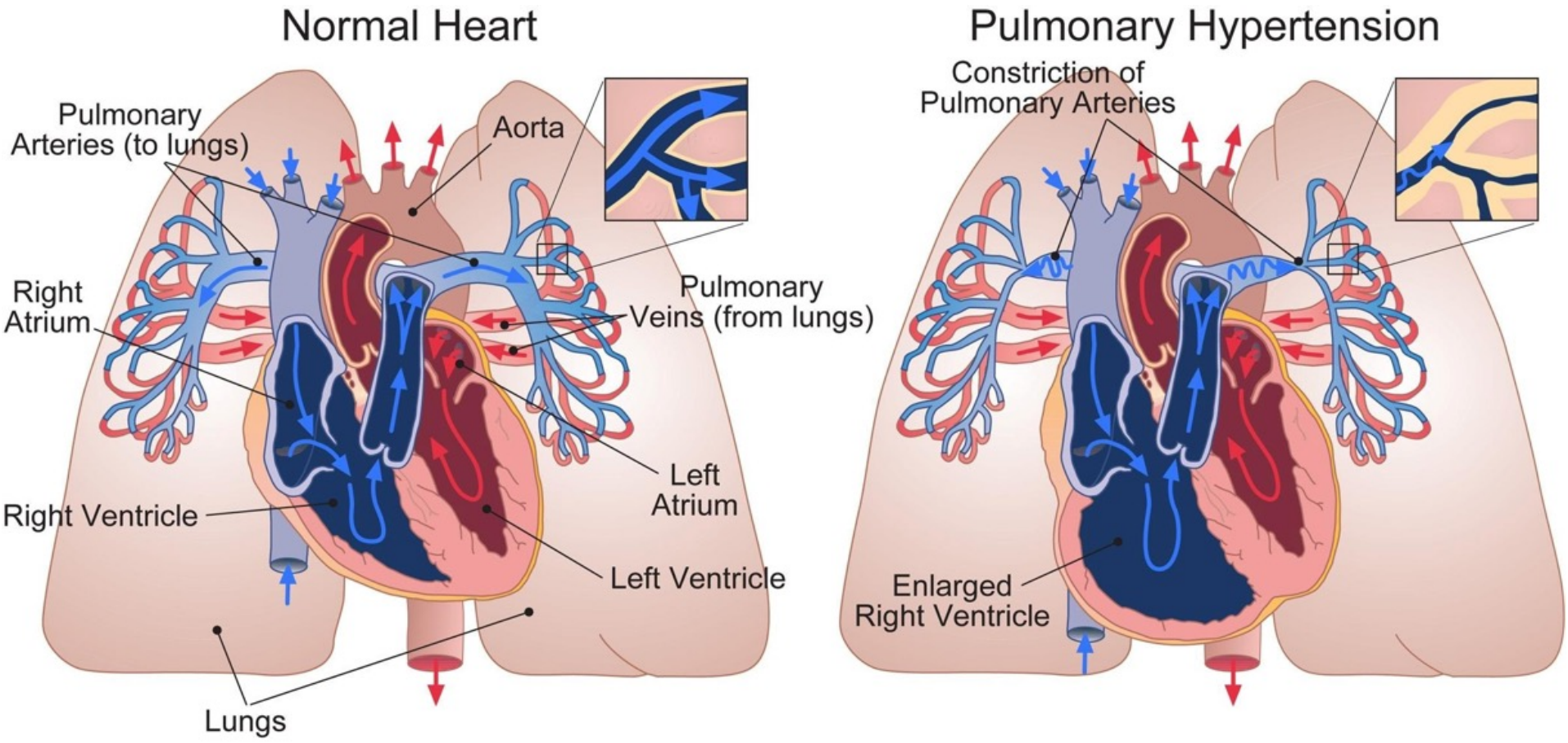
The patient had a history of ingestion of lead paint chips, which explained the intraluminal radiodensities seen throughout the colon on abdominal radiograph. Laboratory studies showed a lead level of greater than 45 µg per deciliter (>2.2 µmol per liter; reference value, <2 µg per deciliter [<0.1 µmol per liter]). A diagnosis of lead poisoning owing to ingestion of lead paint chips in the context of pica from iron-deficiency anemia was made. Intravenous and oral chelation therapy was provided. The patient continues to undergo monitoring owing to her risk of re-exposure to lead paint from housing instability.

Lead-based paint can be found both inside and outside the home. Do you know where to look for lead?

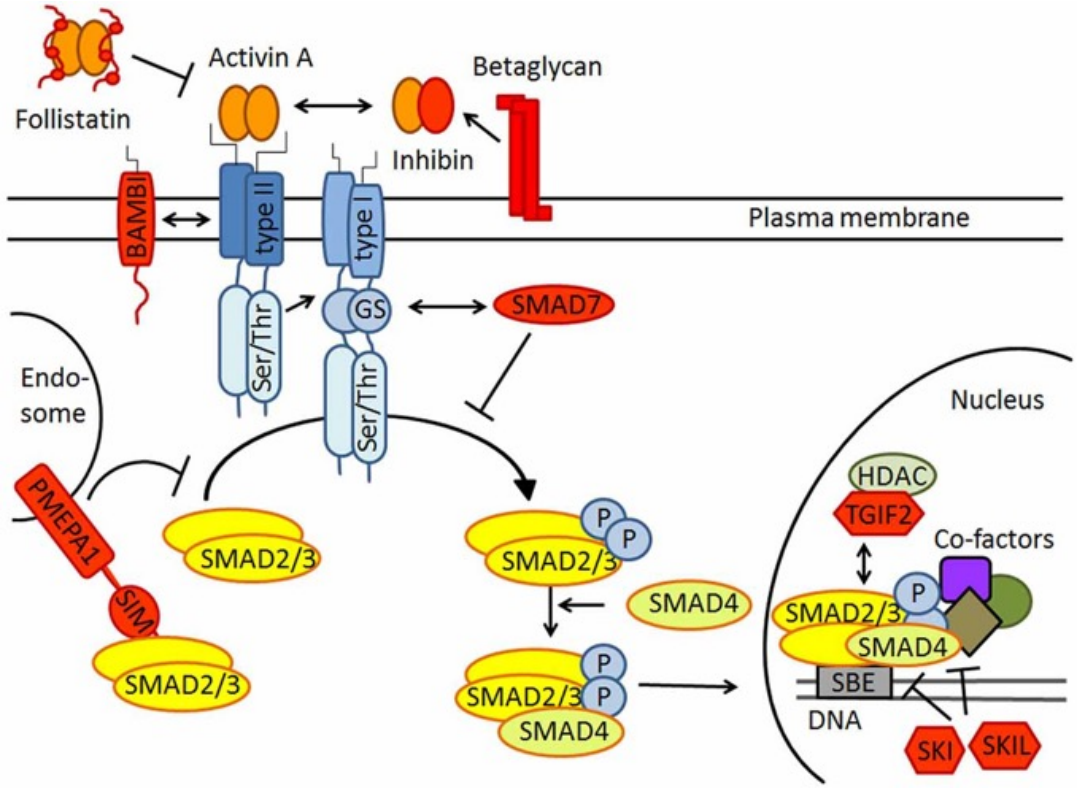


EPA www.epa.gov/lead #leadfreekids

The primary gene associated with heritable pulmonary arterial hypertension (HPAH) is BMPR2. Mutations in this gene, which codes for a receptor in the TGF-beta superfamily, are responsible for a significant portion of familial PAH cases. While BMPR2 mutations are the most common genetic cause, other genes like ACVRL1, CAV1, KCNK3, and SMAD9 have also been implicated in HPAH.

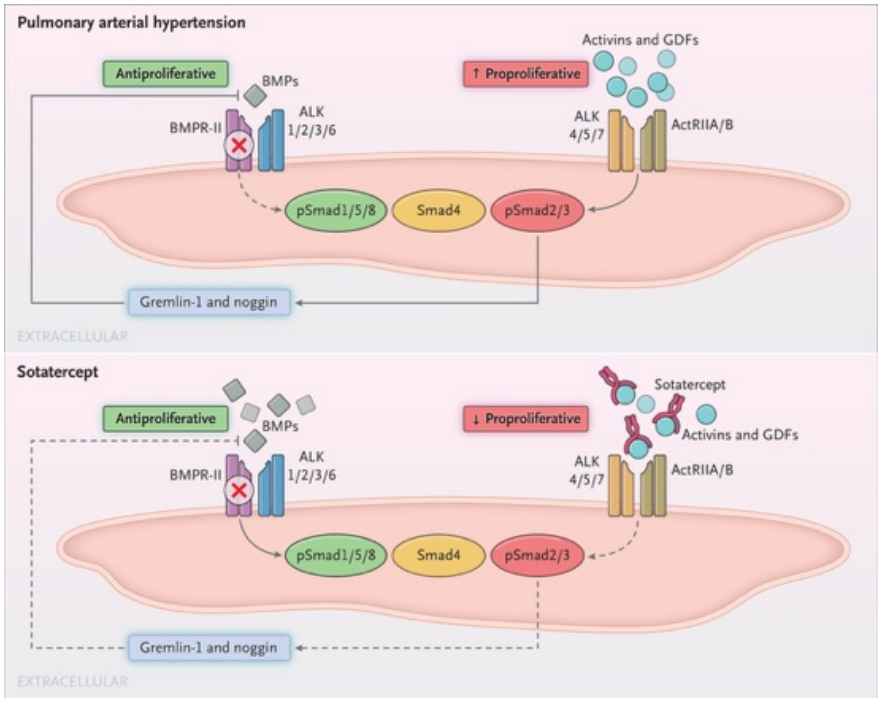


Activine sind eine Gruppe von Proteinen, die zur TGF-β-Superfamilie gehören und eine wichtige Rolle in der Regulation verschiedener physiologischer Prozesse spielen. Sie sind dimere Proteine, die aus zwei Untereinheiten (βA und βB) bestehen und verschiedene Funktionen in Gewebewachstum, -entwicklung und -funktion ausüben.



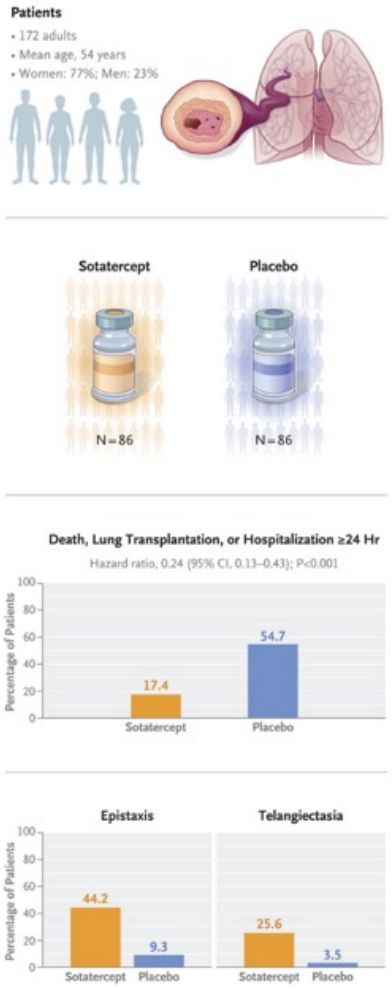
Sotatercept ist ein Medikament, das in der Behandlung der pulmonalen arteriellen Hypertonie (PAH) eingesetzt wird. Es handelt sich um ein Fusionsprotein, das aus der extrazellulären Domäne des Aktivinrezeptors Typ IIA (ActRIIA) und einer humanen IgG1-Fc-Domäne besteht. Sotatercept hemmt die Aktivin-Signalwege, die bei PAH eine Rolle spielen, wodurch die Gefäßentwicklung in der Lunge verbessert wird.

Abfangjäger, Werneuchen



Sotatercept in Patients with Pulmonary Arterial Hypertension at High Risk for Death

Sotatercept improves exercise capacity and delays the time to clinical worsening in patients with World Health Organization (WHO) functional class II or III pulmonary arterial hypertension. The effects of add-on sotatercept in patients with advanced pulmonary arterial hypertension and a high risk of death are unclear. In this phase 3 trial, we randomly assigned patients with pulmonary arterial hypertension (WHO functional class III or IV) and a high 1-year risk of death (Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management Lite 2 risk score, ≥9) who were receiving the maximum tolerated dose of background therapy to receive add-on sotatercept (starting dose, 0.3 mg per kilogram of body weight; escalated to target dose, 0.7 mg per kilogram) or placebo every 3 weeks. The primary end point was a composite of death from any cause, lung transplantation, or hospitalization (≥24 hours) for worsening pulmonary arterial hypertension, assessed in a time-to-first-event analysis.



Pulmonary arterial hypertension is a progressive, potentially fatal disease characterized by remodeling of the pulmonary vasculature. Established treatments for pulmonary arterial hypertension include endothelin-receptor antagonists, phosphodiesterase-5 inhibitors, soluble guanylate cyclase stimulators, and prostacyclin-pathway agents. Although randomized, placebo-controlled trials of existing therapies have shown delays in the time to clinical worsening, these findings primarily reflected functional deterioration rather than major events such as death, lung transplantation, and hospitalization for worsening pulmonary arterial hypertension.
Sotatercept, a first-in-class activin-signaling inhibitor, offers a novel therapeutic alternative to vasodilators in the treatment of pulmonary arterial hypertension by binding proproliferative members of the transforming growth factor β superfamily (e.g., activins), targeting pulmonary vascular remodeling.

Trial Population

Eligible patients were adults (18 to 75 years of age) who had symptomatic WHO group 1 pulmonary arterial hypertension (idiopathic, heritable, drug- or toxin-induced, connective-tissue disease–associated, or with simple congenital systemic-to-pulmonary shunts ≥1 year after repair) in WHO functional class III or IV and had a REVEAL Lite 2 risk score of 9 or higher.

Efficacy End Points

The primary end point was a composite of death from any cause, lung transplantation, or hospitalization lasting at least 24 hours for worsening pulmonary arterial hypertension, assessed in a time-to-first-event analysis.

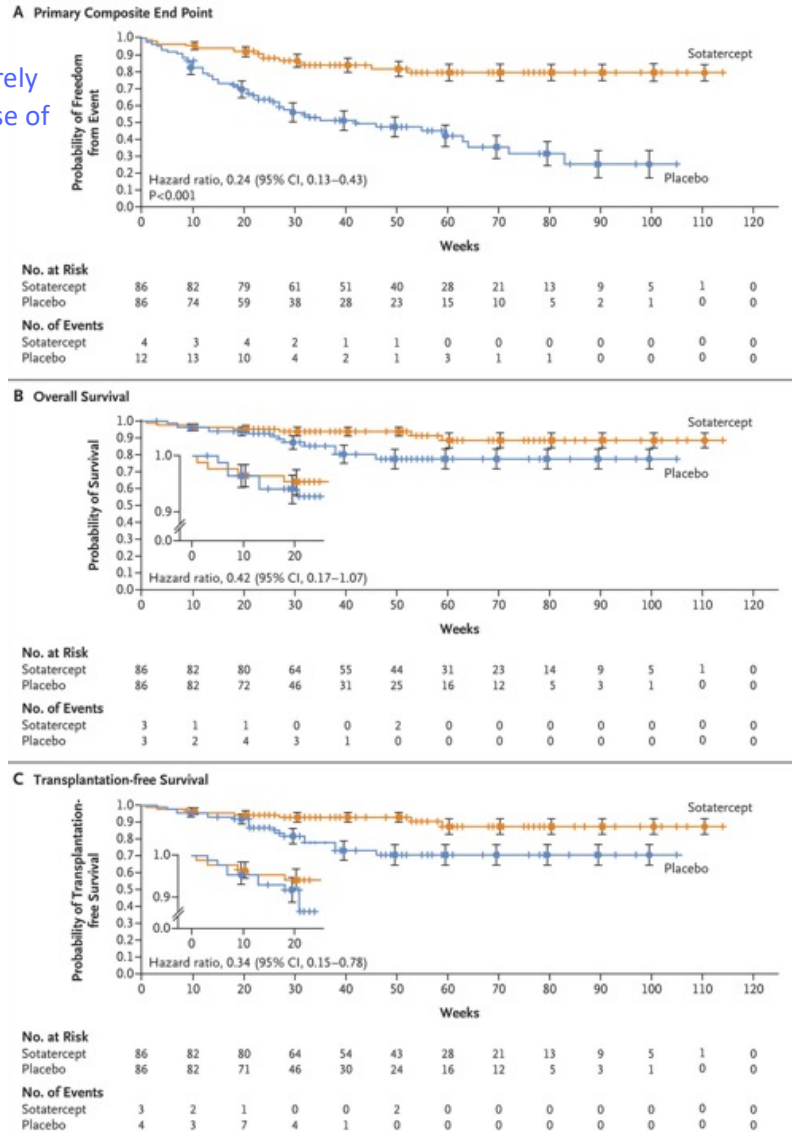
Characteristic	Sotatercept (N=86)	Placebo (N=86)	Total (N=172)
Female sex — no. (%)	61 (70.9)	71 (82.6)	132 (76.7)
Age — yr	55.3±14.3	53.5±14.3	54.4±14.3
Race — no. (%)†			
White	73 (84.9)	76 (88.4)	149 (86.6)
Other‡	12 (14.0)	10 (11.6)	22 (12.8)
Missing	1 (1.2)	0	1 (0.6)
Body-mass index ≥30 — no. (%)§	14 (16.3)	19 (22.1)	33 (19.2)
Time since diagnosis of pulmonary arterial hypertension — yr¶	7.2±5.6	8.2±6.7	7.7±6.2
Classification of pulmonary arterial hypertension — no. (%)			
Idiopathic	42 (48.8)	44 (51.2)	86 (50.0)
Heritable	11 (12.8)	7 (8.1)	18 (10.5)
Associated with connective-tissue disease	22 (25.6)	26 (30.2)	48 (27.9)
Drug-induced or toxin-induced	6 (7.0)	5 (5.8)	11 (6.4)
Associated with corrected congenital shunts	5 (5.8)	4 (4.7)	9 (5.2)
REVEAL Lite 2 risk score — no. (%)‖			
8–10	60 (69.8)	60 (69.8)	120 (69.8)
≥11	26 (30.2)	26 (30.2)	52 (30.2)
WHO functional class — no. (%)**			
III	66 (76.7)	62 (72.1)	128 (74.4)
IV	20 (23.3)	24 (27.9)	44 (25.6)
Background therapy for pulmonary arterial hypertension — no. (%)††			
Prostacyclin infusion therapy‡‡	53 (61.6)	49 (57.0)	102 (59.3)
Double therapy	21 (24.4)	27 (31.4)	48 (27.9)
Triple therapy	65 (75.6)	59 (68.6)	124 (72.1)
6-Minute walk distance — m	270.3±104.8	270.7±99.9	270.5±102.1
NT-proBNP — pg/ml	3603.1±4101.2	2687.3±2771.2	3145.2±3519.8
Mean pulmonary artery pressure — mm Hg	57.0±13.4	55.2±12.1	56.1±12.8
Pulmonary vascular resistance — dyn·sec·cm^{-5}	883.2±410.9	874.7±344.2	879.0±378.2
Cardiac index — liters/min/m^2	2.6±0.6	2.6±0.8	2.6±0.7
Pulmonary artery wedge pressure — mm Hg	10.0±3.3	9.8±3.1	9.9±3.2
Hemoglobin — g/dl	12.9±1.9	12.9±1.9	12.9±1.9
Estimated glomerular filtration rate — ml/min/1.73 m^2	65.1±24.6	73.5±29.7	69.3±27.5

End Point	Sotatercept (N=86)	Placebo (N=86)
Primary end point		
Composite of death from any cause, lung transplantation, or hospitalization ≥24 hr for worsening pulmonary arterial hypertension, assessed in a time-to-first-event analysis		
Hazard ratio (95% CI)†	0.24 (0.13 to 0.43)‡	—
Secondary end points§		
Overall survival, assessed in a time-to-event analysis		
Hazard ratio (95% CI)†	0.42 (0.17 to 1.07)¶	—
Transplantation-free survival, assessed in a time-to-event analysis		
Hazard ratio (95% CI)†	0.34 (0.15 to 0.78)	—
Death from any cause		
Patients who died — no./total no. (%)	7/86 (8.1)	13/86 (15.1)
Between-group percentage-point difference (95% CI)	−7.3 (−17.7 to 2.4)	—
Change from baseline in REVEAL Lite 2 risk score		
Median change estimate (range) from baseline at wk 24‖	−3.0 (−3 to −2)	0.0 (0.0 to 0.0)
Hodges–Lehmann location shift from placebo estimate (95% CI)**††	−3.1 (−4.3 to −1.9)	—
Patients with a low or intermediate REVEAL Lite 2 risk score (≤7) at wk 24 — no./total no. (%)††	34/69 (49.3)	11/72 (15.3)
Between-group percentage-point difference (95% CI)	33.1 (18.4 to 47.0)	—
NT-proBNP — pg/ml		
Median change estimate (range) from baseline at wk 24‖	−1233.0 (−1233 to −1233)	255.4 (211 to 263)
Hodges–Lehmann location shift from placebo estimate (95% CI)**‡‡	−2339.1 (−3378.7 to −1299.4)	—
Mean pulmonary artery pressure — mm Hg		
Median change estimate (range) from baseline at wk 24‖	−13.6 (−14 to −13)	5.5 (5 to 6)
Hodges–Lehmann location shift from placebo estimate (95% CI)**‡‡	−21.2 (−27.8 to −14.6)	—
Pulmonary vascular resistance — dyn·sec·cm^{-5}		
Median change estimate (range) from baseline at wk 24‖	−156.6 (−160 to −152)	46.6 (36 to 104)
Hodges–Lehmann location shift from placebo estimate (95% CI)**‡‡	−339.6 (−511.1 to −168.1)	—
WHO functional class		
Patients with improvement — no./total no. (%)§§	48/86 (55.8)	24/86 (27.9)
Between-group percentage-point difference (95% CI)	27.4 (12.9 to 41.0)	—
6-Minute walk distance — m		
Median change estimate (range) from baseline at wk 24‖	45.4 (45.0 to 46.0)	−5.4 (−9.5 to −1.0)
Hodges–Lehmann location shift from placebo estimate (95% CI)**‡‡	63.0 (23.2 to 102.7)	—
Cardiac output — liters/min		
Median change estimate (range) from baseline at wk 24‖	−0.1 (−0.1 to −0.1)	−0.4 (−0.4 to −0.4)
Hodges–Lehmann location shift from placebo estimate (95% CI)**‡‡	0.5 (−0.2 to 1.2)	—
EQ-5D-5L index score¶¶		
Median change estimate (range) from baseline at wk 24‖‖	0.060 (−1.020 to 0.512)	0.007 (−0.358 to 0.740)

Variable	Sotatercept (N=86)	Placebo (N=86)	Hazard Ratio (95% CI)
No. (%) with ≥1 event	15 (17.4)	47 (54.7)	0.24 (0.13 to 0.43)†
Components of the primary end point — no. (%)‡			
Death from any cause§	7 (8.1)	13 (15.1)	—
Lung transplantation	1 (1.2)	6 (7.0)	—
Hospitalization ≥24 hr for worsening pulmonary arterial hypertension	8 (9.3)	43 (50.0)	—

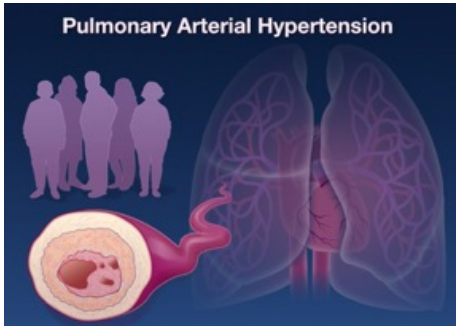
Variable	Sotatercept (N=86)	Placebo (N=86)	Point Estimate (95% CI)†
	number (percent)		*percentage points*
Any adverse event	85 (98.8)	83 (96.5)	2.3 (−3.2 to 8.8)
Adverse event leading to discontinuation of sotatercept or placebo	0	4 (4.7)	−4.7 (−11.4 to −0.3)
Adverse event related to sotatercept or placebo‡	56 (65.1)	28 (32.6)	32.6 (17.8 to 45.9)
Adverse event related to sotatercept or placebo leading to discontinuation of sotatercept or placebo‡	0	1 (1.2)	−1.2 (−6.3 to 3.2)
Adverse event leading to death§	5 (5.8)	12 (14.0)	−8.1 (−17.8 to 0.9)
Adverse event related to sotatercept or placebo leading to death‡	0	0	0.0 (−4.3 to 4.3)
Serious adverse event¶	46 (53.5)	55 (64.0)	−10.5 (−24.8 to 4.3)
Serious adverse event leading to discontinuation of sotatercept or placebo¶	0	4 (4.7)	−4.7 (−11.4 to −0.3)
Serious adverse event related to sotatercept or placebo‡¶	3 (3.5)	2 (2.3)	1.2 (−5.0 to 7.8)
Serious adverse event related to sotatercept or placebo leading to discontinuation of sotatercept or placebo‡¶	0	1 (1.2)	−1.2 (−6.3 to 3.2)
Adverse event of interest or special interest‖			
Any such event	74 (86.0)	59 (68.6)	17.4 (5.0 to 29.7)
Bleeding event	54 (62.8)	30 (34.9)	27.9 (13.1 to 41.5)
Cardiac event	13 (15.1)	26 (30.2)	−15.1 (−27.5 to −2.6)
Increased hemoglobin level	11 (12.8)	1 (1.2)	11.6 (4.8 to 20.5)
Telangiectasia	22 (25.6)	3 (3.5)	22.1 (12.4 to 32.7)
Adverse event with an incidence of ≥10% in either or both groups			
Thrombocytopenia**	11 (12.8)	7 (8.1)	4.7 (−4.8 to 14.5)
Cardiac failure	6 (7.0)	10 (11.6)	−4.7 (−14.1 to 4.4)
Right ventricular failure	3 (3.5)	12 (14.0)	−10.5 (−19.9 to −2.2)
Diarrhea	19 (22.1)	15 (17.4)	4.7 (−7.4 to 16.7)
Nausea	16 (18.6)	13 (15.1)	3.5 (−7.9 to 15.0)
Vomiting	11 (12.8)	5 (5.8)	7.0 (−1.9 to 16.5)
Gingival bleeding	9 (10.5)	2 (2.3)	8.1 (0.9 to 16.7)
Fatigue	12 (14.0)	14 (16.3)	−2.3 (−13.4 to 8.7)
Peripheral edema	12 (14.0)	17 (19.8)	−5.8 (−17.3 to 5.6)
Covid-19	14 (16.3)	14 (16.3)	0.0 (−11.3 to 11.3)
Nasopharyngitis	9 (10.5)	11 (12.8)	−2.3 (−12.4 to 7.7)
Pneumonia	9 (10.5)	5 (5.8)	4.7 (−3.9 to 13.7)
Hypokalemia	15 (17.4)	13 (15.1)	2.3 (−9.0 to 13.7)
Back pain	9 (10.5)	4 (4.7)	5.8 (−2.4 to 14.7)
Headache	20 (23.3)	20 (23.3)	0.0 (−12.7 to 12.7)
Dizziness	9 (10.5)	8 (9.3)	1.2 (−8.3 to 10.7)
Epistaxis	38 (44.2)	8 (9.3)	34.9 (22.4 to 46.7)
Dyspnea	10 (11.6)	21 (24.4)	−12.8 (−24.4 to −1.3)
Pulmonary arterial hypertension††	4 (4.7)	25 (29.1)	−24.4 (−35.4 to −14.0)
Telangiectasia	22 (25.6)	3 (3.5)	22.1 (12.4 to 32.7)
Hypotension	12 (14.0)	9 (10.5)	3.5 (−6.6 to 13.8)

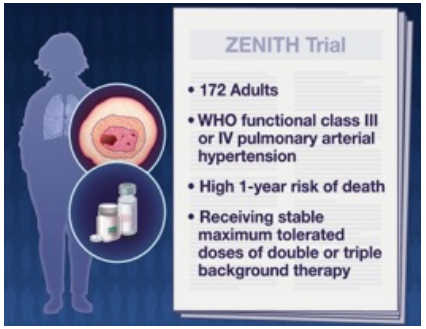
Study prematurely stopped because of this result

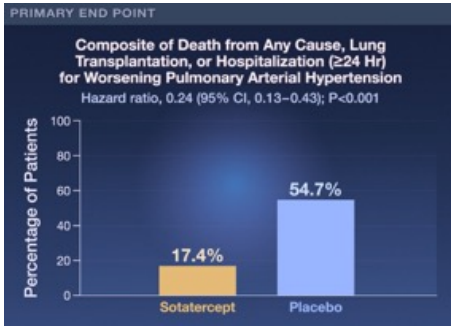


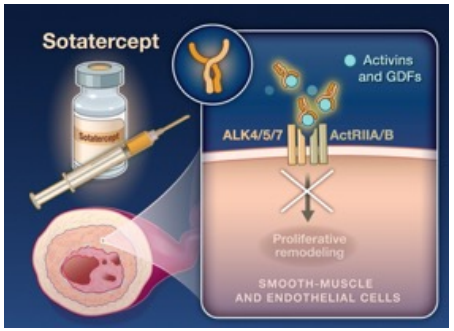
Primary Efficacy End Point, Overall Survival, and Transplantation-free Survival.

Panel A shows the probability of freedom from a first event of death from any cause, lung transplantation, or hospitalization lasting at least 24 hours for worsening pulmonary arterial hypertension. Panel B shows overall survival (defined as the probability of freedom from death from any cause). Panel C shows transplantation-free survival (defined as the probability of freedom from lung transplantation or death from any cause as a first event). The insets in Panels B and C show early event distribution and curve separation on an enlarged y axis. The 95% confidence intervals (indicated by I bars) should not be interpreted as definitive evidence of an effect in the absence of statistical testing. The analyses were performed in the intention-to-treat population, which included all the patients who had undergone randomization, irrespective of whether they received trial medication. The log-rank test was used for comparing sotatercept with placebo, with stratification according to the REVEAL Lite 2 risk score (9 or 10 vs. ≥11) and pulmonary arterial hypertension subtype (associated with connective-tissue disease vs. not associated with connective-tissue disease) in accordance with the randomization schema. Tick marks on each curve indicate censored data. No formal comparisons between the trial groups were made for the individual components of the primary composite end point.

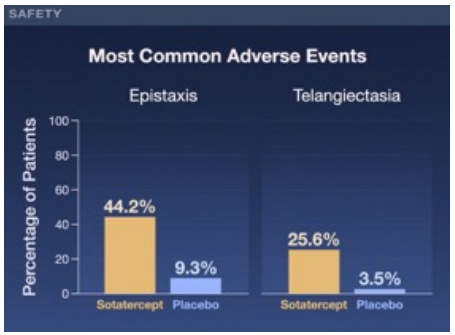

Pulmonary Arterial Hypertension

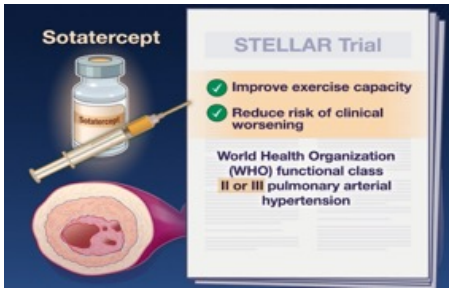

ZENITH Trial
• 172 Adults
• WHO functional class III or IV pulmonary arterial hypertension
• High 1-year risk of death
• Receiving stable maximum tolerated doses of double or triple background therapy

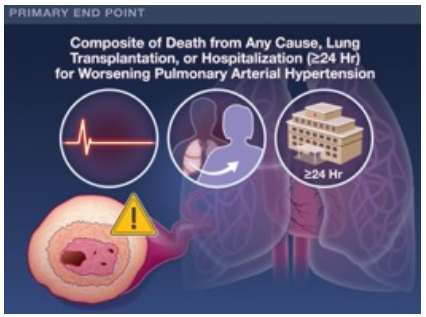

PRIMARY END POINT
Composite of Death from Any Cause, Lung Transplantation, or Hospitalization (≥24 Hr) for Worsening Pulmonary Arterial Hypertension
Hazard ratio, 0.24 (95% CI, 0.13–0.43); P<0.001
Percentage of Patients
100
80
60
40
20
0
17.4%
54.7%
Sotatercept
Placebo


Sotatercept
Activins and GDFs
ALK4/5/7
ActRIIA/B
Proliferative remodeling
SMOOTH-MUSCLE AND ENDOTHELIAL CELLS


ZENITH Trial
Sotatercept
Placebo
Every 21 days
N=86
N=86

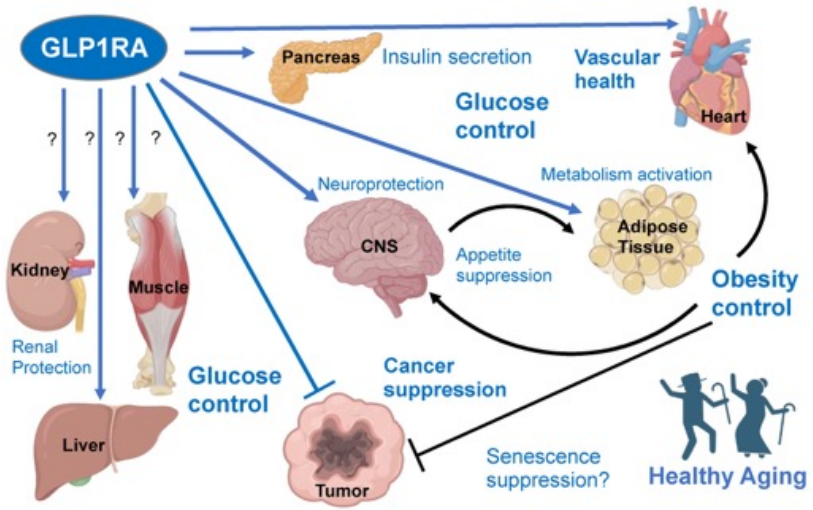

SAFETY
Most Common Adverse Events
Epistaxis
Telangiectasia
Percentage of Patients
100
80
60
40
20
0
44.2%
9.3%
25.6%
3.5%
Sotatercept
Placebo
Sotatercept
Placebo


Sotatercept
STELLAR Trial
Improve exercise capacity
Reduce risk of clinical worsening
World Health Organization (WHO) functional class II or III pulmonary arterial hypertension

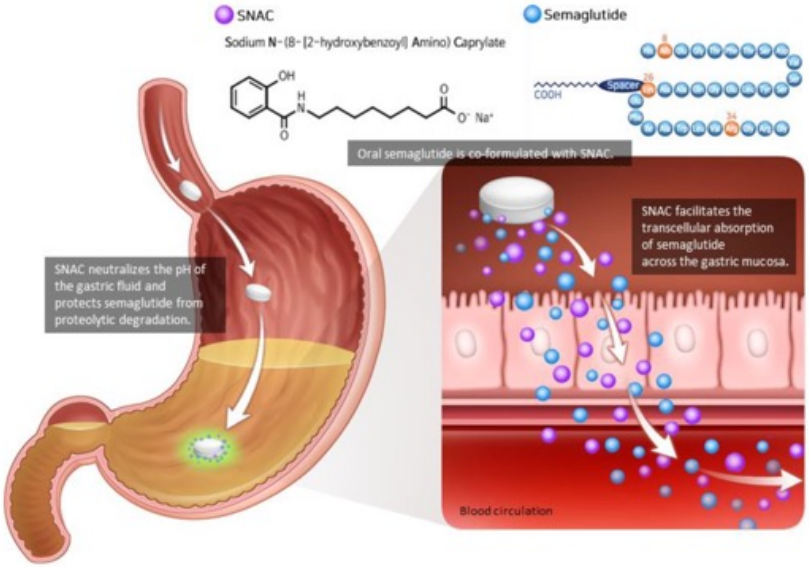

PRIMARY END POINT
Composite of Death from Any Cause, Lung Transplantation, or Hospitalization (≥24 Hr) for Worsening Pulmonary Arterial Hypertension
≥24 Hr


CONCLUSION
Significantly lower risk of a composite of:
≥24 Hr

GLP-1 ist ein Peptidhormon, das im Darm produziert wird und eine wichtige Rolle bei der Steuerung des Blutzuckerspiegels spielt. Es gehört zu den Inkretinen und ist an der Insulinsekretion und der Sättigung beteiligt. In der Medizin werden GLP-1-Rezeptoragonisten zur Behandlung von Typ-2-Diabetes und in einigen Fällen auch zur Gewichtsreduktion eingesetzt.

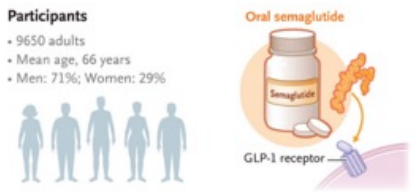


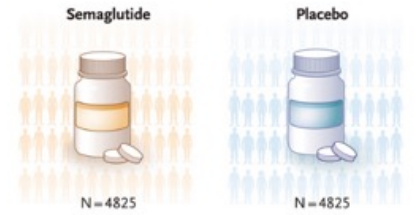
Orales Semaglutid, bekannt unter dem Handelsnamen Rybelsus, ist ein Medikament, das in Tablettenform zur Behandlung von Typ-2-Diabetes eingesetzt wird. Es gehört zur Gruppe der GLP-1-Rezeptoragonisten, die helfen, den Blutzuckerspiegel zu senken. Die Einnahme von Rybelsus sollte in Kombination mit einer angepassten Ernährung und regelmäßiger Bewegung erfolgen.

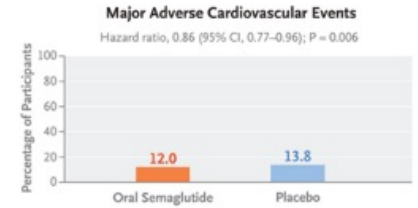


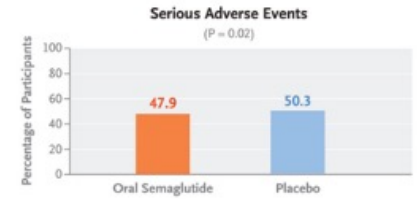
Oral Semaglutide and Cardiovascular Outcomes in High-Risk Type 2 Diabetes

The cardiovascular safety of oral semaglutide, a glucagon-like peptide 1 receptor agonist, has been established in persons with type 2 diabetes and high cardiovascular risk. An assessment of the cardiovascular efficacy of oral semaglutide in persons with type 2 diabetes and atherosclerotic cardiovascular disease, chronic kidney disease, or both is needed. In this double-blind, placebo-controlled, event-driven, superiority trial, we randomly assigned participants who were 50 years of age or older, had type 2 diabetes with a glycated hemoglobin level of 6.5 to 10.0%, and had known atherosclerotic cardiovascular disease, chronic kidney disease, or both to receive either once-daily oral semaglutide (maximal dose, 14 mg) or placebo, in addition to standard care. The primary outcome was major adverse cardiovascular events (a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke), assessed in a time-to-first-event analysis. The confirmatory secondary outcomes included major kidney disease events (a five-point composite outcome).









Semaglutide is a long-acting GLP-1 receptor agonist. For the injectable formulation of semaglutide, cardiovascular efficacy has been established in persons with type 2 diabetes and cardiovascular disease or a high risk of cardiovascular disease, as well as in those with type 2 diabetes and chronic kidney disease. For the oral formulation of semaglutide, cardiovascular safety has been established in persons with type 2 diabetes and high cardiovascular risk, but an assessment of cardiovascular efficacy is needed. The Semaglutide Cardiovascular Outcomes Trial (SOUL) was designed to assess the cardiovascular efficacy of oral semaglutide in persons with type 2 diabetes and established atherosclerotic cardiovascular disease, chronic kidney disease, or both.

Trial Participants

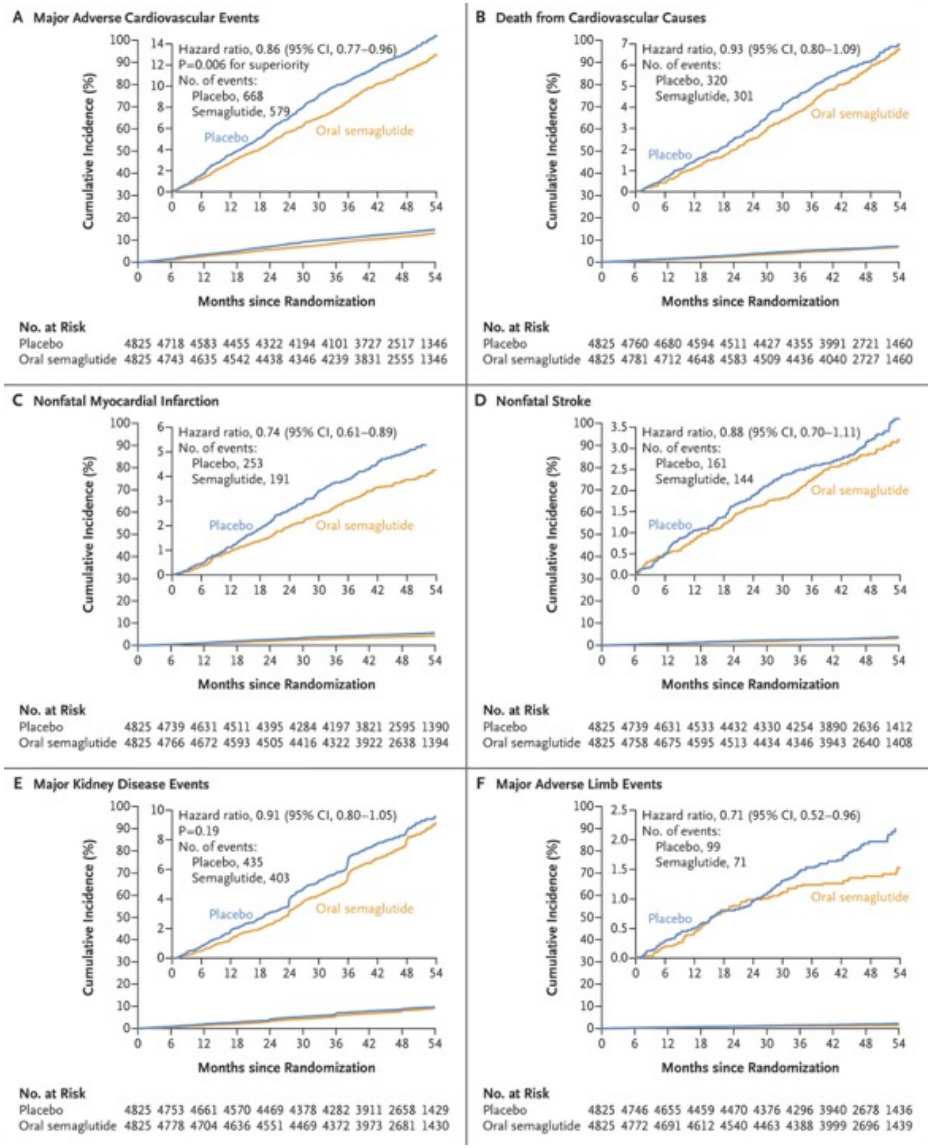
Persons were eligible for inclusion in the trial if they were 50 years of age or older and had type 2 diabetes, a glycated hemoglobin level of 6.5 to 10.0%, and at least one of the following conditions: coronary artery disease, cerebrovascular disease, symptomatic peripheral artery disease, or chronic kidney disease (defined by an estimated glomerular filtration rate [eGFR] of <60 ml per minute per 1.73 m^2).

Trial Outcomes

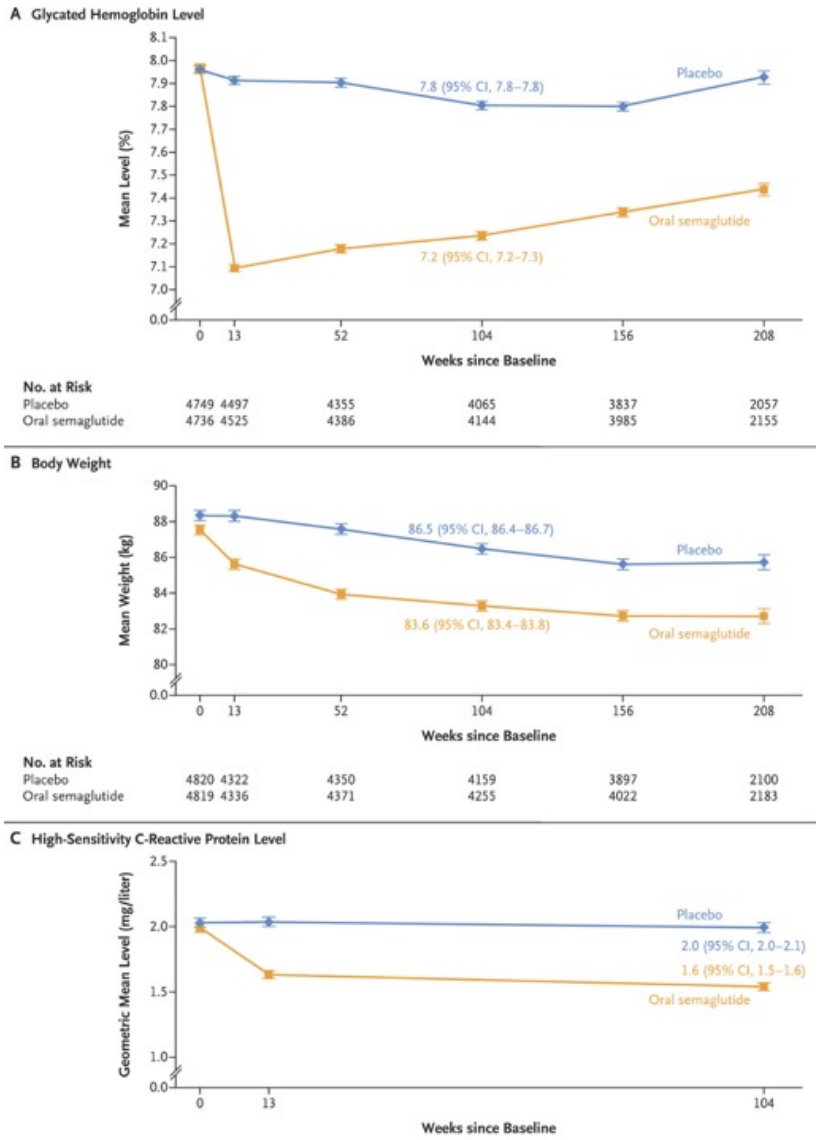
The primary outcome was major adverse cardiovascular events (a three-point composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke), assessed in an analysis of the time from randomization to the first event.

Characteristic	Oral Semaglutide (N=4825)	Placebo (N=4825)
Age — yr	66.1±7.6	66.1±7.5
Female sex — no. (%)	1376 (28.5)	1414 (29.3)
Race or ethnic group — no. (%)†		
White	3327 (69.0)	3321 (68.8)
Black	124 (2.6)	128 (2.7)
Asian	1134 (23.5)	1121 (23.2)
American Indian or Alaska Native	7 (0.1)	12 (0.2)
Native Hawaiian or Pacific Islander	4 (<0.1)	5 (0.1)
Other	185 (3.8)	192 (4.0)
Not reported	44 (0.9)	46 (1.0)
Hispanic or Latino ethnic group — no. (%)†	674 (14.0)	706 (14.6)
Body weight — kg	87.5±19.1	88.3±19.6
Body-mass index‡	31.0±5.7	31.2±5.9
Glycated hemoglobin level — mmol/mol	63.6±12.6	63.5±12.3
Glycated hemoglobin level — %	8.0±1.2	8.0±1.1
Median duration of diabetes (IQR) — yr	14.7 (9.0–20.8)	14.6 (8.9–20.8)
History of cardiovascular or kidney disease — no. (%)§		
Cardiovascular disease only	2730 (56.6)	2738 (56.7)
Chronic kidney disease only	632 (13.1)	609 (12.6)
Both cardiovascular and chronic kidney disease	1303 (27.0)	1317 (27.3)
Hypertension — no. (%)	4378 (90.7)	4381 (90.8)
Current smoking — no. (%)	545 (11.3)	584 (12.1)
Systolic blood pressure — mm Hg	134.6±16.3	134.7±16.4
Diastolic blood pressure — mm Hg	76.6±10.1	76.7±10.1
Pulse — beats/min	72.8±11.1	72.9±11.4
Median high-sensitivity C-reactive protein level (IQR) — mg/liter	2.0 (0.9–4.3)	2.0 (0.9–4.5)
eGFR — ml/min/1.73 m^2¶	74.0±22.6	73.6±22.6

Outcome	Oral Semaglutide (N=4825)		Placebo (N=4825)		Hazard Ratio (95% CI)	P Value†
	no. of participants with event (%)	*no. of events per 100 person-yr*	*no. of participants with event (%)*	*no. of events per 100 person-yr*		
Primary outcome						
Major adverse cardiovascular events, three-point composite‡	579 (12.0)	3.1	668 (13.8)	3.7	0.86 (0.77–0.96)	0.006
Confirmatory secondary outcomes						
Major kidney disease events, five-point composite§	403 (8.4)	2.1	435 (9.0)	2.3	0.91 (0.80–1.05)	0.19
Death from cardiovascular causes	301 (6.2)	1.6	320 (6.6)	1.7	0.93 (0.80–1.09)	—
Major adverse limb events, two-point composite¶	71 (1.5)	0.4	99 (2.1)	0.5	0.71 (0.52–0.96)	—
Supportive secondary outcomes						
Major adverse cardiovascular events, five-point composite‖	670 (13.9)	3.6	777 (16.1)	4.3	0.84 (0.76–0.93)	—
Nonfatal myocardial infarction	191 (4.0)	1.0	253 (5.2)	1.4	0.74 (0.61–0.89)	—
Fatal or nonfatal myocardial infarction	200 (4.1)	1.1	268 (5.6)	1.4	0.73 (0.61–0.88)	—
Nonfatal stroke	144 (3.0)	0.8	161 (3.3)	0.9	0.88 (0.70–1.11)	—
Fatal or nonfatal stroke	164 (3.4)	0.9	171 (3.5)	0.9	0.95 (0.76–1.17)	—
Coronary revascularization	200 (4.1)	1.1	263 (5.5)	1.4	0.75 (0.62–0.90)	—
Hospitalization for unstable angina pectoris	74 (1.5)	0.4	80 (1.7)	0.4	0.92 (0.67–1.26)	—
Death from any cause	528 (10.9)	2.8	577 (12.0)	3.0	0.91 (0.80–1.02)	—
Death from noncardiovascular causes	227 (4.7)	1.2	257 (5.3)	1.4	0.87 (0.73–1.04)	—
Heart failure events, three-point composite**	405 (8.4)	2.1	443 (9.2)	2.4	0.90 (0.79–1.03)	—
Heart failure	146 (3.0)	0.8	167 (3.5)	0.9	0.86 (0.69–1.08)	—
Major kidney disease events, four-point composite††	112 (2.3)	0.6	129 (2.7)	0.7	0.86 (0.66–1.10)	—
Death from kidney-related causes	1 (<0.1)	<0.1	7 (0.1)	<0.1	0.14 (0.01–0.79)	—
Severe hypoglycemic episode	76 (1.6)	0.5	84 (1.7)	0.6	0.90 (0.66–1.22)	—

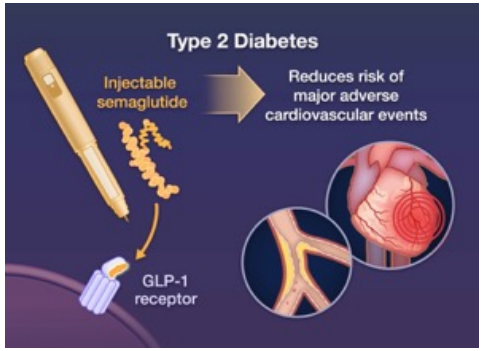


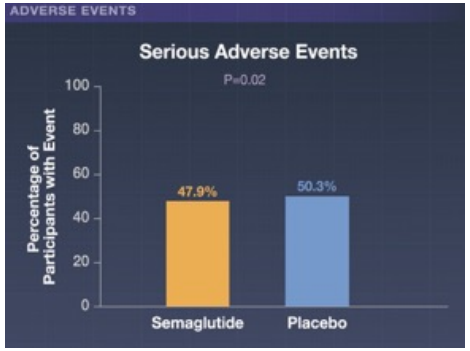
Time-to-First-Event Efficacy Outcomes.
Cumulative-incidence plots are shown for the primary outcome: major adverse cardiovascular events (Panel A), a three-point composite of death from cardiovascular causes (Panel B), nonfatal myocardial infarction (Panel C), or nonfatal stroke (Panel D). Cumulative-incidence plots are also shown for the confirmatory secondary outcomes, which were tested in hierarchical order: major kidney disease events (Panel E), death from cardiovascular causes (Panel B), and major adverse limb events (Panel F). The major kidney disease events outcome is a five-point composite of death from cardiovascular causes, death from kidney-related causes, a persistent reduction from baseline in the estimated glomerular filtration rate (eGFR) of 50% or more as measured with the Chronic Kidney Disease Epidemiology Collaboration method, a persistent eGFR of less than 15 ml per minute per 1.73 m^2, or the initiation of long-term kidney-replacement therapy with either dialysis or transplantation. The major adverse limb events outcome is a two-point composite of hospitalization for acute limb ischemia or hospitalization for chronic limb ischemia. Two-sided P values are shown. Because the results for the first confirmatory secondary outcome were not significant, the results for the two subsequent confirmatory secondary outcomes in the testing hierarchy are reported as point estimates and 95% confidence intervals. The x axis is truncated at 54 months because of the limited number of participants in the trial after that time point. The insets show the same data on an enlarged y axis.



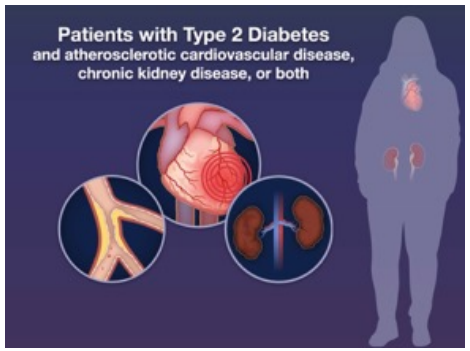
Measures of Metabolism and Inflammation.

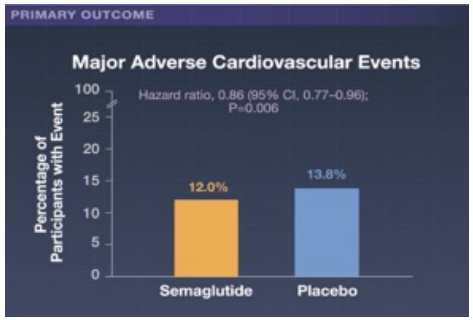
Shown are the observed mean glycated hemoglobin level (Panel A), mean body weight (Panel B), and geometric mean high-sensitivity C-reactive protein level (Panel C) for the intention-to-treat population (all the individual participants who had undergone randomization) during the trial observation period. The change from baseline to week 104 for each of these measures was a prespecified secondary outcome. I bars indicate standard errors.


Type 2 Diabetes
Injectable semaglutide
Reduces risk of major adverse cardiovascular events
GLP-1 receptor

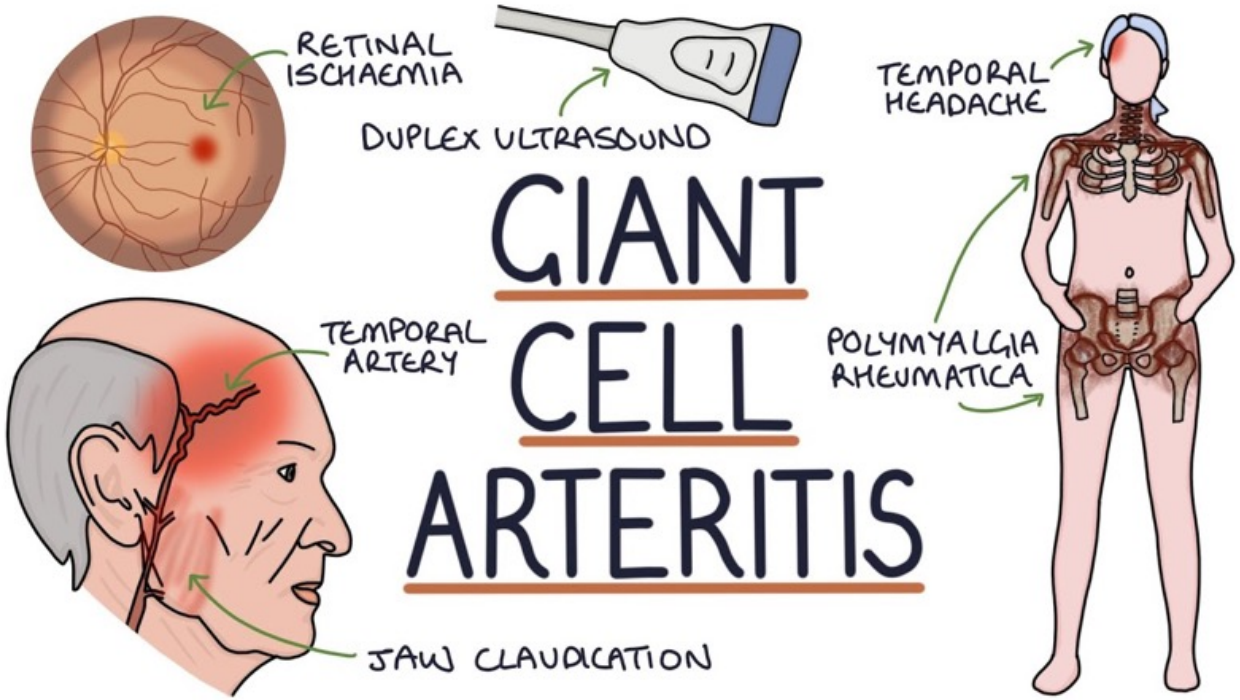

ADVERSE EVENTS
Serious Adverse Events
P=0.02
Percentage of Participants with Event
100
80
60
40
20
0
47.9%
50.3%
Semaglutide
Placebo

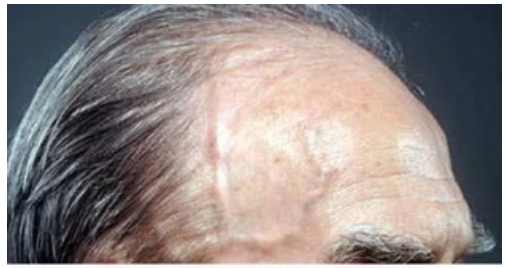

Type 2 Diabetes
with known atherosclerotic disease, chronic kidney disease, or both
Oral semaglutide
Semaglutide
?
Efficacy and safety

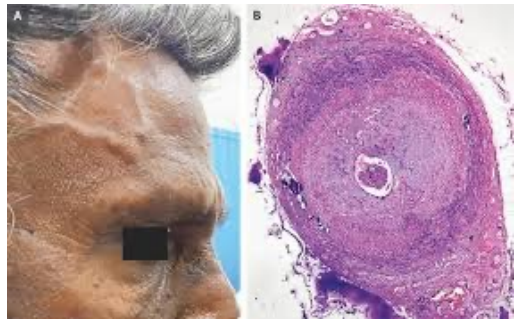

Patients with Type 2 Diabetes
and atherosclerotic cardiovascular disease, chronic kidney disease, or both


PRIMARY OUTCOME
Major Adverse Cardiovascular Events
Hazard ratio, 0.86 (95% CI, 0.77–0.96); P=0.006
Percentage of Participants with Event
100
25
20
15
10
5
0
12.0%
13.8%
Semaglutide
Placebo


Patients with Type 2 Diabetes
and atherosclerotic cardiovascular disease, chronic kidney disease, or both
Oral semaglutide
Semaglutide
Significantly lower risk of major adverse cardiovascular events

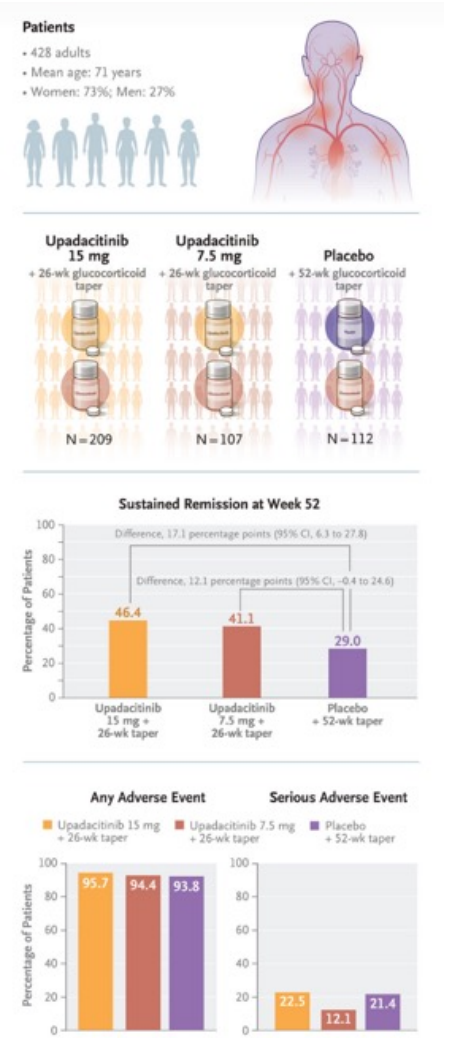






A Phase 3 Trial of Upadacitinib for Giant-Cell Arteritis

Giant-cell arteritis is a systemic vasculitis with limited treatment options. The efficacy and safety of upadacitinib — a selective Janus kinase (JAK) inhibitor that blocks the signaling of several cytokines, including interleukin-6 and interferon-γ — are unknown in patients with giant-cell arteritis. We randomly assigned patients with new-onset or relapsing giant-cell arteritis, in a 2:1:1 ratio, to receive upadacitinib at a dose of 15 mg or 7.5 mg orally once daily plus a 26-week glucocorticoid taper or placebo plus a 52-week glucocorticoid taper. The primary end point was sustained remission at week 52, defined by the absence of signs or symptoms of giant-cell arteritis from week 12 through week 52 and adherence to the protocol-specified glucocorticoid taper.



Eligible patients were adults 50 years of age or older who had a clinical diagnosis of new-onset or relapsing giant-cell arteritis confirmed by temporal-artery biopsy or imaging (ultrasonography, positron-emission tomography, computed tomography, magnetic resonance imaging, or angiography) and in whom the disease was active within 8 weeks before the baseline visit. Active giant-cell arteritis was defined by the presence of unequivocal cranial symptoms of the disease, polymyalgia rheumatica, or both, along with an erythrocyte sedimentation rate (ESR) of more than 30 mm per hour, a C-reactive protein (CRP) level of at least 1 mg per deciliter, or both. New-onset disease referred to the diagnosis of giant-cell arteritis within 8 weeks before baseline; relapsing disease was defined as the reactivation of the disease in patients for whom at least 1 glucocorticoid taper failed to control the disease. At any time before enrollment, patients must have received prednisone at a dose of at least 40 mg daily (or equivalent); at baseline, patients must have been receiving prednisone at a dose of 20 to 60 mg daily. Patients with previous exposure to JAK inhibitors or who had had a disease flare while receiving an interleukin-6 inhibitor were excluded.

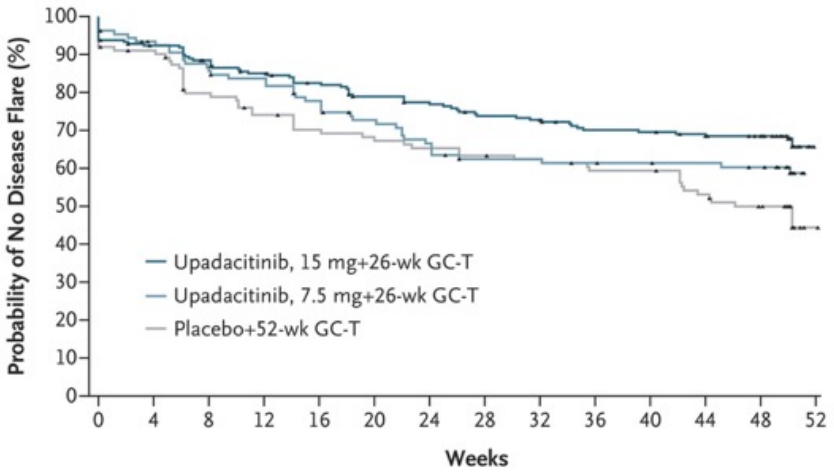
End Points and Safety Assessments

The primary end point was sustained remission at week 52, defined by the absence of signs or symptoms of giant-cell arteritis from week 12 through week 52 and adherence to the protocol-specified glucocorticoid taper.

Characteristic	Placebo + 52-week GC-T (N=112)	Upadacitinib 7.5 mg + 26-week GC-T (N=107)	Upadacitinib 15 mg + 26-week GC-T (N=209)
Female sex — no. (%)	77 (68.8)	80 (74.8)	156 (74.6)
Age — yr	71.6±7.3	71.1±7.6	70.8±7.3
Age group — no. (%)			
<65 yr	17 (15.2)	19 (17.8)	42 (20.1)
≥65 to <75 yr	59 (52.7)	49 (45.8)	102 (48.8)
≥75 yr	36 (32.1)	39 (36.4)	65 (31.1)
Body-mass index†	25.8±4.3	25.2±5.1	25.3±4.6
Race or ethnic group — no. (%)‡			
Asian	6 (5.4)	6 (5.6)	10 (4.8)
Black or African American	2 (1.8)	1 (0.9)	0
Native Hawaiian or other Pacific Islander	0	1 (0.9)	0
White	103 (92.0)	99 (92.5)	199 (95.2)
Multiple races or ethnic groups	1 (0.9)	0	0
Disease status — no. (%)			
New-onset giant-cell arteritis	76 (67.9)	75 (70.1)	148 (70.8)
Relapsing giant-cell arteritis	36 (32.1)	32 (29.9)	61 (29.2)
Duration of new-onset giant-cell arteritis — days			
Mean	38.2±14.8	35.7±11.1	39.5±28.1
Median	37.0	35.0	36.0
Duration of relapsing giant-cell arteritis — days			
Mean	665.7±816.3	999.2±1179.0	664.9±687.5
Median	277.0	539.5	343.0
Glucocorticoid dose — mg	34.6±11.9	34.5±12.5	34.6±12.7
ESR — mm/hr	21.7±25.5	19.9±21.1	19.5±17.5
Median CRP level (range) — mg/dl	0.23 (0.02–5.83)	0.27 (0.02–5.82)	0.24 (0.02–10.10)
Previous use of interleukin-6 inhibitor — no. (%)§	7 (6.2)	7 (6.5)	9 (4.3)
Ischemia-related vision loss — no. (%)¶	22 (19.6)	14 (13.1)	20 (9.6)
History of PMR — no. (%)	69 (61.6)	54 (50.5)	109 (52.2)
History of unequivocal symptoms of PMR without cranial symptoms of giant-cell arteritis — no. (%)	18 (16.1)	7 (6.5)	15 (7.2)
Basis for diagnosis — no. (%)			
History of positive temporal-artery biopsy	44 (39.3)	48 (44.9)	86 (41.1)
Evidence of large-vessel vasculitis on imaging‖	81 (73.0)	83 (77.6)	159 (76.1)
FACIT-Fatigue score**	37.5±11.7	35.6±11.3	36.0±11.2
SF-36 PCS score††	45.0±10.0	44.3±10.2	44.3±9.3

Adverse Events	Placebo + 52-week GC-T (N=112)	Upadacitinib 7.5 mg + 26-week GC-T (N=107)	Upadacitinib 15 mg + 26-week GC-T (N=209)
		number (percent)	
Any adverse event†	105 (93.8)	101 (94.4)	200 (95.7)
Serious adverse events†	24 (21.4)	13 (12.1)	47 (22.5)
Adverse events leading to discontinuation of upadacitinib or placebo†	22 (19.6)	17 (15.9)	31 (14.8)
Death‡	2 (1.8)	0	2 (1.0)
Adverse events of special interest			
Serious infection	12 (10.7)	6 (5.6)	12 (5.7)
Opportunistic infection, excluding herpes zoster	1 (0.9)	0	4 (1.9)
Herpes zoster	3 (2.7)	3 (2.8)	11 (5.3)
Cancer, excluding nonmelanoma skin cancer	2 (1.8)	0	4 (1.9)
Nonmelanoma skin cancer	2 (1.8)	1 (0.9)	5 (2.4)
Major adverse cardiovascular events§	2 (1.8)	0	0
Venous thromboembolism¶	4 (3.6)	4 (3.7)	7 (3.3)
Renal dysfunction	3 (2.7)	0	4 (1.9)
Hepatic disorder	5 (4.5)	2 (1.9)	11 (5.3)
Anemia	3 (2.7)	3 (2.8)	14 (6.7)
Neutropenia	1 (0.9)	0	0
Lymphopenia	0	1 (0.9)	3 (1.4)
Creatine kinase elevation	0	0	6 (2.9)
Retinal detachment	6 (5.4)	6 (5.6)	13 (6.2)
Bone fracture	3 (2.7)	1 (0.9)	3 (1.4)

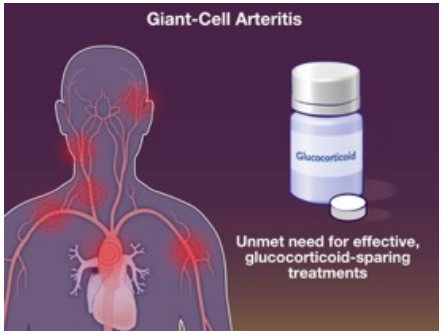
End Points	Placebo + 52-week GC-T (N = 112)	Upadacitinib 7.5 mg + 26-week GC-T (N = 107)	Upadacitinib 15 mg + 26-week GC-T (N = 209)	Treatment Effect, Upadacitinib 7.5 mg (95% CI)	Treatment Effect, Upadacitinib 15 mg (95% CI)	P Value for Treatment Effect, Upadacitinib 15 mg
Primary end point						
Sustained remission at week 52 — no. (% [95% CI])	33 (29.0 [20.6 to 37.5])	44 (41.1 [31.8 to 50.4])	97 (46.4 [39.6 to 53.2])	12.1 (–0.4 to 24.6)	17.1 (6.3 to 27.8)	0.002
Secondary end points						
Sustained complete remission at week 52 — no. (% [95% CI])	18 (16.1 [9.3 to 22.9])	28 (26.2 [17.8 to 34.5])	78 (37.1 [30.5 to 43.7])	9.9 (–0.8 to 20.6)	20.7 (11.3 to 30.2)	<0.001
Median cumulative glucocorticoid exposure through week 52 (95% CI) — mg†	2882 (2762 to 3253)	1905 (1615 to 2265)	1615 (1615 to 1635)	–1206 (–1452 to –802)	–1267 (–1587 to –1133)	<0.001
Median time to first disease flare through week 52 (95% CI) — days‡	323 (249 to >365)	>365 (316 to >365)	>365	0.75 (0.50 to 1.14)	0.57 (0.40 to 0.83)	0.003
≥1 disease flare through week 52 (95% CI) — %§	55.6 (42.9 to 69.2)	41.3 (32.2 to 51.7)	34.3 (27.4 to 42.4)	0.60 (0.35 to 1.03)	0.47 (0.29 to 0.74)	0.001
Complete remission at week 52 — no. (% [95% CI])	22 (19.6 [12.3 to 27.0])	46 (43.0 [33.6 to 52.4])	105 (50.2 [43.4 to 57.1])	23.5 (11.7 to 35.3)	30.3 (20.4 to 40.2)	<0.001
Complete remission at week 24 — no. (% [95% CI])	40 (36.1 [27.2 to 45.1])	42 (39.3 [30.0 to 48.5])	120 (57.2 [50.5 to 64.0])	3.2 (–9.6 to 16.0)	20.8 (9.7 to 31.9)	<0.001
LS mean change from baseline in SF-36 PCS score at week 52 (95% CI)¶	–1.3 (–3.3 to 0.7)	1.3 (–0.7 to 3.3)	2.5 (1.2 to 3.8)	2.6 (–0.2 to 5.4)	3.8 (1.4 to 6.1)	0.002
Mean no. of disease flares through week 52 per patient-year (95% CI)‖	0.7 (0.5 to 0.9)	0.6 (0.4 to 0.7)	0.4 (0.3 to 0.5)	0.8 (0.6 to 1.2)	0.6 (0.4 to 0.8)	0.001
LS mean change from baseline in FACIT-Fatigue score at week 52 (95% CI)**	–2.4 (–4.7 to –0.1)	1.1 (–1.2 to 3.4)	1.7 (0.2 to 3.1)	3.5 (0.3 to 6.7)	4.0 (1.3 to 6.8)	0.004
LS mean TSQM score at week 52 (95% CI)††	68.8 (63.8 to 73.9)	74.3 (69.4 to 79.1)	71.6 (68.3 to 74.8)	5.4 (–1.4 to 12.3)	2.7 (–3.1 to 8.6)	
Mean no. of glucocorticoid-related adverse events through week 52 per patient-year (95% CI)	1.7 (1.3 to 2.3)	1.7 (1.2 to 2.2)	2.0 (1.7 to 2.4)	0.9 (0.6 to 1.4)	1.1 (0.8 to 1.6)‖	

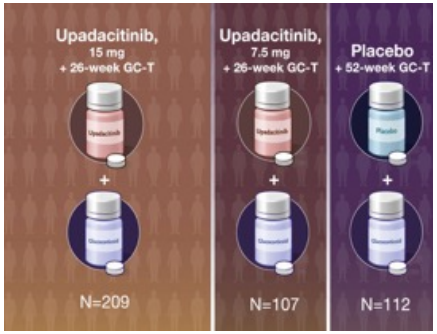


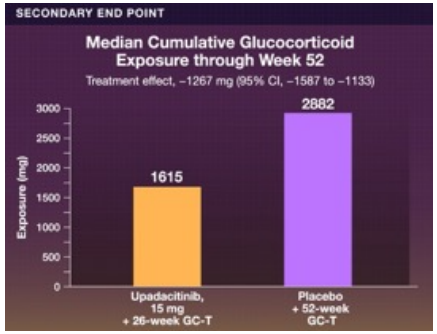
	Median Time to Disease Flare (95% CI)	Hazard Ratio for Disease Flare (95% CI)	P Value

Time to First Flare of Giant-Cell Arteritis through Week 52.

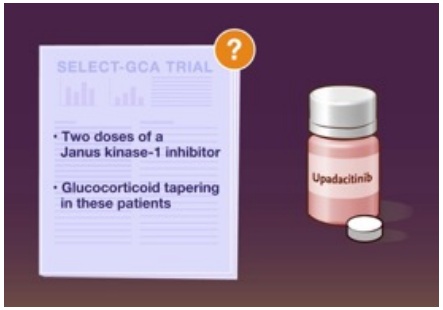
The time to the first disease flare was calculated from the time at which the patients had met three criteria in an assessment: the absence of the signs and symptoms of giant-cell arteritis, normalization of the erythrocyte sedimentation rate, and no increase in the glucocorticoid dose. The Kaplan–Meier curve represents the time in the trial and not the visit schedule. A vertical drop in the curves represents a disease flare, and the black triangles represent censored data. Data from patients who never had a disease flare were censored at the last assessment up to week 52, which is indicated in the graph as the clustering of triangles toward the end of the curve. Hazard ratios were estimated with the use of the Cox proportional-hazards model. The P value was calculated with the use of the log-rank test for upadacitinib at a dose of 15 mg as compared with placebo. Testing of upadacitinib at a dose of 7.5 mg as compared with placebo was not conducted because of the hierarchical approach to control for the type I error rate. GC-T denotes glucocorticoid taper, and NE could not be estimated.

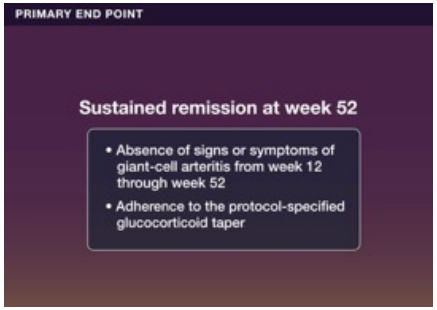

Giant-Cell Arteritis
Glucocorticoid
Unmet need for effective, glucocorticoid-sparing treatments

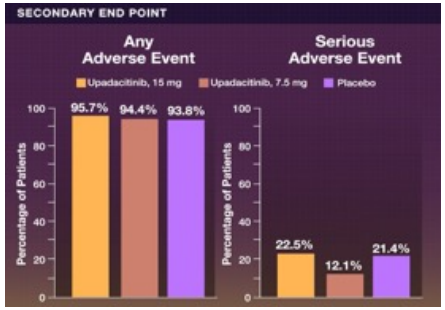

Upadacitinib, 15 mg + 26-week GC-T
Upadacitinib, 7.5 mg + 26-week GC-T
Placebo + 52-week GC-T
N=209
N=107
N=112

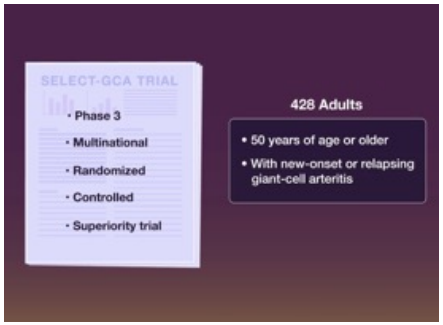

SECONDARY END POINT
Median Cumulative Glucocorticoid Exposure through Week 52
Treatment effect, −1267 mg (95% CI, −1587 to −1133)
Exposure (mg)
1615
2882
Upadacitinib, 15 mg + 26-week GC-T
Placebo + 52-week GC-T

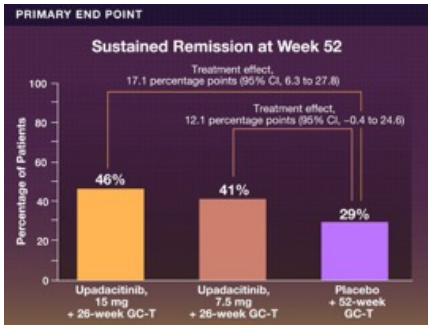

than placebo with a 52-week glucocorticoid taper


SELECT-GCA TRIAL
• Two doses of a Janus kinase-1 inhibitor
• Glucocorticoid tapering in these patients
Upadacitinib


PRIMARY END POINT
Sustained remission at week 52
• Absence of signs or symptoms of giant-cell arteritis from week 12 through week 52
• Adherence to the protocol-specified glucocorticoid taper


SECONDARY END POINT
Any Adverse Event
Serious Adverse Event
Upadacitinib, 15 mg
Upadacitinib, 7.5 mg
Placebo
Percentage of Patients
95.7%
94.4%
93.8%
22.5%
12.1%
21.4%


SELECT-GCA TRIAL
• Phase 3
• Multinational
• Randomized
• Controlled
• Superiority trial
428 Adults
• 50 years of age or older
• With new-onset or relapsing giant-cell arteritis

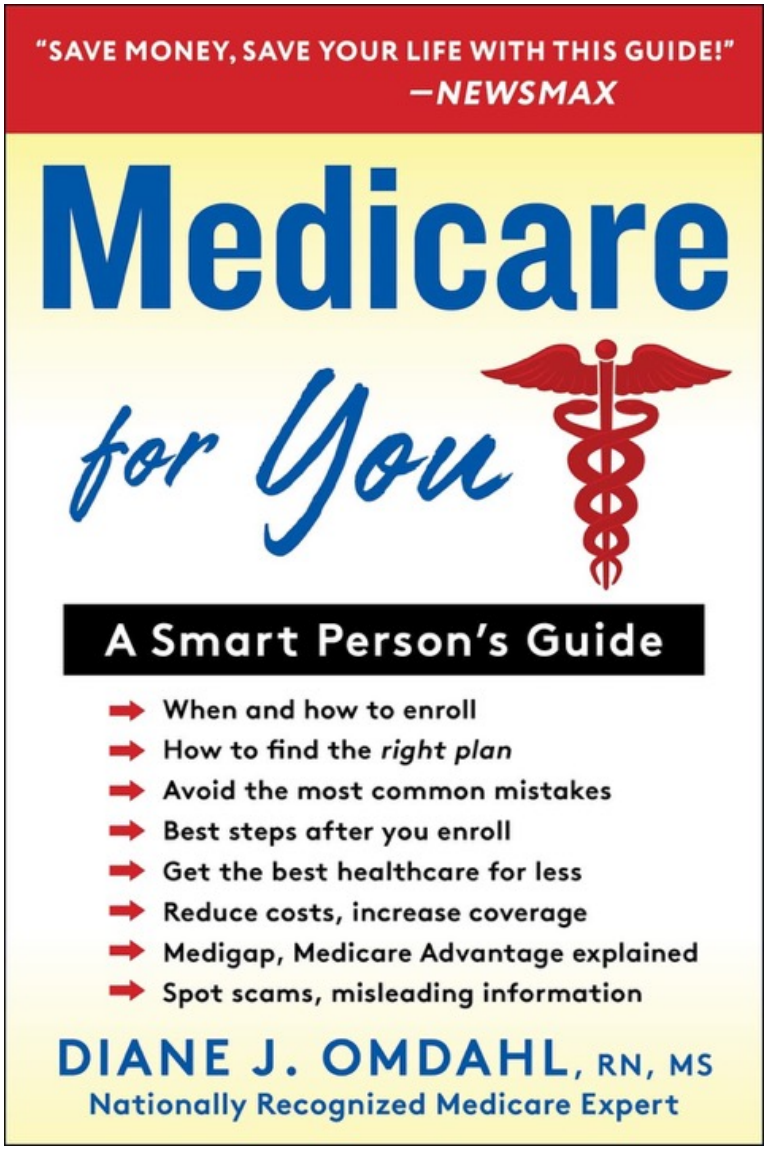

PRIMARY END POINT
Sustained Remission at Week 52
Treatment effect, 17.1 percentage points (95% CI, 6.3 to 27.8)
Treatment effect, 12.1 percentage points (95% CI, −0.4 to 24.6)
Percentage of Patients
46%
41%
29%
Upadacitinib, 15 mg + 26-week GC-T
Upadacitinib, 7.5 mg + 26-week GC-T
Placebo + 52-week GC-T


Upadacitinib
Glucocorticoid
Upadacitinib at a daily dose of 15 mg with a 26-week glucocorticoid taper was more likely to result in sustained remission at 52 weeks

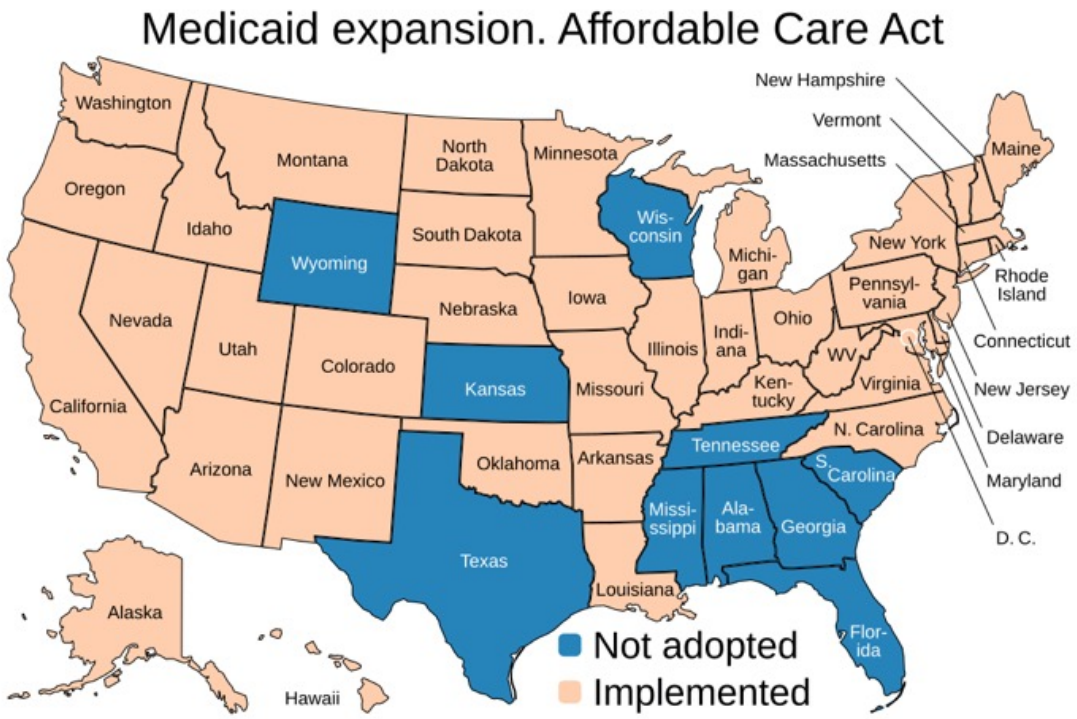
Medicare ist die öffentliche und bundesstaatliche Krankenversicherung innerhalb des Gesundheitssystems der USA für über 65-jährige oder Bürger mit Behinderung.

Medicare wurde am 30. Juli 1965 durch Zusätze zum Social Security Act im Rahmen der Great Society in das Sozialversicherungssystem der Vereinigten Staaten eingefügt und ist neben der Rentenversicherung die zweite bundesstaatliche Pflichtversicherung. Jeder Bürger ab dem Alter von 65 Jahren und Bürger jeden Alters mit einer anerkannten Behinderung oder mit akutem Nierenversagen, das eine dauerhafte Dialyse oder eine Nierentransplantation erforderlich macht, kann Medicare in Anspruch nehmen.
Zusätzlich gibt es Medicaid, ein steuerfinanziertes Gesundheitsfürsorgeprogramm für Bürger mit geringem Einkommen.

2018 versicherte Medicare 59,9 Millionen Personen. 2020 betrug der Beitrag der US-Bundesregierung für Medicare 776,2 Milliarden US-Dollar



Medicaid (Medical Assistance) ist ein Gesundheitsfürsorgeprogramm für Personenkreise mit geringem Einkommen, Kinder, ältere Menschen und Menschen mit Behinderungen in den USA, das von den einzelnen Bundesstaaten organisiert und paritätisch zusammen mit der Bundesregierung finanziert wird.



Loss of Subsidized Drug Coverage and Mortality among Medicare Beneficiaries

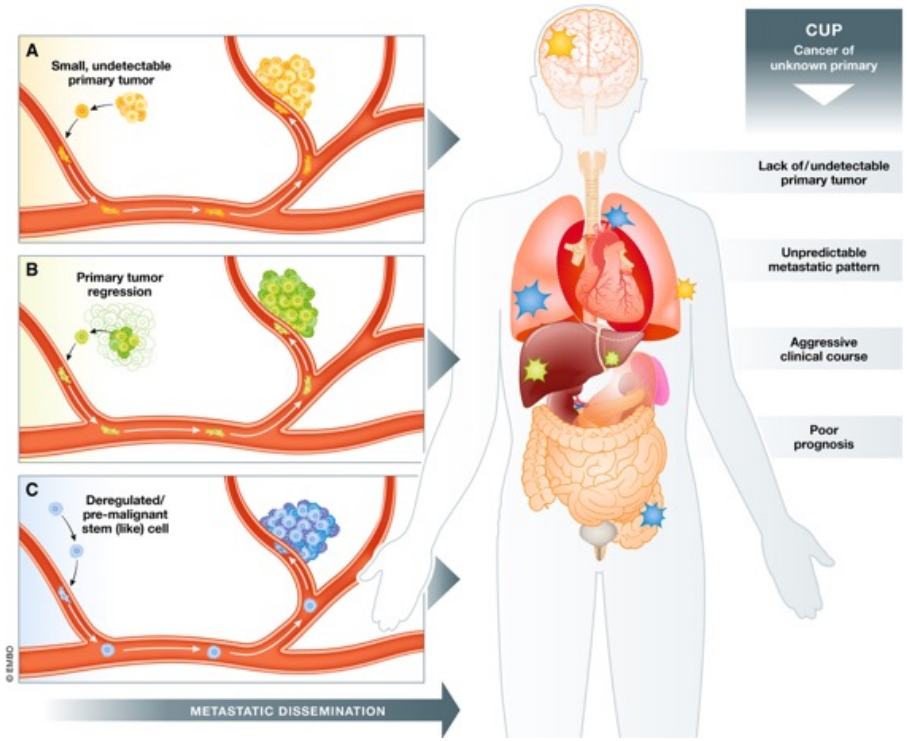
Background
A total of 14 million Medicare beneficiaries receive the Low-Income Subsidy (LIS), which reduces cost sharing in Medicare Part D. Losing the LIS may impede medication access and affect mortality.

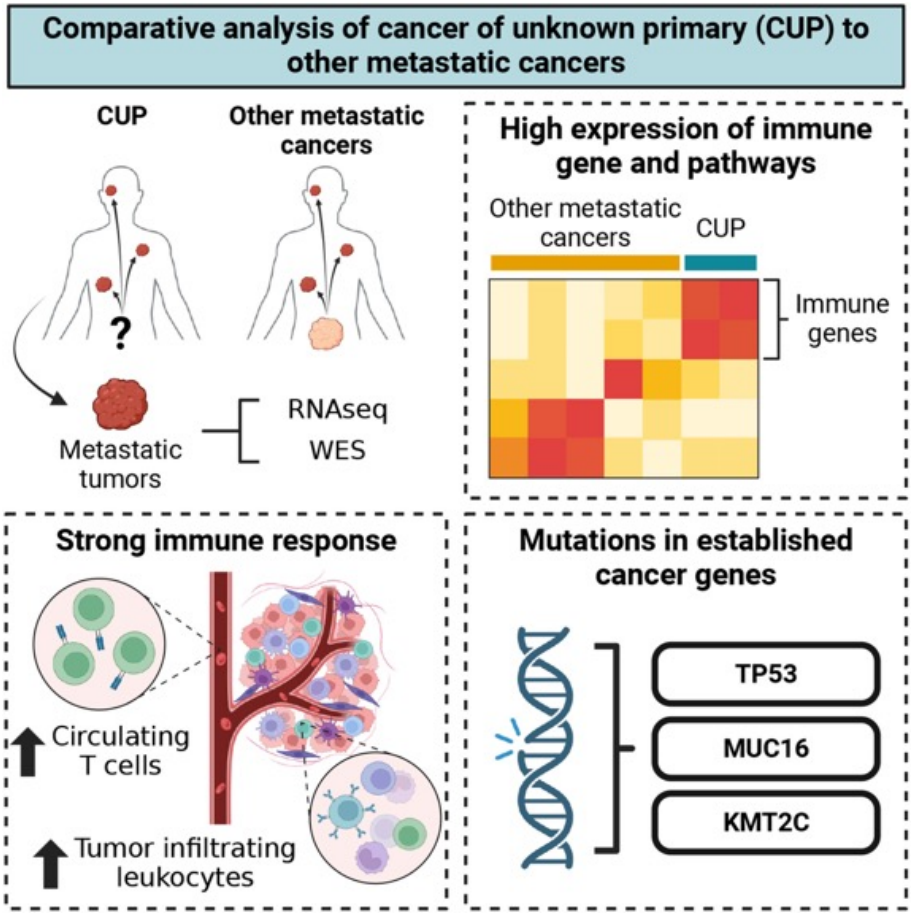
Methods
Using 2015–2023 Medicare data, we identified dual-eligible Medicare–Medicaid beneficiaries, who automatically receive the LIS, and calculated annual rates of Medicaid and LIS loss. To examine the relationship between LIS loss and mortality, we leveraged a natural experiment arising from the relationship between the timing of Medicaid disenrollment and subsequent LIS loss. We compared beneficiaries disenrolling from Medicaid in January through June, who kept the LIS through December (6 to 11 additional months), with those disenrolling in July through December, who kept the LIS through the following December (12 to 17 additional months). Among persons disenrolling from Medicaid during 2015–2017, we examined cumulative mortality 7 to 17 months after disenrollment, when those with earlier disenrollment were more likely to lose the LIS.

Results
The sample included 969,606 persons with early (January though June) Medicaid disenrollment and 920,158 with late (July though December) Medicaid disenrollment. Those with early Medicaid disenrollment averaged 13.6 cumulative months of the LIS in the 17 months after disenrollment, as compared with 15.3 months for those with late disenrollment. At 17 months after Medicaid disenrollment, cumulative mortality was higher among persons with early disenrollment (78.3 per 1000) than among those with late disenrollment (75.3 per 1000), a difference of 3.0 deaths per 1000 (95% confidence interval [CI], 2.1 to 3.9). Mortality differences between persons with early disenrollment and those with late disenrollment were amplified among those in the highest quintile of baseline Part D spending (5.6 deaths per 1000; 95% CI, 3.3 to 7.9) and users of medications for cardiovascular disease, chronic lung disease, or human immunodeficiency virus infection.

Conclusions
Loss of drug subsidies after Medicaid disenrollment was associated with higher mortality among low-income Medicare beneficiaries.
(Funded by the National Institute on Aging and others.)

Cancer of unknown primary (CUP)





Cancer of Unknown Primary Site

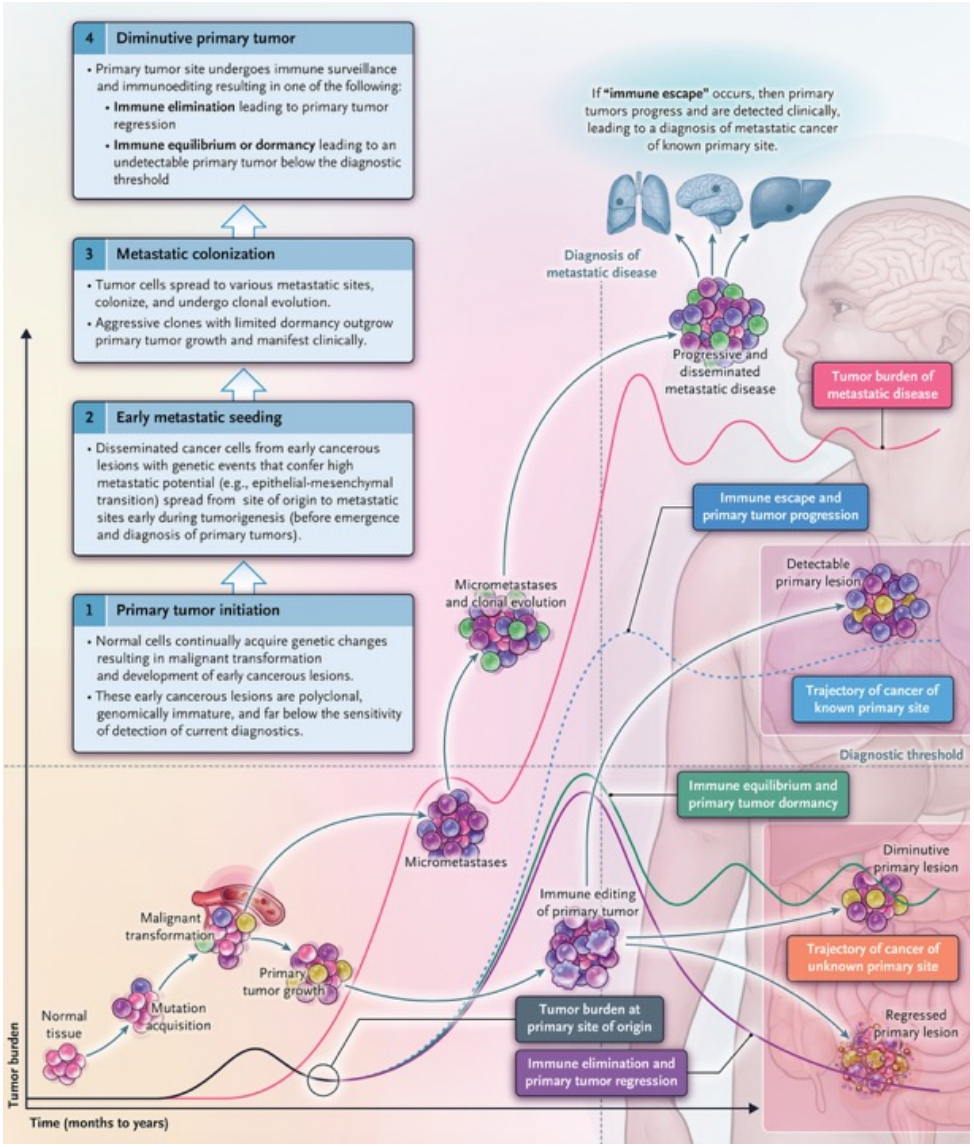
A previously healthy 47-year-old woman presented with abdominal bloating and discomfort that had worsened over the previous 3 months. Her examination was notable for abdominal distention with bulging flanks and shifting dullness consistent with ascites. Further workup revealed a normocytic anemia (hemoglobin level, 10.4 g per deciliter; reference range, 12.0 to 14.0), elevated serum cancer antigen 125 level (168 U per milliliter; reference value, <38), and elevated carcinoembryonic antigen level (14.7 ng per milliliter; reference value, <3.8). A computed tomographic (CT) scan of her chest, abdomen, and pelvis with the use of contrast material showed liver, lymph node, and peritoneal tumors with ascites. She was referred to an oncologist because of suspicion of cancer, and an omental biopsy revealed poorly differentiated carcinoma with immunohistochemical assays positive for CK20, CDX2, and SATB2 (lower gastrointestinal tract immunostains) and negative for multiple other immunostains. A subsequent fluorodeoxyglucose (FDG) positron-emission tomographic (PET) scan showed FDG-avid liver, lymph node, and peritoneal metastases. Further testing with mammography, colonoscopy, and upper endoscopy failed to identify any primary site. Molecular profiling to find the tissue of origin and identify targetable genomic alterations was deemed indeterminate. How would you further evaluate and treat this patient?

Cancer of Unknown Primary Site

- Cancer of unknown primary site is a heterogeneous group of histologically confirmed metastatic cancers, with the primary anatomical site of origin remaining unidentified after a standard diagnostic workup.
- Baseline evaluation involves a detailed history; physical, laboratory, and imaging assessments (ideally, a contrast-enhanced computed tomographic scan of the chest, abdomen, and pelvis); and a thorough pathological workup of adequate tumor tissue.
- Although immunophenotyping is the mainstay of diagnosis, recent advances have led to the integration of molecular profiling in predicting the tissue of origin and identifying targetable alterations in the management of cancer of unknown primary site.
- Both site-specific therapy (treatment of a putative primary site) and empirical chemotherapy (with a platinum-based cytotoxic regimen) are acceptable options for treatment.
- The overall prognosis for patients with cancer of unknown primary site remains poor. Participation in clinical trials should be encouraged.

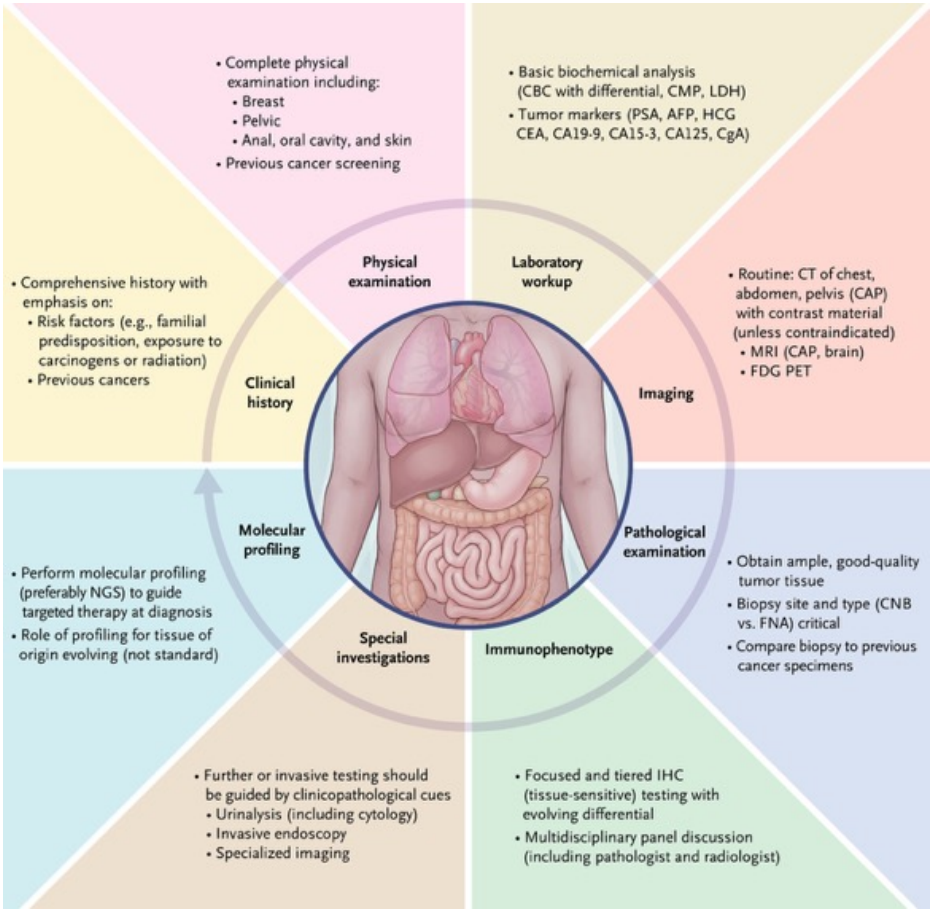
Manifestation	Analogous Known Primary Site	Therapeutic Strategy
Clinicopathological		
Blastic bone metastases with elevated prostate-specific antigen level (in men)	Prostate cancer	Combination androgen-deprivation therapy
Carcinoma (serous) with peritoneal carcinomatosis (in women)	Ovarian cancer	Chemotherapy (paclitaxel and carboplatin with or without bevacizumab)
Carcinoma with isolated axillary lymphadenopathy (in women)	Breast cancer	Chemotherapy, surgery, and radiation therapy (according to breast cancer guidelines)
Solitary or oligometastatic disease	Any tissue of origin	Chemotherapy with or without radiation therapy or chemoradiation with or without surgery
Squamous-cell carcinoma with cervical lymphadenopathy	Head and neck squamous-cell cancer	Surgery with or without radiation therapy or chemoradiation with or without chemotherapy (according to head and neck squamous-cell cancer guidelines)
Immunohistochemical		
CK20+ and CDX2+	Lower gastrointestinal or colorectal cancer	FOLFOX, XELOX, FOLFIRI, or FOLFOXIRI
Molecular		
BRAF V600E mutation	Any tissue of origin	Dabrafenib with trametinib
Fusions		
NTRK	Any tissue of origin	Entrectinib, larotrectinib, or repotrectinib
RET	Any tissue of origin	Selpercatinib
HER2 amplification or overexpression†	Any tissue of origin	Trastuzumab deruxtecan
Immunotherapy eligible		
Mismatch repair–deficient and microsatellite instability–high	Any tissue of origin	PD-1 and PD-L1 monoclonal antibodies
High tumor mutational burden‡	Any tissue of origin	Pembrolizumab

Study†	Study Type and Primary End Point	Tissue-of-Origin Profiling	Sample Size (Site-Specific vs. Empirical Therapy)	Empirical Therapy Regimen	Sites of Common Predicted Tumors	Outcomes‡
Fudan CUP-001[40]	RCT, PFS	Canhelp-Origin, a 90-gene expression assay (archived FFPE)	182 (91 vs. 91)	Platinum and paclitaxel or gemcitabine	Stomach or esophagus, lung, ovary, cervix, breast	Median PFS, 9.6 vs. 6.6 mo (HR, 0.68; 95% CI, 0.49–0.93; P=0.017) Median OS, 28.2 vs. 19.0 mo (HR, 0.74; 95% CI, 0.52–1.06; P=0.09) Objective response, 49% vs. 46% (P=0.76)§
New South Wales[43]	Retrospective	Clinicopathological (tissue-based)	57 (26 vs. 31)	Platinum and gemcitabine or carboplatin and paclitaxel	Head and neck, colon or rectum, pancreas, lung, stomach or esophagus	Median PFS, 9.8 vs. 7.3 mo (HR, 0.70; 95% CI, 0.40–1.30; P=0.29) Median OS, 25.9 vs. 13.2 mo (P=0.30)
Japan-8 CUP[44]	Retrospective	Clinicopathological (tissue-based)	144 (60 vs. 84)	Various	Lung, stomach or esophagus, pancreas, colon or rectum, ovary	Median OS, 10.0 vs. 10.1 mo (HR, 1.01; 95% CI, 0.70–1.45; P=0.95)
CUP-NGS[21]	RCT, OS	Microarray-based gene expression analysis (fresh frozen)	101 (50 vs. 51)¶	Carboplatin and paclitaxel	Pancreas, stomach or esophagus, lymphatic system, bladder, cervix	Median PFS, 5.1 vs. 4.8 mo (HR, 0.88; 95% CI, 0.59–1.33; P=0.55) Median OS, 9.8 vs. 12.5 mo (HR, 1.03; 95% CI, 0.68–1.56; P=0.89) Overall response, 34.7% vs. 41.2% (P=0.50)§
GEFCAPI-04[41]	RCT, PFS	92-Gene RT-PCR (tissue-based)	243 (123 vs. 120)	Gemcitabine and cisplatin	Pancreas, gallbladder, or bile duct; squamous-cell carcinoma; kidney, lung, intestines	Median PFS, 4.6 vs. 5.3 mo (HR, 0.95; 95% CI, 0.72–1.25; P=0.71) Median OS, 10.7 vs. 9.9 mo (HR, 0.92; 95% CI, 0.69–1.23; P=0.72)
Aichi CUP[45]	Retrospective	Clinicopathological (tissue-based)	122 (90 vs. 32)	Platinum-based therapy	Colon or rectum, gynecologic system, lung, pancreas, neuroendocrine system	Median PFS, 5.1 vs. 4.2 mo (P=0.02) Median OS, 15.7 vs. 10.7 mo (P=0.07)
EPICUP[46]	Retrospective	Microarray DNA methylation signatures (tissue-based)	92 (31 vs. 61)	Various	Lung, head and neck, breast, colon or rectum, liver	Median OS, 13.6 vs. 6.0 mo (P=0.008)
Sarah Cannon[47]	Prospective, OS	92-Gene RT-PCR (tissue-based)	223 (194 vs. 29)	Various	Biliary tract, bladder, colon or rectum, lung, pancreas	Median OS, 12.5 vs. 9.1 mo (historical control)
Lower GI CUP[48]	Retrospective	Immunohistochemical test (tissue-based)	68 (53 vs. 15)	Gemcitabine- or taxane-based therapy	Lower gastrointestinal tract	OS (HR, 0.52; 95% CI, 0.22–1.22; P=0.13)
CancerTYPE ID-GI[49]	Retrospective	92-Gene RT-PCR (tissue-based)	42 (24 vs. 18)	Various	Colon or rectum	Median PFS, 8.5 vs. 6 mo (P=0.11)



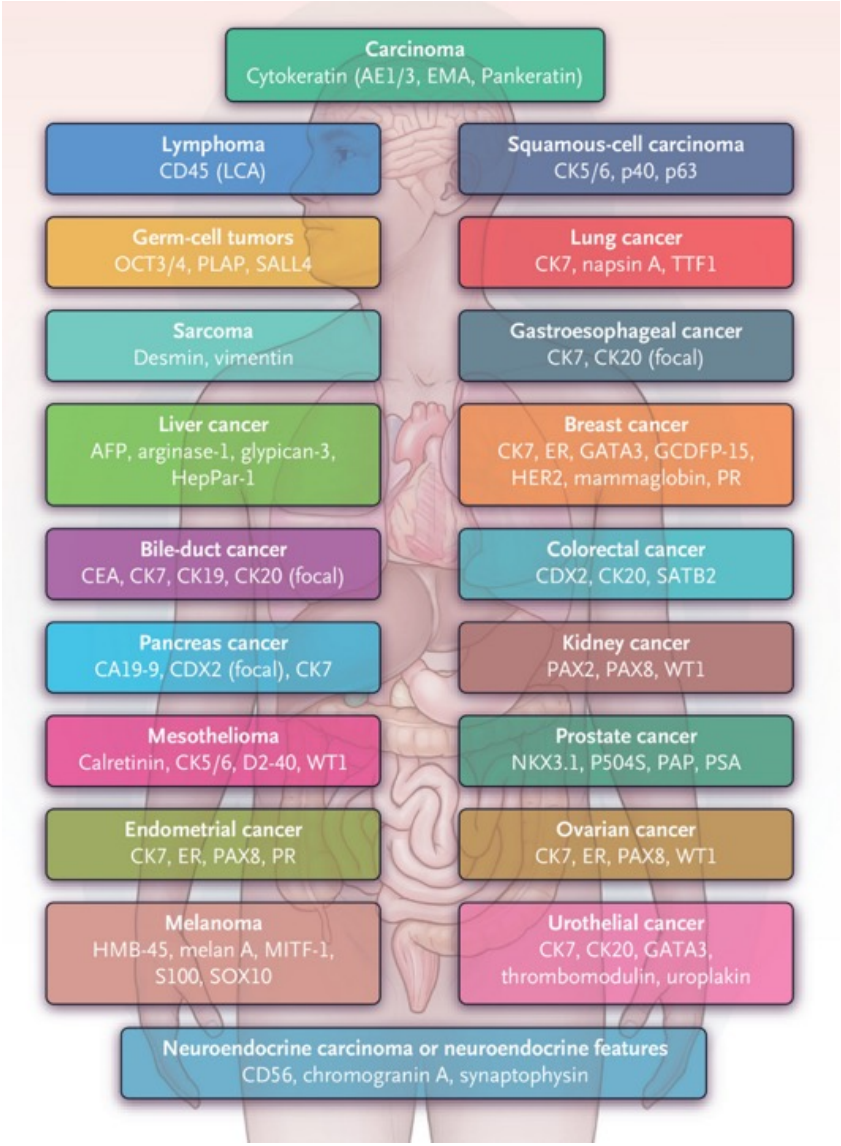
Development of Cancer of Unknown Primary Site.

The hallmark of cancer of unknown primary site is the presence of detectable metastatic disease without an identifiable primary lesion. The biologic features of cancer of unknown primary site, as opposed to cancer of known primary site, favor an aggressive phenotype with a propensity for early metastases and metastatic tumor outgrowth. While the metastatic disease grows, the primary tumor undergoes extensive immunoediting that is orchestrated by diverse anti- and protumorigenic immune cells and cytokines. Unlike cancer of known primary site, in which the primary tumor will progress by evading the immune system, cancer of unknown primary site involves a process that results in either immune elimination with regression of the primary tumor or an immune equilibrium (a state of dormancy) that leads to a subclinical primary lesion below the limits of diagnostic sensitivity. The graph shows tumor-burden growth over time in both metastatic and primary disease. Biologic features of the disease leading to differences between the primary tumor and the metastatic disease with respect to growth trajectory and diagnostic sensitivity result in the entities known as cancer of known primary site and cancer of unknown primary site.



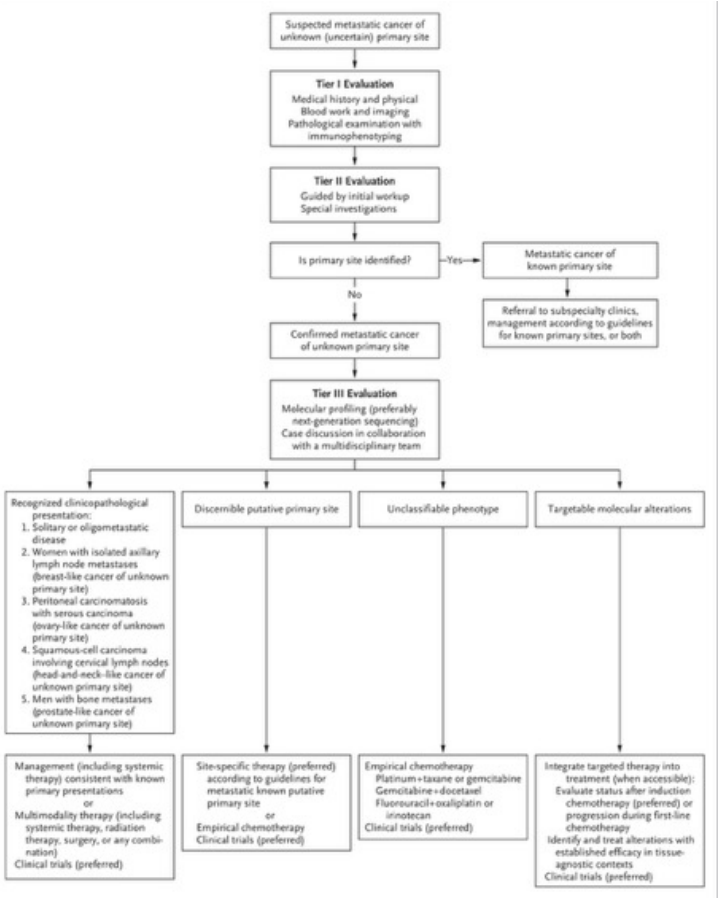
Diagnostic Workup for Patients with Cancer of Unknown Primary Site.

Cancer of unknown primary site is a diagnosis of exclusion, with workup designed to rule out any known primary site. Investigations should follow a tiered format with emphasis on tailoring the workup with each subsequent test. The critical decision is centered on striking the appropriate balance between the intensity of and time required for testing and the indication for and ability to start treatment guided by the patient's clinical status, disease trajectory, and goals of care. Immunophenotyping takes center stage in the diagnosis, but no one stain is sensitive or specific enough; therefore, a modular approach is necessary. With respect to imaging, magnetic resonance imaging (MRI), positron emission tomography (PET), or both can be performed in patients with contraindication to CT with the use of intravenous contrast material. The multidisciplinary team includes a medical oncologist, pathologist (with or without a molecular pathologist), radiologist, and in certain cases a surgical oncologist, radiation oncologist, and interventional radiologist. Special investigations include urinalysis, invasive endoscopy (involving colonoscopy and esophagogastroduodenoscopy [if clinical history or symptoms or immunohistochemical findings suggest a gastrointestinal primary cancer], cystoscopy, or panendoscopy with biopsies and tonsillectomy [for cases in which head and neck carcinoma is suspected]), and specialized imaging (such as breast imaging [mammography or breast MRI] and ^{18}F-fluorodeoxyglucose [FDG] PET), among others. Molecular profiling to determine the tissue of origin is useful as an adjunct to standard workup and preferably in a research context. The value of molecular profiling over the diagnostic methods currently used is yet to be established. AFP denotes α-fetoprotein, CA cancer antigen, CA19-9 carbohydrate antigen 19-9, CBC complete blood count, CEA carcinoembryonic antigen, CgA chromogranin A, CMP complete metabolic profile, CNB core needle biopsy, FNA fine-needle aspiration, HCG β-human chorionic gonadotropin, LDH lactate dehydrogenase, IHC immunohistochemical, NGS next-generation sequencing, and PSA prostate-specific antigen.



Immunophenotyping in Cancer of Unknown Primary Site.

Shown are key positive immunostains that are indicative of specific tumor types during phenotyping.



Conclusions and Recommendations

Regarding the patient in the vignette with cancer of unknown primary site, I would manage her care according to the most likely putative cancer of known primary site given the phenotype and genotype. She had an immunophenotype suggestive of a gastrointestinal primary cancer (colon-like cancer of unknown primary site) on the basis of assays positive for CK20, CDX2, and SATB2, which are immunostains used for samples from the lower gastrointestinal tract. I would start by obtaining a repeat biopsy and sending tissue for genomic profiling to identify targetable alterations. Alternatively, genomic profiling with blood-based assays can also be used to detect potential actionable genetic alterations (e.g., dMMR, *BRAF* V600E, human epidermal growth factor receptor 2 amplification).

I would then recommend palliative systemic chemotherapy that corresponded to the best treatments known for the presumed primary cancer. In this case, I would use fluorouracil (plus leucovorin), oxaliplatin, and irinotecan (FOLFOXIRI), drawing from evidence supporting the role of triplet cytotoxic chemotherapy in metastatic colorectal cancer. The use of doublet fluorouracil-based therapy with oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) is also defensible, but a 47-year-old patient should be able to receive the more aggressive and more effective FOLFOXIRI therapy. The results of molecular profiling can enable the integration of molecularly guided therapy in a treatment continuum that is based on response to therapy, the level of evidence that supports targeting the alteration, and the availability of molecularly guided therapies, preferably within the context of clinical trials. I would also seek early referral to a center with a multidisciplinary program focused on cancer of unknown primary site and enroll the patient in a clinical trial, if she were willing.

Case 15-2025: A 52-Year-Old Man with Fever, Nausea, and Respiratory Failure

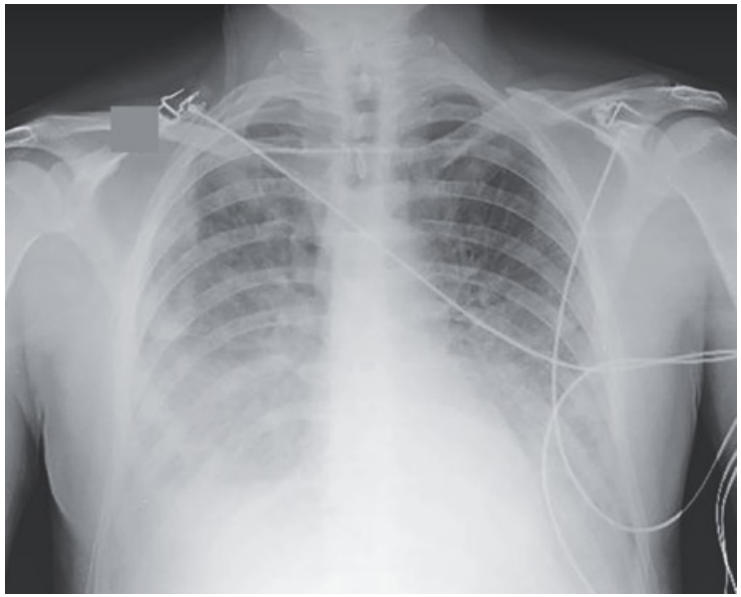
A 52-year-old man presented to the emergency department of Centro de Educación Médica e Investigaciones Clínicas (CEMIC) in Buenos Aires in early autumn with fever that had persisted for 1 week. The patient had been in his usual state of good health until 7 days before the current presentation, when fever developed. He presented to the emergency department of CEMIC for evaluation. The temperature was 38.0°C, and testing of a nasopharyngeal swab for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA was negative.

During the next 7 days, fever persisted and additional symptoms developed, including nausea, abdominal pain, and watery diarrhea. The patient had poor oral intake and became concerned about his ability to maintain adequate hydration. He returned to the emergency department for further evaluation. The temporal temperature was 36.3°C, the blood pressure 100/75 mm Hg, the pulse 91 beats per minute, the respiratory rate 22 breaths per minute, and the oxygen saturation 89% while he was breathing ambient air. The oxygen saturation increased to 93% after the administration of supplemental oxygen through a simple face mask at a rate of 2 liters per minute. The patient appeared to be confused but had no focal neurologic deficits.

Portable chest radiography, performed in the emergency department, revealed diffuse ground-glass opacities in both lungs, predominantly in the lower lobes, with associated reticular opacities. These findings were suggestive of volume overload or vascular redistribution; an underlying infection such as atypical pneumonia could not be ruled out.

The patient's medical history was notable for cholelithiasis, for which cholecystectomy had been performed 2 years earlier. He was fully vaccinated against SARS-CoV-2 but not against influenza virus. He took no medications and had no known adverse drug reactions. The patient lived in Buenos Aires with his wife and son, had no pets, and worked in an office setting without occupational exposures. He reported no recreational drug use or high-risk sexual behaviors. His family history was notable for hypertension and diabetes. Approximately 1 month before the current presentation, he had undergone a dental root-canal procedure. The patient had recently visited a rural area in the region of Chascomús, located in the Buenos Aires Province of Argentina. While in Chascomús, he had camped outdoors in a tent. He reported no known insect bites, contact with rodents, or other exposures.

On admission to the ICU, the patient had persistent hypoxemia, with an oxygen saturation of 88%, and supplemental oxygen was administered through a high-flow nasal cannula. On examination, dry mucous membranes were noted. The oropharynx appeared to be congested, and there was evidence of poor dental hygiene, with decayed teeth. Crackles were heard at the base of both lungs. There was no murmur, jugular venous distention, or peripheral signs of embolic disease. The abdomen was soft, bowel sounds were present, and there was mild epigastric tenderness on palpation. No edema of the arms or legs was noted.



Laboratory studies revealed an elevated hematocrit (56.9%; reference range, 41 to 53), leukocytosis (16,500 white cells per microliter; reference range, 4500 to 11,000) with a predominance of neutrophils, and thrombocytopenia (54,000 platelets per microliter; reference range, 150,000 to 400,000). In addition, the blood urea nitrogen level was elevated (49 mg per deciliter [17.5 mmol per liter]; reference range, 8 to 25 mg per deciliter [2.9 to 8.9 mmol per liter]), with a normal creatinine level (1.23 mg per deciliter [109 µmol per liter]; reference range, 0.60 to 1.50 mg per deciliter [53 to 133 µmol per liter]); no previously obtained values were available.

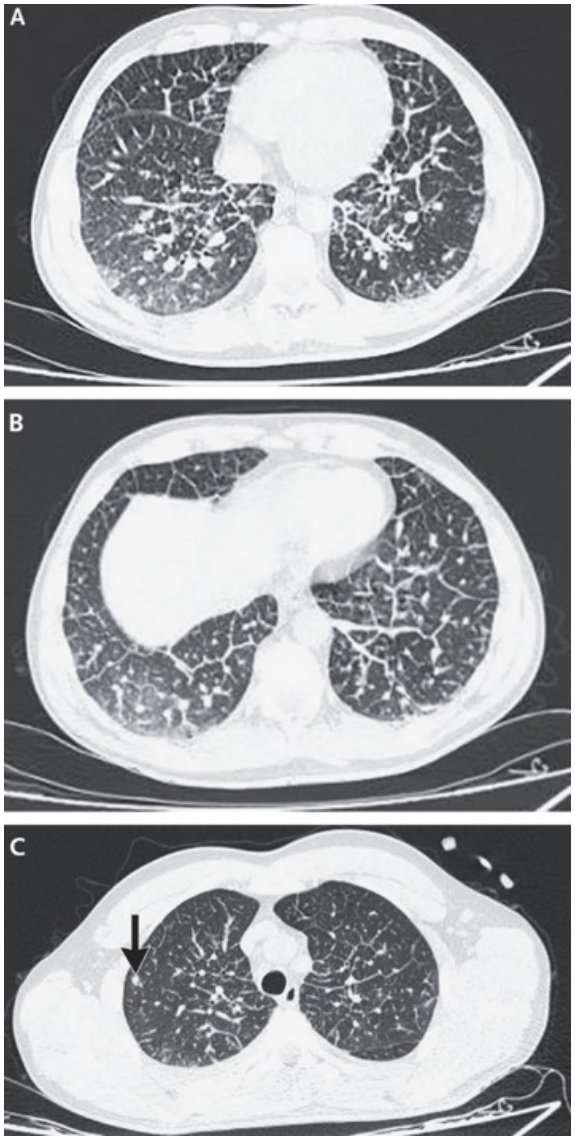
Blood and sputum were obtained for culture. Testing for SARS-CoV-2 and influenza virus types A and B, was negative, as was urinary antigen testing for *Streptococcus pneumoniae*. Serologic testing for human immunodeficiency virus (HIV), dengue virus, and leptospira was also performed.

Variable	Reference Range, Adults†	On Admission
Hemoglobin (g/dl)	13.5–17.5	19.7
Hematocrit (%)	41.0–53.0	56.9
White-cell count (per µl)	4500–11,000	16,500
Platelet count (per µl)	150,000–400,000	54,000
Sodium (mmol/liter)	135–145	133
Potassium (mmol/liter)	3.4–5.0	4.7
Chloride (mmol/liter)	98–108	95
Carbon dioxide (mmol/liter)	23–32	22
Urea nitrogen (mg/dl)	8–25	49
Creatinine (mg/dl)	0.60–1.50	1.23
Aspartate aminotransferase (U/liter)	10–40	56
Alanine aminotransferase (U/liter)	10–55	31
Alkaline phosphatase (U/liter)	15–115	49
Total bilirubin (mg/dl)	<1.2	0.4
Arterial blood gas measurements		
Partial pressure of arterial oxygen — mm Hg	80–100	42
Partial pressure of arterial carbon dioxide — mm Hg	35–45	70
Arterial pH	7.35–7.45	7.14

Empirical antimicrobial therapy with ceftriaxone, vancomycin, clarithromycin, and oseltamivir was initiated. The patient continued to receive supplemental oxygen through a high-flow nasal cannula at a rate of 50 liters per minute, with a fraction of inspired oxygen of 100%. However, the partial pressure of arterial oxygen was 42 mm Hg (reference range, 80 to 100), with a partial pressure of arterial carbon dioxide of 70 mm Hg (reference range, 35 to 45) and an arterial pH of 7.14 (reference range, 7.35 to 7.45). The trachea was intubated, and mechanical ventilation was initiated.

Owing to persistent abdominal pain and severe hypoxemia, point-of-care ultrasonography of the heart, chest, and abdomen was performed. No visceromegaly was noted in the abdomen. Pleuropulmonary findings included a severe diffuse alveolar–interstitial syndrome with bibasilar consolidations and mild bilateral pleural effusions. Focused cardiac ultrasonography showed normal biventricular function.

A diagnostic test was performed.



Community-Acquired Pneumonia

The patient's syndrome could be compatible with community-acquired pneumonia. In an immunocompetent adult presenting with a severe case of community-acquired pneumonia, the most likely causes include bacterial pathogens (e.g., *S. pneumoniae*, *Haemophilus influenzae*, *Legionella pneumoniae*, and *Mycoplasma pneumoniae*), as well as respiratory viruses (e.g., influenza virus, SARS-CoV-2, and respiratory syncytial virus).

Myeloproliferative Disorder

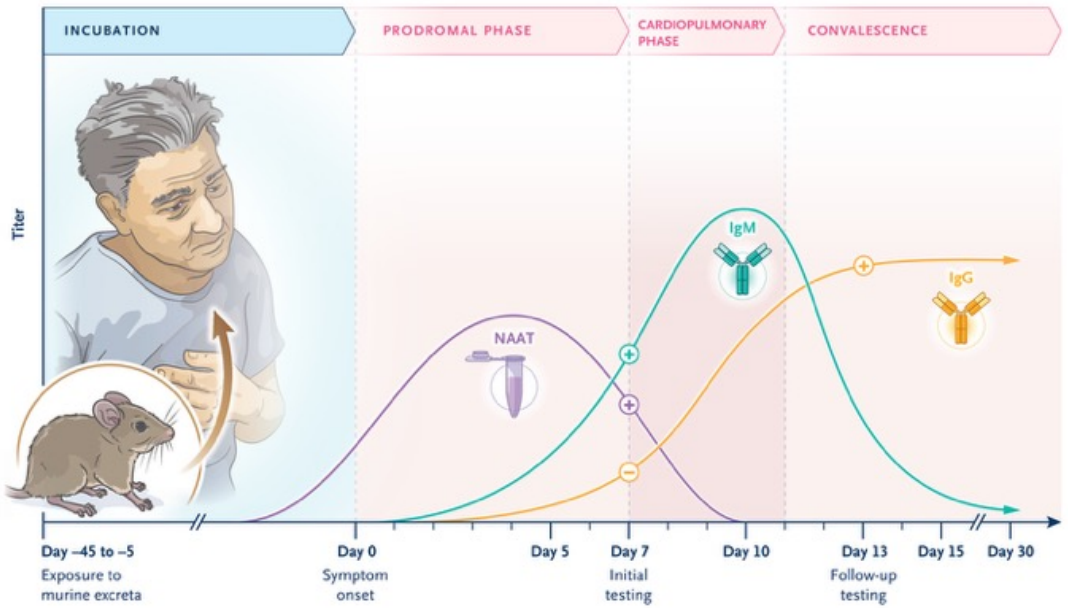
The patient had an elevated hematocrit, leukocytosis, and epigastric abdominal tenderness that might have suggested splenomegaly. These findings initially pointed toward an underlying myeloproliferative disorder, such as polycythemia vera. In this context, an invasive fungal infection, such as pulmonary aspergillosis, could have been responsible for the pulmonary findings.

Pulmonary–Renal Syndrome

Possible noninfectious causes of this patient's presentation included pulmonary–renal syndrome, which may manifest with diffuse alveolar hemorrhage and lead to hypoxemic respiratory failure. Diffuse alveolar hemorrhage can result from coagulopathy, the use of anticoagulant therapy, or pulmonary capillaritis, which can occur in the context of an autoimmune disorder such as anti–glomerular basement membrane disease (Goodpasture's syndrome) or antineutrophil cytoplasmic antibody–associated vasculitis (granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, or microscopic polyangiitis).

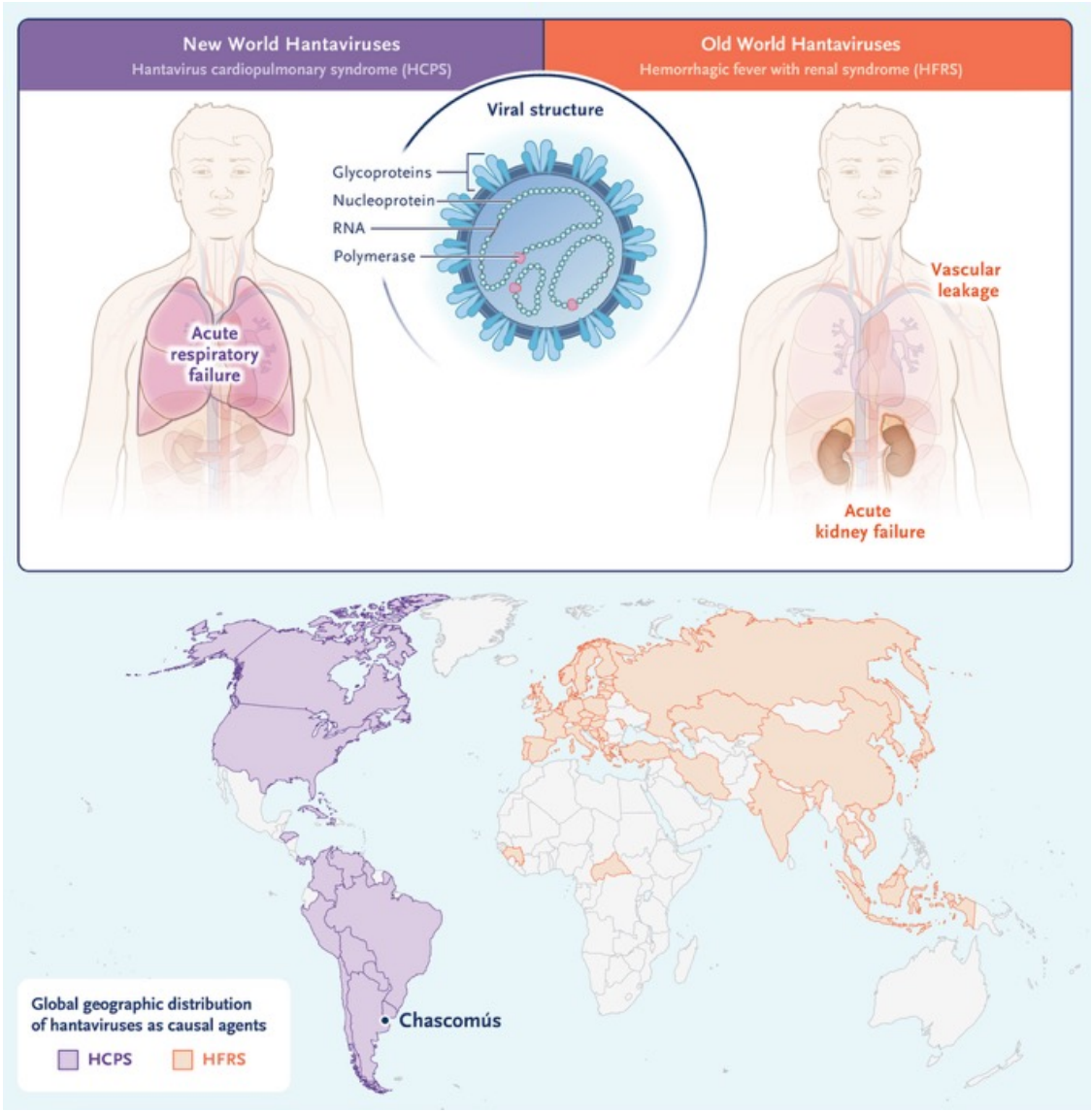
Hantavirus Cardiopulmonary Syndrome

The patient had hemoconcentration and bilateral pulmonary opacities, features suggestive of capillary leak syndrome, which is characterized by marked endothelial permeability with subsequent hemoconcentration and hemodynamic instability. Capillary leak syndrome can be caused by severe sepsis, toxic shock, envenomation, anaphylaxis, and viral infections. Given the patient's acute disease course, infectious diseases were prioritized in the initial evaluation.



Diagnostic Testing for Hantavirus Infection.

The kinetics of diagnostic testing for human hantavirus infection are shown relative to symptom onset. IgM levels become detectable 1 to 3 days after symptom onset, peak at approximately day 10, and decline by approximately day 30. IgG levels start to rise 3 to 5 days after symptom onset, and elevation continues for a prolonged period. Viral RNA can be detected on nucleic acid amplification testing (NAAT) before and up to approximately 10 days after symptom onset. Results of serologic and molecular testing performed in this case are also shown. The patient initially had detectable IgM and positive NAAT, and IgG was later detected. These findings confirmed the diagnosis of hantavirus infection manifesting as hantavirus cardiopulmonary syndrome. Hantavirus cardiopulmonary syndrome progresses through four phases, which can vary in length; typical durations are shown.



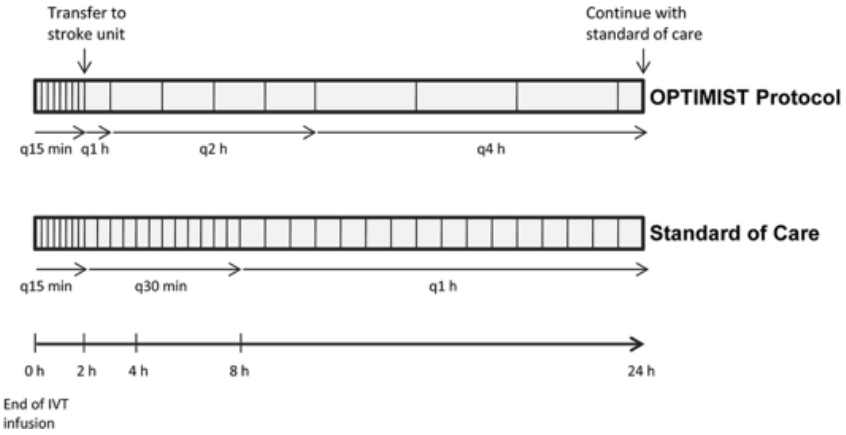
Global Geographic Distribution and Clinical Manifestations of Hantavirus Infection.

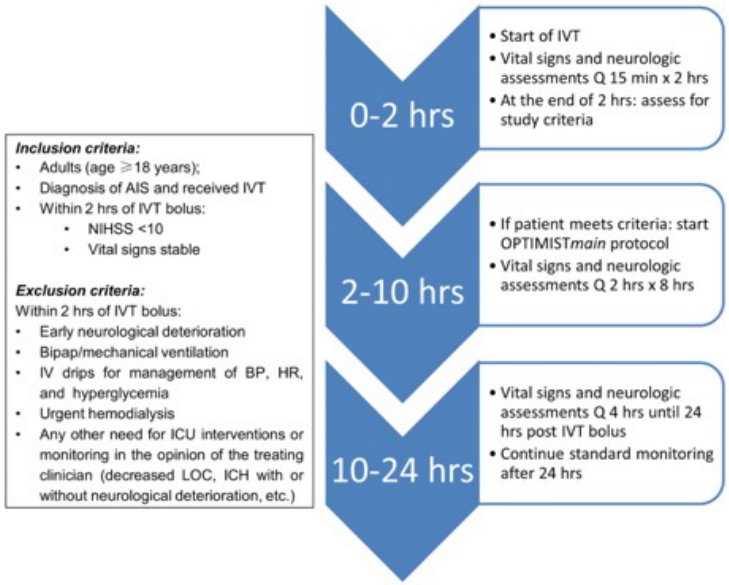
The global distribution of hantavirus infection is shown according to clinical manifestations. Infection with genotypes that are prevalent predominantly in Europe and Asia (Old World hantaviruses) manifests as hemorrhagic fever with renal syndrome. Infection with genotypes that are prevalent across South America and North America (New World hantaviruses) manifests as hantavirus cardiopulmonary syndrome. In this case, hantavirus exposure most likely occurred in the region of Chascomús, located in the Buenos Aires Province of Argentina.

Final Diagnosis

Hantavirus cardiopulmonary syndrome.

Following IV alteplase (tPA) administration for stroke, standard monitoring includes frequent checks of vital signs, neurological status, and blood pressure for the first 24 hours. Specifically, vital signs and neurological assessments are typically monitored every 15 minutes for the first two hours, then every 30 minutes for the next 6 hours, and every hour thereafter. This is to detect any signs of intracranial hemorrhage or adverse drug reactions.





Safety and efficacy of low-intensity versus standard monitoring following intravenous thrombolytic treatment in patients with acute ischaemic stroke (OPTIMISTmain): an international, pragmatic, stepped-wedge, cluster-randomised, controlled non-inferiority trial

Summary

Background The universally accepted best practice protocol for monitoring patients who receive intravenous thrombolysis for acute ischaemic stroke was established in the 1990s. However, the protocol is burdensome for nurses, disrupts the sleep of patients, and is potentially less relevant in patients at low risk of symptomatic intracerebral haemorrhage. We aimed to assess whether implementing a low-intensity monitoring protocol would be as safe and effective as standard high-intensity monitoring for patients with acute ischaemic stroke at low risk.

Methods OPTIMISTmain was an international, pragmatic, multicentre, stepped-wedge, cluster-randomised, controlled, non-inferiority, blinded-endpoint trial conducted at hospitals (clusters) in eight countries. It was designed to test the non-inferiority of a low-intensity monitoring protocol to a standard protocol among consecutive adults with acute ischaemic stroke who were clinically stable with mild to moderate neurological impairment (score <10 on the National Institutes of Health Stroke Scale) within 2 h of initiation of intravenous thrombolysis according to local guidelines. Participating hospitals were randomly allocated to three sequences of implementation across four periods, stratified by country and projected numbers of participants, in which sites switched from standard monitoring (control) to low-intensity monitoring (intervention) in a stepped manner. The low-intensity monitoring protocol included assessments of neurological and vital signs every 15 min for 2 h, every 2 h for 8 h (*vs* every 30 min for 6 h for standard monitoring), and every 4 h (*vs* every 1 h for standard monitoring) until 24 h after thrombolysis. The primary outcome was the proportion of participants with an unfavourable functional outcome defined by a score from 2 (indicating some disability) to 6 (death) on the modified Rankin Scale at 90 days, measured by research staff masked to group allocation. The non-inferiority margin was set at 1·15 for the risk ratio (RR) in the intention-to-treat population. A generalised linear mixed model was used for analysis with adjustments for cluster (hospital site) and time (6-month periods from April, 2021), and imputation of missing outcome data. This trial is registered at Clinicaltrials.gov (NCT03734640) and the Australian New Zealand Clinical Trial Registry (ACTRN 12619001556134p) and is completed.

Findings Of 181 hospitals assessed for eligibility, 120 hospitals agreed to join the trial and were randomly allocated between April 28, 2021, and Sept 30, 2024; however, one hospital withdrew, one was not activated, and four did not enrol any patients. Overall, 4922 participants were enrolled at 114 hospitals, with 2789 participants assigned to the low-intensity monitoring group and 2133 to the standard monitoring group. 809 (31·7%) of 2552 participants in the low-intensity group and 606 (30·9%) of 1963 in the standard monitoring group had a modified Rankin Scale score of 2–6 at 90 days (RR 1·03 [95% CI 0·92–1·15], $p_{non\text{-}inferiority}$=0·057). Symptomatic intracerebral haemorrhage occurred in five (0·2%) of 2783 patients in the low-intensity group and eight (0·4%) of 2122 patients in the standard monitoring group. The numbers of participants with a serious adverse event were similar between the low-intensity monitoring group (309 [11·1%] of 2789) and the standard monitoring group (240 [11·3%] of 2133).

Interpretation OPTIMISTmain provides weak evidence that low-intensity monitoring is non-inferior to standard monitoring in patients with a mild or moderate level of neurological impairment who receive thrombolysis treatment for acute ischaemic stroke. Hospitals could consider incorporating this approach into stroke services according to local circumstances.

Funding National Health and Medical Research Council of Australia; New South Wales Health Investigator Development Grant; University of New South Wales Medicine Non Communicable Diseases Theme Early–Mid

Introduction

Acute ischaemic stroke accounts for approximately two-thirds (7·8 million) of strokes that occur globally each year, and has considerable variation in its risk factors, management, and outcomes by age, sex, geography, and socioeconomic status.[1,2] The 1995 National Institute of Neurological Disorders and Stroke (NINDS) trial[3] that established the efficacy of thrombolysis treatment with intravenous recombinant tissue plasminogen activator (or alteplase) in patients with acute ischaemic stroke has had a major influence on clinical practice that extends beyond the main results. The stringent inclusion and exclusion criteria chosen to maximise the balance between efficacy and safety and the consensus-based protocol that was used to monitor the vital signs and neurological function of participants were incorporated verbatim into the licence and guidelines to ensure that alteplase could be safely administered in clinical practice.[4] Subsequent upskilling of nurses, improved systems of care, and increased familiarity in the use of thrombolysis treatment, alone or in combination with endovascular thrombectomy, have allowed many patients worldwide to be monitored in wards outside of an intensive care unit (ICU), as originally recommended, after receiving reperfusion therapy. However, guidelines[5,6] and prescribing information[7] continue to recommend that patients be closely monitored according to the NINDS protocol over the first 24 h after thrombolysis treatment to allow for early detection of symptomatic intracerebral haemorrhage, neurological deterioration, and other complications. Thus, modern stroke services include areas with a high ratio of nurses to beds, necessary to provide the recommended high frequency of checks of vital signs and neurological assessments over 24 h.[5–8] However, such monitoring disrupts the sleep of patients, adversely affects nursing resources, and shifts attention away from other aspects of care, such as education, counselling, and mobilisation. Moreover, it might be unnecessary for patients who are at low risk of adverse outcomes.[9,10]

We undertook the main phase Optimal Post rtPA-IV Monitoring in Ischaemic Stroke Trial (OPTIMISTmain) to assess whether a low-intensity monitoring protocol would be as safe and effective as standard monitoring on the functional outcome of patients with a level of neurological impairment considered mild to moderate in severity when receiving thrombolysis treatment for acute ischaemic stroke.

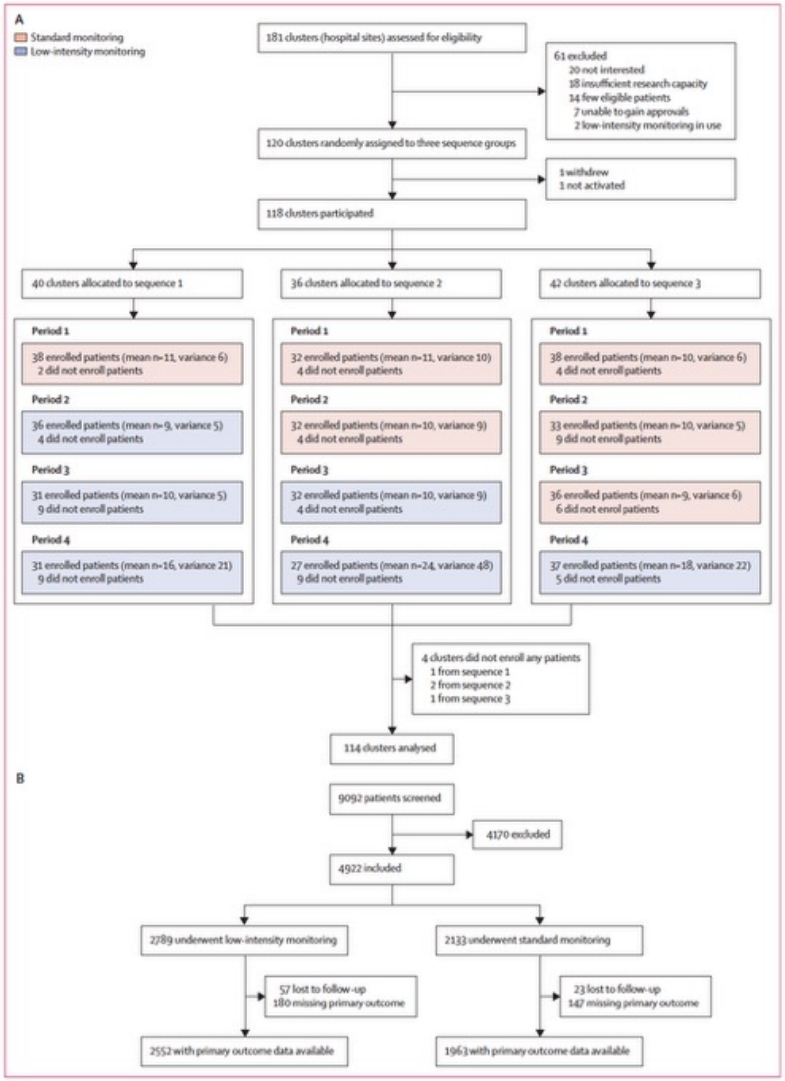


Figure 2: Trial profile
(A) Clusters. (B) Patients.

	Low-intensity monitoring (N=2789)	Standard monitoring (N=2133)
Age, years	66·0 (13·2)	65·8 (13·2)
Sex*		
Female	1086/2789 (38·9%)	804/2127 (37·8%)
Male	1702/2789 (61·0%)	1323/2127 (62·2%)
Other	1/2789 (<0·1%)	0/2127
Ethnicity		
Asian	1418/2786 (50·9%)	1105/2127 (52·0%)
Black	104/2786 (3·7%)	84/2127 (3·9%)
Hispanic	343/2786 (12·3%)	186/2127 (8·7%)
White	856/2786 (30·7%)	718/2127 (33·8%)
Other or uncertain	65/2786 (2·3%)	34/2127 (1·6%)
Medical history		
Hypertension	1715/2786 (61·6%)	1296/2127 (60·9%)
Intracerebral haemorrhage	20/2786 (0·7%)	10/2126 (0·5%)
Ischaemic stroke	572/2786 (20·5%)	427/2127 (20·1%)
Coronary artery disease	404/2786 (14·5%)	282/2127 (13·3%)
Other heart disease	247/2786 (8·9%)	179/2127 (8·4%)
Atrial fibrillation	212/2786 (7·6%)	169/2127 (7·9%)
Diabetes	691/2786 (24·8%)	530/2127 (24·9%)
Hypercholesterolaemia	601/2786 (21·6%)	488/2127 (22·9%)
Current smoker	660/2785 (23·7%)	492/2126 (23·1%)
mRS score before onset†		
0	1733/2779 (62·4%)	1315/2126 (61·9%)
1	428/2779 (15·4%)	322/2126 (15·1%)
2	266/2779 (9·6%)	229/2126 (10·8%)
3	221/2779 (8·0%)	146/2126 (6·9%)
4	124/2779 (4·5%)	106/2126 (5·0%)
5	7/2779 (0·3%)	8/2126 (0·4%)
Medications		
Antihypertensive medication	1086/2786 (39·0%)	880/2126 (41·4%)
Blood glucose-lowering agents	441/2786 (15·8%)	304/2126 (14·3%)
Statin or other lipid-lowering agent	664/2786 (23·8%)	506/2126 (23·8%)
Aspirin or other antiplatelet agent	550/2786 (19·7%)	412/2126 (19·4%)
Anticoagulation agent	52/2786 (1·9%)	45/2126 (2·1%)
Systolic blood pressure, mm Hg	152·4 (23·0), N=2783	153·6 (22·5), N=2125
Diastolic blood pressure, mm Hg	86·6 (14·2), N=2780	87·2 (14·5), N=2124
Glasgow Coma Scale score‡	15 (15–15), N=2593	15 (15–15), N=1987
NIHSS score§		
At presentation to hospital	4 (2–7), N=2786	5 (3–7), N=2125
Immediately after thrombolysis treatment	2 (1–5), N=2753	3 (1–5), N=2094
Median time from the onset of symptoms to commencement of thrombolysis treatment, h	2·5 (1·8–3·5)	2·6 (1·9–3·4)
Type of thrombolytic agent		
Alteplase	1995/2786 (71·6%)	1729/2126 (81·3%)
Tenecteplase	536/2786 (19·2%)	236/2126 (11·1%)
Other	255/2786 (9·2%)	161/2126 (7·6%)
Use of endovascular therapy	76/2786 (2·7%)	97/2127 (4·6%)

(Table 1 continues on next page)

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	Low-intensity monitoring (N=2789)	Standard monitoring (N=2133)
Final diagnosis¶		
Acute ischaemic stroke	2497/2782 (89·8%)	1944/2124 (91·5%)
Large vessel atheroma‖	625/2497 (25·0%)	538/1944 (27·7%)
Small vessel or perforating vessel disease	929/2497 (37·2%)	708/1944 (36·4%)
Cardioemboli	350/2497 (14·0%)	291/1944 (15·0%)
Dissection	17/2497 (0·7%)	22/1944 (1·1%)
Uncertain aetiology	516/2497 (20·7%)	333/1944 (17·1%)
Other definite pathological mechanism	60/2497 (2·4%)	52/1944 (2·7%)
Stroke mimic (other diagnosis)	285/2782 (10·2%)	180/2124 (8·5%)
Location of patients for immediate post-thrombolysis care		
Acute stroke unit	1331/2786 (47·8%)	1114/2126 (52·4%)
Intensive care unit	356/2786 (12·8%)	357/2126 (16·8%)
Intermediate care, stepdown, or high-dependency unit	710/2786 (25·5%)	435/2126 (20·5%)
Other	389/2786 (14·0%)	220/2126 (10·3%)
Condition stable or improving after thrombolysis	2714/2786 (97·5%)	2075/2126 (97·6%)
Monitoring for immediate post-thrombolysis care		
Adherence to monitoring protocol	2581/2786 (92·6%)	1991/2126 (93·7%)
Median duration, h	24·7 (24·0–26·0), N=2785	24·0 (24·0–24·0), N=2121
Median number of neurological assessments	17 (16–17), N=2784	37 (30–37), N=2125
Median number of vital sign measurements	17 (17–18), N=2784	37 (33–37), N=2125

Data are mean (SD), n (%), median (IQR), or n/N (%). mRS=modified Rankin Scale. NIHSS=National Institutes of Health Stroke Scale. *According to self-reported category ("female", "male", or "other") on the patient's case report form. †Scores indicate functional recovery, ranging from 0 (no symptoms) to 6 (death); a score of 2 or less indicates functional independence; the mRS score before stroke onset was assessed by the treating physician with the use of information obtained from patients (if possible) or their family members. ‡Scores indicate level of consciousness, ranging from 15 (normal) to 3 (deep coma). §Scores range from 0 to 42, with higher scores indicating more severe neurological deficits. ¶Reported by clinician investigators; multiple options recorded. ‖Defined as evidence of stenosis of 50% or more of an extracranial or intracranial artery on angiography or ultrasonography.

Table 1: **Patient characteristics at baseline and monitoring in the first 24 h after thrombolysis treatment**

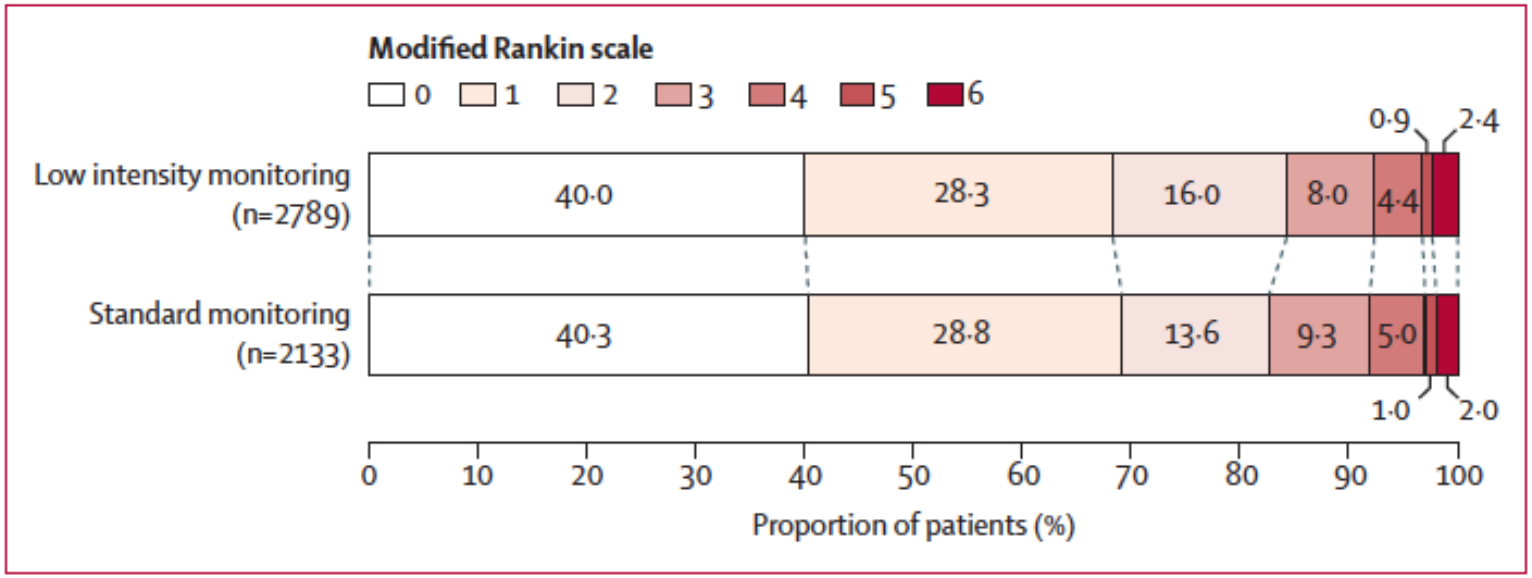


Figure 3: **Raw distribution of mRS scores at 90 days in the low-intensity and standard monitoring groups**
Scores on the mRS range from 0 to 6, with 0 indicating no symptoms, 1 symptoms without clinical significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death. There was a significant difference between the more-intensive and less-intensive groups in the overall distribution of scores (p=0·14 by proportional odds test). The common odds ratio indicating greater odds of worse functional outcome on the mRS was 1·03 (95% CI 0·89 to 1·20). mRS=modified Rankin Scale.

	Low-intensity monitoring (n=2789)	Standard monitoring (n=2133)	Effect size (95% CI)*	p value
Primary outcome				
mRS score 2–6 at 90 days†	809/2552 (31·7%)	606/1963 (30·9%)	RR 1·03 (0·92 to 1·15)	0·057‡
Secondary outcomes				
NIHSS score at 7 days or at hospital discharge, if sooner§	1·9 (2·8)	2·1 (3·1)	Mean difference −0·11 (−0·36 to 0·13)	..
NIHSS score category or death by 7 days§	..	..	Ordinal OR 0·85 (0·67 to 1·08)	..
Score 0–4	2185/2487 (87·9%)	1615/1874 (86·2%)	..	..
Score 5–9	242/2487 (9·7%)	214/1874 (11·4%)	..	..
Score 10–14	35/2487 (1·4%)	26/1874 (1·4%)	..	..
Score 15–19	8/2487 (0·3%)	10/1874 (0·5%)	..	..
Score 20–24	2/2487 (0·1%)	3/1874 (0·2%)	..	..
Score 25–42	4/2487 (0·2%)	1/1874 (0·1%)	..	..
Death	11/2487 (0·4%)	5/1874 (0·3%)	..	..
Sleep-related impairment¶	1·6 (1·3 to 2·1)	1·8 (1·4 to 2·3)	Median difference 0·02 (−0·05 to 0·08)	..
Patient-reported experience‖	1·1 (1·0 to 1·5)	1·1 (1·0 to 1·5)	Median difference −0·03 (−0·07 to 0·01)	..
Time to discharge from hospital, days	7 (3 to 10)	7 (4 to 10)	HR 1·14 (1·04 to 1·24)	..
Shift in the distribution of mRS scores at 90 days	..	..	Ordinal OR 1·03 (0·89 to 1·20)	..
mRS score 3–6 at 90 days	401/2562 (15·7%)	340/1963 (17·3%)	RR 0·95 (0·79 to 1·13)	..
Death at 90 days	60/2716 (2·2%)	39/2099 (1·9%)	RR 1·35 (0·84 to 2·17)	..
mRS score 3–5 at 90 days	341/2552 (13·4%)	301/1963 (15·3%)	RR 0·91 (0·75 to 1·10)	..
Time to from last monitoring to request for CT brain scan, h	22·4 (14·0 to 24·0)	16·7 (6·2 to 23·7)	Median difference 2·3 (−22·5 to 27·1)	..
Symptomatic intracerebral haemorrhage**	5/2783 (0·2%)	8/2122 (0·4%)	RR 0·57 (0·15 to 2·13)	..
Health-related quality of life on EQ-5D-5L at 90 days††				
Number of patients with assessment	2448	1876	..	..
Overall score on the visual analogue scale	82·2 (19·2), N=2411	81·6 (19·2), N=1864	Mean difference −0·46 (−1·98 to 1·05)	..
Safety outcomes				
Serious adverse events during follow-up‡‡				
Events reported	389	312	..	..
Patients with at least one event	309/2789 (11·1%)	240/2133 (11·3%)	..	0·67
Time from enrolment to onset of serious adverse event, days	5 (1 to 39)	7 (1 to 40)	..	0·29

Data are n/N (%), mean (SD), or median (IQR), except where otherwise stated. HR=hazard ratio. mRS=modified Rankin scale. NIHSS=National Institutes of Health Stroke Scale. OR=odds ratio. RR=risk ratio. *Estimates from either a logistic or linear regression model with a random effect of cluster (hospital site), group assignment (low-intensity or standard intensity monitoring) as a fixed effect, and calendar time (6-month window) as a fixed categorical effect, and in either multiple imputation of missing data assuming missingness at random (for all the mRS related outcomes) or all the available data (complete case analysis). †The mRS evaluates global disability with scores ranging from 0 (no symptoms) to 6 (death), and a score of 2–5 indicating some degree of disability. ‡p value for non-inferiority; the interclass correlation coefficient in the study was 0·039. §Scores on the NIHSS range from 0 to 42, with higher scores indicating more severe neurological deficits. ¶Mean scores of completed questions on the eight-item short-form questionnaire on sleep-related impairment (mean score range 1–5, with low scores indicating less sleep-related impairment), developed by the Patient-Reported Outcome Measurement Information System, in which all questions were answered in 3078 patients. ‖Mean scores of completed questions on a patient-reported experience measurement questionnaire (mean score range 1–5, with low scores indicating a better experience), which included eight of 12 questions from the Australian Hospital Patient Experience Question Set used in hospitals outside of the USA, with all questions answered in 3638 patients. **Symptomatic intracranial haemorrhage was according to a parenchymal haematoma occupying ≥30% of the infarcted tissue with obvious mass effect as judged by the clinician investigator. ††Scores on the visual analogue scale of the EQ-5D-5L were analysed in a linear mixed model. ‡‡Any serious adverse event was defined by standard criteria to include any of the following events that may or may not be considered related to the treatment that results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or results in medical or surgical intervention to prevent permanent impairment to body structure or function; a patient could have more than one event.

Table 2: **Primary and secondary efficacy and safety outcomes**

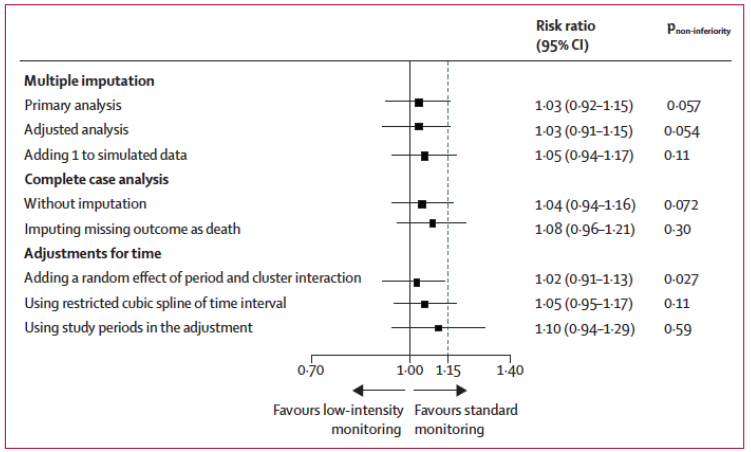


Figure 4: **Primary and sensitivity analyses of poor functional outcome (scores 2–6 on the modified Rankin Scale) in the low-intensity and standard monitoring groups**
The dashed line shows the prespecified non-inferiority threshold (risk ratio 1·15).

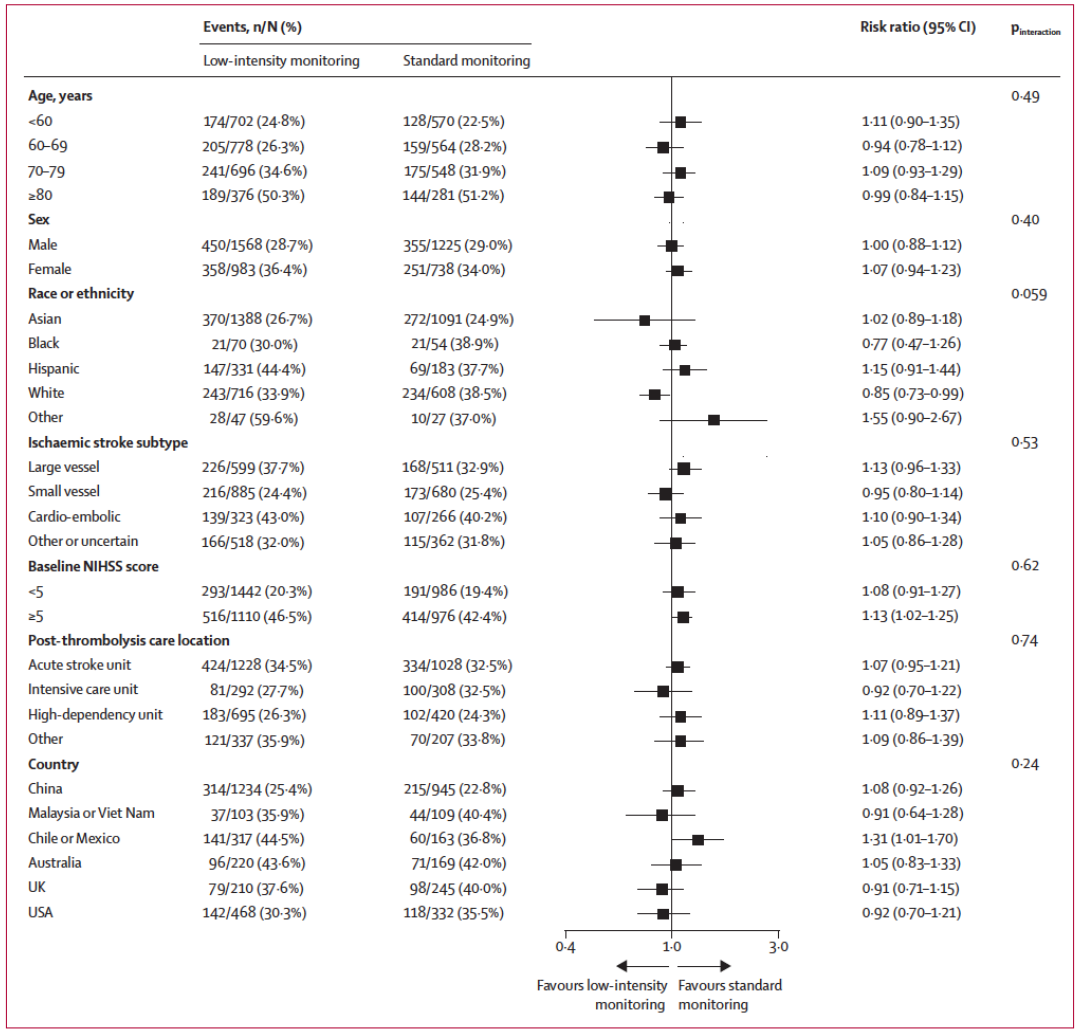


Figure 5: **Risk of poor functional outcome (scores 2–6 on the modified Rankin Scale) at 90 days in prespecified patient subgroups**
NIHSS=National Institute of Health Stroke Scale.

Research in context

Evidence before this study

We searched PubMed (from Jan 1, 1970, to Jan 6, 2025) and Embase (from Jan 1, 1947, to Jan 6, 2025) on Jan 7, 2025, with no language or data restrictions, for publications with relevant text words in the title or abstract or keywords that included the following: "stroke" OR "ischaemic stroke", "thrombolysis" OR "reperfusion treatment" OR "tissue plasminogen activator", "monitoring" OR "monitor", "nursing care" OR "acute care". Studies were eligible for inclusion if they assessed the effectiveness of reduced monitoring care post-thrombolysis treatment on clinical outcomes. We identified only one completed trial, a single-centre, single-arm, safety trial conducted between March 1, 2014, and March 31, 2018, the OPTIMIST pilot trial, which showed a low-intensity protocol in 35 patients with minor stroke (NIHSS score <10) was safe, with no patient requiring transfer to an intensive care unit (ICU) or needing a critical care intervention in the 24 h period after thrombolysis. A retrospective, single-centre study that enrolled 122 patients in Michigan, USA, between Jan 1, 2017, and March 30, 2019, showed that in comparison to 24 h monitoring in an ICU, a shorter 12 h period of monitoring after thrombolysis for patients with a minor acute ischaemic stroke (NIHSS score 0–5) was not associated with any increase in adverse outcomes. A before and after study published as an abstract showed that among 731 patients enrolled over 8 years, there was no significant difference in mortality at 3 months between standard and reduced frequency of monitoring (37 *vs* 17 assessments, respectively) over 24 h after thrombolysis for acute ischaemic stroke. No ongoing trials were identified through a search of registered trials at ClinicalTrials.gov. There is scant evidence of the safety and efficacy of low-intensity monitoring after thrombolysis treatment in patients with minor acute ischaemic stroke.

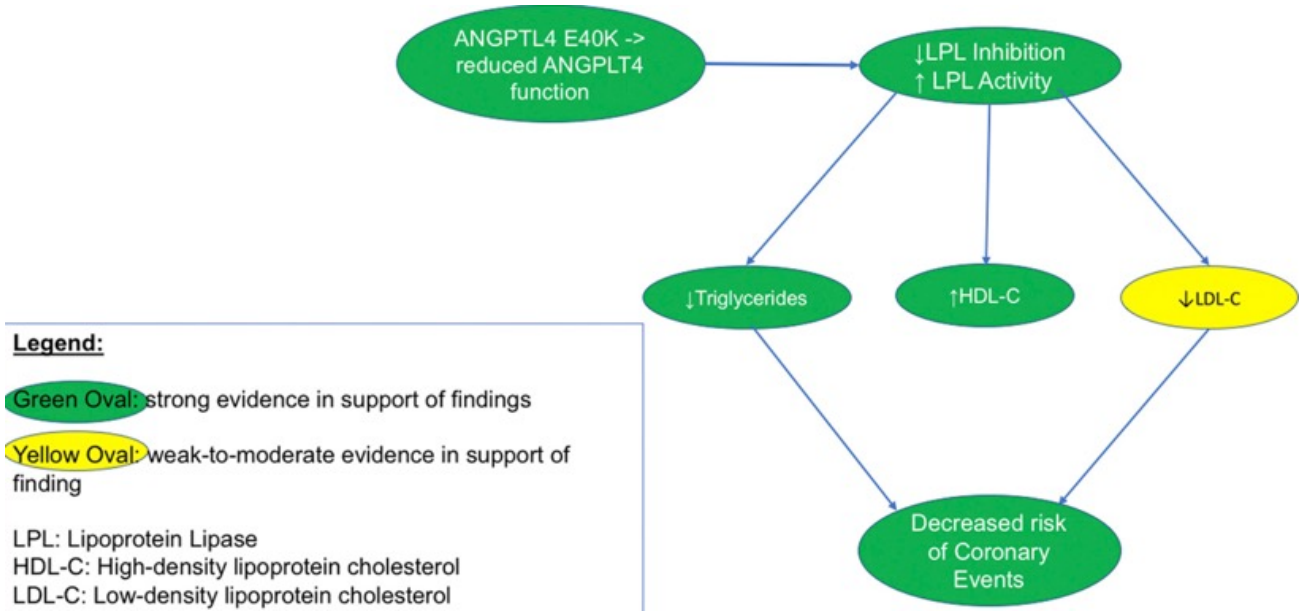
Added value of this study

OPTIMISTmain is the only randomised controlled trial of a low-intensity monitoring protocol for the care of patients who receive thrombolysis treatment for acute ischaemic stroke. The primary result was that the implementation of low-intensity monitoring across participating hospitals showed weak evidence of being non-inferior for unfavourable functional outcome (a score of 2–6 on the modified Rankin Scale) at 90 days compared with standard monitoring. Moreover, there were no clinically meaningful differences in the effects on other outcomes, including levels of functional recovery, death, quality of sleep, patient-reported satisfaction with the quality of care, and health-related quality of life. There were no significant differences in serious adverse events, and symptomatic intracerebral haemorrhage was very low in both randomised groups.

Implications of all the available evidence

We conclude that low-intensity monitoring is probably non-inferior to standard high-intensity monitoring in stable patients with a mild to moderate level of neurological impairment, defined by a score of 0–9 on the National Institute of Health Stroke Scale at the end of thrombolysis treatment for acute ischaemic stroke. In the current study, the intervention did not compromise the recovery of patients nor increase harms associated with serious adverse events, including the potential to miss intracerebral haemorrhage. The intervention was acceptable and feasible to be done outside of an ICU in many countries, with the benefits of flexibility in nursing workflow and release of intensive care resources. Hospitals could consider incorporating this approach to improve systems of care for acute stroke.

Angiopoietin-like 4 (Angptl4) is a secreted protein modulating triacylglycerol homeostasis. Its transcription is induced by glucocorticoids, which act to elevate circulating Angptl4 levels during fasting. In investigating the role of Angptl4 in glucocorticoid action, we identified that in addition to its known ability to inhibit lipoprotein lipase, Angptl4 stimulates intracellular adipocyte lipolysis. Fatty acid release by murine adipocytes following fasting or treatment with glucocorticoids or catecholamines is highly Angptl4-dependent. In fact, Angptl4 can directly stimulate cAMP-dependent PKA signaling and lipolysis when added to adipocytes. Here, we detail this novel Angptl4-dependent lipolytic regulatory mechanism and discuss its physiological and therapeutic implications.



Safety and efficacy of a novel ANGPTL4 inhibitory antibody for lipid lowering: results from phase 1 and phase 1b/2a clinical studies

Summary

Background Genetic studies have established angiopoietin-related protein 4 (ANGPTL4) as a key regulator of triglyceride metabolism and a promising target to reduce atherosclerotic cardiovascular disease (ASCVD) risk beyond traditional risk factors. Human *ANGPTL4* loss-of-function shows no adverse consequences and is associated with reduced triglycerides and remnant cholesterol, and a reduced risk of type 2 diabetes and ASCVD. Nonetheless, development of *ANGPTL4* inhibitors has been delayed due to adverse findings in *ANGPTL4*-knockout mice fed a high saturated fat diet, including lipid accumulation in mesenteric lymph nodes, systemic inflammation, adverse clinical signs, and reduced survival. We previously reported the development and preclinical characterisation of MAR001, an ANGPTL4 inhibitory antibody. Here, we report a comprehensive safety assessment of *ANGPTL4* inhibition, including novel analysis of genetic *ANGPTL4* loss on mesenteric lymph node architecture in humans and two early-phase clinical trials.

Methods MAR001 was evaluated in a first-in-human, randomised, placebo-controlled, single-ascending-dose phase 1 study with three parts in which participants received a single subcutaneous injection of MAR001 or placebo. The study was developed and conducted by Novartis Biomedical Research (Cambridge, MA, USA). Eligible participants enrolled in part 1A were healthy men and women aged between 18 years and 65 years with a bodyweight of at least 50 kg and a BMI of 18–30 kg/m^2. Participants in part 1B weighed at least 70 kg and had a BMI of 30–40 kg/m^2. Participants in part 1C weighed at least 59 kg and had fasting triglycerides in the range of 200–500 mg/dL. The primary objectives were to assess the safety and tolerability of a single subcutaneous injection of MAR001 up to and including 141 days post-dose and to assess the pharmacokinetics of single-dose subcutaneous administration in healthy participants. MAR001 was subsequently assessed in a randomised, double-blind, placebo-controlled phase 1b/2a study in participants with metabolic dysfunction. The study was done at two sites in Australia. Eligible participants were adults with hypertriglyceridaemia (in the screening range of ≥1·7 mmol/L and ≤5·6 mmol/L; ≥151 mg/dL and ≤496 mg/dL) and a history of type 2 diabetes, or a screening homeostatic model assessment for insulin resistance (HOMA-IR) value greater than 2·2 and abdominal obesity (defined as waist circumference >88 cm for women and >102 cm for men; > 80 cm for Asian women and >90 cm for Asian men). The primary objective was to characterise the safety and tolerability of multiple doses of MAR001 in participants with metabolic dysfunction. The phase 1b/2a study is registered with ClinicalTrials.gov, NCT05896254.

Findings We found no evidence of clinical adversity in human germline *ANGPTL4* loss-of-function, adding to preclinical support for initiating human studies. Between Nov 20, 2017, and Sept 10, 2019, in the first-in-human, randomised, placebo-controlled, single-ascending-dose phase 1 study, part 1A enrolled 32 healthy participants: six each received 15 mg, 50 mg, 150 mg, or 450 mg of MAR001, and eight received placebo. Part 1B enrolled 12 participants: nine received 450 mg of MAR001 and three received placebo. Part 1C enrolled 12 participants: eight received 450 mg of MAR001 and four received placebo. Between Nov 24, 2013, and July 1, 2024, in the multidose phase 1b/2a randomised, double-blind, placebo-controlled study, 55 participants were randomly assigned to receive subcutaneous injections of placebo (19 participants) or MAR001 at doses of 150 mg (ten participants), 300 mg (nine participants), or 450 mg (17 participants), followed by a 12-week safety follow-up period. MAR001 was safe and generally well tolerated, and we observed no treatment-related systemic inflammatory biomarker elevations or changes in mesenteric lymph node size or inflammation assessed by MRI. MAR001 (450 mg) yielded placebo-adjusted week 12 mean reductions in triglycerides of 52·7% (90% CI –77·0 to –28·3) and in remnant cholesterol of 52·5% (–76·1 to –28·9).

Interpretation ANGPTL4 inhibition with MAR001 can safely and effectively reduce circulating triglycerides and remnant cholesterol. The findings of these trials support further research and development of MAR001 as a promising potential lipid-lowering therapy to reduce risk of ASCVD.

Funding Marea Therapeutics.

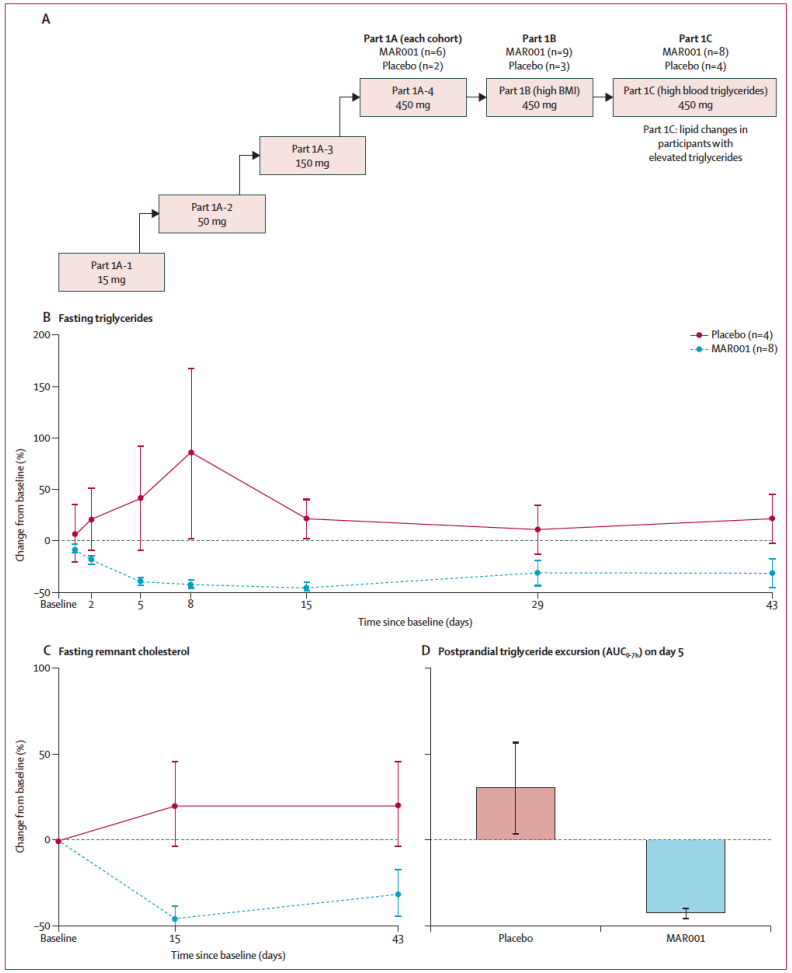


Figure 1: **First-in-human single-dose clinical study**
(A) Study design. All participants received a single subcutaneous injection of MAR001 or placebo. Part 1A in healthy participants comprised four dose-escalation cohorts (15 mg to 450 mg of MAR001) and placebo. In part 1B, 12 participants with high BMI (30–40 kg/m^2) received 450 mg MAR001 or placebo. In part 1C, 12 participants weighing at least 59 kg and with high triglycerides (200–500 mg/dL) at screening received 450 mg MAR001 or placebo. (B–D) Percentage change from baseline in biomarkers in participants with high triglycerides (part 1C) after a single-dose of MAR001 (450 mg subcutaneous). (B) Fasting triglycerides. (C) Fasting remnant cholesterol. (D) Postprandial triglyceride AUC. AUC was measured during a meal tolerance test at baseline and on day 5 after MAR001 administration. Error bars represent SE of the mean. For figure 1C, note fasting triglyceride values were assessed more densely than other lipid parameters such as remnant cholesterol (appendix p 15). AUC=area under the curve.

	Part 1A					Part 1B		Part 1C		Total (n=56)
	MAR001 15 mg (n=6)	MAR001 50 mg (n=6)	MAR001 150 mg (n=6)	MAR001 450 mg (n=6)	Placebo (n=8)	MAR001 450 mg (n=9)	Placebo (n=3)	MAR001 450 mg (n=8)	Placebo (n=4)	
Overall	3, 3 (50%)	4, 3 (50%)	4, 3 (50%)	1, 1 (17%)	4, 2 (25%)	1, 1 (11%)	0	8, 5 (63%)	1, 1 (25%)	26, 19 (34%)
Mild intensity	3, 3 (50%)	4, 3 (50%)	2, 2 (33%)	1, 1 (17%)	4, 2 (25%)	1, 1 (11%)	0	7, 4 (50%)	1, 1 (25%)	23, 17 (30%)
Moderate intensity	0	0	2, 1 (17%)	0	0	0	0	1, 1 (13%)	0	3, 2 (4%)
Severe intensity	0	0	0	0	0	0	0	0	0	0
Study treatment-related adverse events	0	0	1, 1 (17%)	0	0	1, 1 (11%)	0	0	0	2, 2 (4%)
Serious adverse events	0	0	0	0	0	0	0	0	0	0
Adverse events leading to discontinuation of study treatment	0	0	0	0	0	0	0	0	0	0
Study treatment-related adverse events leading to discontinuation of study treatment	0	0	0	0	0	0	0	0	0	0

Data are number of events, number of participants with at least one adverse event in the category (%).

Table 1: **Overall incidence of adverse events observed in the single-dose study**

	Placebo (n=19)	MAR001 150 mg (n=10)	MAR001 300 mg (n=9)	MAR001 450 mg (n=17)
Age, years	49·0 (38·0–56·0)	54·5 (41·0–59·0)	40·0 (34·0–42·0)	50·0 (40·0–58·0)
Sex				
Female	11 (58%)	8 (80%)	3 (33%)	7 (41%)
Male	8 (42%)	2 (20%)	6 (67%)	10 (59%)
Race				
White	15 (79%)	5 (50%)	6 (67%)	12 (71%)
Asian	3 (16%)	4 (40%)	1 (11%)	1 (6%)
Other	1 (5%)	1 (10%)	2 (22%)	4 (24%)
Hispanic or Latino ethnicity	0	0	1 (11%)	1 (6%)
BMI, kg/m²	34·5 (32·0–38·1)	35·4 (33·1–37·3)	34·3 (33·3–37·1)	34·5 (32·6–36·0)
Waist circumference, cm	109·8 (9·7)	106·3 (9·0)	112·9 (13·5)	110·6 (7·4)
Triglycerides, mg/dL	181·6 (49·9)	169·9 (46·2)	191·4 (58·0)	219·2 (100·7)
≥150	13 (68%)	7 (70%)	8 (89%)	14 (82%)
≥200	9 (47%)	3 (30%)	4 (44%)	9 (53%)
Remnant cholesterol, mg/dL	32·2 (8·8)	29·4 (7·0)	33·6 (9·1)	40·1 (18·8)
≥30	11 (58%)	3 (30%)	6 (67%)	11 (65%)
≥40	2 (11%)	1 (10%)	2 (22%)	5 (29%)
Very low-density lipoprotein cholesterol, mg/dL	36·0 (9·9)	33·6 (9·0)	37·9 (11·4)	43·5 (19·8)
Non-HDL cholesterol, mg/dL	159·5 (31·2)	139·1 (35·7)	163·9 (38·9)	175·1 (44·7)
HDL cholesterol, mg/dL	46·1 (9·7)	47·7 (10·5)	41·1 (8·3)	42·8 (6·9)
LDL cholesterol, mg/dL	122·5 (31·4)	104·8 (38·8)	125·6 (45·3)	131·1 (33·9)
Homeostatic model assessment of insulin resistance score	3·3 (1·7)	3·7 (3·2)	4·6 (3·8)	2·9 (1·4)
Glycated haemoglobin	5·9 (0·6)	6·0 (0·6)	5·6 (0·4)	5·6 (0·3)
Type 2 diabetes	3 (16%)	0	0	1 (6%)
Liver fat fraction by MRI-proton density fat fraction	12·7 (9·1)	12·7 (9·5)	11·3 (9·6)	9·7 (7·2)
Fat fraction > 5%	15 (79%)	7 (70%)	6 (67%)	9 (53%)
Current medication use				
Metformin	3 (16%)	1 (10%)	1 (11%)	2 (12%)
Statin	1 (5%)	1 (10%)	1 (11%)	2 (12%)
SGLT2 inhibitors	2 (11%)	0	0	0

Data are median (IQR), mean (SD), or n (%).

***Table 2*: Baseline characteristics of participants in the multidose clinical study**

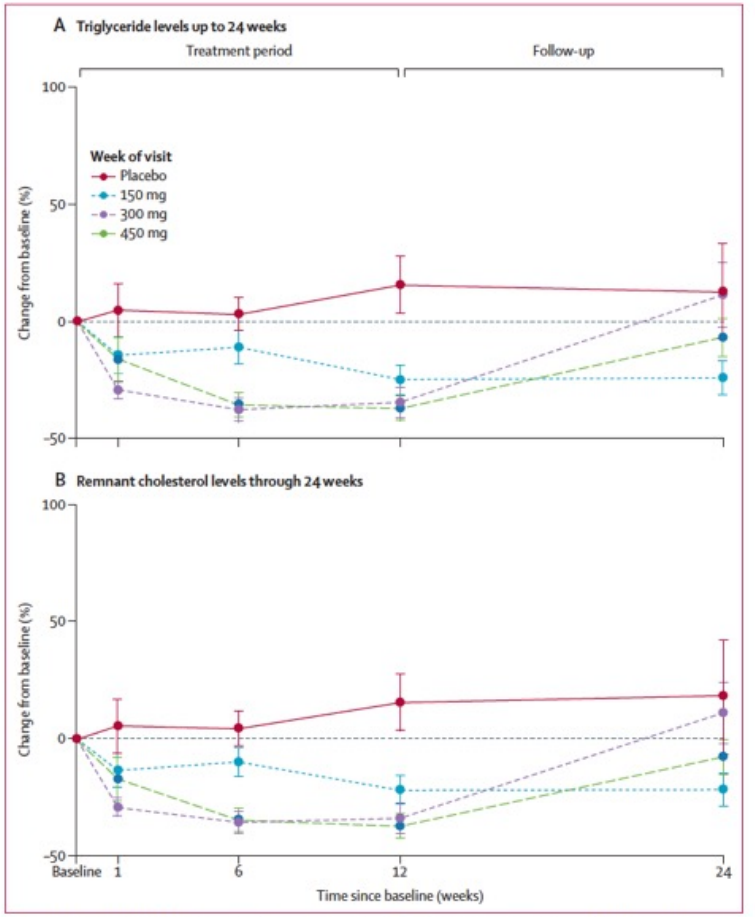


***Figure 2*: Effect of MAR001 on triglyceride and remnant cholesterol levels up to 24 weeks in the multidose clinical study**
Error bars indicate SE of the mean.

	Placebo (n=19)	MAR001 150 mg (n=10)	MAR001 300 mg (n=9)	MAR001 450 mg (n=17)
Triglycerides				
Triglyceride concentrations at baseline, mg/dL	181·6 (49·9)	169·9 (46·2)	191·4 (58·0)	219·2 (100·7)
Change from baseline at week 12, mg/dL	26·6 (−12·8 to 65·9)	−42·5 (−64·0 to −21·0)	−76·2 (−105·0 to −47·4)	−85·0 (−115·6 to −54·4)
Placebo-adjusted percentage change from baseline at week 12*	..	−40·6 (−70·1 to −11·2)	−50·3 (−88·0 to −12·7)	−52·7 (−77·0 to −28·3)
Remnant cholesterol				
Remnant cholesterol concentrations at baseline, mg/dL	32·2 (8·8)	29·4 (7·0)	33·6 (9·1)	40·1 (18·8)
Change from baseline at week 12, mg/dL	5·3 (−2·0 to 12·6)	−6·2 (−10·1 to −2·4)	−12·8 (−17·8 to −7·8)	−15·6 (−21·5 to −9·7)
Placebo-adjusted percentage change from baseline at week 12*	..	−37·4 (−66·1 to −8·8)	−49·3 (−85·8 to −12·8)	−52·5 (−76·1 to −28·9)

Data are mean (SD) or mean (90% CI). *Hodges–Lehmann estimators.

Table 3: **Change in triglyceride and remnant cholesterol at week 12 in the multidose clinical study**

	Placebo (n=19)	MAR001 150 mg (n=10)	MAR001 300 mg (n=9)	MAR001 450 mg (n=17)	Total (n=55)
Any adverse event	16 (84%)	7 (70%)	8 (89%)	16 (94%)	47 (85%)
Adverse events of special interest	5 (26%)	2 (20%)	2 (22%)	6 (35%)	15 (27%)
Adverse event leading to treatment discontinuation	1 (5%)	0	0	0	1 (2%)
Adverse event likely related to study drug	5 (26%)	6 (60%)	5 (56%)	5 (29%)	21 (38%)
Serious adverse event	0	0	0	0	0
Adverse event associated with death	0	0	0	0	0
Adverse event by maximum severity					
Grade 1	5 (26%)	5 (50%)	4 (44%)	8 (47%)	22 (40%)
Grade 2	10 (53%)	2 (20%)	4 (44%)	8 (47%)	24 (44%)
Grade 3	0	0	0	0	0
Grade 4	1 (5%)	0	0	0	1 (2%)
Grade 5	0	0	0	0	0

Data are n (%). Values represent the number of participants in each category. Maximum severity is reported for participants with multiple adverse events.

Table 4: **Overview of adverse events in the multidose clinical study**

Research in context

Evidence before this study

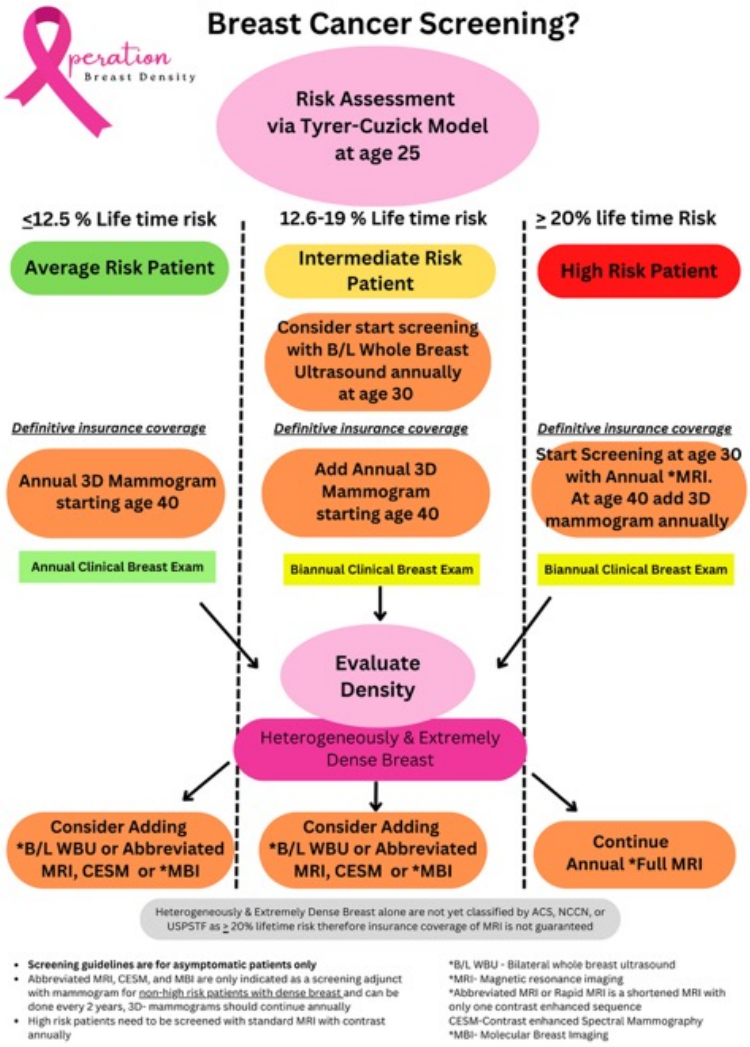
We searched PubMed for studies published from database inception up to March 25, 2025, using the terms "ANGPTL4 inhibition", "triglyceride-rich lipoproteins", "residual ASCVD risk", and "lipid-lowering therapies", with no language restrictions. Previous research, including human genetic studies and preclinical models, has suggested that angiopoietin-related protein 4 (ANGPTL4) inhibition can substantially reduce triglyceride and remnant cholesterol concentrations, potentially lowering atherosclerotic cardiovascular disease risk. Human genetic studies have also shown that germline inhibition of ANGPTL4 does not result in adverse clinical outcomes. These studies, which have primarily focused on the p.E40K variant, a near-complete loss-of-function mutation in *ANGPTL4* found in approximately 1·7% of the population, have shown no evidence of increased risk for negative health outcomes. In contrast to human genetics, previous studies showed that *ANGPTL4*-knockout mice fed a high saturated fat diet showed severe adverse effects, such as mesenteric lymphadenopathy and systemic inflammation. These findings have reduced enthusiasm for therapeutic development of ANGPTL4 inhibitors. To date, one study on pharmacological ANGPTL4 inhibition in non-human primates found no adverse safety signals, though it was limited to a single dose. To our knowledge, no studies have examined the safety and efficacy effects of pharmacological inhibition of ANGPTL4 in humans.

Added value of this study

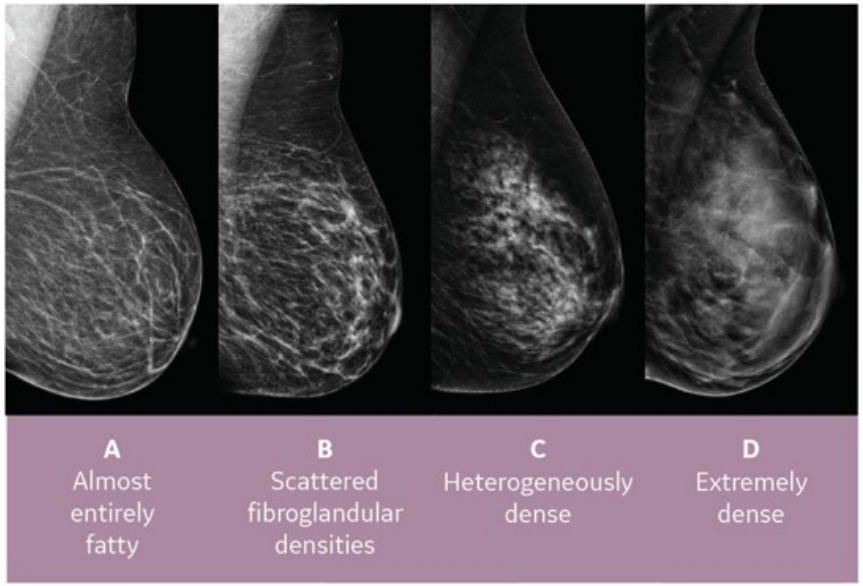
We extended the human genetics safety predictions of ANGPTL4 inhibition by evaluating abdominal MRI of individuals with homozygous *ANGPTL4* loss. Additionally, for the first time, we report analysis of the electronic health records of individuals who are homozygous carriers of a frameshift loss-of-function mutation. Both analyses supported the safety of ANGPTL4 inhibition in humans. Data presenting the development of MAR001, an ANGPTL4 inhibitory antibody, and showing its safety and tolerability when administered for 9 months to non-human primates, supported progression to human studies. We present, for the first time to our knowledge, clinical studies with pharmacological ANGPTL4 inhibition in humans. We found that single-dose and 12-week multidose administration of MAR001 was generally safe and well tolerated, and did not induce the symptoms seen in mouse knockout models. We also observed improvement in lipid profiles in individuals with high baseline triglycerides, including dose-dependent and robust lowering of fasting triglycerides and remnant cholesterol. We also observed lowering of postprandial triglycerides and non-HDL cholesterol, and an increase in HDL cholesterol.

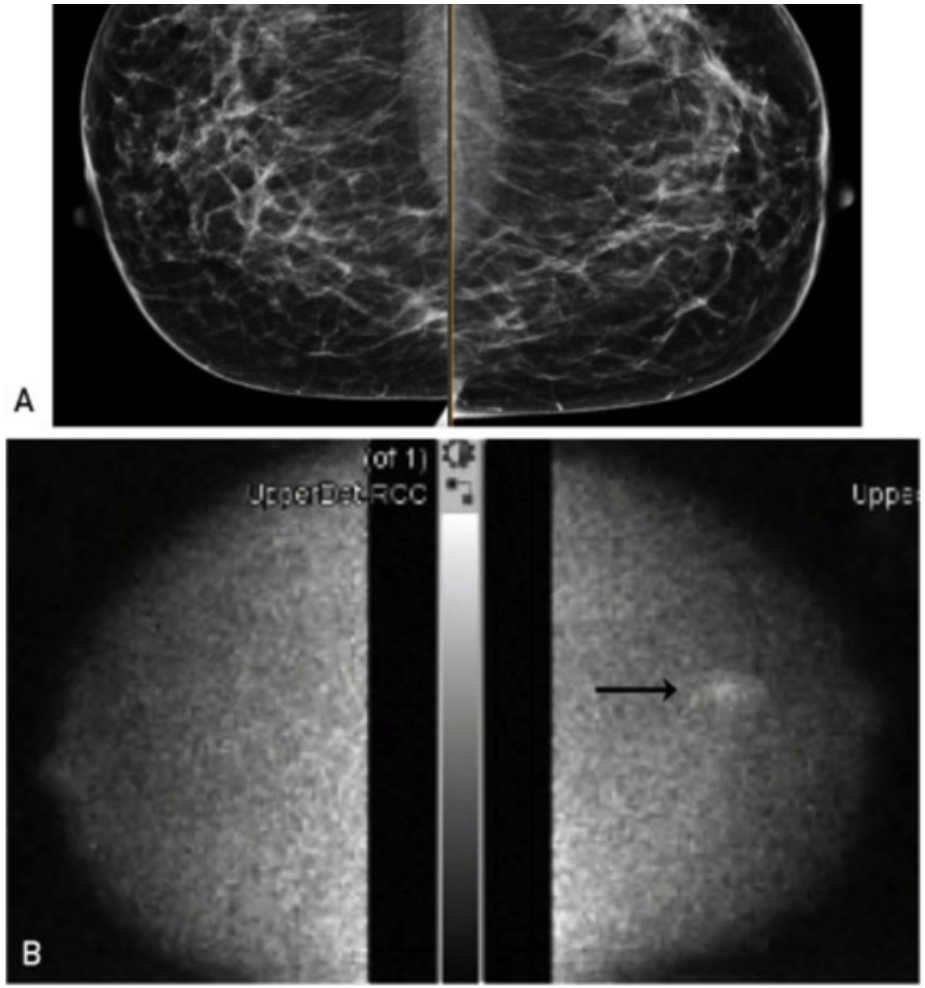
Implications of all the available evidence

Our findings reinforce the potential of ANGPTL4 inhibition as a promising strategy to address residual cardiovascular risk, particularly in individuals with high triglyceride and remnant cholesterol levels. The substantial triglyceride-lowering and residual cholesterol-lowering effects of MAR001 exceed those of existing therapies, such as fibrates and omega-3 fatty acids, and are similar to those seen with therapies in development, such as apolipoprotein C3 and angiopoietin-related protein 3 inhibitors, in similar populations with dyslipidaemia. The distinct mechanism of ANGPTL4 inhibition—facilitating triglyceride storage in metabolically favourable adipose tissue—might underlie the potential benefits beyond traditional lipid-lowering therapies. These findings support further clinical development of MAR001 as a targeted therapy for high-risk individuals with residual cardiovascular risk.



Supplemental breast cancer screening involves using additional imaging tests, such as tomosynthesis, whole-breast ultrasound, molecular breast imaging, or MRI, in addition to a standard mammogram, to improve breast cancer detection, particularly in women with dense breast tissue.



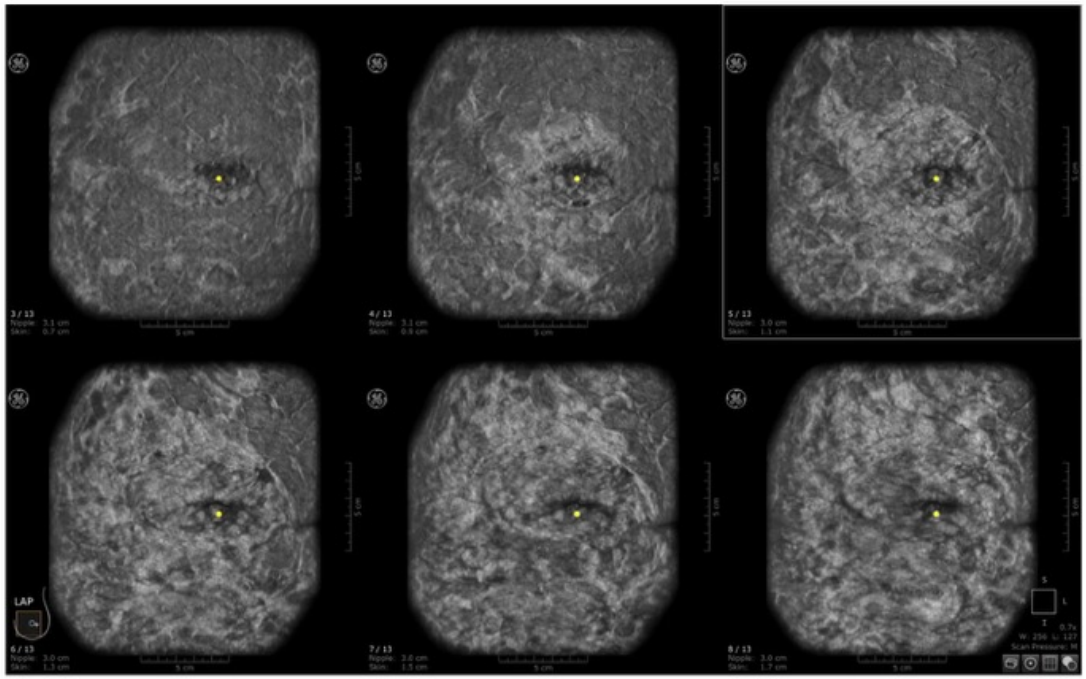


MAYO CLINIC PROCEEDINGS

A 40-year-old woman with heterogeneously dense breasts. A, Baseline screening mammography examination. Two craniocaudal views showing a normal screening mammogram (Breast Imaging–Reporting and Data System category score 1). B, Molecular breast imaging supplemental screening examination 3 months after the normal screening mammogram (A) demonstrates focal uptake in the left central breast mid-depth (arrow). Surgical pathologic analysis reported corresponding 7-mm invasive ductal carcinoma, histologic grade 1, at surgical excision.

Experience with Automated Breast Ultrasound Drives Understanding of Success Factors

The benefits of adding whole breast automated ultrasound (ABUS) screening to clinical practice, enhancing cancer detection in the setting of dense breast tissue



In a detailed overview held during the Radiological Society of North America's (RSNA) 2021 annual meeting, promising results from an Institutional Review Board (IRB)-approved study were presented by Georgia Giakoumis Spear, MD. She serves as chief of the department of breast imaging with NorthShore University HealthSystem, and is an associate professor of radiology at the University of Chicago Pritzker School of Medicine.

Comparison of supplemental breast cancer imaging techniques—interim results from the BRAID randomised controlled trial

Summary

Background It is not known which supplemental imaging technique is most beneficial for women with dense breasts attending breast screening. This study compares abbreviated MRI, automated whole breast ultrasound (ABUS), and contrast-enhanced mammography versus standard of care in women with dense breasts and a negative mammogram. We report on interim results from the first round of supplemental imaging.

Methods In this UK randomised controlled trial, at ten breast screening sites, women (aged 50–70 years) were independently allocated by batches (day/mobile screening van) to either abbreviated MRI, ABUS, or contrast-enhanced mammography or standard of care (full-field digital mammography) varied by modality availability at each centre. Women were invited if their mammogram was negative and they had dense breasts. Primary outcome was detection rate, defined as the percentage of women with a positive result on supplemental imaging that resulted in histologically confirmed breast cancer. Analysis was by imaging received (intention to treat) using network meta-analysis, treating each site as a study in the meta-analysis, with two analyses carried out: one using only the three active intervention arms (primary analysis) that compared the three supplemental imaging techniques with respect to cancer detection, recall, and biopsy rates in addition to those resulting from full-field digital mammography alone; and one with the addition of the observational data from Cambridge on full-field digital mammography alone. This trial is closed for recruitment and is registered with ClinicalTrials.gov, NCT04097366.

Findings From October 18, 2019, to March 30, 2024, 9361 eligible women were recruited and randomly assigned (2318 to abbreviated MRI, 2240 to ABUS, 2235 to contrast-enhanced mammography, and 2568 to standard of care). Of those, 6305 completed supplementary imaging (2130 in the abbreviated MRI, 2141 in the ABUS, and 2035 in the contrast-enhanced mammography) and were included in the outcome analysis. The cancer detection rate was 17·4 (95% CI 12·2–23·9, n=37) per 1000 examinations for abbreviated MRI, 4·2 (1·9–8·0, n=9) per 1000 examinations for ABUS, and 19·2 (13·7–26·1, n=39) per 1000 examinations for contrast-enhanced mammography, of which 15·0 (10·3–21·1, n=32) per 1000 women for abbreviated MRI, 4·2 (1·9–8·0, n=9) per 1000 examinations for ABUS, and 15·7 (10·8–22·1, n=32) per 1000 examinations for contrast-enhanced mammography were invasive cancers. The detection rates for abbreviated MRI were significantly higher than for ABUS (p=0·047) and non-significantly higher than for contrast-enhanced mammography (p=0·62). There was one case of extravasation in the abbreviated MRI arm (0·5 events per 1000 examinations), no adverse events in the ABUS arm, and 24 iodinated contrast reactions (17 minor [8·4 events per 1000 examinations], six moderate [2·9 events per 1000 examinations], and one severe [0·5 events per 1000 examinations]) and three extravasations (1·5 extravasations per 1000 examinations) in the contrast-enhanced mammography arm.

Interpretation Abbreviated MRI and contrast-enhanced mammography detected three times as many invasive cancers compared with ABUS, with cancers being half the size. This study shows that supplemental imaging could lead to earlier detection of cancer in women with dense breasts but does not estimate the level of overdiagnosis.

Funding Cancer Research UK, GE Healthcare, and Bayer Healthcare.

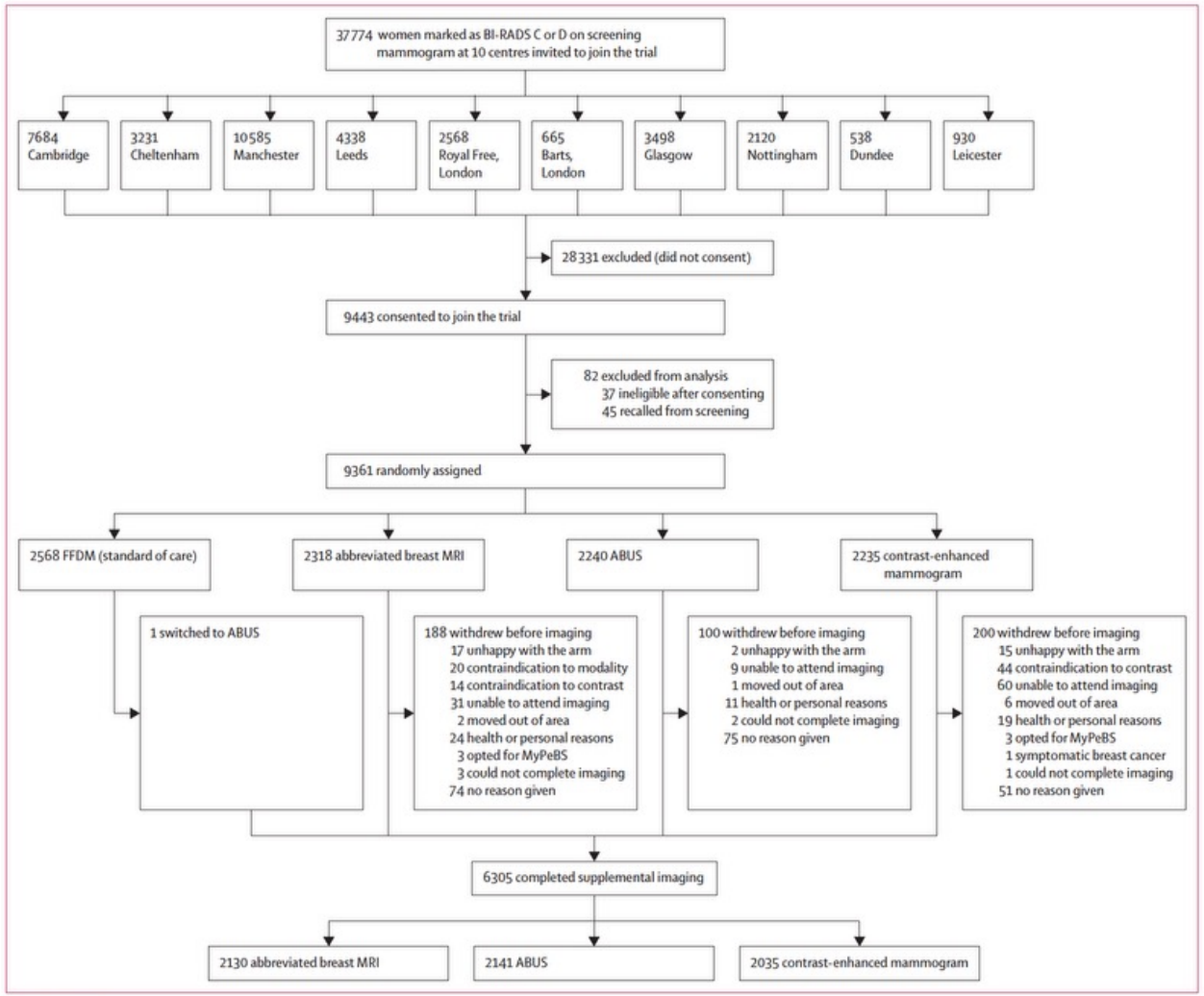


Figure: Trial profile
ABUS=automated whole breast ultrasound. BI-RADS=Breast Imaging Reporting and Data System. FFDM=full-field digital mammography. MyPeBS=My Personal Breast Screening.

	Supplemental imaging			Standard of care (n=2568)
	Abbreviated breast MRI (n=2318)	ABUS (n=2240)	Contrast-enhanced mammogram (n=2235)	
Median age at screening mammogram, years (IQR)	56 (52–61)	56 (52–62)	56 (52–61)	56 (52–61)
Mammographic breast density				
C	1936 (83·5%)	1943 (86·7%)	1769 (79·1%)	2151 (83·8%)
D	382 (16·5%)	297 (13·3%)	466 (20·9%)	417 (16·2%)
Trial centre				
Cambridge	548	874	502	357
Cheltenham	445	0	387	521
Manchester	419	818	0	416
Leeds	186	548	202	282
Royal Free, London	233	0	258	209
Barts, London	76	0	169	191
Glasgow	243	0	208	21
Nottingham	0	0	366	242
Dundee	52	0	55	41
Leicester	116	0	88	96

Data are n (%) unless otherwise stated. Standard of care was full-field digital mammography. ABUS=automated whole breast ultrasound.

Table 1: Characteristics of cohort at baseline

	Abbreviated breast MRI (n=2318)	ABUS (n=2240)	Contrast-enhanced mammogram (n=2235)
Withdrew before imaging	188	100	200
Examinations by centre			
Cambridge	532	853	477
Cheltenham	417	0	360
Manchester	344	765	0
Leeds	173	523	169
Royal Free, London	220	0	229
Barts, London	66	0	152
Glasgow	218	0	185
Nottingham	0	0	334
Dundee	49	0	47
Leicester	111	0	82
Total	2130	2141	2035
Median time in days between screening mammogram and supplemental imaging (IQR)	143 (98–183)	111 (77–150)	134 (91–173)
Received supplemental imaging 0–89 days after screening mammogram	434/2130 (20·4%)	721/2141 (33·7%)	478/2035 (23·5%)
Received supplemental imaging 90–179 days after screening mammogram	1113/2130 (52·3%)	1173/2141 (54·8%)	1111/2035 (54·6%)
Received supplemental imaging 180–269 days after screening mammogram	515/2130 (24·2%)	230/2141 (10·7%)	395/2035 (19·4%)
Received supplemental imaging 270–365 days after screening mammogram	57/2130 (2·7%)	13/2141 (0·6%)	42/2035 (2·1%)
Received supplemental imaging over 365 days after screening mammogram	6/2130 (0·3%)	1/2141 (<0·1%)	4/2035 (0·2%)

ABUS=automated whole breast ultrasound.

Table 2: Supplemental imaging

	Abbreviated breast MRI (n=2130)	ABUS (n=2141)	Contrast-enhanced mammogram (n=2035)
Recalled	206	85	197
Recall rate	9·7% (8·4–11·0)	4·0% (3·2–4·9)	9·7% (8·4–11·0)
Biopsied	105	32	89
Biopsy rate	4·9% (4·0–5·9)	1·5% (1·0–2·1)	4·4% (3·5–5·4)
Cancer detected	37	9	39
Cancer detection rate (arm) per 1000	16·0 (11·3–21·9)	4·0 (1·8–7·6)	17·4 (12·4–23·8)
Cancer detection rate (imaged) per 1000	17·4 (12·2–23·9)	4·2 (1·9–8·0)	19·2 (13·7–26·1)
PPV1	18·0% (13·0–23·9)	10·6% (5·0–19·2)	19·8% (14·5–26·1)
PPV3	35·2% (26·2–45·2)	28·1% (13·7–46·7)	43·8% (33·3–54·7)
Cancer type			
DCIS only	5/37 (13·5%)	0/9	7/39 (17·9%)
Invasive cancer	32/37 (86·5%)	9/9 (100·0%)	32/39 (82·1%)

Data are n or % (95% CI). ABUS=automated whole breast ultrasound. DCIS=ductal carcinoma in situ. PPV=positive predictive value.

Table 3: Supplemental imaging performance metrics

	Abbreviated breast MRI	ABUS	Contrast-enhanced mammogram
Invasive grade			
1	10	3	11
2	18	6	21
3	3	0	0
Unknown	1	0	0
DCIS grade			
Low	2	0	0
Intermediate	0	0	1
High	3	0	6
Tumour size, mm			
Invasive (IQR)	10 (8–15)	22 (14–35)	11 (7–15)
DCIS (IQR)	10 (3–55)	NA	27 (13–40)
Invasive cancer receptor status (positive/total tested)			
Oestrogen receptor	29/35 (82·9%)	7/9 (77·8%)	31/36 (86·1%)
HER2	8/34 (23·5%)	0/9	3/33 (9·1%)
Progesterone receptor	13/19 (68·4%)	7/9 (77·8%)	19/22 (86·4%)
Confirmed triple-negative breast cancer	3	2	2
Lymph node status (positive/total tested)	3/32 (9·4%)	1/9 (11·1%)	2/32 (6·3%)

ABUS=automated whole breast ultrasound. DCIS=ductal carcinoma in situ. NA=not applicable.

Table 4: Characteristics of cancer detected by supplemental imaging

Research in context

Evidence before this study

Mammography screening in women with dense breast tissue has low sensitivity and detected cancers can be large. Supplemental imaging with MRI or ultrasound have both been shown to be effective in early cancer detection. A detailed search of the literature and clinical trials website was conducted to determine whether or not a direct comparison had been made between abbreviated MRI, contrast-enhanced mammography, and whole breast ultrasound as supplemental imaging tools in women with dense breasts. No prospective trials were found.

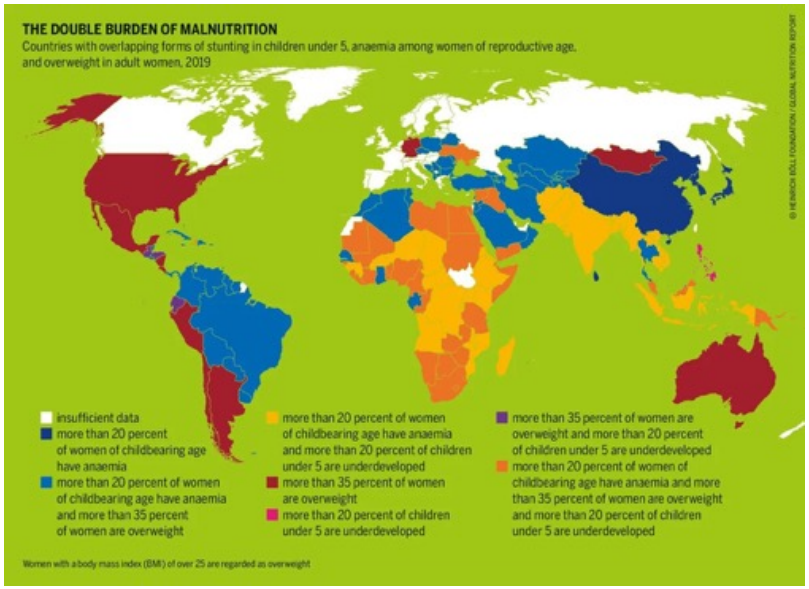
Added value of this study

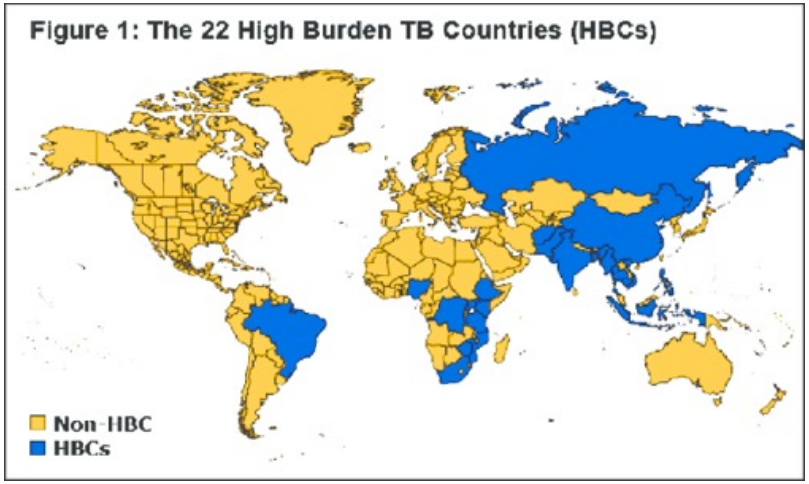
This study is the first large scale randomised trial comparing these supplemental imaging techniques in women with normal mammograms and dense breast tissue. In this protocol-defined analysis the objective was to determine which modality detected more early breast cancers and the recall rate of each technique. This study shows that contrast techniques detect an additional 17 cancers per 1000 examinations compared with four cancers per 1000 examinations with ultrasound. The majority of the cancers were less than 2 cm in size and lymph-node-negative.

Implications of all the available evidence

These results demonstrate that supplemental imaging can be delivered in a screening programme to women with dense breast tissue. The small size of the additional cancers found shows that the tools are effective in early detection. Contrast techniques find almost three times as many cancers with twice the recall rate compared to ultrasound. However, the health benefit of the additional cancer detection is not established.

Multi-burden countries are defined as those experiencing a high burden of communicable, maternal, or nutritional diseases in adolescents. They are characterized by a high number of Disability Adjusted Life Years (DALYs) due to these diseases, particularly in adolescents. In 1990, a significant portion of countries, including those in sub-Saharan Africa, central, south, and east Asia, and some in Latin America, were classified as multi-burden. The definition often involves more than 2,500 DALYs per 100,000 due to these diseases.





A call to action: the second *Lancet* Commission on adolescent health and wellbeing

Key messages

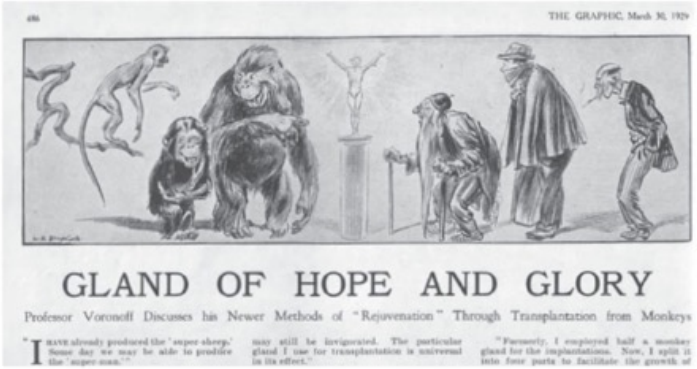
- Investments across adolescence—ie, the period between age 10 years and 24 years—will reap a triple dividend, with benefits for young people today, for the adults they will become, and for the next generation of children whom they will parent.
- Despite progress in some areas, without increasing investments, our projections suggest that by the end of the Sustainable Development Goal era in 2030, at least half of the world's adolescents (1 billion people) will be living in multiburden countries where adolescents experience a complex and excess burden of disease. We project that, in 2030, 464 million adolescents globally will be overweight or obese (143 million more than in 2015) and 42 million years of health life will be lost to mental disorders or suicide (2 million more than in 2015).
- Funding for adolescent health and wellbeing is not commensurate with the magnitude of the challenge and is not targeted to the areas of greatest need. For example, specific funding for adolescent health accounted for only 2·4% of total development assistance for health in 2016–21, despite adolescents accounting for 25·2% of the world population.
- Today's adolescents are the first human cohort who will live their entire lives under the shadow of climate change. Intergenerational justice demands that current and future generations of adolescents have the resources they need for health and wellbeing.
- Central to effective action is the meaningful engagement of adolescents in policy, research, interventions, and accountability mechanisms that affect them.
- Better indicators and improvement in data systems at the national and global level are required to monitor systemic changes in health and wellbeing outcomes and in the circumstances in which adolescents are growing up.
- Enabling laws and policies provide the foundational environments for sustained improvements in adolescent health and wellbeing. These environments should protect adolescent sexual and reproductive health and rights, reduce the impact of the commercial determinants of health, and promote the healthy use of social media and online spaces.
- Multisectoral actions on mental health, nutrition, sexual and reproductive health, and violence are required to amplify gains made in adolescent health. Coordination is needed between ministries of health and of education with regard to interventions in schools.

The organ farm

Gene-edited pig kidneys are finally moving the long-stymied field of xenotransplantation forward

On 8 January, a 66-year-old retiree in New Hampshire named Timothy Andrews sent a Facebook Messenger note to a 53-year-old stranger in New York City, Towana Looney, with an unusual question. He wanted to know how her new pig kidney was doing.

Six weeks earlier, surgeons at New York University (NYU) Langone Health had made international news when they gave Looney the organ from a pig genetically altered so its tissues would be less likely to be rejected by her body. Andrews himself was 2 weeks away from receiving a similar, engineered pig kidney. “There’s one person on the planet that has one, and I’m going to talk to her,” he told his doctors at Massachusetts General Hospital (MGH). “I was just curious if there was anything different, what she felt about it.”



THE GRAPHIC, March 30, 1929

GLAND OF HOPE AND GLORY

Professor Voronoff Discusses his Newer Methods of "Rejuvenation" Through Transplantation from Monkeys

"I HAVE already produced the 'super-sheep.' Some day we may be able to produce the 'super-man.'"

may still be invigorated. The particular gland I use for transplantation is universal in its effect."

"Formerly, I employed half a monkey gland for the implantations. Now, I split it into four parts to facilitate the growth of

1929 Serge Voronoff popularizes transplanting monkey and chimp gonads. CREDIT: *THE GRAPHIC: AN ILLUSTRATED WEEKLY NEWSPAPER* 20 MARCH 1929

Late Sports

Los Angeles Times

Morning Final

Friday, November 16, 1984

Heart Fails—Baby Fae Dies

Lived for 20 Days With Implant From Baboon

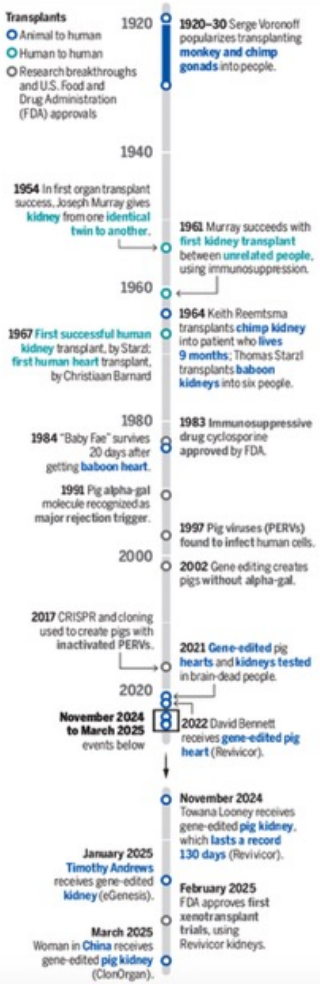
U.S. There 31 Years

DMZ: Blend of Tension and Tedium

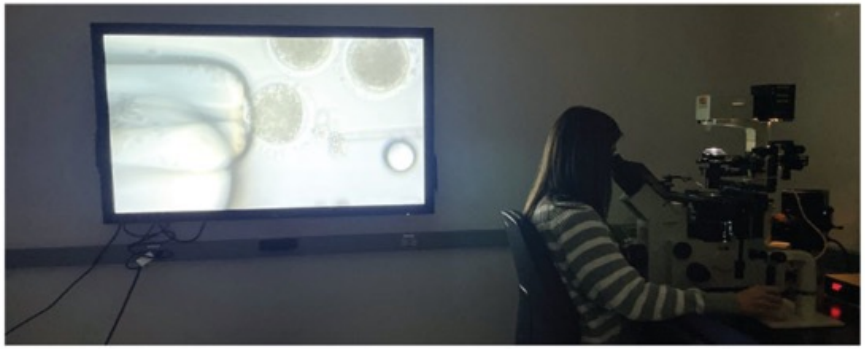
1984 Baby Fae survives 20 days after getting a baboon heart. CREDIT: *THE LOS ANGELES TIMES*, 16 NOVEMBER 1984

Xeno's checkered history

Efforts to transplant animal organs into people— xenotransplantation— date back more than a century, but have been marked by failure after failure. Progress in human-tohuman transplants, coupled with improved immunosuppressive drugs and gene-editing advances, have prompted new enthusiasm for xeno. Still, success remains far from certain.



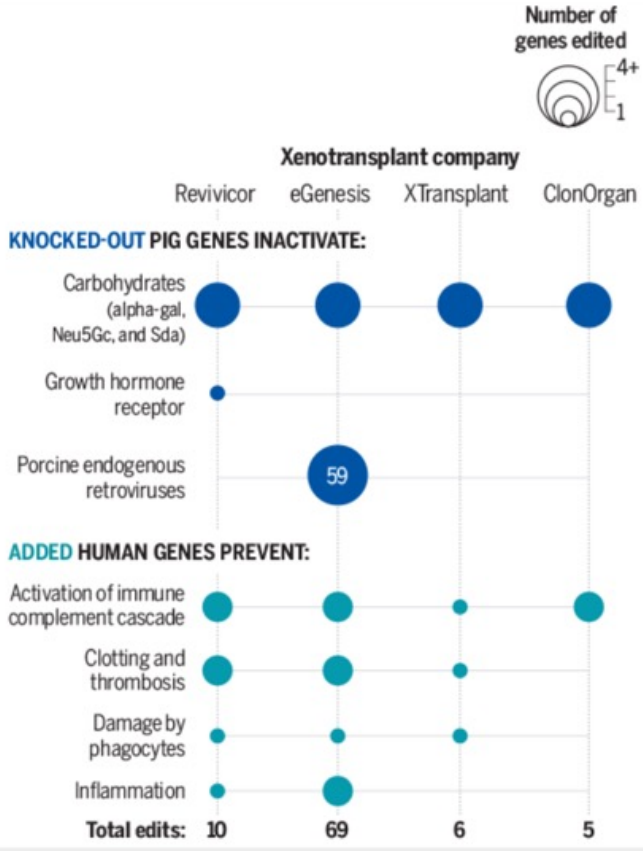
Revivicor's David Ayares holds a piglet with 10 edited genes. PHOTO: J. COHEN/*SCIENCE*



A company researcher removes DNA from a pig egg as part of the cloning process used to breed the edited animals. PHOTO: J. COHEN/*SCIENCE*

Brave new pigs

Various gene-editing strategies aim to create pigs whose organs will survive in a human body. Inactivating pig genes or adding human genes can limit immune rejection or keep organs small, for example.



Towana Looney's xenotransplant functioned for 130 days, a new record. PHOTO: JACKIE MOLLOY/*THE NEW YORK TIMES* VIA REDUX

Timothy Andrews (right), leaving the hospital after his xenotransplant, thanks Tatsuo Kawai, who led the surgical team. PHOTO: KATE FLOCK/MASSACHUSETTS GENERAL HOSPITAL

LOONEY, UNFORTUNATELY, didn't make it that far. Seventeen days after the transplant, protein levels in her blood rose, and a biopsy revealed an antibody onslaught against the kidney. After plasmapheresis, Montgomery says, "the antibody never comes back." But the immune system has myriad actors, and something else began to damage Looney's new organ in late March.

Anderson was hospitalized with an infection unrelated to the xenotransplant. He since has recovered and returned home. "I know there are no guarantees, but it is sobering to see it happened," he said about Looney's xenostransplant ultimately failing. "Two things I live by now: It is what it is, and this is what we signed up for," he said. "I was already committed to death with dialysis, so it wasn't that hard of a leap for me," Andrews added. "I did it knowing that no matter what happened, I did something for humanity."

Six days after having her kidney removed, Looney was back home and having her hair dyed orange. Her hairdresser posted a video of them on Facebook in which she asked her client what's the word for the day? "Blessed," a smiling Looney said. "And highly favored," the hairdresser said.

"And highly favored," Looney agreed.

4 ways women are physically stronger than men

Brute force and sprint speeds are qualities associated with male physiology. But female bodies excel in other areas.

In September, Tara Dower became the fastest person ever to complete the Appalachian Trail. Her record — 40 days, 18 hours and 6 minutes — was 13 hours faster than the previous record holder, a man.

Jasmin Paris in 2024 became one of only 20 people ever to finish the brutal 100-mile Barkley Marathons race in under 60 hours — while pumping breast milk.

Built to endure

Recovery and resilience

Pain tolerance

Human bodies endure all kinds of pain — from menstrual cramps and childbirth to back injuries and broken bones. Pain is subjective, so difficult to measure, but most research agrees with your grandma — women seem to handle pain better.

Immunity

Among mammals, including humans, it is widely accepted that females have stronger immune systems than males. That's due to the power of estrogen, and also of the XX chromosome carried by women but not men, which provides more variability in immune function. As the University of Minnesota evolutionary biologist Marlene Zuk wrote in a 2009 article, "There is no contest about the identity of the sicker sex — it is males, almost every time.

Resilience

Women's bodies seem better built for the long haul — less wear and tear, more staying power, according to the limited research. The data on long-term exercise suggests women may also pay a lower price for physical strain. For instance, the British Heart Foundation studied the vascular condition of 300 Masters' athletes (meaning over age 40), that included a mix of long-distance runners, cyclists, rowers and swimmers. In men, vascular aging increased among the athletes — by some markers up to 10 years, increasing their risk of cardiovascular issues. Among the female athletes, the reverse was true, they had biologically younger vascular systems, lowering their risk of heart problems.

Longevity

Arguably, the truest test of any body is longevity. And with rare exceptions, no matter the species or culture, women live longer.