

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

The weekly Clinical Journal Club by Dr. Friedrich C. Luft

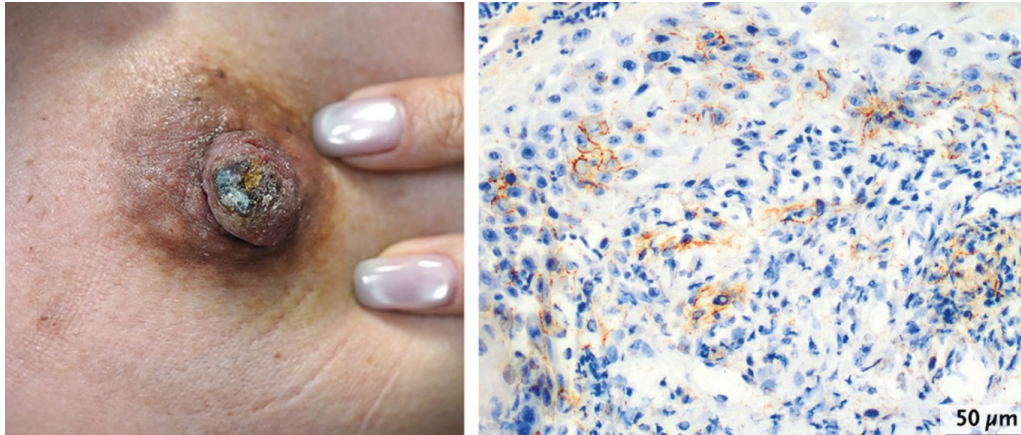
Usually every Wednesday 17:00 - 18:00



Klinische Forschung

Experimental and Clinical Research Center (ECRC) von MDC und Charité

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 35-year-old woman presented with a 20-day history of a painless nipple ulcer without other associated symptoms or skin findings. Histopathologic analysis of a nipple-biopsy specimen showed epidermal necrosis with inflammatory exudate, dermal capillary proliferation, and dense perivascular lymphoplasmacytic infiltrates. Physical examination and immunohistochemical analysis of the biopsy are shown. What is the most likely diagnosis?

An assay for *Treponema pallidum* particle agglutination was positive, and the rapid plasma reagin titer was 1:8. Immunohistochemistry of the biopsy showed *T. Pallidum* organisms. These findings, alongside a subacute, painless lesion, were consistent with a primary syphilitic chancre. Primary syphilitic chancres can occur at any site of inoculation, including extragenital erogenous locations.

Eczema

Erosive adenomatosis

Idiopathic granulomatous mastitis

Mammary Paget disease

Syphilitic chancre

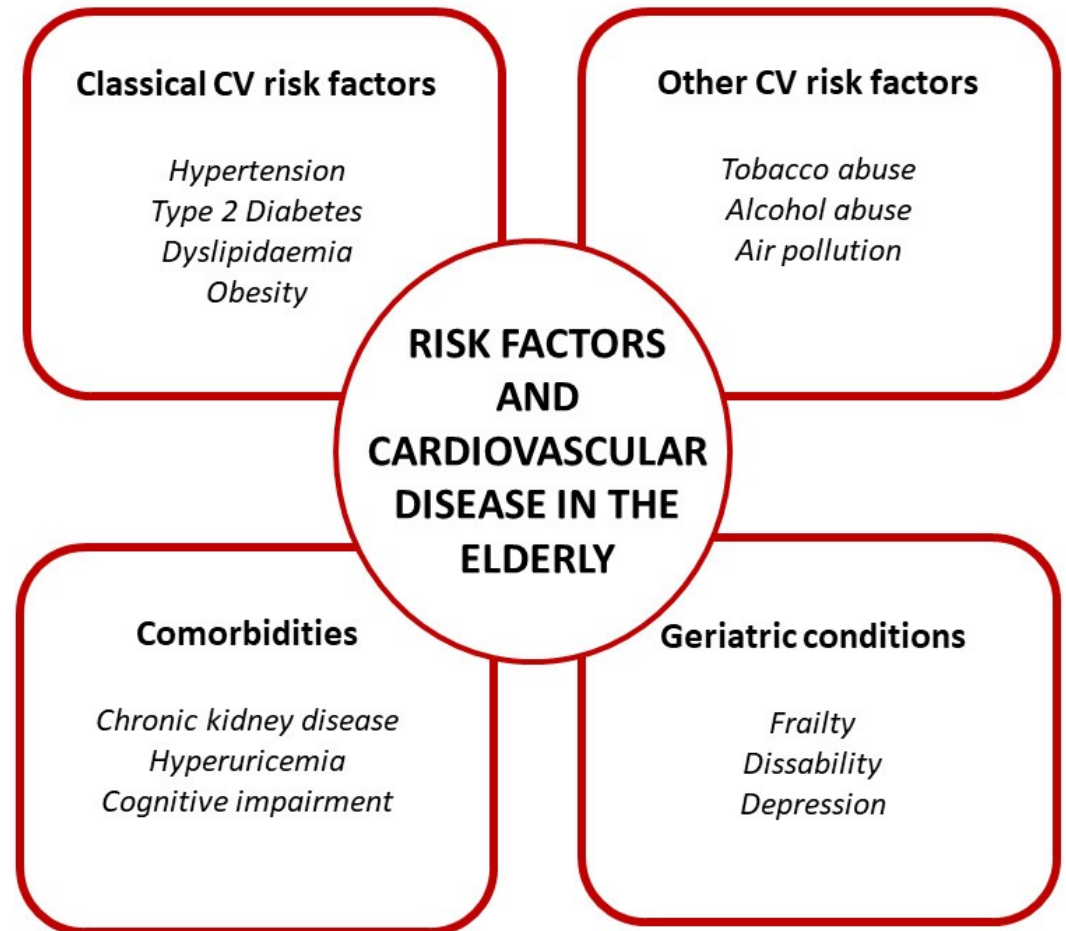
The syphilis spirochete (*Treponema pallidum*) is typically 6 to 15 micrometers (μ m) long



Cardiovascular disease is the leading cause of illness and death in older adults, driven by age-related arterial stiffness, cumulative risk factors, and frailty.

Key Risk Factors

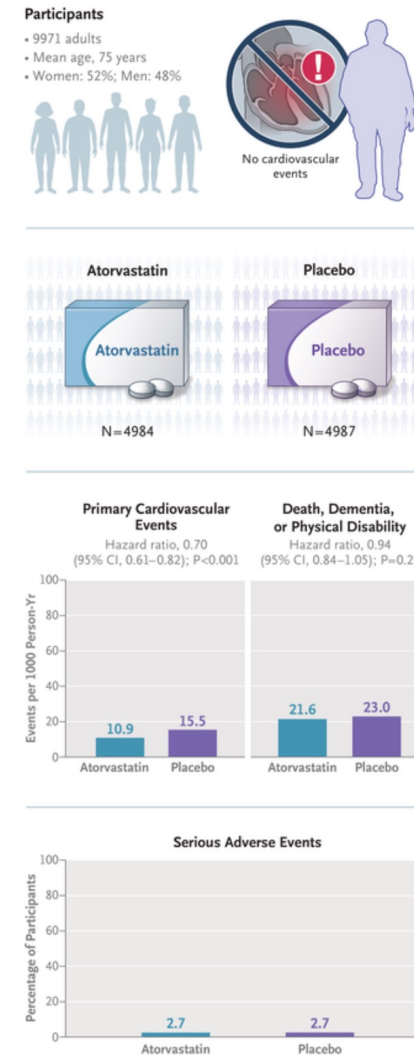
- **Traditional triggers:** High blood pressure (hypertension), type 2 diabetes, high cholesterol (dyslipidemia), and obesity heavily impact aging hearts.
- **Age-related changes:** Arteries stiffen and calcify over time, forcing the heart muscle to work harder and thicken.
- **Hidden triggers:** Frailty, cognitive impairment, depression, chronic kidney disease, and social isolation significantly increase heart risk in older populations.



Atorvastatin, Cardiovascular Events, and Disability-free Survival in Older Adults

The effectiveness and safety of statins for the primary prevention of cardiovascular events and the extension of disability-free survival among older adults remain uncertain.

We conducted a double-blind, randomized, placebo-controlled trial at general medical practices across Australia. Community-dwelling adults at least 70 years of age with no history of cardiovascular disease, diabetes, or dementia were randomly assigned in a 1:1 ratio to receive atorvastatin at a dose of 40 mg once daily or identical placebo. The two primary end points were a composite of death from cardiovascular causes, nonfatal myocardial infarction or stroke, or coronary revascularization (to assess effects on major cardiovascular events) and a composite of death from any cause, dementia, or persistent physical disability (to assess effects on disability-free survival). Analyses were performed according to a hierarchical testing plan.



Few randomized trials have assessed the effects of statins on dementia and disability. The Heart Protection Study included participants with a wide range of ages (40 to 82 years) and used a single cognitive test that probably lacked the sensitivity to detect subtle cognitive decline, with the number of newly identified cases of dementia being too low for a definitive analysis. Both the PROSPER (Prospective Study of Pravastatin in the Elderly at Risk) and HOPE-3 (Heart Outcomes Prevention Evaluation 3) trials included cognitive measures but did not formally assess newly diagnosed dementia as a clinical end point. The JUPITER (Justification for the Use of Statins in Prevention) trial tracked dementia as an adverse event but did not use standardized, objective cognitive assessments and, despite enrolling 17,802 participants, identified very few cases of dementia (12 in the rosuvastatin group and 9 in the placebo group). Data from large-scale, randomized trials evaluating disability-free survival (i.e., survival free of dementia or physical disability) as a prespecified primary end point are lacking.

Trial Population

Adults 70 years of age or older who were living independently and had no history of cardiovascular disease, diabetes, dementia, or other life-limiting conditions were identified from the clinical databases of 1013 general medical practices, among 1583 registered practices across metropolitan, regional, and rural areas of Australia. For trial eligibility, cardiovascular disease was defined as myocardial infarction, angina, heart failure, stroke, transient ischemic attack, carotid stenosis, abdominal aortic aneurysm, peripheral artery disease, or any coronary-artery blockage or narrowing leading to angioplasty, stent implantation, or bypass graft surgery. Eligible participants were invited to take part in **two baseline screening visits** 4 weeks apart. These baseline visits included the completion of cognitive tests to ascertain cognitive performance, assessment of physical independence with the use of a modified Katz Index of Independence in Activities of Daily Living, and laboratory assessments. During the period between visits, the participants were asked to take a once-daily placebo tablet to assess adherence to a daily medication regimen. All the participants provided written informed consent.

Trial End Points

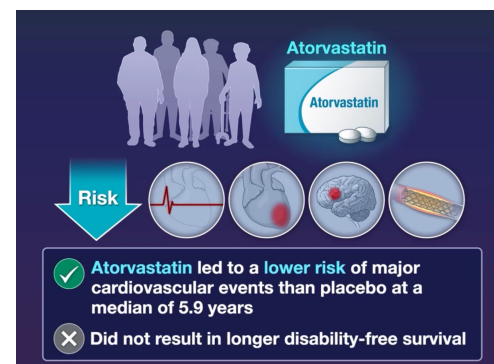
The two primary end points were a **composite of death from cardiovascular causes, nonfatal myocardial infarction or stroke, or coronary revascularization** and a **composite of death from any cause, dementia, or persistent physical disability** (a measure of disability-free survival).

Half
overweight
25% obese

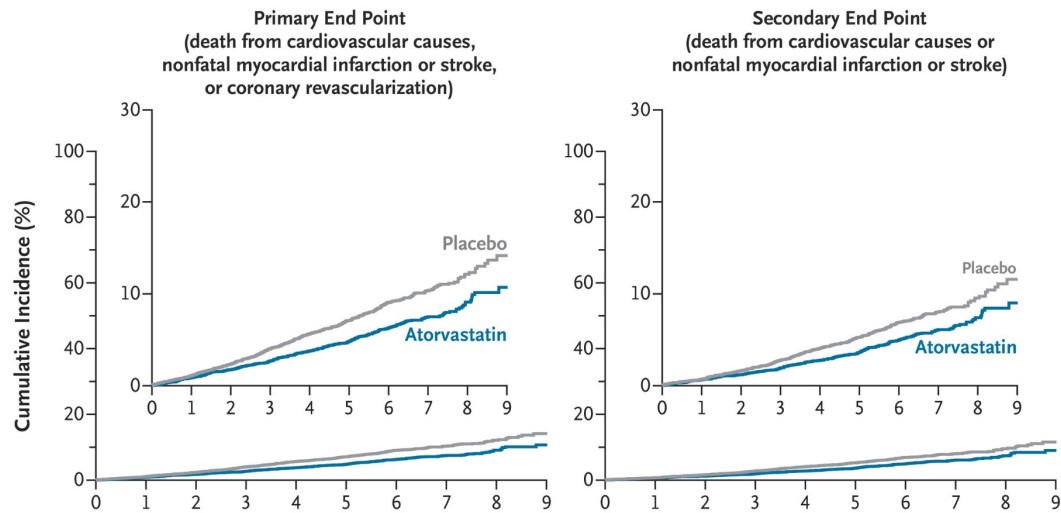
Characteristic	Overall (N = 9971)	Atorvastatin (N = 4984)	Placebo (N = 4987)
Age group — no. (%)			
70–74 yr	5948 (59.7)	2959 (59.4)	2989 (59.9)
75–79 yr	2503 (25.1)	1274 (25.6)	1229 (24.6)
80–84 yr	1112 (11.2)	562 (11.3)	550 (11.0)
≥85 yr	408 (4.1)	189 (3.8)	219 (4.4)
Gender — no. (%)			
Man	4797 (48.1)	2411 (48.4)	2386 (47.8)
Woman	5174 (51.9)	2573 (51.6)	2601 (52.2)
Race or ethnic group — no. (%)†			
White	9803 (98.3)	4901 (98.3)	4902 (98.3)
Asian	84 (0.8)	40 (0.8)	44 (0.9)
Aboriginal or Torres Strait Islander	23 (0.2)	13 (0.3)	10 (0.2)
Other	61 (0.6)	30 (0.6)	31 (0.6)
First language — no./total no. (%)			
English	9535/9967 (95.7)	4768/4981 (95.7)	4767/4986 (95.6)
Other	432/9967 (4.3)	213/4981 (4.3)	219/4986 (4.4)
Smoking status — no./total no. (%)			
Current smoker	245/9967 (2.5)	130/4981 (2.6)	115/4986 (2.3)
Former smoker	4252/9967 (42.7)	2134/4981 (42.8)	2118/4986 (42.5)
Never smoker	5470/9967 (54.9)	2717/4981 (54.5)	2753/4986 (55.2)
BMI category — no./total no. (%)			
≥30.0	2483/9612 (25.8)	1248/4794 (26.0)	1235/4818 (25.6)
25.0–29.9	4078/9612 (42.4)	2043/4794 (42.6)	2035/4818 (42.2)
<25.0	3051/9612 (31.7)	1503/4794 (31.4)	1548/4818 (32.1)
Medication use — no. (%)			
Blood-pressure-lowering agents	4612 (46.3)	2306 (46.3)	2306 (46.2)
Agents for acid-related disorders	2700 (27.1)	1398 (28.0)	1302 (26.1)
Analgesic agents	2055 (20.6)	1060 (21.3)	995 (20.0)
Anticoagulant or antiplatelet agents	1486 (14.9)	728 (14.6)	758 (15.2)
Lipid levels — mg/dl			
Total cholesterol	211.2±32.0	210.8±31.6	211.6±32.5
LDL cholesterol	126.6±28.0	126.2±27.8	127.0±28.1
HDL cholesterol	61.6±17.5	61.6±17.7	61.7±17.3
Non-HDL cholesterol	149.6±30.7	149.2±30.4	149.9±31.0
Triglycerides	113.1±53.6	113.1±53.4	113.2±53.8
Blood pressure — mm Hg			
Systolic	135.8±16.1	135.8±16.0	135.7±16.2
Diastolic	80.1±9.4	80.1±9.3	80.2±9.6
Score on 3MS (IQR)‡			
In-person assessment	95.0 (91.0–97.0)	95.0 (91.8–97.0)	95.0 (91.0–97.0)
Telephone assessment	70.0 (67.0–71.0)	70.0 (67.0–71.0)	70.0 (67.0–71.0)

Primary and Secondary End Points.

End Point	Overall (N=9971)	Atorvastatin (N=4984)	Placebo (N=4987)	Hazard Ratio (95% CI)†
<i>no. of events per 1000 person-yr (no. of participants with event)</i>				
Death from cardiovascular causes, nonfatal myocardial infarction or stroke, or coronary revascularization: primary end point	13.2 (709)	10.9 (297)	15.5 (412)	0.70 (0.61–0.82)‡
Death from cardiovascular causes or nonfatal myocardial infarction or stroke	10.1 (551)	8.6 (236)	11.7 (315)	0.73 (0.62–0.87)
Death from cardiovascular causes	2.4 (148)	2.4 (74)	2.4 (74)	1.00 (0.72–1.37)
Fatal or nonfatal myocardial infarction	3.9 (216)	2.9 (79)	5.0 (137)	0.57 (0.43–0.75)
Nonfatal myocardial infarction	3.8 (207)	2.8 (77)	4.8 (130)	0.58 (0.44–0.77)
Fatal or nonfatal stroke	4.7 (260)	4.4 (122)	5.1 (138)	0.87 (0.68–1.11)
Nonfatal stroke	4.2 (230)	3.7 (103)	4.7 (127)	0.80 (0.62–1.04)
Any arterial revascularization	6.4 (348)	4.6 (127)	8.2 (221)	0.56 (0.45–0.70)
Coronary revascularization	5.5 (300)	4.0 (110)	7.0 (190)	0.57 (0.45–0.72)
Death from any cause, dementia, or persistent physical disability: primary end point	22.3 (1313)	21.6 (637)	23.0 (676)	0.94 (0.84–1.05)§
Death from any cause	13.7 (828)	13.0 (395)	14.3 (433)	0.91 (0.79–1.04)
Dementia	10.5 (570)	10.6 (290)	10.3 (280)	1.03 (0.87–1.21)
Persistent physical disability	2.5 (140)	2.2 (60)	2.9 (80)	0.74 (0.53–1.04)
Hospitalization for any cause	149.9 (5515)	148.9 (2744)	150.9 (2771)	0.99 (0.94–1.04)



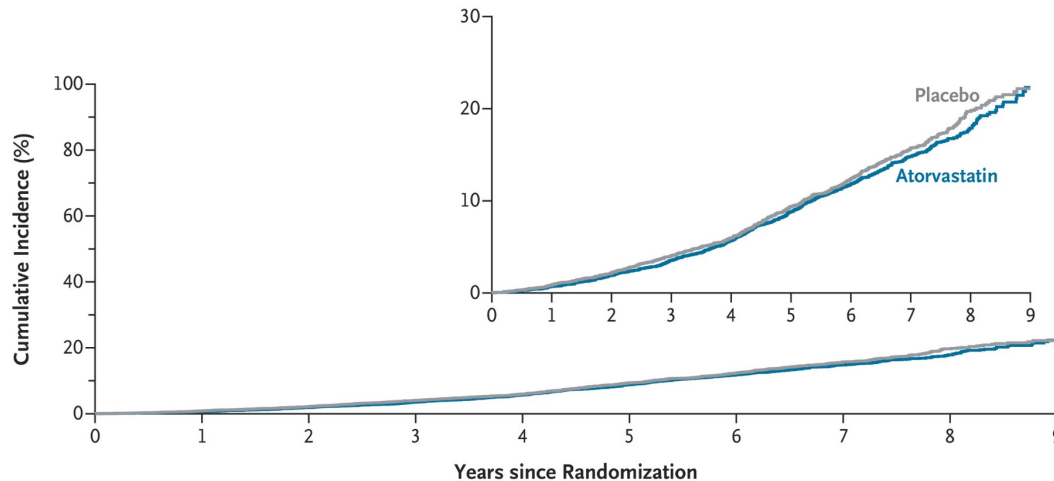
A Major Cardiovascular Events



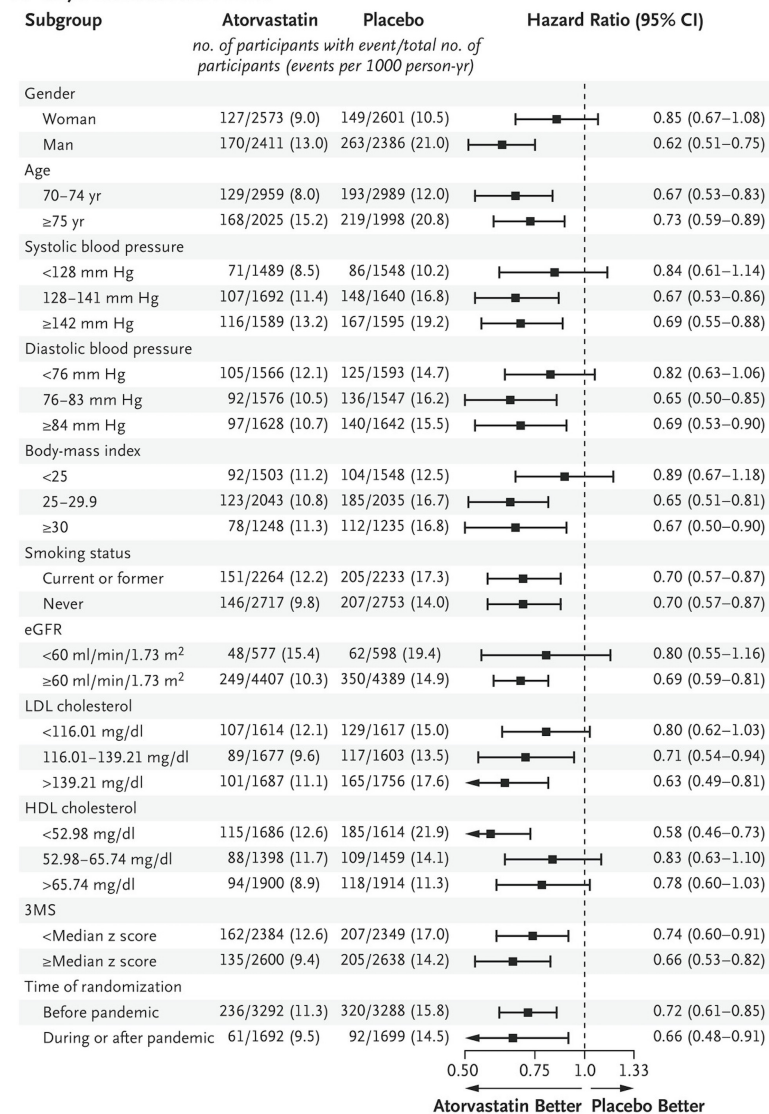
Major Cardiovascular Events and Disability-free Survival According to Trial Group.

Panel A shows the cumulative incidence of major cardiovascular events. The graphs on the left show the cumulative incidence of primary end-point events (death from cardiovascular causes, nonfatal myocardial infarction or stroke, or coronary revascularization, whichever occurred first), and those on the right the cumulative incidence of composite secondary end-point events (death from cardiovascular causes, myocardial infarction, or stroke, whichever occurred first). Panel B shows the cumulative incidence of death from any cause, dementia, or persistent physical disability, whichever occurred first, as a measure of disability-free survival. Insets show the same data on an expanded y axis.

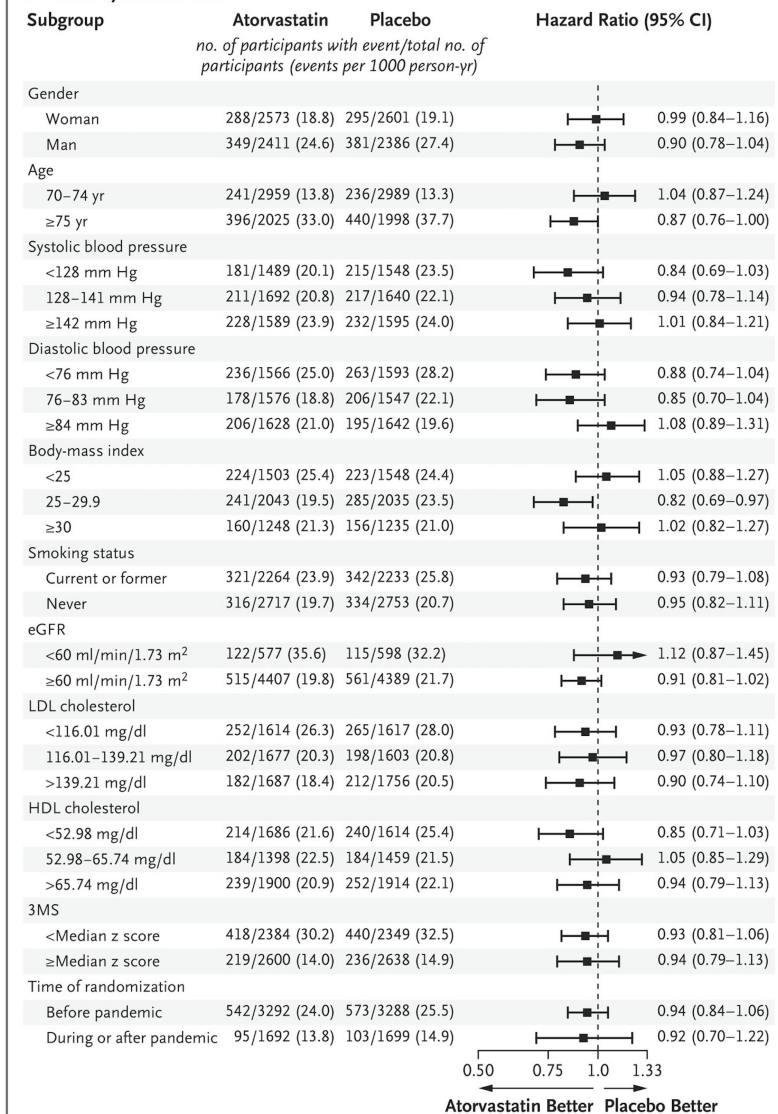
B Death from Any Cause, Dementia, or Persistent Physical Disability



A Major Cardiovascular Events



B Disability-free Survival

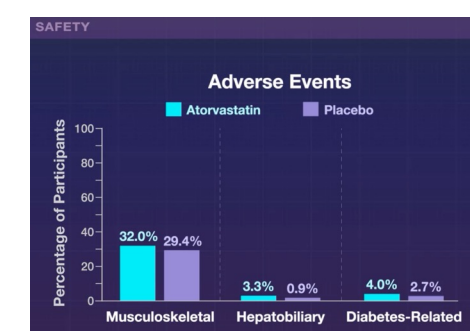
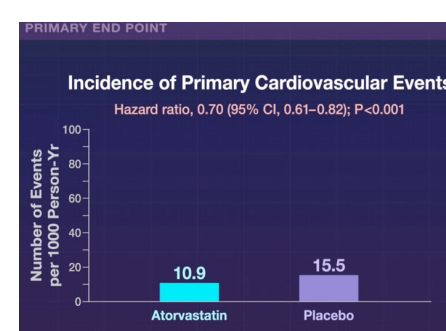
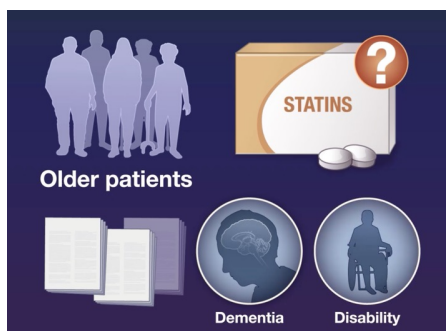
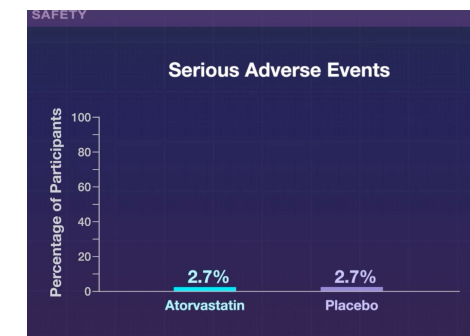
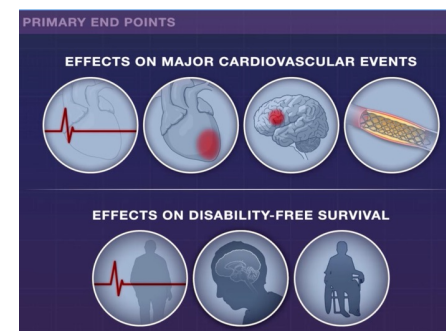
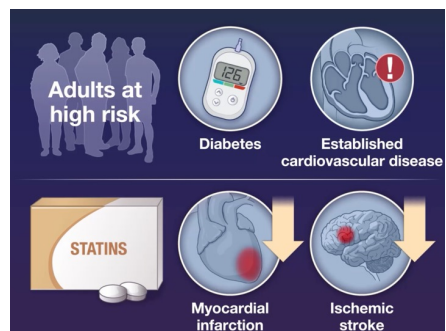
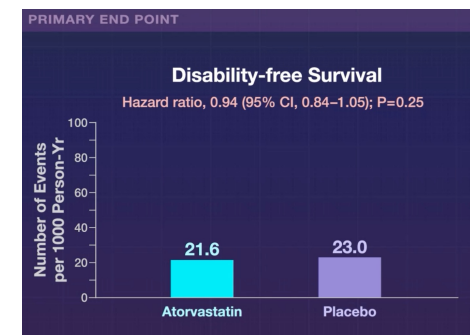
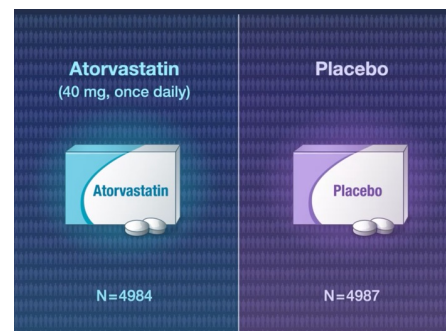
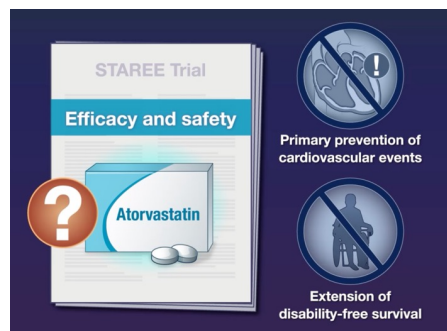
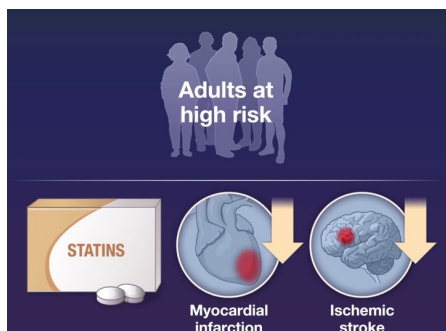


Trial-Related Safety Events (Modified Intention-to-Treat Population).

Event	Atorvastatin (N = 4876)	Placebo (N = 4847)
<i>no. of participants (%)</i>		
Any adverse event	3073 (63.0)	2846 (58.7)
Serious adverse event	131 (2.7)	129 (2.7)
Medically important adverse event	430 (8.8)	324 (6.7)
Discontinuation of trial regimen due to adverse event	349 (7.2)	297 (6.1)
Adverse events of special interest		
Musculoskeletal and connective-tissue disorders		
Any adverse event	1562 (32.0)	1423 (29.4)
Serious adverse event	8 (0.2)	8 (0.2)
Medically important adverse event	54 (1.1)	43 (0.9)
Hepatobiliary disorders		
Any adverse event	163 (3.3)	44 (0.9)
Serious adverse event	9 (0.2)	4 (0.1)
Medically important adverse event	69 (1.4)	14 (0.3)
Diabetes and diabetes-related disorders		
Any adverse event	195 (4.0)	132 (2.7)
Serious adverse event	2 (<0.1)	1 (<0.1)
Medically important adverse event	56 (1.1)	33 (0.7)
Nervous system disorders		
Any adverse event	1148 (23.5)	1141 (23.5)
Serious adverse event	11 (0.2)	7 (0.1)
Medically important adverse event	20 (0.4)	29 (0.6)

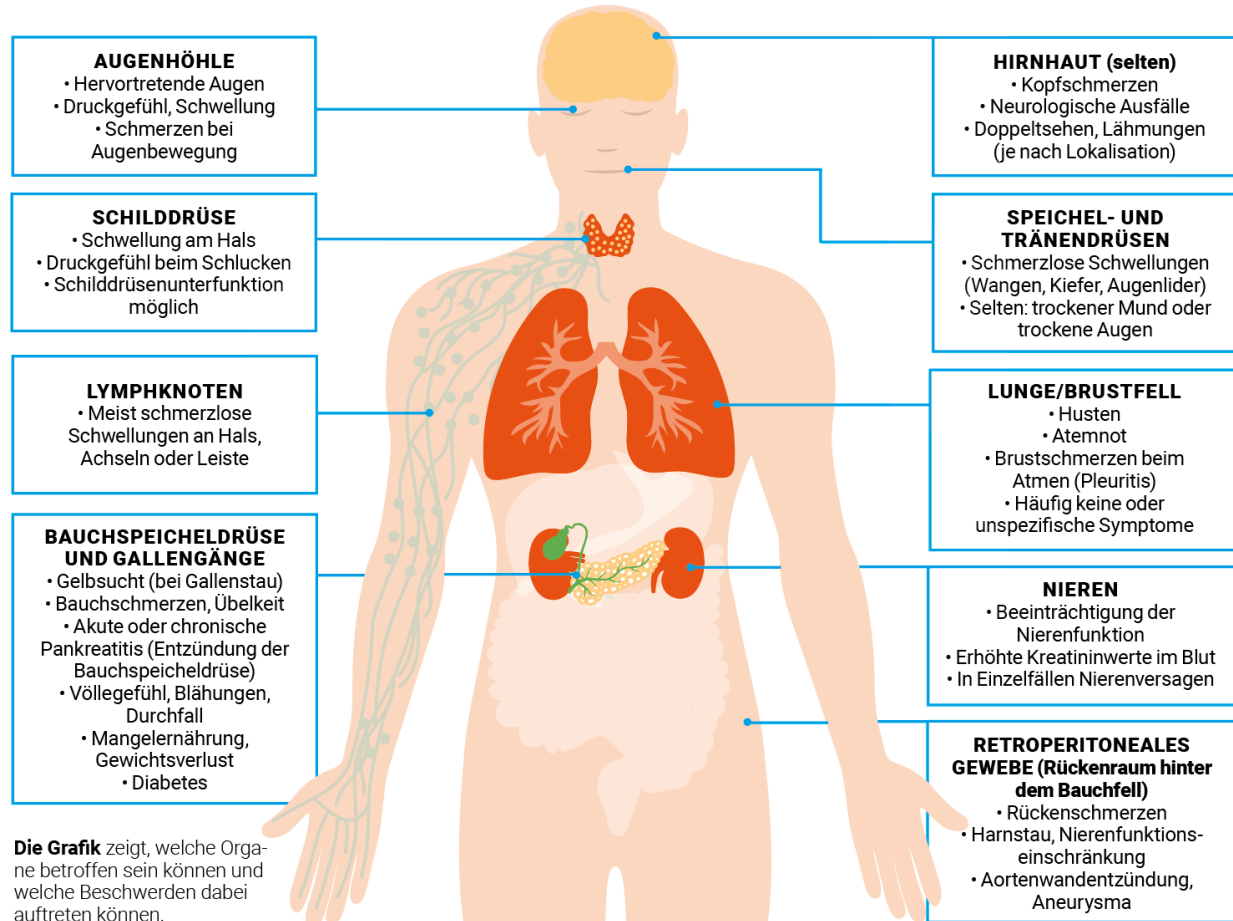
Safety

Adverse events in the modified intention-to-treat population that were considered by the trial physician to be related to the trial regimen are summarized. Adverse events of any kind, medically important adverse events, and adverse events that led to discontinuation of the trial regimen were more commonly reported in the atorvastatin group than in the placebo group. In cases of discontinuation of the assigned trial regimen, **the most cited reason was “participant unwilling”** (in 15.6% of the participants in the atorvastatin group and in 16.2% of those in the placebo group), with adverse events or an unacceptable side-effect profile leading to discontinuation in 7.2% and in 6.1%, respectively.



IgG4-Syndrome Von Augen bis Nieren:

Je nach betroffenen Organen kann eine IgG4-RD sehr unterschiedliche Beschwerden auslösen.^{2,7,10}



Obexelimab ist ein neuartiger, experimenteller monoklonaler Antikörper, der primär für die Behandlung der seltenen chronisch-entzündlichen IgG4-assoziierten Erkrankung (IgG4-RD) sowie des systemischen Lupus erythematoses (SLE) von dem Pharmaunternehmen [Zenas BioPharma](#) entwickelt wird.

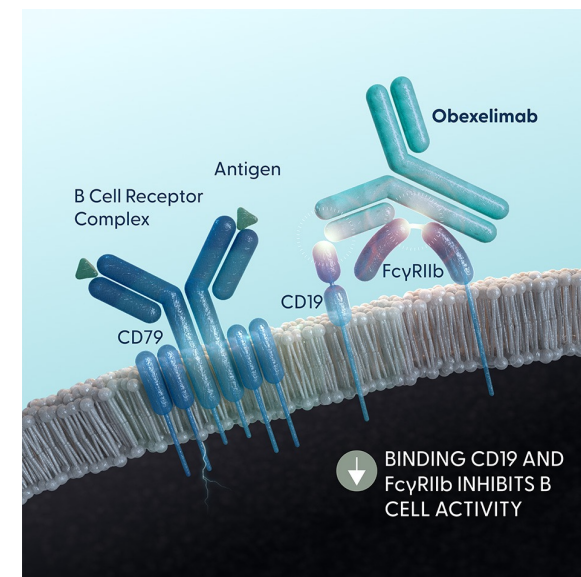
Im Gegensatz zu klassischen B-Zell-Therapien tötet Obexelimab die Zellen nicht ab, sondern inaktiviert sie lediglich.

Wirkmechanismus

Obexelimab ist ein **bispezifischer (bifunktionaler), nicht-zytolytischer Antikörper**. Er ahmt natürliche Antigen-Antikörper-Komplexe nach und bindet gleichzeitig an zwei Strukturen auf B-Zellen:

1. **CD19:** Ein Oberflächenmolekül, das auf einer breiten Masse von B-Zellen (inklusive Plasmablasten) vorkommt.
2. **FcγRIIb (Fc-Gamma-Rezeptor IIb):** Ein inhibitorischer Rezeptor, der der Zelle ein negatives Signal zur Dämpfung der Aktivität übermittelt

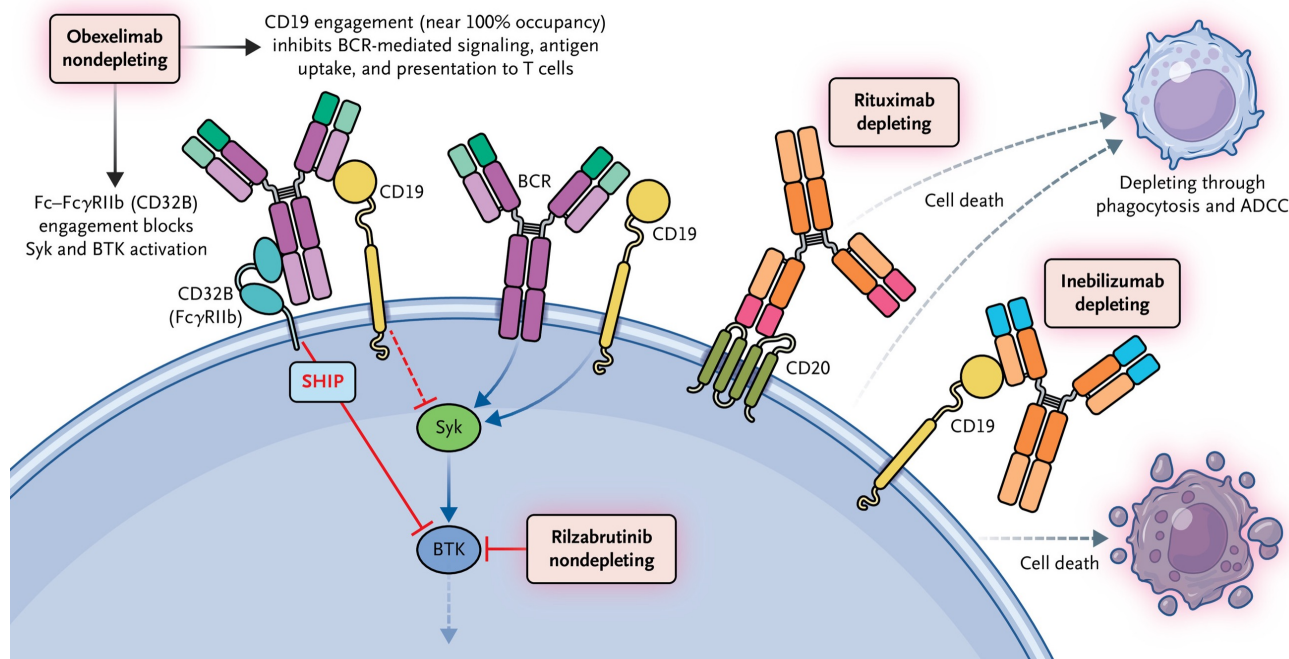
- **CD19:** Appears earlier in B-cell development (starting on early pre-B cells) and stays on late-stage antibody-secreting cells like **plasmablasts and plasma cells**.
CD20: Appears a bit later in development and is completely **lost** when B cells mature into plasma cells.



Der **Fcγ-Rezeptor IIb** (auch **CD32b** genannt) ist ein wichtiges hemmendes Protein auf der Oberfläche von Immunzellen, das überschießende Immunreaktionen kontrolliert.

B-Cell–Targeted Therapies and Their Mechanisms of Action in IgG4-Related Disease.

B-cell–directed therapies can be classified on the basis of whether they deplete B cells or functionally inhibit B-cell activation, albeit often with a reduction in the number of circulating B cells. Rituximab targets CD20 and induces B-cell depletion through phagocytosis and antibody-dependent cellular cytotoxicity. Inebilizumab targets CD19 and depletes CD19-expressing B-lineage cells. Obexelimab coengages CD19 and the inhibitory receptor FcγRIIb, which leads to inhibition of B-cell–receptor signaling through blockade of spleen tyrosine kinase (Syk) and Bruton’s tyrosine kinase (BTK) activation. Near-complete CD19 occupancy may also reduce antigen uptake and presentation to T cells. Rilzabrutinib inhibits BTK and thereby blocks downstream B-cell activation without directly depleting B cells. ADCC denotes antibody-dependent cellular cytotoxicity, BCR B-cell receptor, FcγRIIb Fc gamma receptor IIb, and SHIP SH2-containing inositol 5′-phosphatase.



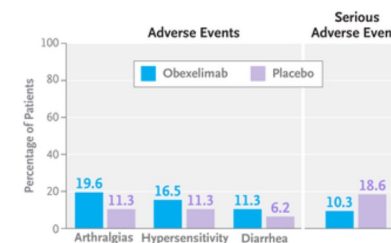
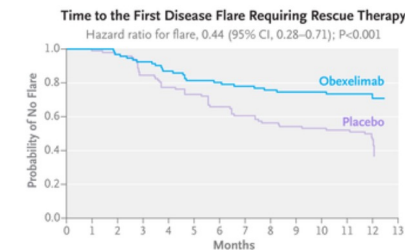
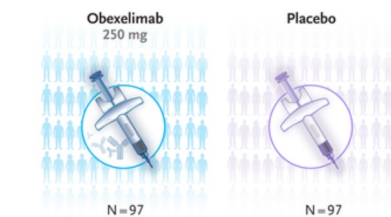
Obexelimab for the Treatment of IgG4-Related Disease

IgG4-related disease is a chronic fibroinflammatory condition that can affect virtually any organ system. Glucocorticoid agents are a cornerstone of therapy but are limited by toxic effects, and relapse is common after discontinuation.

Obexelimab is a bifunctional monoclonal antibody that inhibits B-cell activity through coengagement of CD19 and FcγRIIb without inducing B-cell depletion. In this phase 3, double-blind, randomized, placebo-controlled trial, patients with active IgG4-related disease received subcutaneous obexelimab at a dose of 250 mg or placebo once weekly for 52 weeks. For patients in both groups, glucocorticoids were tapered in a standardized schedule to discontinuation at week 8. The primary end point was the time to the first flare of IgG4-related disease for which rescue therapy was required, as determined by both the investigator and the independent adjudication committee. Key secondary end points included complete remission at week 52 and the cumulative dose of glucocorticoid rescue therapy through week 52.

Patients

- 194 adults
- Mean age, 59 years
- Men: 67%; Women: 33%



At a cellular level, IgG4-related disease is driven by dysregulated B-cell activation and aberrant interactions with CD4+ and CD8+ cytotoxic T lymphocytes as well as follicular helper T cells, which result in class switching to IgG4, lymphoplasmacytic tissue infiltration, tertiary lymphoid structure formation, and progressive fibrosis. Expanded and activated B-cell populations, as well as circulating plasmablasts, correlate with disease activity and treatment response; these findings have led to the use of B-cell–depleting therapies targeting CD20 or CD19 for management of the disease. However, this chronic, relapsing disease commonly warrants extended therapy, and prolonged B-cell depletion prompts concern about class-related side effects, such as infections, impaired vaccine response, and hypogammaglobulinemia.

Obexelimab is a humanized, bifunctional monoclonal antibody designed to inhibit B cells through coengagement of CD19 and FcγRIIb, which results in broad inhibition of B-cell receptor–dependent and B-cell receptor–independent activity.

Assessments and End Points

The primary end point was the time to the first flare of IgG4-related disease for which rescue therapy was required, as determined by both the investigator and an independent adjudication committee.

Patients

Eligible patients were at least 18 years of age and had a clinical diagnosis of IgG4-related disease involving one or more organs and fulfilling the classification criteria of the **American College of Rheumatology–European League against Rheumatism for IgG4-related disease**. An independent adjudication committee consisting of disease experts who remained unaware of the trial-group assignments throughout the trial confirmed that each patient met the classification criteria. Patients were also required to have active IgG4-related disease (flare) at screening for which either initiation of glucocorticoid therapy or a dose increase of a prednisone equivalent from a stable regimen of 10 mg or less per day was determined by the investigator to be necessary. Key exclusion criteria were active infection, receipt of a dose of more than 60 mg per day of a prednisone equivalent within 4 weeks before screening, and receipt of B-cell–depleting therapy or other immunomodulatory agents within 6 months before randomization.

Treatment and Randomization

Glucocorticoid induction therapy during the screening period consisted of 20 to 60 mg of a prednisone equivalent daily for 3 to 6 weeks, **with tapering to 20 mg per day by the day of randomization**. Patients with no disease activity, as determined by the investigator, were then stratified according to the number of affected organs (1 vs. >1) and disease status (newly diagnosed vs. recurrent) and randomly assigned to receive subcutaneous obexelimab at a dose of 250 mg once weekly or matching placebo for 52 weeks

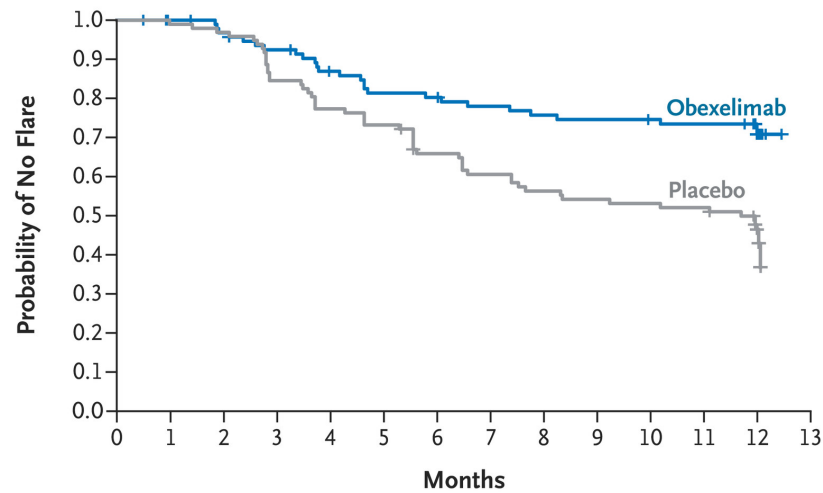
Characteristic	Obexelimab (N=97)	Placebo (N=97)	Total (N=194)
Age — yr	59.6±13.4	58.7±12.0	59.1±12.7
Male sex — no. (%)	65 (67.0)	64 (66.0)	129 (66.5)
Race or ethnic group — no. (%)†			
Asian	59 (60.8)	51 (52.6)	110 (56.7)
White	27 (27.8)	39 (40.2)	66 (34.0)
Other	11 (11.3)	7 (7.2)	18 (9.3)
Geographic region — no. (%)			
Asia	51 (52.6)	48 (49.5)	99 (51.0)
United States or Canada	24 (24.7)	16 (16.5)	40 (20.6)
Europe	19 (19.6)	28 (28.9)	47 (24.2)
Latin America‡	3 (3.1)	5 (5.2)	8 (4.1)
Body-mass index§	24.8±4.3	25.4±5.3	25.1±4.8
IgG4-related disease manifestation — no. (%)			
Recurrent	64 (66.0)	65 (67.0)	129 (66.5)
Newly diagnosed	33 (34.0)	32 (33.0)	65 (33.5)
Number of organs involved — no. (%)			
1	6 (6.2)	7 (7.2)	13 (6.7)
2 to 4	59 (60.8)	58 (59.8)	117 (60.3)
>4	32 (33.0)	32 (33.0)	64 (33.0)
Most commonly affected organs — no. (%)			
Salivary glands	60 (61.9)	66 (68.0)	126 (64.9)
Lacrimal glands	54 (55.7)	49 (50.5)	103 (53.1)
Pancreas	45 (46.4)	46 (47.4)	91 (46.9)
Lymph nodes	41 (42.3)	46 (47.4)	87 (44.8)
Disease duration — yr¶	3.1±4.2	2.5±3.2	2.8±3.7
Median ACR–EULAR score (IQR)‖	38 (30–45)	38 (31–44)	38 (30–45)
Median peak IgG4 level (IQR) — mg/dl	511.0 (255.3–982.0)	747.0 (278.0–1450.0)	624.8 (270.0–1297.6)
Previous rituximab use — no. (%)	12 (12.4)	11 (11.3)	23 (11.9)

Primary and Key Secondary Efficacy End Points

End Point	Obexelimab (N=97)	Placebo (N=97)	Effect vs. Placebo (95% CI)	P Value
Primary: time to the first adjudicated IgG4-related disease flare that required rescue therapy — no. (%)†	26 (26.8)	53 (54.6)	0.44 (0.28 to 0.71)‡	<0.001
Key secondary				
Time to the first IgG4-related disease flare that required rescue therapy — no. (%)§	26 (26.8)	56 (57.7)	0.41 (0.26 to 0.66)‡	<0.001
No. of adjudicated IgG4-related disease flares that required rescue therapy — adjusted annualized flare rate (95% CI)¶	0.34 (0.21 to 0.53)	0.70 (0.47 to 1.03)	0.48 (0.32 to 0.74)¶	<0.001
Percentage of patients with complete remission at wk 52 (95% CI)‖	37.1 (27.5 to 47.5)	19.6 (12.2 to 28.9)	17.7 (5.4 to 30.0)**	0.005
Cumulative dose of glucocorticoid rescue therapy for IgG4-related disease — mg††	329.5±200.8	929.8±198.9	−600.3 (−1011.1 to −189.5)††	0.004

Adverse events

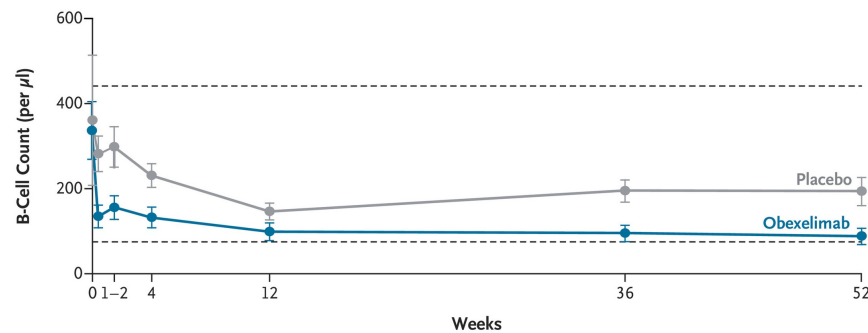
	Obexelimab (N=97)	Placebo (N=97)	Total (N=194)
	<i>no. of patients (%)</i>		
Most common adverse events†			
Arthralgia	19 (19.6)	11 (11.3)	30 (15.5)
Nasopharyngitis	18 (18.6)	14 (14.4)	32 (16.5)
Upper respiratory tract infection	15 (15.5)	22 (22.7)	37 (19.1)
Insomnia	13 (13.4)	10 (10.3)	23 (11.9)
Back pain	11 (11.3)	12 (12.4)	23 (11.9)
Diarrhea	11 (11.3)	6 (6.2)	17 (8.8)
Injection-site erythema	8 (8.2)	6 (6.2)	14 (7.2)
Eczema	7 (7.2)	5 (5.2)	12 (6.2)
Injection-site pruritus	7 (7.2)	4 (4.1)	11 (5.7)
Pyrexia	7 (7.2)	3 (3.1)	10 (5.2)
Cough	6 (6.2)	7 (7.2)	13 (6.7)
Dizziness	6 (6.2)	3 (3.1)	9 (4.6)
Fatigue	6 (6.2)	9 (9.3)	15 (7.7)
Mania	6 (6.2)	6 (6.2)	12 (6.2)
Nausea	6 (6.2)	5 (5.2)	11 (5.7)
Edema peripheral	6 (6.2)	6 (6.2)	12 (6.2)
Urticaria	6 (6.2)	1 (1.0)	7 (3.6)
Serious adverse events	10 (10.3)	18 (18.6)	28 (14.4)
Adverse events of special interest	22 (22.7)	15 (15.5)	37 (19.1)
Hypersensitivity‡	16 (16.5)	11 (11.3)	27 (13.9)
Cancer§	3 (3.1)	0	3 (1.5)
Infection¶	2 (2.1)	4 (4.1)	6 (3.1)
Injection-site reaction‖	2 (2.1)	1 (1.0)	3 (1.5)



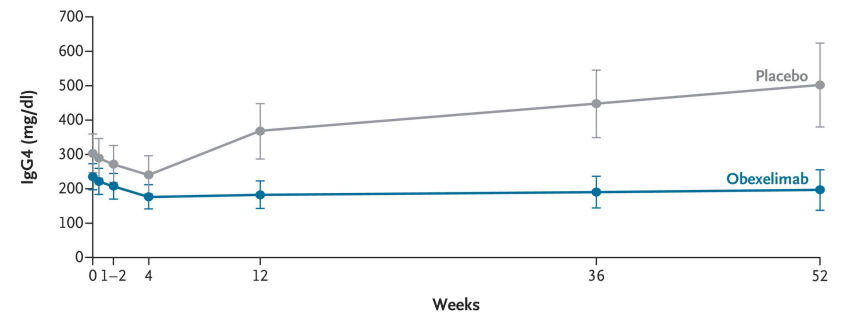
First Adjudicated Flare of IgG4-Related Disease for Which Rescue Therapy Was Required (Intention-to-Treat Population).

Shown are estimates over time of the probability of a first flare of IgG4-related disease for which rescue therapy was required, as determined by both the investigator and the adjudication committee (the primary end point). Tick marks indicate censored data. The intention-to-treat population included all the patients who had undergone randomization. NC denotes not calculable.

A CD20+ B-Cell Counts

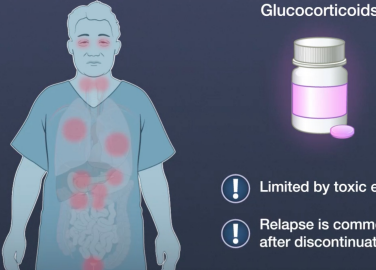


Serum IgG4 Levels



IgG4-Related Disease

Chronic fibroinflammatory condition



Glucocorticoids

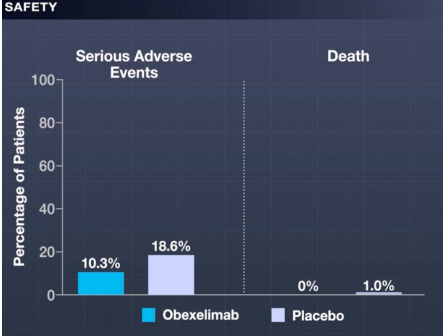
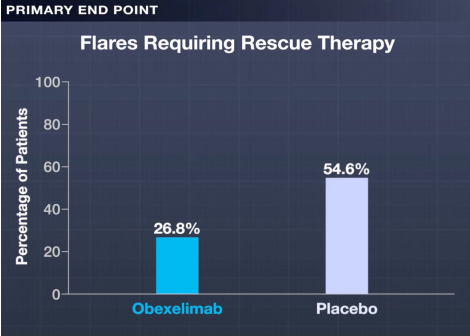
- ! Limited by toxic effects
- ! Relapse is common after discontinuation

Obexelimab
(N=97)
 

(250 mg, weekly)

Placebo
(N=97)
 

For 52 weeks



Obexelimab

Inhibits B-cell activity without depleting B cells



Bifunctional monoclonal antibody

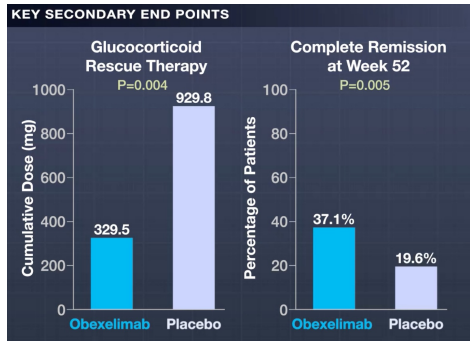
B cell

Obexelimab
(N=97)
 

(250 mg, weekly)

Placebo
(N=97)
 

Glucocorticoids were tapered on a standardized schedule and discontinued by week 8





Obexelimab



IgG4-Related Disease

- ✓ Significantly lower risk of flare
- ✓ Significantly less glucocorticoid exposure

Obexelimab

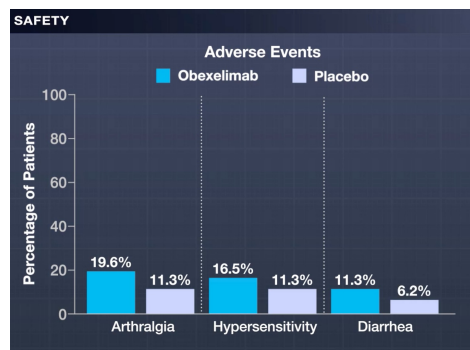
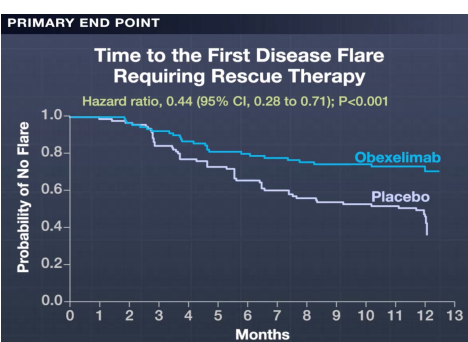
Inhibits B-cell activity without depleting B cells



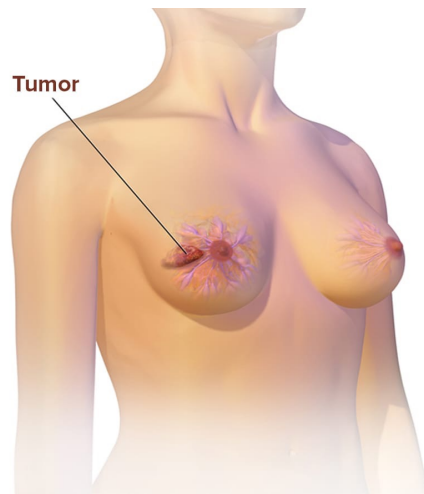
Bifunctional monoclonal antibody

B cell

? Efficacy and safety



Advanced estrogen positive breast cancer

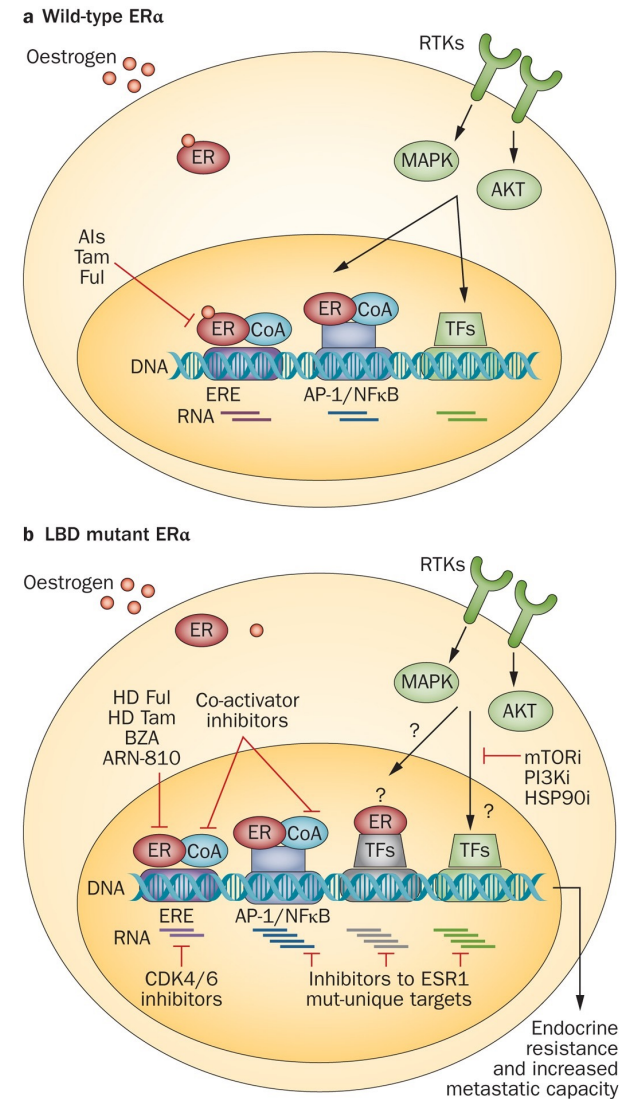


Therapieform	Wirkweise & Medikamente	Ziel
Endokrine Basistherapie	Aromatasehemmer (z. B. Letrozol, Anastrozol) senken den Östrogenspiegel im Körper. Antiöstrogene (z. B. Fulvestrant) blockieren die Rezeptoren direkt.	Entzug des Wachstumssignals für die Tumorzellen.
CDK4/6-Inhibitoren (Standard in der Erstlinie)	Medikamente wie Palbociclib, Ribociclib oder Abemaciclib blockieren bestimmte Eiweiße, die für die Zellteilung verantwortlich sind.	Werden mit der Hormontherapie kombiniert, um deren Wirksamkeit drastisch zu verlängern.
Resistenz-Blocker (bei Mutationen)	Bei einer Weiterentwicklung des Tumors (z. B. einer <i>ESSR1</i> -Mutation) kommen neue Wirkstoffe wie Elacestrant oder neuere Kombinationen (z. B. mit Capivasertib)	Durchbrechen von Mechanismen, mit denen der Krebs versucht, die Hormontherapie zu umgehen.

Eine **ESR1-Mutation** ist eine erworbene genetische Veränderung des Östrogenrezeptor-1-Gens bei Brustkrebs. Sie führt dazu, dass der Tumor unabhängig von Östrogen wachsen kann und unempfindlich gegenüber bestimmten Standard-Hormontherapien wird.

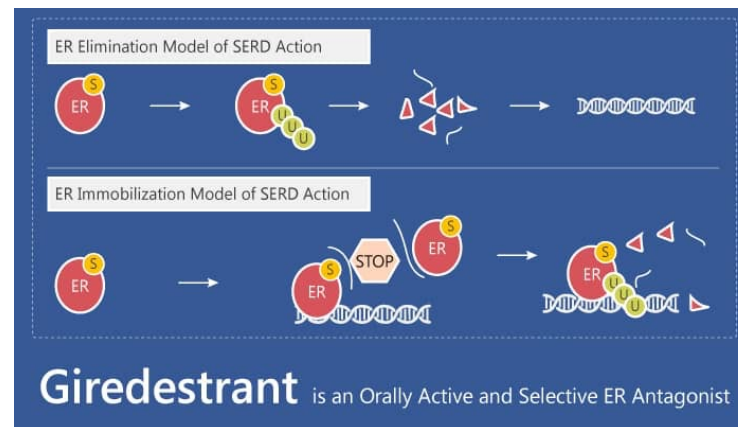
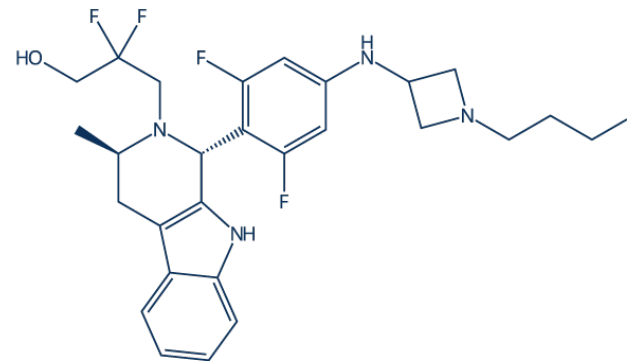
Das Wichtigste auf einen Blick

- **Wann tritt sie auf?** Bei einer Erstdiagnose (Therapie-naiver Brustkrebs) ist die Mutation extrem selten (< 0,5 %). Sie entwickelt sich meist erst im Laufe der Behandlung von **metastasiertem, hormonrezeptorpositivem (ER+) und HER2-negativem Brustkrebs**, insbesondere unter dem Selektionsdruck von **Aromatasehemmern**. Bis zu 40 % der Patientinnen und Patienten entwickeln diese Resistenz in späteren Therapielinien.
- **Die Auswirkung:** Normalerweise blockieren Antihormontherapien das Östrogen oder dessen Bildung, um dem Tumor die Nahrung zu entziehen. Die ESR1-Mutation verändert den Rezeptor jedoch so, dass er dauerhaft „**eingeschaltet**“ ist – ganz ohne Östrogen. Der Krebs wächst trotz der Blockade weiter



Giredestrant ist ein innovativer, in der Entwicklung befindlicher Wirkstoff des Schweizer Pharmakonzerns [Roche](#), der als oraler SERD (selektiver Östrogenrezeptor-Degrader) klassifiziert wird. Er wird primär für die Behandlung von **Hormonrezeptor-positivem (HR+) und HER2-negativem Brustkrebs** erforscht.

Das Medikament blockiert und baut den Östrogenrezeptor in den Krebszellen vollständig ab, um deren Wachstum zu stoppen. Im Gegensatz zu älteren SERDs (wie Fulvestrant, das intramuskulär gespritzt werden muss) wird Giredestrant als **Tablette** eingenommen

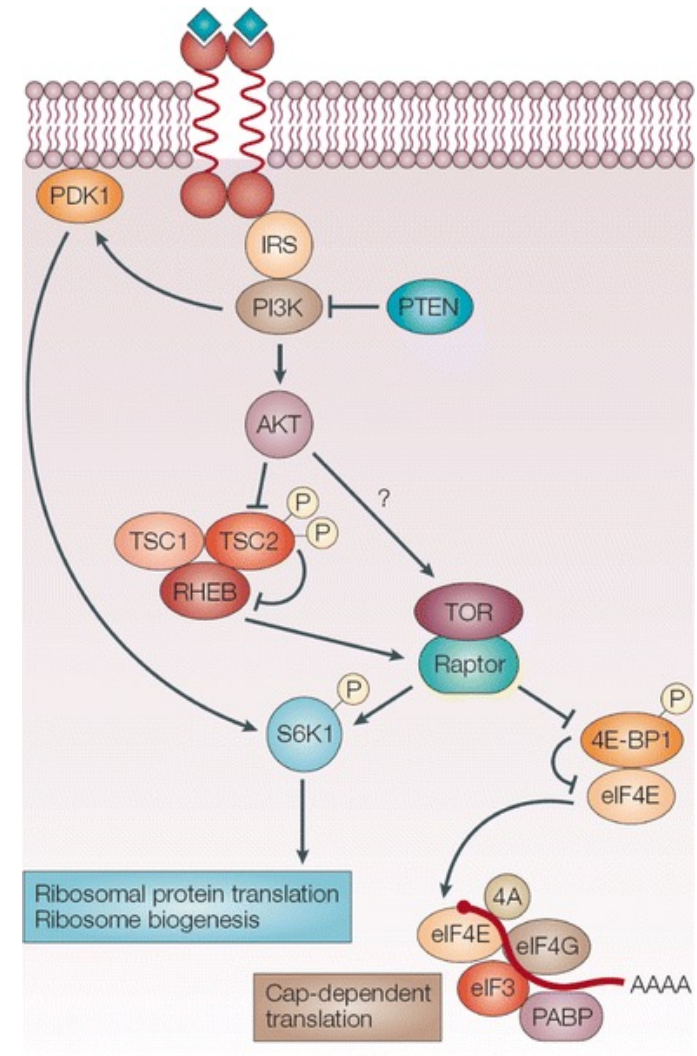


Everolimus ist ein verschreibungspflichtiger Arzneistoff aus der Gruppe der mTOR-Inhibitoren. Er wird sowohl in der Krebsheilkunde (Onkologie) als auch in der Transplantationsmedizin (Immunsuppression) eingesetzt.

Wirkungsweise

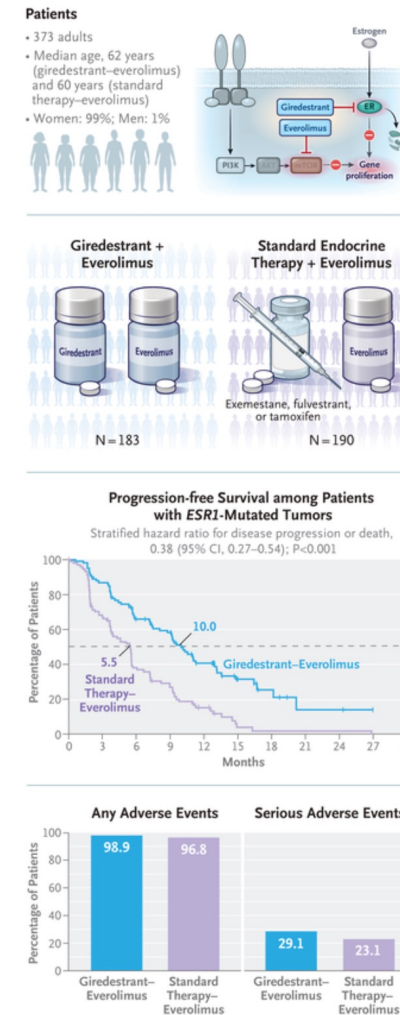
Der Wirkstoff bindet im Zellinneren an ein bestimmtes Protein (FKBP-12). Dieser Komplex blockiert das Enzym **mTOR** (*mechanistic Target of Rapamycin*). Dadurch wird die Weiterleitung von Wachstumssignalen in den Zellen unterbrochen.

- **In der Onkologie:** Es hemmt das Wachstum und die Teilung von Tumorzellen sowie die Neubildung von Blutgefäßen (Angiogenese), die den Tumor versorgen.
- **In der Transplantationsmedizin:** Es unterdrückt die Aktivierung und Vermehrung von T-Lymphozyten (Abwehrzellen), um die Abstoßung eines Spenderorgans zu verhindern.



Giredestrant plus Everolimus in Advanced Breast Cancer

Giredestrant and everolimus target the estrogen receptor (ER) pathway and the phosphatidylinositol 3-kinase (PI3K)–protein kinase B (AKT)–mammalian target of rapamycin (mTOR) pathway, respectively, which are implicated in endocrine-therapy resistance. In this phase 3, open-label, randomized trial, we enrolled patients with ER-positive, human epidermal growth factor receptor 2 (HER2)–negative locally advanced or metastatic breast cancer who had disease progression or recurrence after receipt of a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor plus endocrine therapy. Patients were assigned, in a 1:1 ratio, to receive giredestrant plus everolimus (each given orally) or standard endocrine therapy (i.e., exemestane, fulvestrant, or tamoxifen) plus everolimus. The primary end point was investigator-assessed progression-free survival, evaluated first among patients with *ESR1*-mutated tumors and then in the overall trial population.



For the first-line treatment of patients with estrogen receptor (ER)–positive, human epidermal growth factor receptor 2 (HER2)–negative advanced breast cancer, a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor plus endocrine therapy is the standard approach worldwide. However, in patients with disease progression during first-line CDK4/6 inhibitor therapy, effective treatment options remain limited, and responses to subsequent endocrine-based therapies are often not durable.

Key mechanisms of resistance to a CDK4/6 inhibitor and endocrine therapy include aberrant phosphatidylinositol 3-kinase (PI3K)–protein kinase B (AKT)–mammalian target of rapamycin (mTOR) signaling and mutations in the estrogen receptor 1 gene (*ESR1*) encoding ER alpha, respectively. *ESR1* mutations are acquired primarily under the selective pressure of aromatase inhibitors, which results in ligand-independent constitutive ER activity. In patients with disease progression after the receipt of a CDK4/6 inhibitor plus endocrine therapy, approximately 40% will have tumors with acquired *ESR1* mutations.

Everolimus, an established oral inhibitor of the mTOR signaling pathway, is one of the recommended standard-therapy options in combination with endocrine therapy (i.e., exemestane, fulvestrant, or tamoxifen) after first-line therapy in patients with ER-positive, HER2-negative advanced breast cancer. Giredestrant is a potent new oral selective ER degrader (SERD) and full ER antagonist with the potential to improve outcomes. Giredestrant targets both estrogen-dependent and estrogen-independent ER activity, whereas aromatase inhibitors target only estrogen-dependent activity.

Patients

Women (of any menopausal status) and men with ER-positive, HER2-negative locally advanced unresectable or metastatic breast cancer, **which was not amenable to treatment with curative intent, were enrolled**. Patients must have had disease progression after at least 6 months of treatment with a CDK4/6 inhibitor plus endocrine therapy in the context of locally advanced or metastatic disease or must have had recurrence during, or within 12 months after receiving, adjuvant treatment with a CDK4/6 inhibitor plus endocrine therapy (i.e., ≥ 12 months of adjuvant endocrine therapy, 6 months of which was in combination with a CDK4/6 inhibitor). If a CDK4/6 inhibitor plus endocrine therapy was not the most recent therapy, the patient must also have had disease progression after at least 4 months of the most recent endocrine therapy.

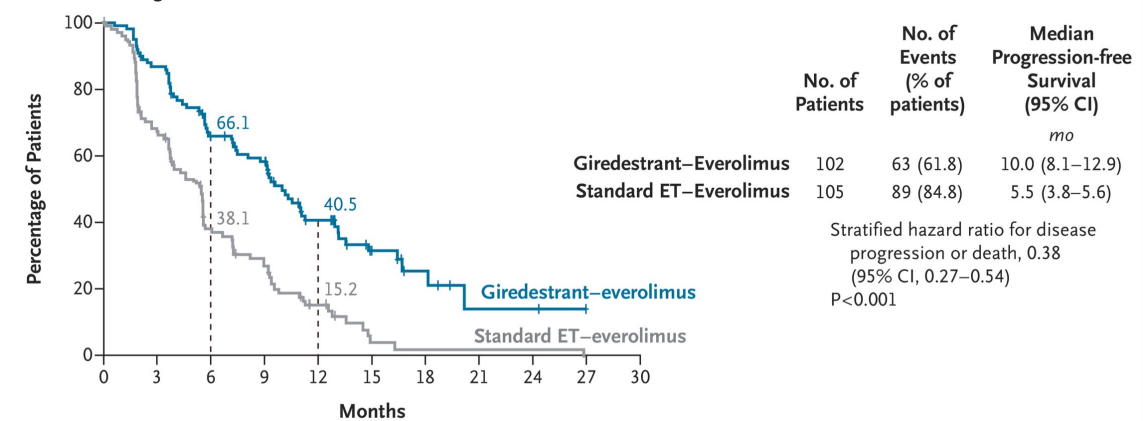
End Points

The primary end point was investigator-assessed **progression-free survival**, which was evaluated first among patients with *ESR1*-mutated tumors and then in the overall trial population, which included all the patients who had undergone randomization. Progression-free survival was defined as the time from randomization to disease progression (according to RECIST, version 1.1) or death from any cause, whichever occurred first.

Characteristic	Patients with <i>ESR1</i> -Mutated Tumors		Overall Trial Population	
	Giredestrant– Everolimus (N = 102)	Standard Endocrine Therapy–Everolimus (N = 105)	Giredestrant– Everolimus (N = 183)	Standard Endocrine Therapy–Everolimus (N = 190)
Age				
Median (range) — yr	61 (32–83)	59 (39–82)	62 (27–83)	60 (28–84)
≥65 yr — no. (%)	39 (38.2)	28 (26.7)	74 (40.4)	57 (30.0)
Sex — no. (%)				
Male	1 (1.0)	2 (1.9)	1 (0.5)	3 (1.6)
Female	101 (99.0)	103 (98.1)	182 (99.5)	187 (98.4)
Race or ethnic group — no. (%) [†]				
White	65 (63.7)	72 (68.6)	103 (56.3)	119 (62.6)
Asian	30 (29.4)	24 (22.9)	66 (36.1)	57 (30.0)
Black	4 (3.9)	5 (4.8)	9 (4.9)	9 (4.7)
Other	3 (2.9)	4 (3.8)	5 (2.7)	5 (2.6)
ECOG performance-status score—no. (%) [‡]				
0	68 (66.7)	75 (71.4)	126 (68.9)	139 (73.2)
1	34 (33.3)	30 (28.6)	57 (31.1)	51 (26.8)
Menopausal status at randomization — no. (%) [§]				
Premenopausal or perimenopausal	15 (14.7)	17 (16.2)	27 (14.8)	31 (16.3)
Postmenopausal	87 (85.3)	88 (83.8)	156 (85.2)	159 (83.7)
No. of organs with metastases — no. (%)				
1	14 (13.7)	13 (12.4)	37 (20.2)	33 (17.4)
2	31 (30.4)	40 (38.1)	57 (31.1)	69 (36.3)
≥3	57 (55.9)	52 (49.5)	89 (48.6)	88 (46.3)
<i>ESR1</i> mutation — no. (%) [¶]				
102 (100)	102 (100)	105 (100)	102 (55.7)	105 (55.3)
<i>PIK3CA</i> , <i>AKT1</i> , or <i>PTEN</i> alteration — no. (%) ^{¶¶}				
47 (46.1)	47 (46.1)	42 (40.0)	82 (44.8)	80 (42.1)
<i>PIK3CA</i> mutation	35 (34.3)	29 (27.6)	64 (35.0)	51 (26.8)
<i>AKT1 E17K</i> alteration	10 (9.8)	5 (4.8)	14 (7.7)	12 (6.3)
<i>PTEN</i> alteration	10 (9.8)	15 (14.3)	13 (7.1)	28 (14.7)
No. of previous lines of therapy for advanced breast cancer — no. (%) ^{**}				
0	2 (2.0)	1 (1.0)	3 (1.6)	5 (2.6)
1	82 (80.4)	74 (70.5)	140 (76.5)	132 (69.5)
2	18 (17.6)	30 (28.6)	40 (21.9)	52 (27.4)
Previous chemotherapy for early breast cancer — no. (%)	41 (40.2)	48 (45.7)	86 (47.0)	86 (45.3)
Duration of most recent CDK4/6 inhibitor therapy in the context of metastatic disease — no. (%) ^{††}				
<12 mo	20 (19.6)	18 (17.1)	44 (24.0)	50 (26.3)
≥12 mo	80 (78.4)	86 (81.9)	136 (74.3)	135 (71.1)
12 to <24 mo	37 (36.3)	37 (35.2)	61 (33.3)	60 (31.6)
≥24 mo	43 (42.2)	49 (46.7)	75 (41.0)	75 (39.5)

Event	Giredestrant– Everolimus (N = 182)		Standard Endocrine Therapy– Everolimus (N = 186)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
<i>number of patients (percent)</i>				
Stomatitis	86 (47.3)	5 (2.7)	91 (48.9)	6 (3.2)
Diarrhea	49 (26.9)	0	42 (22.6)	2 (1.1)
Anemia	43 (23.6)	11 (6.0)	39 (21.0)	16 (8.6)
Nausea	40 (22.0)	1 (0.5)	31 (16.7)	2 (1.1)
Fatigue	38 (20.9)	2 (1.1)	37 (19.9)	2 (1.1)
Decreased appetite	34 (18.7)	0	26 (14.0)	3 (1.6)
Pneumonitis	31 (17.0)	5 (2.7)	23 (12.4)	5 (2.7)
Rash	29 (15.9)	1 (0.5)	26 (14.0)	1 (0.5)
Aspartate aminotransferase increased	27 (14.8)	3 (1.6)	24 (12.9)	1 (0.5)
Peripheral edema	26 (14.3)	0	23 (12.4)	0
Cough	26 (14.3)	1 (0.5)	19 (10.2)	0
Headache	24 (13.2)	2 (1.1)	30 (16.1)	0
Hyperglycemia	23 (12.6)	6 (3.3)	18 (9.7)	4 (2.2)
Arthralgia	22 (12.1)	2 (1.1)	28 (15.1)	0
Hypokalemia	22 (12.1)	7 (3.8)	20 (10.8)	5 (2.7)
Vomiting	21 (11.5)	0	25 (13.4)	1 (0.5)
Back pain	20 (11.0)	0	20 (10.8)	0
Alanine aminotransferase increased	20 (11.0)	2 (1.1)	24 (12.9)	2 (1.1)
Dysgeusia	19 (10.4)	0	18 (9.7)	0
Platelet count decreased	19 (10.4)	1 (0.5)	18 (9.7)	2 (1.1)
Neutrophil count decreased	19 (10.4)	4 (2.2)	22 (11.8)	6 (3.2)
Weight decreased	19 (10.4)	4 (2.2)	16 (8.6)	6 (3.2)
Constipation	16 (8.8)	0	28 (15.1)	2 (1.1)
Insomnia	15 (8.2)	0	23 (12.4)	1 (0.5)
Pruritus	9 (4.9)	0	21 (11.3)	0

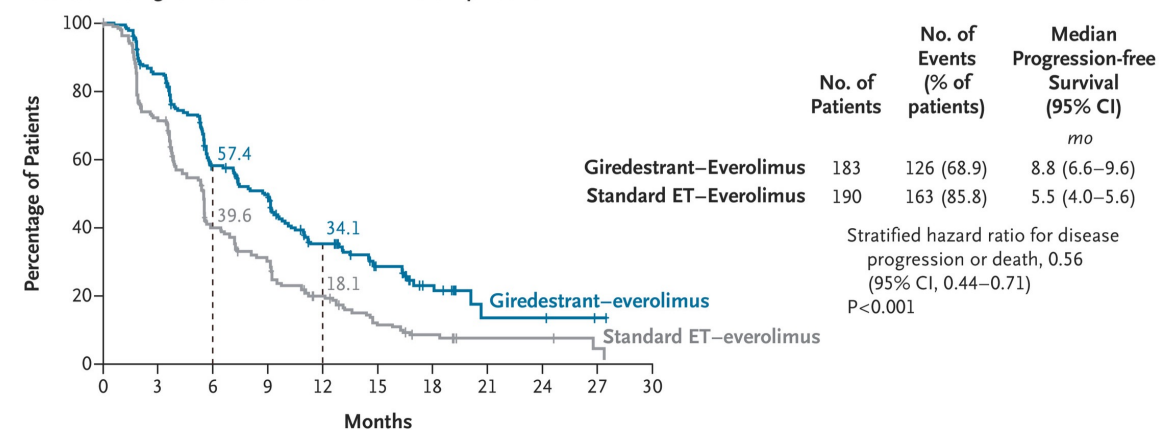
A Progression-free Survival among Patients with *ESR1*-Mutated Tumors



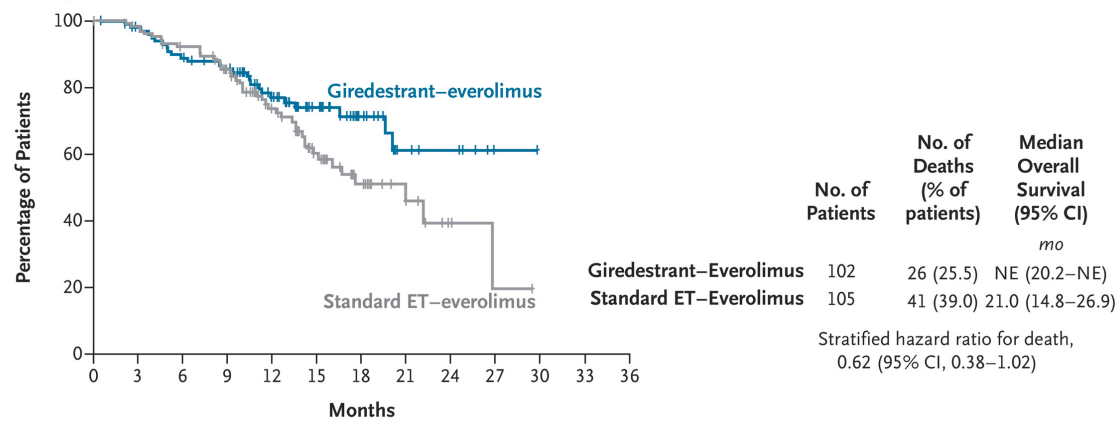
Investigator-Assessed Progression-free Survival.

Panel A shows progression-free survival as assessed by the investigator among all the patients who underwent randomization and had *ESR1*-mutated tumors. Progression-free survival was defined as the time from randomization to disease progression (as assessed by the investigator according to the Response Evaluation Criteria in Solid Tumors, version 1.1²⁵) or death from any cause, whichever occurred first. Panel B shows progression-free survival as assessed by the investigator in the overall trial population. In both panels, tick marks indicate censored data. Data from patients who were alive and without disease progression at the time of the analysis were censored at the time of the patients' last disease evaluation; data for patients with no postbaseline disease assessment were censored at the randomization date plus 1 day.

Progression-free Survival among All Patients in the Overall Trial Population



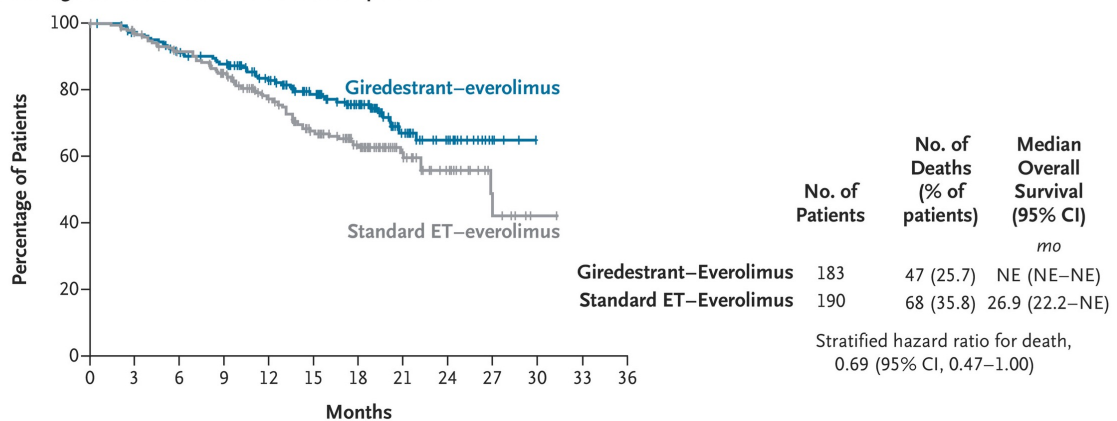
A Overall Survival among Patients with *ESR1*-Mutated Tumors

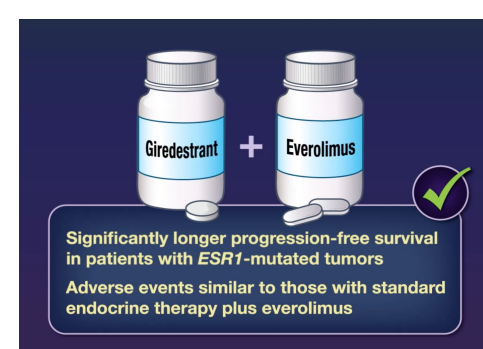
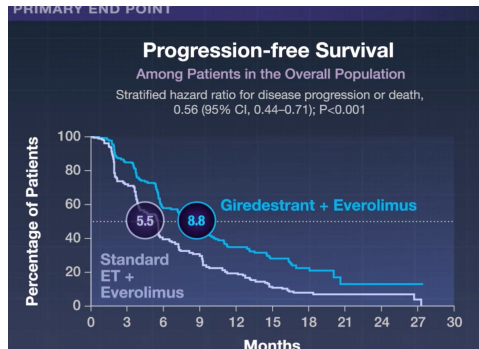
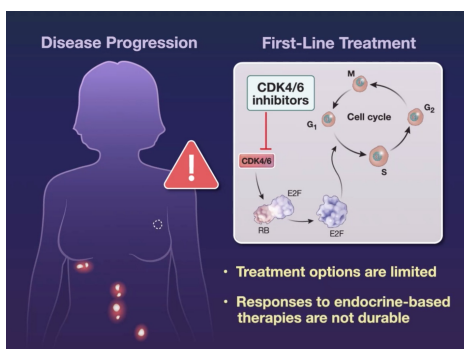
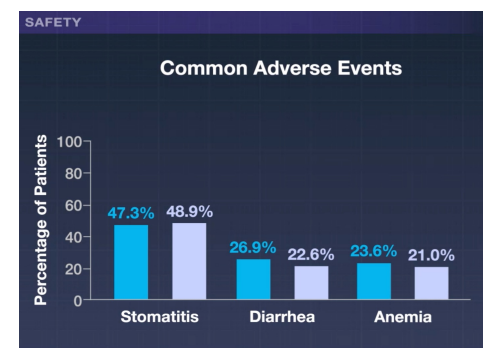
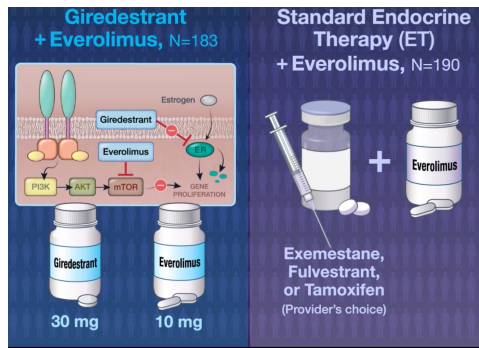
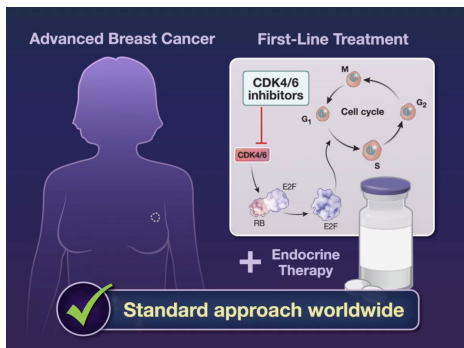
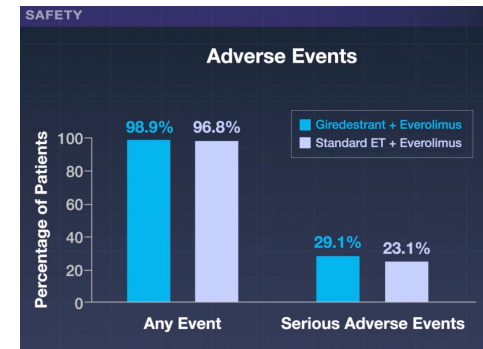
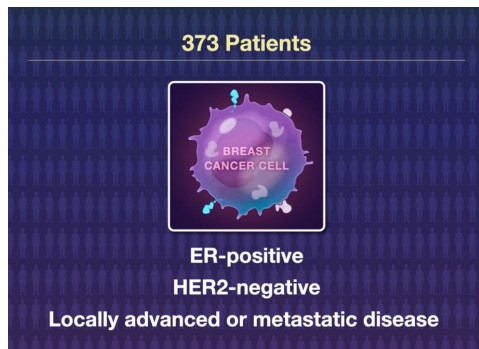
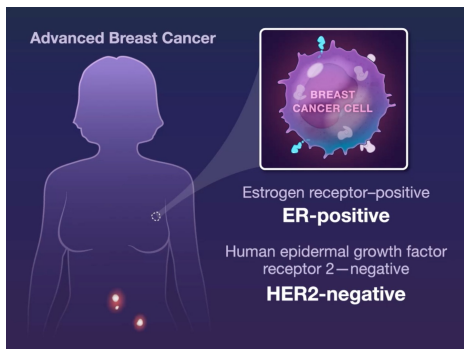


Overall Survival.

Panel A shows overall survival (secondary end point) among all patients with *ESR1*-mutated tumors who underwent randomization. The P value did not cross the prespecified boundary (based on the Lan–DeMets function approximating the O’Brien–Fleming boundary²⁸) for a two-sided significance level of 0.0097. Panel B shows overall survival among all patients who underwent randomization (overall trial population). The P value did not cross the prespecified boundary for significance of 0.0146 (two-sided). In both panels, tick marks indicate censored data. Data from patients who were alive at the time of the analysis were censored at the time they were last known to be alive. The widths of the confidence intervals were not adjusted for multiplicity and should not be used to infer definitive treatment effects. NE denotes not evaluable.

B Overall Survival among All Patients in the Overall Trial Population

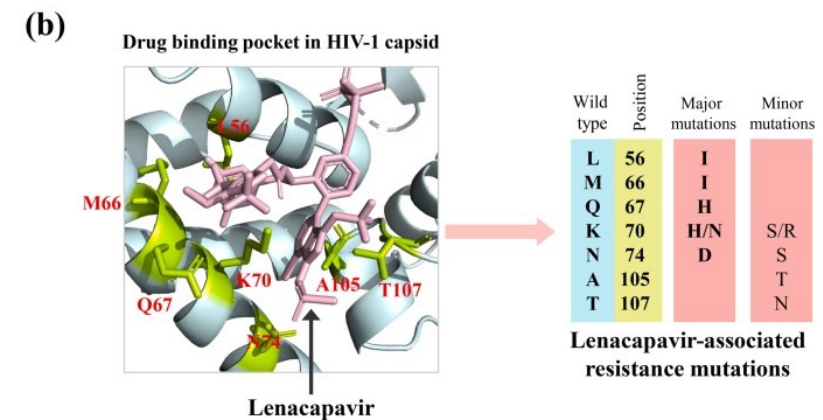
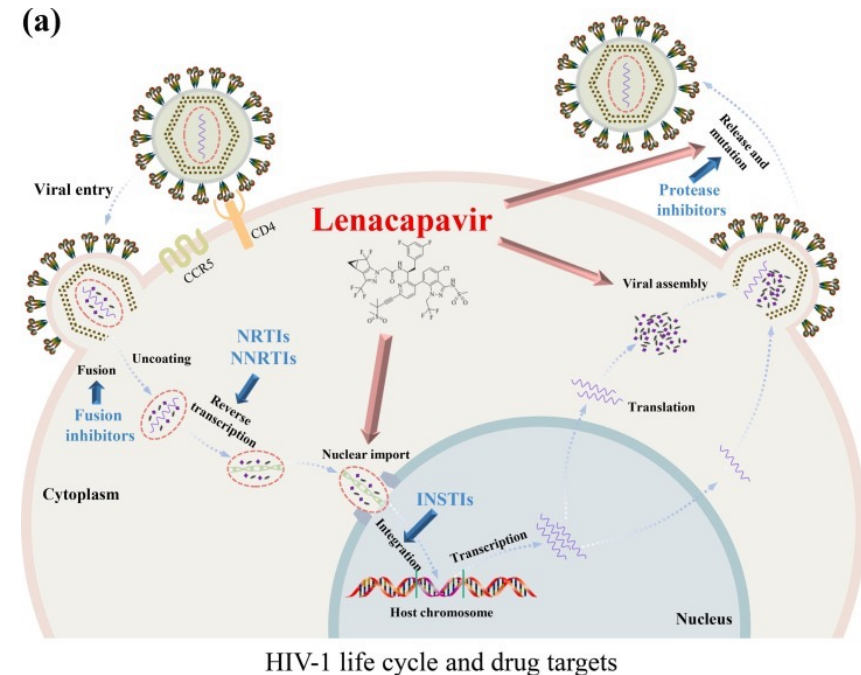




Islatravir und Lenacapavir werden gemeinsam als neuartige, einmal wöchentlich einzunehmende orale Kombinationstherapie zur Behandlung von HIV-1 erforscht.

Wichtigste Fakten zur Kombination

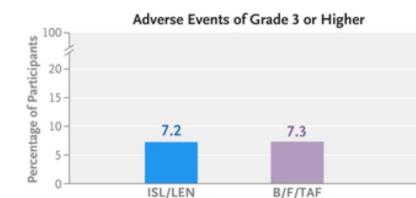
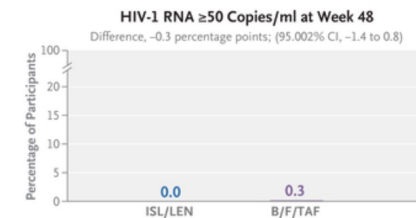
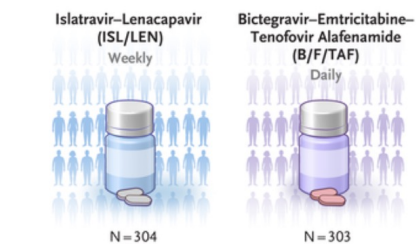
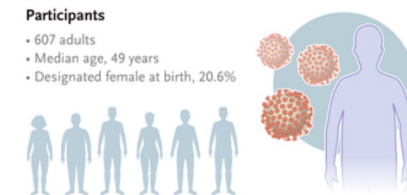
- **Wirkstoffe und Dosis:** Die Kombination besteht aus Islatravir (2 mg) und Lenacapavir (300 mg) als wöchentliche orale Dosis.
- **Wirkmechanismus:**
 - *Islatravir* ist ein nukleosidischer Reverse-Transkriptase-Translokationsinhibitor (NRTTI).
 - *Lenacapavir* ist ein Kapsidinhibitor, der die Hülle des Virus stört



Phase 3 Trial of Weekly Oral Islatravir–Lenacapavir for HIV-1 Treatment

Once-daily, single-tablet regimens have transformed care for persons living with human immunodeficiency virus type 1 (HIV-1); however, challenges to adherence continue to limit effective treatment. Long-acting oral-drug combinations could offer new options with less frequent dose administration.

We conducted a phase 3, double-blind, randomized, active-controlled, noninferiority trial in 12 countries to evaluate the efficacy and safety of a switch to once-weekly oral islatravir–lenacapavir (ISL/LEN) from once-daily oral bictegravir–emtricitabine–tenofovir alafenamide (B/F/TAF) in adults in whom HIV-1 had been virologically suppressed for at least 6 months while they were receiving B/F/TAF. Participants were assigned in a 1:1 ratio to receive once-weekly ISL/LEN (2 mg/300 mg) or to continue once-daily B/F/TAF for 96 weeks; all received matched placebo for the alternative regimen. **The primary end point was the percentage of participants with an HIV-1 RNA level of 50 copies per milliliter or higher at week 48,** as determined by the Food and Drug Administration–defined snapshot algorithm. Noninferiority was determined at a margin of 4 percentage points.



Islatravir, a nucleoside reverse-transcriptase translocation inhibitor, is approved for use in combination with doravirine for the treatment of HIV type 1 (HIV-1) infection.

Lenacapavir is a first-in-class selective inhibitor of HIV-1 capsid function. Twice-yearly subcutaneous lenacapavir is approved for use in adults with multidrug resistance and limited options for treatment in combination with antiretroviral therapy, as well as for the prevention (preexposure prophylaxis) of HIV-1 infection. Both islatravir and lenacapavir have pharmacokinetic profiles that support once-weekly oral administration.

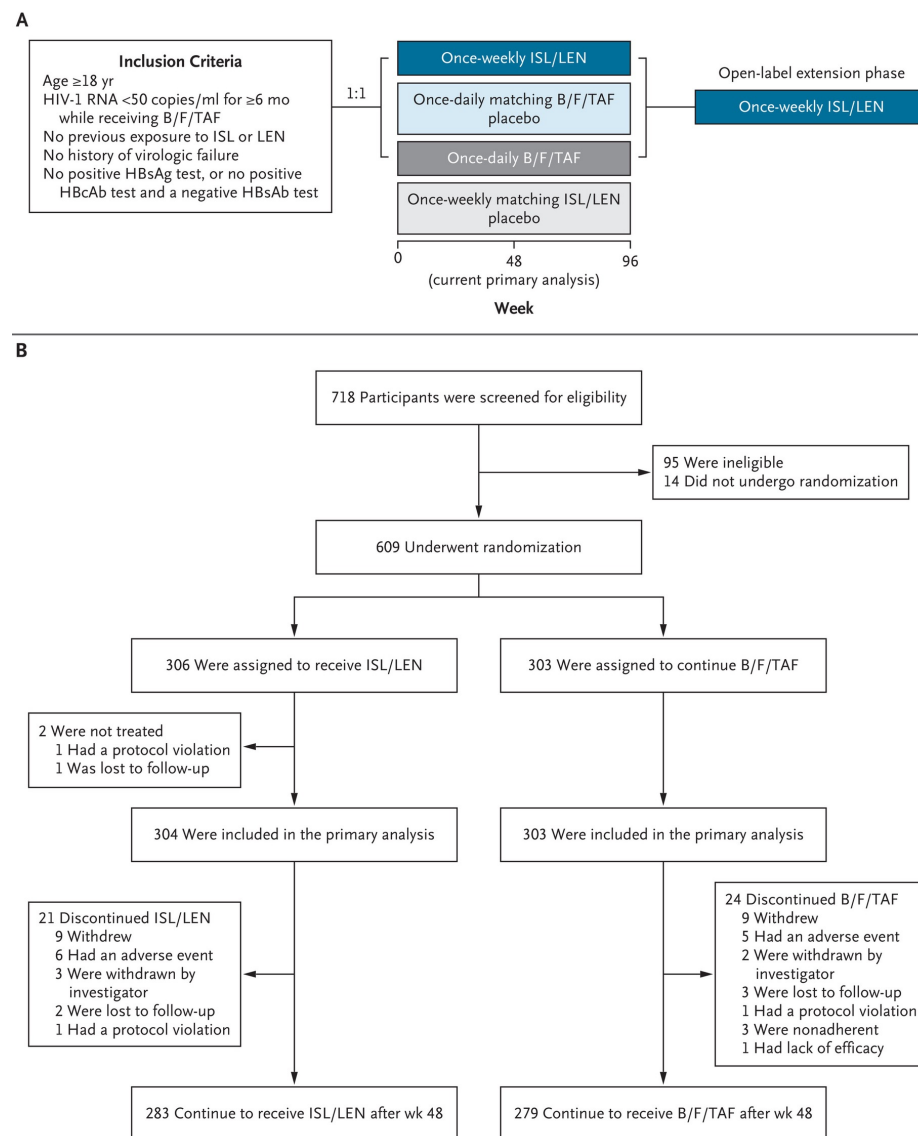
Given their distinct mechanisms of action and resistance profiles, islatravir in combination with lenacapavir (ISL/LEN) has the potential to be a long-acting, once-weekly, single-tablet oral regimen for the treatment of HIV-1. In a phase 3 trial, we evaluated the efficacy and safety of a switch to ISL/LEN from once-daily bictegravir–emtricitabine–tenofovir alafenamide (B/F/TAF) in adults with virologically suppressed HIV-1, with a planned follow-up period of 96 weeks. Here, we report the results for the primary efficacy end point and for the secondary and safety end points at week 48.

Participants and Procedures

Participants were eligible if they were adults (≥ 18 years of age) with virologically suppressed HIV-1 (a documented plasma HIV-1 RNA level of < 50 copies per milliliter) for at least 6 months before screening while they were receiving B/F/TAF and had no previous exposure to islatravir or lenacapavir, no previous virologic failure, and no active hepatitis B virus (HBV) infection.

Trial Design and Participant Flow through the Trial.

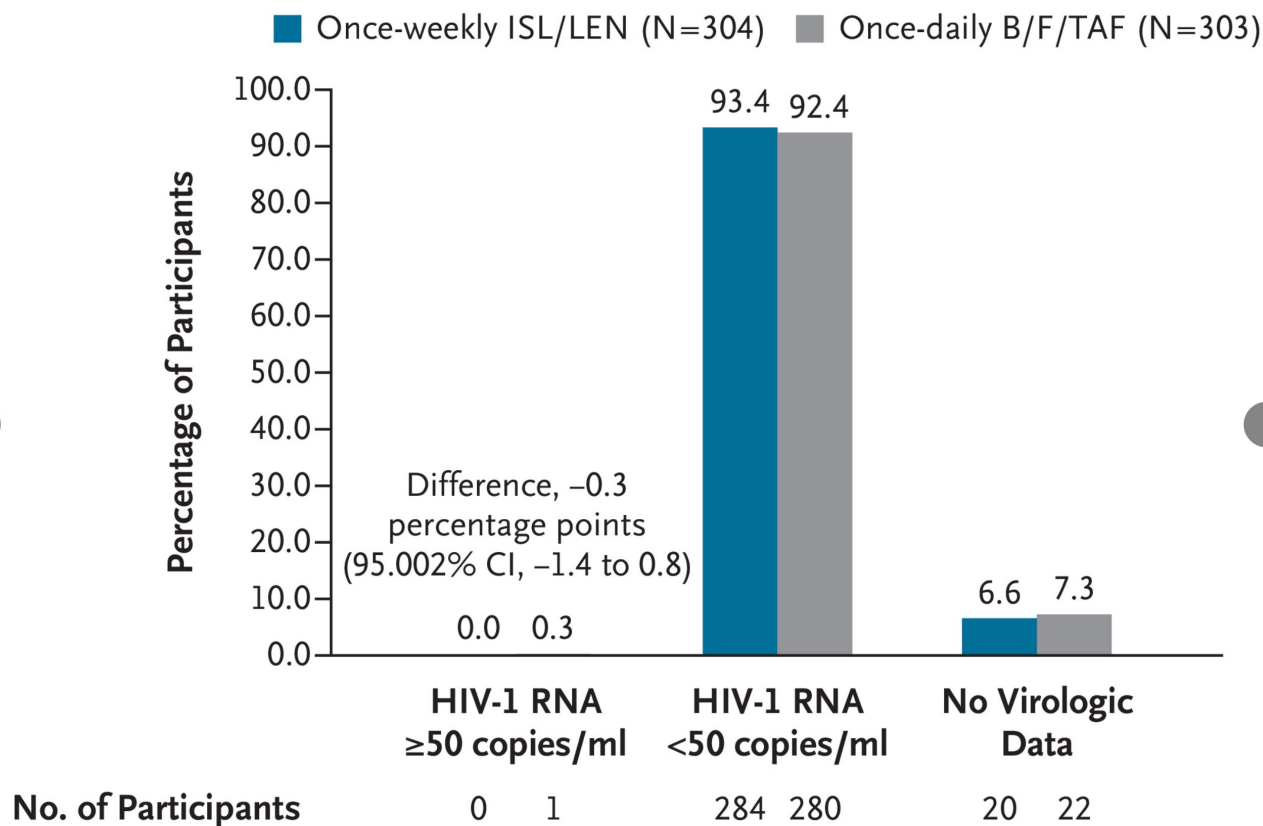
Panel A shows a diagram of the trial design. Panel B shows the screening, randomization, and follow-up of the participants. A total of 57 participants did not meet inclusion criteria, and 50 participants met exclusion criteria (the reasons, not mutually exclusive, are shown). The reasons for not undergoing randomization were withdrawal of consent (9 participants), loss to follow-up (3 participants), and other reason (2 participants). The reasons for withdrawal by the investigator were extended time off treatment, personal issues, immunocompromise due to chemotherapy, use of investigational product not allowed at behavioral health facility, and nonadherence (in 1 participant each). B/F/TAF denotes bictegravir–emtricitabine–tenofovir alafenamide, HBcAb hepatitis B core antibody, HBsAb hepatitis B surface antibody, HBsAg hepatitis B surface antigen, and ISL/LEN islatravir–lenacapavir.



Characteristic	Once-Weekly ISL/LEN (N = 304)	Once-Daily B/F/TAF (N = 303)	Total (N = 607)
Age			
Median (IQR) — yr	49 (38–60)	48 (38–60)	49 (38–60)
Range — yr	20–87	21–87	20–87
Distribution			
≥50 yr — no. (%)	151 (49.7)	143 (47.2)	294 (48.4)
≥65 yr — no. (%)	52 (17.1)	40 (13.2)	92 (15.2)
Female sex assigned at birth — no. (%)	67 (22.0)	58 (19.1)	125 (20.6)
Median weight (IQR) — kg	80.5 (72.0–95.2)	79.8 (71.4–93.0)	80.0 (71.7–94.0)
Gender identity — no. (%)			
Cisgender man or woman	299 (98.4)	296 (97.7)	595 (98.0)
Transgender, gender nonbinary, or gender nonconforming	5 (1.6)	7 (2.3)	12 (2.0)
Race — no. (%)†			
White	148 (48.7)	128 (42.2)	276 (45.5)
Black	89 (29.3)	100 (33.0)	189 (31.1)
Asian	32 (10.5)	33 (10.9)	65 (10.7)
Hispanic or Latine ethnic group — no. (%)†	73 (24.0)	87 (28.7)	160 (26.4)
Geographic region — no. (%)			
United States	182 (59.9)	183 (60.4)	365 (60.1)
Outside the United States	122 (40.1)	120 (39.6)	242 (39.9)
HIV-1 RNA level ≥50 copies/ml — no. (%)	5 (1.6)	5 (1.7)	10 (1.6)
CD4+ T-cell count — cells/μl	739±289.2	745±319.3	742±304.4
CD4+ T-cell count <200 cells/μl — no. (%)	3 (1.0)	6 (2.0)	9 (1.5)
Median eGFR (IQR) — ml/min‡	101.6 (81.3–125.8)	101.0 (82.8–121.6)	101.0 (82.0–124.2)
Absolute lymphocyte count — cells/μl§	1860±524	1900±617	1880±572
History of AIDS — no. (%)	13 (4.3)	8 (2.6)	21 (3.5)
Median duration of HIV-1 from diagnosis (IQR) — yr¶	14.2 (7.3–23.0)	14.2 (7.3–23.0)	14.2 (7.3–23.0)
Median duration of HIV-1 treatment (IQR) — yr	12.3 (7.1–19.3)	13.1 (7.1–19.1)	12.3 (7.1–19.2)

Safety Summary

Adverse Event*	Once-Weekly ISL/LEN (N = 304)	Once-Daily B/F/TAF (N = 303)	Unattributed†
	<i>no. of participants (%)</i>		<i>no. of participants (% in either group)</i>
Adverse event of any grade	241 (79.3)	238 (78.5)	
Adverse event of grade ≥3	22 (7.2)	22 (7.3)	
Treatment-related adverse event of any grade	41 (13.5)	40 (13.2)	
Treatment-related adverse event of grade ≥3			1 (0.3)
Serious adverse event	16 (5.3)	14 (4.6)	
Treatment-related serious adverse event			1 (0.3)‡
Adverse event leading to discontinuation of trial treatment	6 (2.0)	5 (1.7)	
Treatment-related adverse event leading to discontinuation of trial treatment			4 (1.3)
Death	0	0	

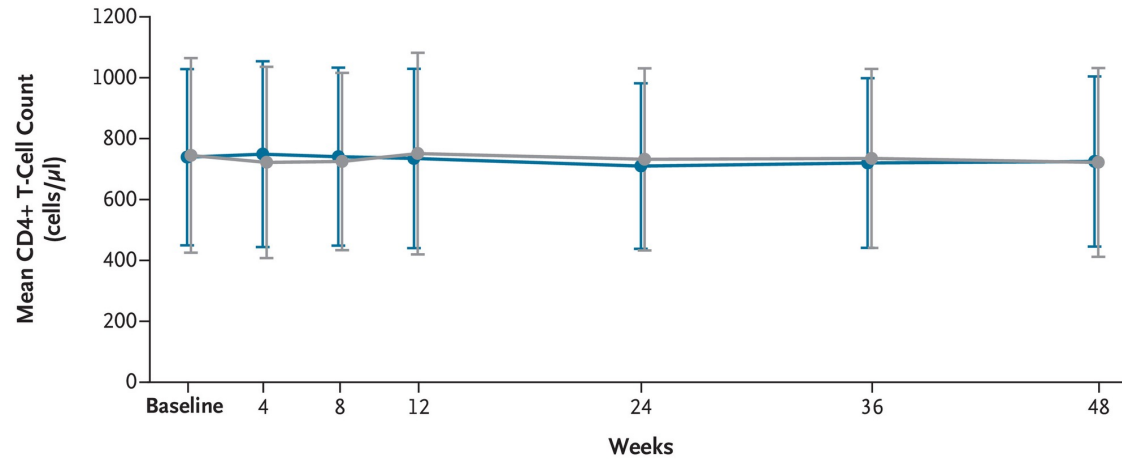


Virologic Outcomes at Week 48.

Two-sided 95.002% confidence intervals were constructed on the basis of stratum-adjusted Mantel–Haenszel proportions, with adjustment according to geographic region (United States vs. outside the United States). The percentage of participants with a human immunodeficiency virus type 1 (HIV-1) RNA level of 50 copies per milliliter or higher at week 48 (primary end point) was determined by the Food and Drug Administration–defined snapshot algorithm. Among the participants who had an HIV-1 RNA level of less than 50 copies per milliliter at 48 weeks, 1 participant discontinued the assigned trial treatment (B/F/TAF) owing to “other reasons” and had a last available HIV-1 RNA level of 50 copies per milliliter or higher. Among the participants who had no virologic data, 6 in the ISL/LEN group and 4 in the B/F/TAF group had discontinued the trial regimen owing to an adverse event; 13 and 15, respectively, had discontinued the trial regimen for other reasons and had a last available HIV-1 RNA level of less than 50 copies per milliliter; and 1 and 3, respectively, had missing data during the analysis window but were still receiving the trial treatment. “Other reasons” for discontinuing the trial regimen included withdrawal by the investigator, withdrawal by the participant, loss to follow-up, nonadherence to the trial regimen, and pregnancy.

● Once-weekly ISL/LEN ● Once-daily B/F/TAF

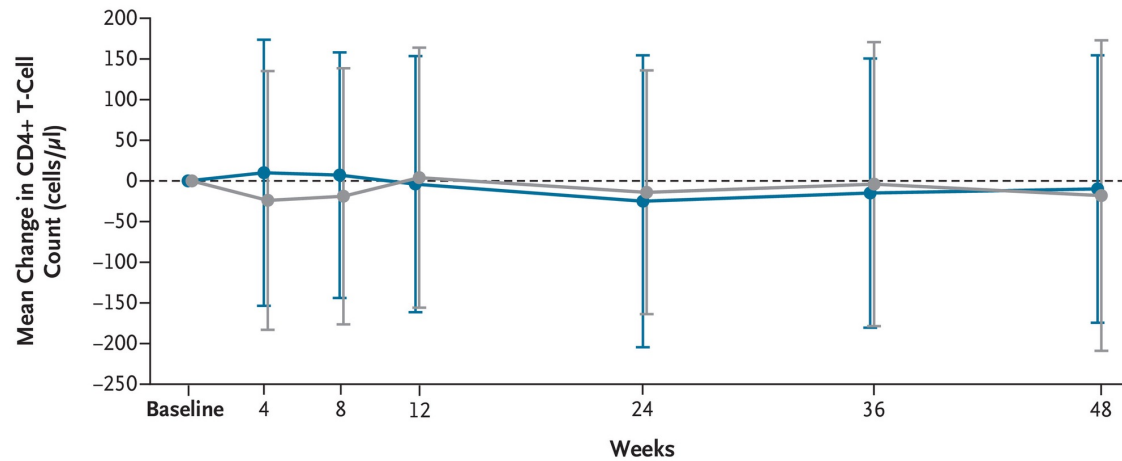
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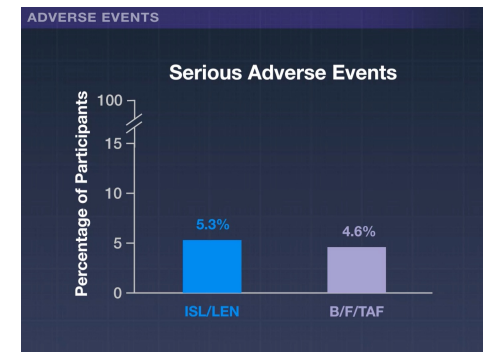
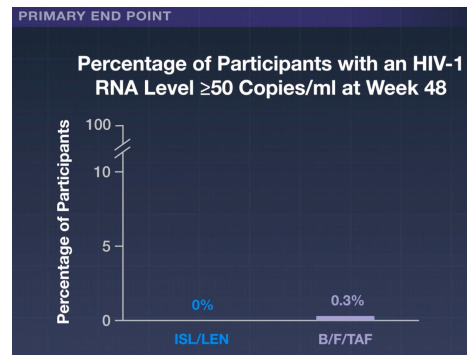
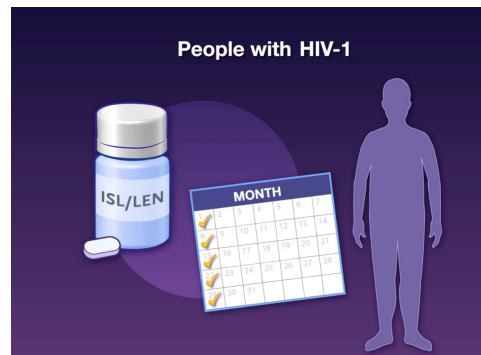
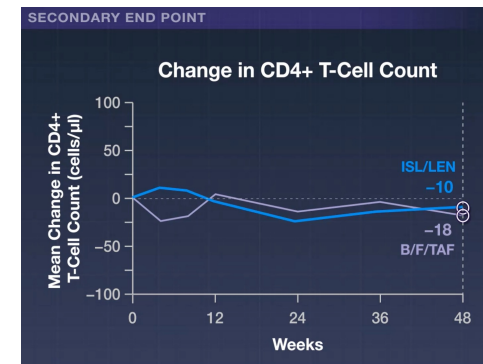
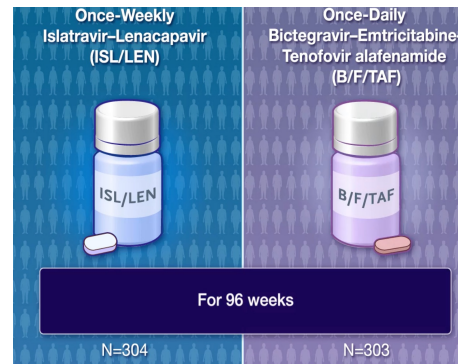


CD4+ T-Cell Count through Week 48

Panel A shows the mean absolute CD4+ T-cell counts and Panel B the change from baseline in CD4+ T-cell counts through week 48. I bars indicate the standard deviation.

B



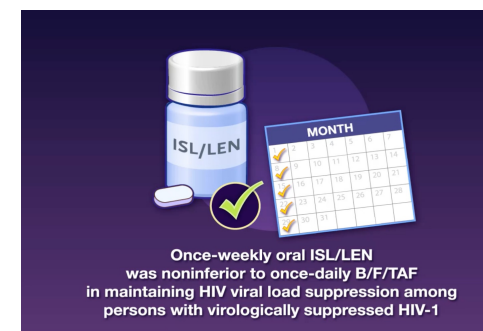
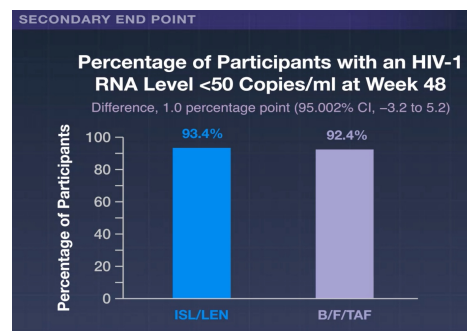


ISLEND-1 Trial

- Phase 3
- Double-blind
- Randomized
- Active-controlled
- Noninferiority
- Across 12 countries

607 Adults

- With HIV-1
- Virologically suppressed for at least 6 months with once-daily bictegravir, emtricitabine, and tenofovir alafenamide, or B/F/TAF



The hantavirus cases on the cruise ship were confirmed to be the Andes virus (ANDV).

During the **April to June 2026 outbreak** aboard the Dutch-flagged expedition cruise ship *MV Hondius*, laboratory testing and viral sequencing quickly identified the pathogen specifically as the **Andes strain of hantavirus**.

Key Details of the Outbreak

- **The Pathogen:** While initially reported broadly as a hantavirus cluster, South African and international health authorities confirmed on May 6, 2026, that the specific culprit was **Andes virus (ANDV)**.
- **The Toll:** The outbreak resulted in **13 total cases** (12 confirmed, 1 probable) and **3 deaths** before the [World Health Organization \(WHO\)](#) officially declared the outbreak contained and over on July 2, 2026.
- **Origin & Transmission:** The index cases were a Dutch couple who had traveled through Patagonia (Argentina/Chile) on a bird-watching trip prior to boarding the ship in Ushuaia. They were exposed to the virus via its natural rodent reservoir, the long-tailed pygmy rice rat.



What We Know So Far

Hantaviruses found in the Western Hemisphere, including the U.S., can cause **Hantavirus Pulmonary Syndrome (HPS)**, a severe and potentially deadly disease that affects the lungs.

Experts say the **Andes virus**—a rare and highly deadly hantavirus strain, **known to spread person-to-person**—is behind a cruise ship outbreak that has killed three people and sickened at least four others.

@amermedicalassn

Andes Virus — A Clinical Review

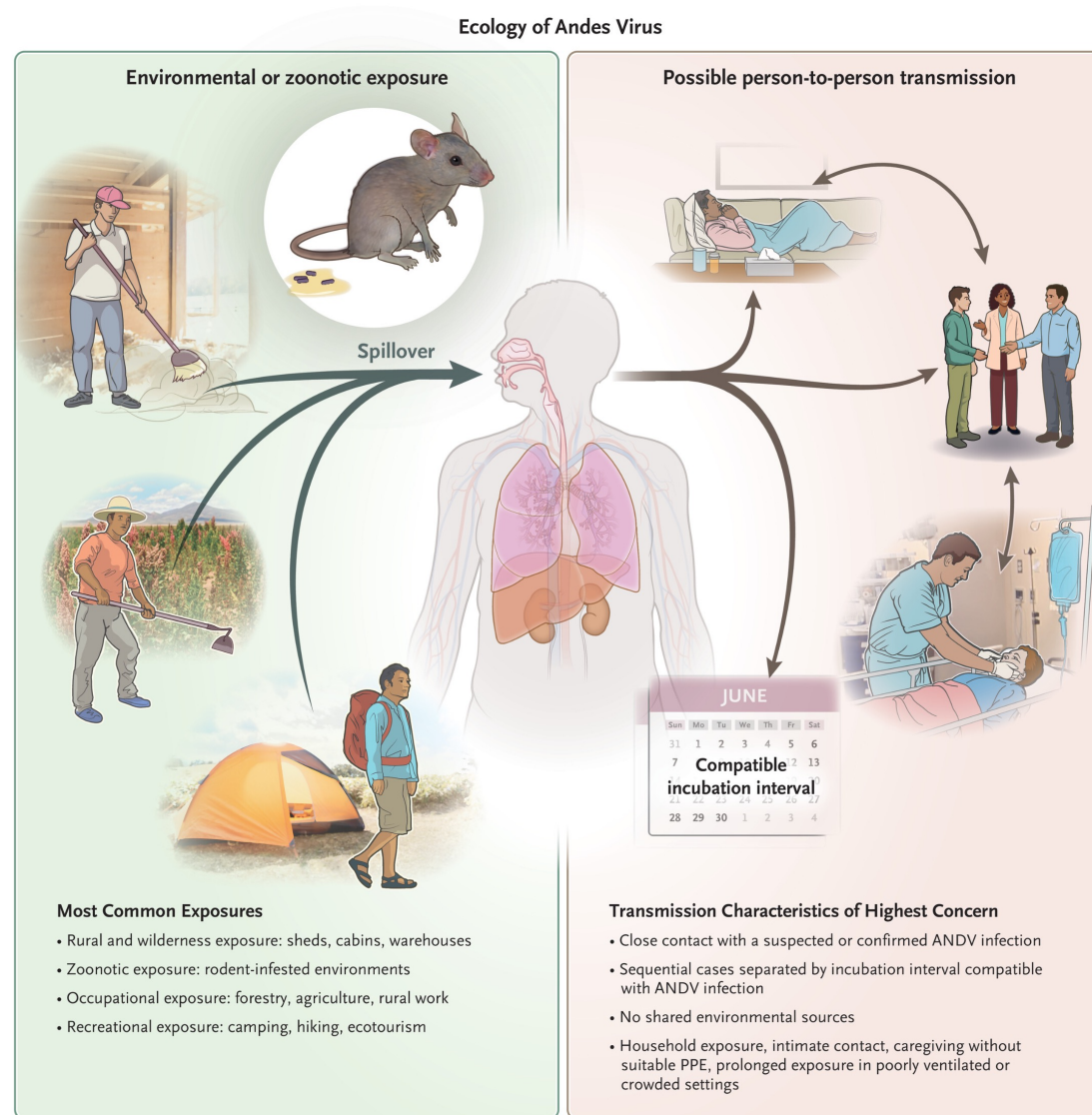
Summary

Andes virus (ANDV) is the sole orthohantavirus with documented human-to-human transmission.

We summarize the epidemiology and clinical features of ANDV infection and review best practices in clinical management, as based on published expert consensus guidelines, field experience, and clinical trials. We also evaluate currently available and investigational treatments (including the use of antiviral agents), assess emerging monoclonal antibody therapies, and outline prospects for vaccine development. Finally, we discuss important infection prevention and control measures.

Andes virus (ANDV) is a member of the species *Orthohantavirus andesense* and the only orthohantavirus with documented human-to-human transmission. Orthohantaviruses are trisegmented, negative-sense, single-stranded RNA viruses. Rodents are the primary natural reservoir, although the virus has also been found in other small mammals, including moles and shrews. Like other orthohantaviruses in the Western hemisphere, infection with ANDV may cause hantavirus pulmonary syndrome (previously also known as hantavirus cardiopulmonary syndrome), which is associated with a high case fatality rate (25 to 40%). Survival depends on host and viral factors; early identification of hantavirus pulmonary syndrome followed by initiation of optimal supportive care has been associated with better outcomes in severe cases. This review summarizes the epidemiology, clinical features, diagnostics, infection-prevention considerations, and emerging therapeutics for ANDV infection.

The hantavirus cases on the cruise ship were confirmed to be the Andes virus (ANDV).



Epidemiology

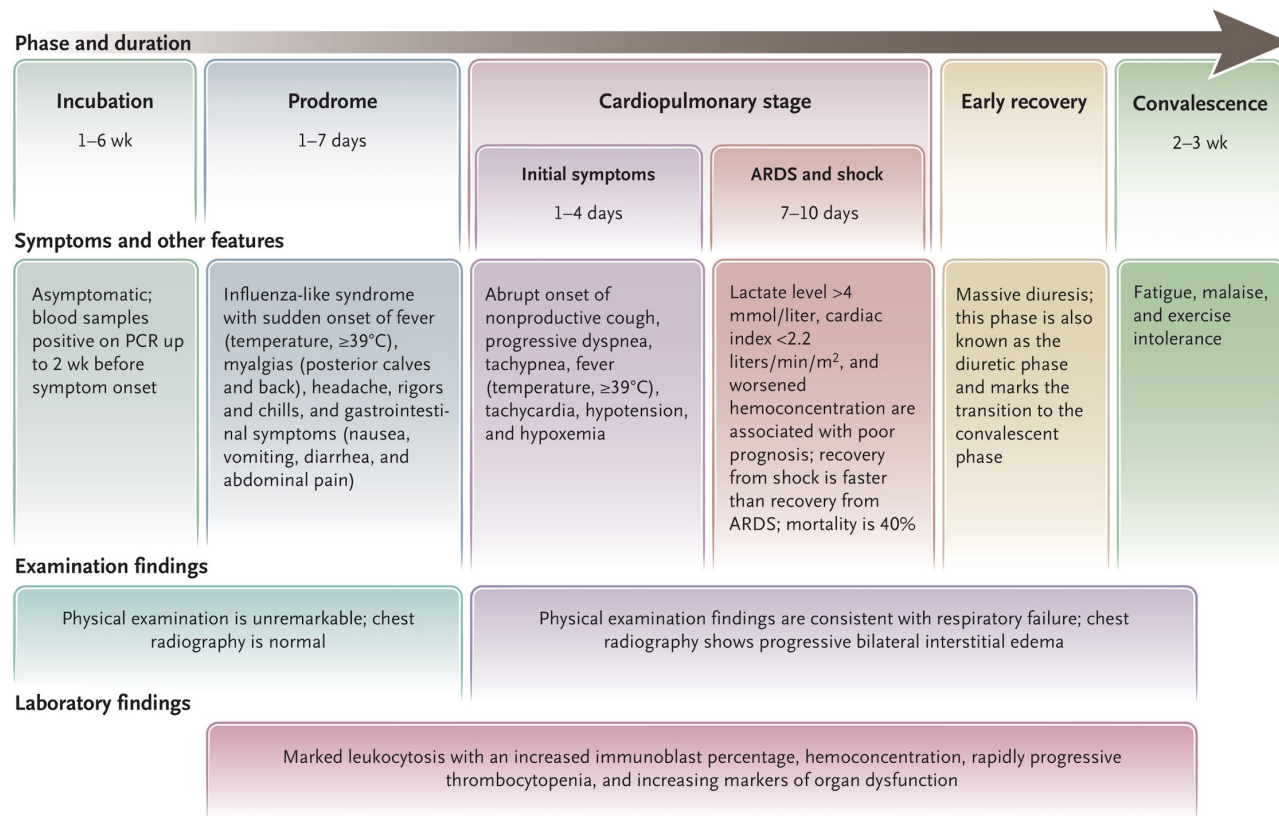
The first known cases of ANDV infection in humans were documented in Argentina and Chile in 1995, after which hantavirus pulmonary syndrome was recognized as an endemic zoonosis in the Southern Cone of South America. Cases of human infection cluster in focal areas where ANDV is hyperendemic, but the majority of cases of hantavirus pulmonary syndrome across Argentina and Chile appear to be caused by other orthohantaviruses. Human infection primarily occurs through inhalation of aerosolized rodent excreta or direct contact with contaminated materials. Cases have traditionally been associated with exposure to rodent-infested rural dwellings or structures, landfills, dumps, or poorly ventilated spaces where aerosolization of contaminated dust may occur. Less common routes of human infection include inoculation during rodent bites and human-to-human transmission.

Observations of household and nosocomial clusters of ANDV infection have implicated prolonged or extensive contact with a person infected with ANDV as a risk factor for human-to-human transmission. Human-to-human transmission of ANDV has been documented in both Argentina (notably the Epuyén outbreak in 2018 and 2019) and Chile (household and nosocomial clusters). Human transmission has also been linked to the related Buenos Aires genotype (HU39694), but the effect of different variants on transmission is unclear. Nevertheless, human-to-human transmission is generally thought to be uncommon and is associated with household exposure, intimate contact, caregiving without suitable personal protective equipment (PPE), and prolonged exposure in poorly ventilated or crowded settings. No evidence supporting efficient community transmission of ANDV exists.

KEY POINTS

Andes Virus

- Andes virus (ANDV) is the sole orthohantavirus with demonstrated human-to-human transmission and has a prolonged incubation period of up to 6 to 8 weeks.
- ANDV causes hantavirus pulmonary syndrome, a disease with a high case fatality rate (25 to 40%) that rapidly progresses from a febrile illness to severe respiratory failure and shock within hours to days.
- Clinicians should maintain a high index of suspicion for ANDV in any patient presenting with fever and severe rapidly progressive respiratory illness in conjunction with a relevant travel or exposure history; early diagnostic clues include marked leukocytosis, thrombocytopenia, and the presence of immunoblasts.
- No licensed targeted antiviral therapy or vaccine currently exists; management is focused on early recognition and aggressive supportive critical care.
- Strict infection prevention and control measures are essential to reduce the risk of transmission and include prompt isolation, use of appropriate personal protective equipment, and urgent public health notification.



Clinical Course of Hantavirus Pulmonary Syndrome.

During the cardiopulmonary phase, acute respiratory distress syndrome (ARDS) and shock occur in patients with the most severe progressive form of hantavirus pulmonary syndrome, potentially resulting in the use of venoarterial extracorporeal membrane oxygenation in selected patients. PCR denotes polymerase chain reaction.

Conclusions

ANDV is an important emerging pathogen that is capable of causing rapidly progressive disease and high mortality. Clinicians should maintain a high index of suspicion in any patient who presents with fever and a severe, rapidly progressive respiratory illness and who has had exposure to the virus or a history of travel to a region where ANDV is endemic. Rapid onset of leukocytosis, **an increased immunoblast percentage, and thrombocytopenia are important early clues**. Notification to public health authorities to coordinate testing along with isolation of suspected and confirmed cases is essential. The cornerstone of **treatment remains largely supportive** and includes prompt, appropriate care with circulatory support in the ICU for hantavirus pulmonary syndrome; circulatory support may include venoarterial ECMO. Investigational medical countermeasures are in development and should be administered in research settings only. Infection prevention and control measures are crucial in reducing community and persistent transmission of the disease.

Thyroglossal Duct Cyst



A 6-year-old boy was brought to the pediatric surgery clinic with a 2-year history of an asymptomatic, stable lump on his neck. Physical examination revealed a nontender, mobile, midline mass in the anterior neck (Panel A) that moved up with tongue protrusion and swallowing. Ultrasonography of the neck revealed a well-defined, thin-walled hypoechoic mass and a normal thyroid gland. A thyroglossal duct cyst was suspected. A thyroglossal duct cyst is a common congenital cervical anomaly that results from incomplete or failed obliteration of the embryonic thyroglossal duct, which leaves behind fluid-secreting epithelia that generate a cyst. Magnetic resonance imaging (MRI) of the neck was subsequently conducted to plan the operative approach (although cross-sectional imaging is not typically needed for this condition in children). Sagittal T2-weighted MRI showed a hyperintense, beaded fistulous duct (Panel B, arrow) originating from the tongue base, coursing inferiorly through the hyoid bone, and terminating in a cyst anterior to the thyroid cartilage. The cyst (Panel C, asterisk) and the central portion of the hyoid bone (Panel C, arrow) were excised. Histopathological analysis showed no evidence of infection or cancer. The patient recovered well and had no recurrence at 2 years of follow-up.

Serotonin Syndrome



A 23-year-old man with depression was brought to the emergency department 1 hour after a witnessed ingestion of 2000 mg of sertraline in a suicide attempt. His depression had been treated with daily sertraline and clonazepam. Initial physical examination was notable only for slight drowsiness. Urine toxicologic screening was positive only for benzodiazepines. Six hours after the ingestion, the patient's temperature rose to 38.0°C. On repeat assessment, he was agitated, and restraints were needed for the examination to continue. The pupils in both eyes were dilated to 6 mm. Spontaneous clonus was observed in the calves ([Video 1A](#)), and sustained, inducible clonus and patellar hyperreflexia were also noted in both legs ([Video 1B](#); identifying information has been blurred in the video and in the still images [above] from Video 1B). No ocular clonus, diaphoresis, muscular rigidity, or tremor was noted. A diagnosis of serotonin syndrome was made. In serotonin syndrome, clonus and hyperreflexia are typically more pronounced in the legs than in other parts of the body. Treatment with intravenous diazepam was given. Over the next 24 hours, the patient's symptoms abated. He was discharged to a psychiatric facility. At follow-up 1 month later, his depression was abating.

VIDEO 1



Clonus in the Legs and Patellar Hyperreflexia 0m 34s

An Echo Unheard (Wortspiel)

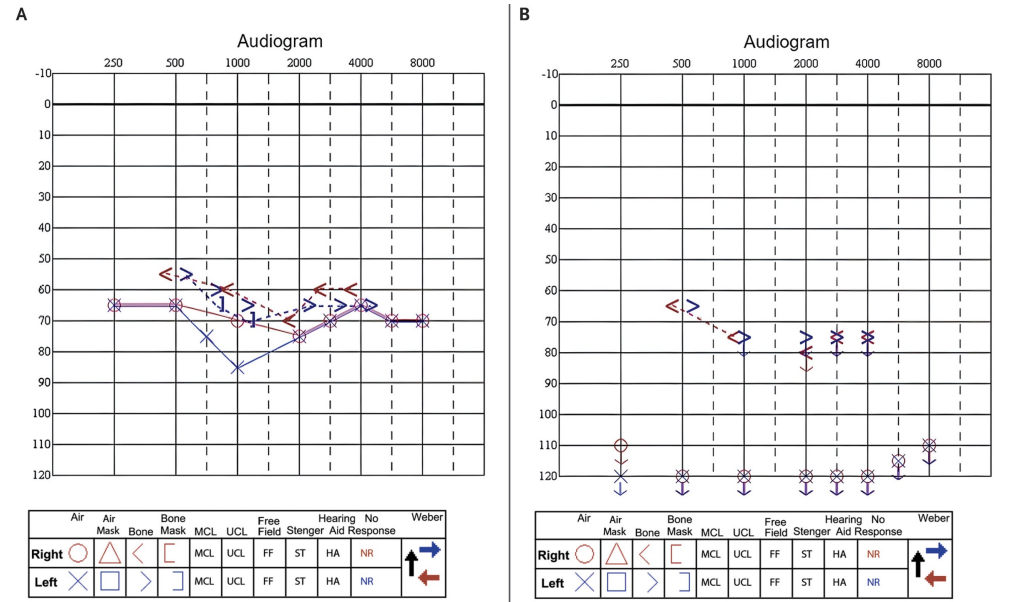
A 58-year-old woman was admitted to the hospital for rapidly progressive bilateral hearing loss. She reported no headache, vertigo, tinnitus, or dizziness. She had a childhood-onset **hearing impairment of unknown cause**, which had been stable since childhood and for which **she used hearing aids**.

The medical history was notable for a **20-year history of rheumatoid arthritis** and a **6-year history of myasthenia gravis**. Rheumatoid arthritis was managed with weekly subcutaneous methotrexate (15 mg) and **twice-yearly rituximab** (most recent infusion, 5 months earlier), with prednisone (20 mg per day) added 2 weeks before the current presentation for a disease flare and currently being tapered. Immunoglobulin levels before rituximab therapy were normal (IgG, 842 mg per deciliter; IgM, 87 mg per deciliter; IgA, 94 mg per deciliter).

Myasthenia gravis was treated with pyridostigmine and intermittent intravenous immune globulin (IVIG), with the most recent course administered 2 years earlier. She also had hypertension, treated with metoprolol, and diet-managed diabetes. She reported no history of smoking or use of illicit drugs.

Two weeks before admission, **she noted a gradual decline in hearing**. This gradual decline was followed several days later by an abrupt worsening.

Pure-tone audiometry showed **bilateral moderate-to-severe sensorineural hearing loss** with overlapping air- and bone-conduction thresholds ([Figure 1A](#)). The patient was admitted to the otolaryngology service, where treatment with high-dose prednisone (60 mg per day) was initiated for suspected idiopathic sudden sensorineural hearing loss. Inhalation of carbogen (a gas mixture of 5% CO₂ and 95% O₂) was also administered to promote cochlear vasodilation and increase oxygen delivery. **No improvement was noted despite treatment.**



Sequential Audiometry.

Panel A shows bilateral moderate-to-severe sensorineural hearing loss with no substantial air–bone gap. Panel B, obtained 12 days later, shows progression to severe-to-profound hearing loss. The x axis shows frequency (Hz), and the y axis shows hearing level (dB HL); thresholds plotted lower on the graph indicate poorer hearing. Red denotes the right ear and blue the left. Circles and crosses indicate air conduction, and angle brackets and square brackets indicate unmasked and masked bone conduction, respectively. Downward arrows indicate no response at the maximum output of the audiometer. The apparent air–bone gap at 500 Hz in Panel B should not be interpreted as a true conductive component, since the bone-conduction responses at this intensity probably reflect vibrotactile perception rather than true hearing.

Laboratory studies showed a **white-cell count of 13,200 per cubic millimeter** (95% neutrophils), a hemoglobin level of 13.2 g per deciliter, and a platelet count of 213,000 per cubic millimeter. The glycated hemoglobin level was 7.3% (reference range, 4 to 5.7). **The alanine aminotransferase (ALT) level was 50 U per liter (reference range, 10 to 40), and the C-reactive protein (CRP) level was 18 mg per liter (reference range, <5).** Results of other routine chemical and liver-function tests were normal. Salvage intratympanic glucocorticoid therapy was initiated, but hearing continued to deteriorate; a follow-up audiogram obtained 12 days after the first showed progression to severe-to-profound bilateral sensorineural hearing loss across all tested frequencies ([Figure 1B](#)).

Given the progressive hearing loss and concern for vasculitis, **intravenous methylprednisolone was initiated.** Tests for antinuclear antibodies, antineutrophil cytoplasmic antibodies, antiphospholipid antibodies, and rheumatoid factor were negative, and complement levels were normal. Treponemal antibody testing was negative. A chest radiograph was normal. Magnetic resonance imaging (MRI) of the head revealed scattered, nonspecific punctate hyperintensities on T2-weighted fluid-attenuated inversion recovery images without pathologic enhancement, restricted diffusion, vasculitis, or leptomeningeal infiltration. High-resolution MRI of the inner ear with gadolinium enhancement showed no abnormal enhancement of the cochlea, labyrinth, or vestibulocochlear nerve.

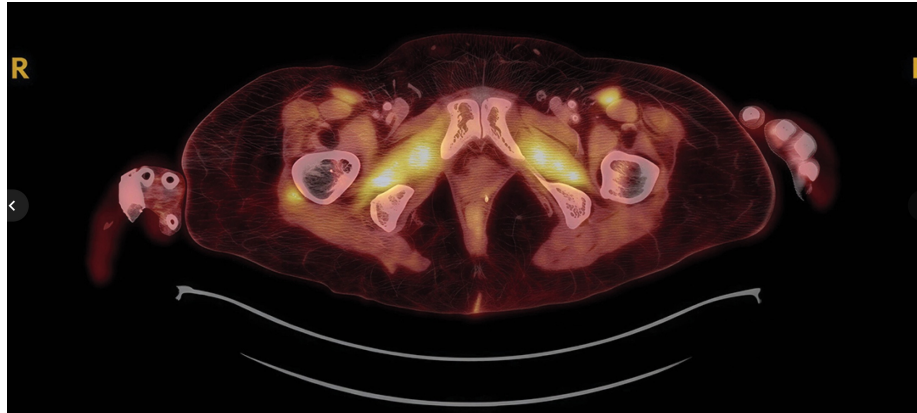
On hospital day 9, the patient's clinical course was complicated by the **onset of low-grade fever, diarrhea, and myalgias localized to the hips and calves**. The white-cell count increased to 14,900 per cubic millimeter, and the CRP level increased to 189 mg per liter. The **ALT level was 61 U per liter, and the aspartate aminotransferase (AST) level was 90 U per liter**. Blood and stool cultures were positive for *Salmonella enterica* serotype Enteritidis. The patient was transferred to the internal medicine service for management of disseminated infection. Intravenous ceftriaxone was administered, and glucocorticoids were tapered. No exposure to suspected contaminated food or to ill children was reported. The IgG level was 484 mg per deciliter (reference range, 650 to 1600), the IgA level 49 mg per deciliter (reference range, 70 to 400), and the IgM level 25 mg per deciliter (reference range, 50 to 300). HIV serologic testing was negative. CT angiography of the chest, abdomen, and pelvis showed no evidence of aortitis or mycotic aneurysms. Despite antimicrobial therapy, the patient's **clinical status continued to decline, with persistent intermittent fevers, new-onset thrombocytopenia (platelet count, 132,000 per cubic millimeter), an elevated creatine kinase level (941 U per liter; reference range, 40 to 200), an increased lactate dehydrogenase level (964 U per liter; reference range, 125 to 220), and progressive transaminitis (ALT level, 78 U per liter; AST level, 113 U per liter)**.

On hospital day 15, proximal weakness in the legs and worsening myalgias developed, predominantly on the left side. There were no visual changes. Examination revealed 3/5 strength in the left iliopsoas and quadriceps, 4/5 in the left hamstrings, and 4/5 in the corresponding right proximal muscle groups. Bilateral leg edema was present. Tenderness to palpation was noted in the hips and calves, greater on the left side. Sensation was mildly reduced over the left hip and ankle. Patellar reflexes were symmetrically diminished with normal Achilles, plantar, and Babinski reflexes. There was no ptosis, and muscle strength remained stable during repeated effort. The gait was ataxic, and walking was limited to short distances. A single episode of bowel and bladder incontinence was reported.

MRI of the thoracic and lumbar spine showed disc protrusions from L2 to L5 with mild left-predominant impingement of the L3, L4, and L5 nerve roots. MRI with gadolinium enhancement showed no epidural abscess, vertebral osteomyelitis, cord compression, or myelitis.

Nerve-conduction studies revealed a symmetric reduction in sensory and motor amplitudes across the arms and legs, with normal F-wave latencies, findings consistent with mild axonal neuropathy. Needle electromyography showed widespread spontaneous activity in the upper and lower limbs and the lumbar and thoracic paraspinal musculature. Low-amplitude polyphasic motor-unit potentials, suggestive of a myopathic pattern, were identified in several muscles, most prominently in the left iliopsoas and vastus lateralis, corresponding to the side of greater clinical weakness.

¹⁸F-fluorodeoxyglucose PET-CT showed bilateral uptake along the internal obturator muscles bilaterally ([Figure 2](#)) as well as along the sartorius muscles, without mass or lymphadenopathy.



Positron-Emission Tomography–Computed Tomography. Increased uptake of ^{18}F -fluorodeoxyglucose was observed along the obturator internus muscles bilaterally.

Lumbar puncture was performed. Analysis of the cerebrospinal fluid (CSF) revealed a white-cell count of 49 per cubic millimeter (73.5% neutrophils). The glucose level was 43 mg per deciliter (serum glucose level, 84 mg per deciliter), and the protein level was 63 mg per deciliter (normal range, 15 to 60).

Immunophenotyping and cytologic assessment of the CSF were negative for malignant cells. Testing for paraneoplastic autoimmune antibodies was negative. Bacterial cultures were negative; however, their sensitivity may have been compromised by the ongoing administration of ceftriaxone for the recent salmonella bacteremia. A polymerase-chain-reaction (PCR) assay of the CSF for herpes simplex virus and VZV was negative. Given the diagnostic uncertainty, an expanded molecular workup was undertaken; a multiplex PCR panel (BioFire Diagnostics Meningitis/Encephalitis Panel) was positive for enterovirus.

After the initiation of IVIG, the patient's fever and myalgia resolved, motor function improved gradually, and aminotransferase and creatine kinase levels normalized over a 4-week period. Viral clearance was confirmed by negative whole-blood PCR testing 3 weeks later. However, there was no appreciable improvement in hearing, and the patient was referred for an evaluation for a cochlear implant. At 4-month follow-up, she remained otherwise asymptomatic with no recurrence of fever or myalgia, and liver-function tests and creatine kinase levels had normalized.

Commentary

This patient presented to the otolaryngology service with sudden sensorineural hearing loss. Despite a history of rheumatoid arthritis, myasthenia gravis, and known immunosuppression, the presentation was initially managed as idiopathic sudden sensorineural hearing loss with high-dose glucocorticoids. However, the bilateral presentation and lack of response to this treatment prompted a broader differential diagnosis. It was only after the emergence of neuromuscular symptoms that further evaluation — including PCR assays of the CSF and blood — led to the diagnosis of disseminated chronic enteroviral infection.

Ultimately, this case underscores the potential for atypical presentations of infection in patients with immunodeficiency, especially that resulting from rituximab.

The name **ECHO** stands for Enteric Cytopathic Human Orphan. They were called "orphans" when first discovered in the 1950s because they caused observable changes in lab cells but were not yet linked to any specific diseases. They are a subgroup within the Enterovirus genus.

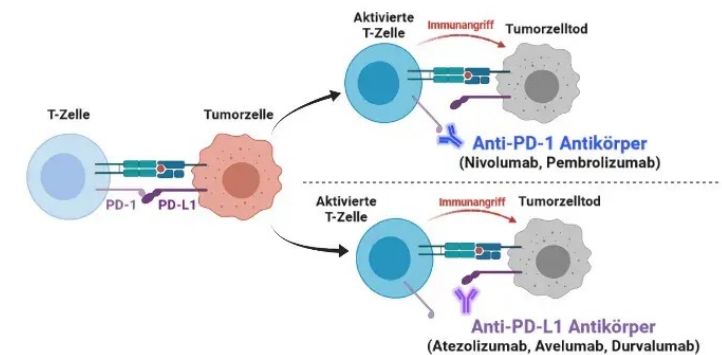
THE LANCET

Atezolizumab ist ein humanisierter monoklonaler Antikörper, der als [Checkpoint-Inhibitor](#) in der Krebstherapie eingesetzt wird.

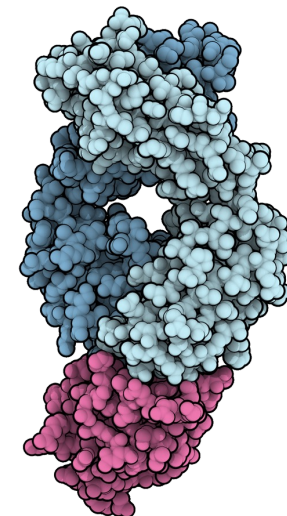
- **Zielstruktur:** Bindet an das Protein PD-L1 auf Tumorzellen und Immunzellen.
- **Funktion:** Blockiert die Wechselwirkung von PD-L1 mit PD-1, wodurch die T-Zell-Antwort reaktiviert und die körpereigene Immunabwehr gegen den Tumor gesteigert wird.

Wichtigste Anwendungsgebiete (Indikationen)

- **Lungenkrebs:** Nicht-kleinzelliges (NSCLC) und kleinzelliges Lungenkarzinom (SCLC), oft in Kombination mit Chemotherapie.
- **Brustkrebs:** Triple-negatives Mammakarzinom (TNBC) bei nachgewiesener PD-L1-Expression.
- **Leberzellkarzinom (HCC):** Fortgeschrittenes hepatozelluläres Karzinom (in Kombination mit Bevacizumab).
- **Urothelkarzinom:** Behandlung von Blasen- und Harnwegstumoren.



**GELBE
LISTE.**
PHARM NOEX



In inoperable NSCLC, Checkpoint inhibitor did not help beyond irradiation

Induction and consolidation atezolizumab with stereotactic body radiation therapy versus radiation alone in high-risk, early-stage non-small-cell lung cancer (SWOG/NRG S1914): a multicentre, open-label, superiority, phase 3, randomised controlled trial

Summary

Background Stereotactic body radiation therapy (SBRT) is the standard of care for early-stage, medically inoperable non-small-cell lung cancer (NSCLC). We aimed to test the addition of neoadjuvant, concurrent, and adjuvant atezolizumab with SBRT for early-stage NSCLC.

Methods In this multicentre, open-label, phase 3, randomised controlled trial, eligible patients from 146 institutions across the USA who had T1–T3N0M0 NSCLC ≤ 7 cm, and were medically inoperable or declined surgery, and had at least one risk factor suggestive of increased risk of recurrence, were included in the study. Patients underwent open-label equal and stratified randomisation to SBRT over three to eight fractions with or without up to eight cycles of neoadjuvant, concurrent, and adjuvant atezolizumab 1200 mg intravenously every 21 days for up to eight cycles, with SBRT initiated with cycle three. The primary objective was to compare overall survival between the two groups. The group sequential design included four interim analyses. Target accrual was 480 patients (432 eligible). The trial is registered with ClinicalTrials.gov (NCT04214262) and is closed to new participants.

Findings Between March 25, 2020, and Sept 9, 2024, 417 patients were enrolled and randomly assigned to atezolizumab plus SBRT (n=210) or SBRT alone (n=207). 402 were eligible and made up the modified intention-to-treat population (201 per group). The median age was 72·8 years (IQR 67·4–78·4), 218 (54%) of 402 participants were female, and 184 (46%) were male. Accrual closed at the first interim analysis of all randomly assigned participants for futility with 76 progression-free survival (PFS) events and 41 deaths among 400 eligible participants (200 per group). An updated analysis was performed with 140 PFS events, 92 deaths, and a median of 24·8 months (range 0·1–64·9; IQR 18·6–36·0) of follow-up among living patients. The overall survival hazard ratio was 1·04 (95% CI 0·69–1·58; one-sided p=0·58). Estimated 2-year overall survival was 82% in both groups (95% CI 75–87). Grade 3 or higher adverse event rates were 12% with atezolizumab plus SBRT and 3% with SBRT. Two grade 5 respiratory events occurred in the atezolizumab plus SBRT group.

Interpretation In the first fully reported phase 3 cooperative group trial to assess immunotherapy in inoperable early-stage NSCLC, we observed no improvement in overall survival with atezolizumab plus SBRT, and more grade 3 or higher adverse events were reported with atezolizumab combined with SBRT.



	Atezolizumab plus SBRT group (n=201)	SBRT group (n=201)	All participants (n=402)
Age, years	72.3 (67.5–77.7)	73.5 (67.4–79.0)	72.8 (67.4–78.4)
Sex			
Female	100 (50%)	118 (59%)	218 (54%)
Male	101 (50%)	83 (41%)	184 (46%)
BMI	27.0 (23.5–30.8)	26.0 (22.7–30.8)	26.6 (22.9–30.8)
Race or ethnicity			
White	169 (84%)	162 (81%)	331 (82%)
Black	18 (9%)	27 (13%)	45 (11%)
Asian	4 (2%)	6 (3%)	10 (2%)
Native American	2 (1%)	2 (1%)	4 (1%)
Multiracial	1 (<1%)	2 (1%)	3 (1%)
Unknown	7 (3%)	2 (1%)	9 (2%)
Hispanic ethnicity	8 (4%)	5 (2%)	13 (3%)
Tumour size, cm	2.4 (1.7–3.2)	2.3 (1.7–3.3)	2.3 (1.7–3.2)
Tumour size ≥4 cm	29 (14%)	29 (14%)	58 (14%)
Tumour size <4 cm	172 (86%)	172 (86%)	344 (86%)
Central tumour location	63 (31%)	64 (32%)	127 (32%)
ECOG performance status			
0–1	178 (89%)	180 (90%)	358 (89%)
2	23 (11%)	21 (10%)	44 (11%)
FEV ₁	1.6 (1.1–2.2)	1.5 (1.2–2.0)	1.6 (1.1–2.1)
DLCO, mL/min per mm Hg	13.2 (9.7–18.1)	12.7 (9.5–16.6)	13.0 (9.6–17.3)
DLCO, %	58.5 (45.0–72.0)	54.0 (43.0–68.0)	56.0 (44.0–71.0)
Smoking status			
Current	67 (33%)	66 (33%)	133 (33%)
Recent	20 (10%)	25 (12%)	45 (11%)
Former	109 (54%)	105 (52%)	214 (53%)
Never	5 (2%)	5 (2%)	10 (2%)
Maximum standardised uptake value	7.6 (3.9–12.8)	7.9 (3.9–12.3)	7.7 (3.9–12.7)
Grade			
Cannot be assessed	44 (22%)	36 (18%)	80 (20%)
Well	11 (5%)	16 (8%)	27 (7%)
Moderately	76 (38%)	72 (36%)	148 (37%)
Poorly	34 (17%)	33 (16%)	67 (17%)
Undifferentiated	2 (1%)	0	2 (<1%)
Unknown	34 (17%)	44 (22%)	78 (19%)
Number of high-risk factors			
0	0	2 (1%)	2 (<1%)
1	75 (37%)	84 (42%)	159 (40%)
2	82 (41%)	72 (36%)	154 (38%)
3	44 (22%)	43 (21%)	87 (22%)
Histological type of cancer			
Non-squamous	129 (64%)	130 (65%)	259 (64%)
Squamous	72 (36%)	71 (35%)	143 (36%)

(Table 1 continues on next page)

	Atezolizumab plus SBRT group (n=201)	SBRT group (n=201)	All participants (n=402)
(Continued from previous page)			
T substage			
T1A	11 (5%)	10 (5%)	21 (5%)
T1B	63 (31%)	68 (34%)	131 (33%)
T1C	67 (33%)	61 (30%)	128 (32%)
T2A	33 (16%)	33 (16%)	66 (16%)
T2B	15 (7%)	11 (5%)	26 (6%)
T3	12 (6%)	18 (9%)	30 (7%)

Data are median (IQR) or n (%). DLCO=diffusing capacity of the lungs for carbon monoxide. ECOG=Eastern Cooperative Oncology Group. FEV₁=forced expiratory volume in 1 sec. SBRT=stereotactic body radiation therapy.

Table 1: Participant characteristics in the modified intention-to-treat population

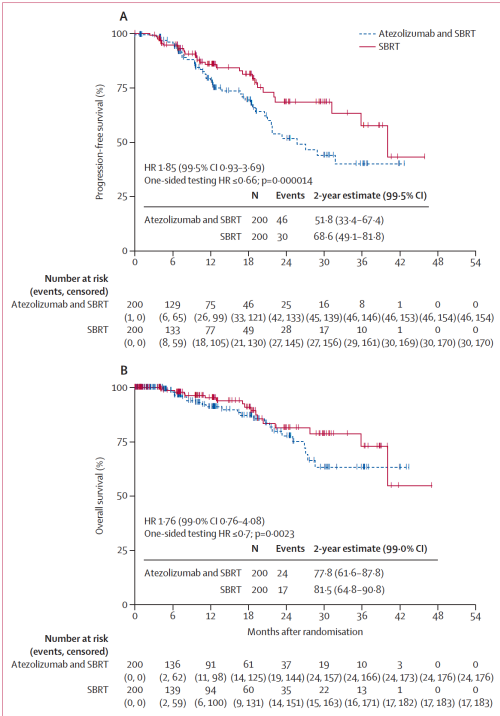


Figure 2: Progression-free survival and overall survival in the modified intention-to-treat population at the first interim analysis evaluating early stopping for futility
(A) Progression-free survival. (B) Overall survival. SBRT=stereotactic body radiation therapy. HR=hazard ratio.

Progression free survival
Worse

Toxicity
Worse

	Atezolizumab and SBRT (n=193)	SBRT (n=194)
Any grade 2–5 treatment emergent adverse event	144 (75%)	49 (25%)
Any grade 3–5 treatment emergent adverse event	69 (36%)	27 (14%)
Any serious adverse event	42 (22%)	0
Any grade 2–5 treatment-related adverse event	88 (46%)	22 (11%)
Any grade 3–5 treatment-related adverse event	24 (12%)	5 (3%)
Any treatment-related adverse event resulting in death	2 (1%)	0

SBRT=stereotactic body radiation therapy.

Table 2: Grades 2–5 adverse events in the toxicity-evaluable population

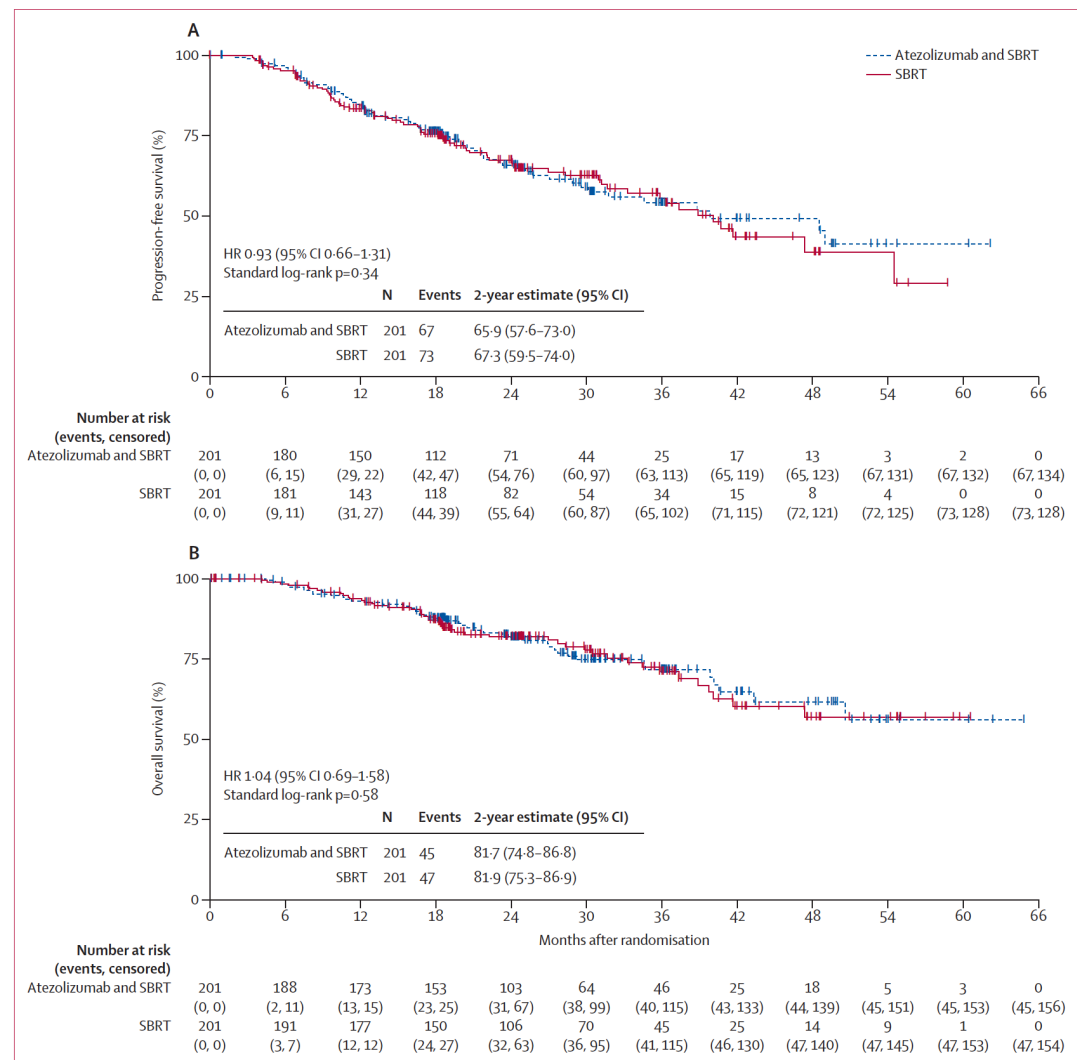
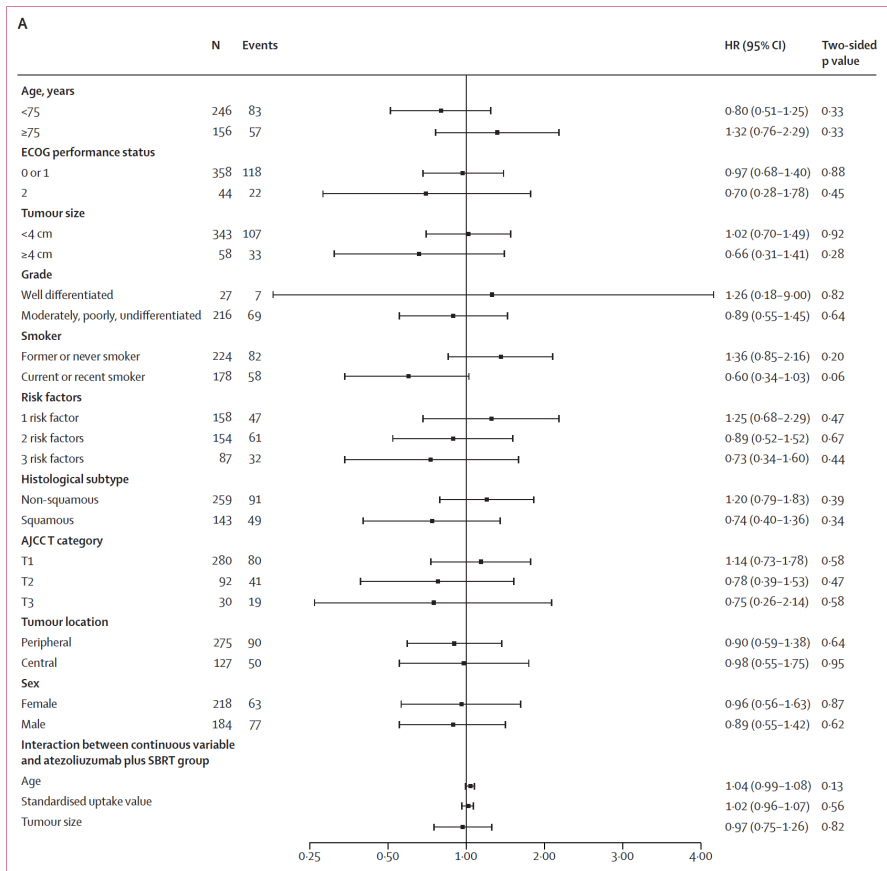


Figure 3: Updated progression-free survival and overall survival in the modified intention-to-treat population
(A) Progression-free survival. (B) Overall survival. SBRT=stereotactic body radiation therapy. HR=hazard ratio.



(Figure 4 continues on next page)

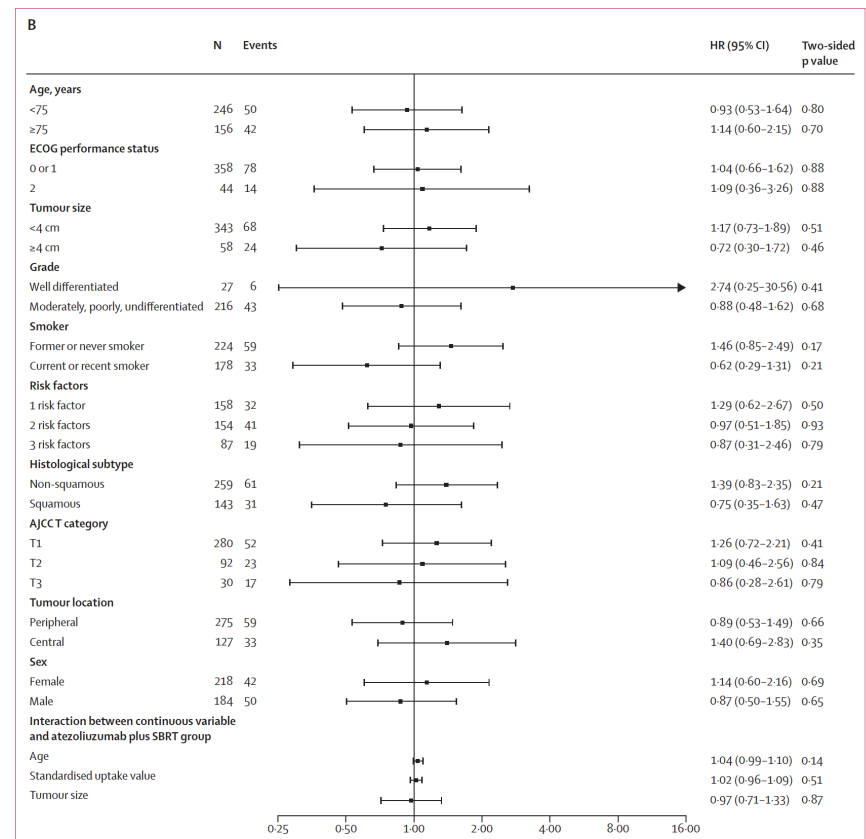


Figure 4: Subgroup hazard ratios and confidence intervals in the modified intention-to-treat population
(A) Progression-free survival. (B) Overall survival. HR=hazard ratio. AJCC T=American Joint Committee on Cancer Tumor Stage. ECOG=Eastern Cooperative Oncology Group.

Research in context

Evidence before this study

We conducted a search of PubMed from database inception up to June 25, 2026, using the search terms (“early stage lung cancer” OR “stage 1 lung cancer” or “early stage NSCLC” OR “stage 1 NSCLC”) AND (SBRT OR “Stereotactic Body Radiation Therapy” OR SABR OR “Stereotactic Ablative Radiotherapy”) AND (Immunotherapy OR “immune checkpoint inhibitor”). We identified one randomised phase 2 trial (I-SABR) that investigated the addition of the immune checkpoint inhibitor nivolumab to stereotactic body radiation therapy (SBRT) in early-stage non-small-cell lung cancer (NSCLC). The I-SABR trial identified improved 4-year event-free survival from 53% (95% CI 42–67%) to 77% (95% CI 66–91%; hazard ratio 0.38 [95% CI 0.19–0.75]; $p=0.0056$). No randomised phase 3 trials have been published. The SWOG Cancer Research Network/NRG Oncology S1914 trial investigated the incorporation of immunotherapy with SBRT in early-stage inoperable NSCLC in a randomised phase 3 setting.

Added value of this study

No completed, randomised phase 3 trials have been published to date. SWOG/NRG Oncology S1914 specifically evaluated a strategy of neoadjuvant, concurrent, and adjuvant immunotherapy with SBRT in patients with early-stage inoperable NSCLC with risk factors suggestive of an increased risk of recurrence. In contrast to the single institution, randomised phase 2 I-SABR trial, S1914 found no benefit to immunotherapy for either overall or progression-free survival, and increased toxicity with immunotherapy.

Implications of all the available evidence

SBRT remains the standard of care for early-stage, inoperable NSCLC. Randomised phase 3 data do not support routine incorporation of immunotherapy for patients with early-stage NSCLC treated with SBRT.



Physiotherapy in
ER saved time and
money

Physiotherapist-led care for musculoskeletal conditions in the emergency department (RESHAP-ED): a randomised controlled trial with economic evaluation

Summary

Background Long stays in the emergency department compromise patient safety and health system performance. Physiotherapist-led models of care may improve care and emergency department performance, but their effects have not been rigorously evaluated in randomised trials. We compared the effectiveness, safety, and cost-effectiveness of physiotherapist-led care with usual care for patients presenting to the emergency department with musculoskeletal conditions.

Methods RESHAP-ED was an open-label, pragmatic, randomised trial that recruited adults aged 18 years and older at five emergency departments in New South Wales, Australia, with uncomplicated musculoskeletal conditions (eg, soft tissue conditions, neck and back pain, and fractures or dislocations not requiring orthopaedic review or surgery). Participants were randomly assigned (1:1), using statistician-generated randomly permuted blocks, to either physiotherapist-led care (intervention) or usual physician-led or nurse practitioner-led care (control). The primary outcome was length of stay in the emergency department, calculated as time from arrival to discharge, analysed in the intention-to-treat population using a linear mixed-effects model. The trial was prospectively registered on the Australian New Zealand Clinical Trials Registry (ACTRN12623000782639) and is completed.

Findings Between Nov 22, 2023 and March 29, 2025, 4219 patients were screened, 2728 were deemed ineligible for inclusion, and 1491 participants were randomly assigned (746 assigned to the physiotherapy-led intervention group and 745 assigned to the physician-led or nurse-led practitioner control group). Following the exclusion of 16 participants after randomisation, 1475 were included in the analysis (737 in the intervention group and 738 in the control group). The mean age of participants was 40·1 years (SD 16·5). 719 (48·7%) participants were male, 755 (51·2%) were female, and one (0·1%) participant had unreported sex data. Follow-up for the primary outcome was 100% complete. The mean length of stay in the emergency department was 2·4 h in the intervention group and 3·4 h in the control group (−1·0 h [95% CI −1·2 to −0·8]). Adverse events were reported by 39 (6·6%) of 591 participants in the intervention group versus 33 (5·9%) of 555 in the control group ($p=0·72$). The intervention group had lower costs (−\$35·1 [95% CI −69·0 to −1·7]) and a high probability (98·1%) of being cost-effective.

Interpretation A physiotherapist-led model of care in the emergency department reduced length of stay among patients presenting with uncomplicated musculoskeletal conditions, without compromising health outcomes or safety, and was cost-effective.

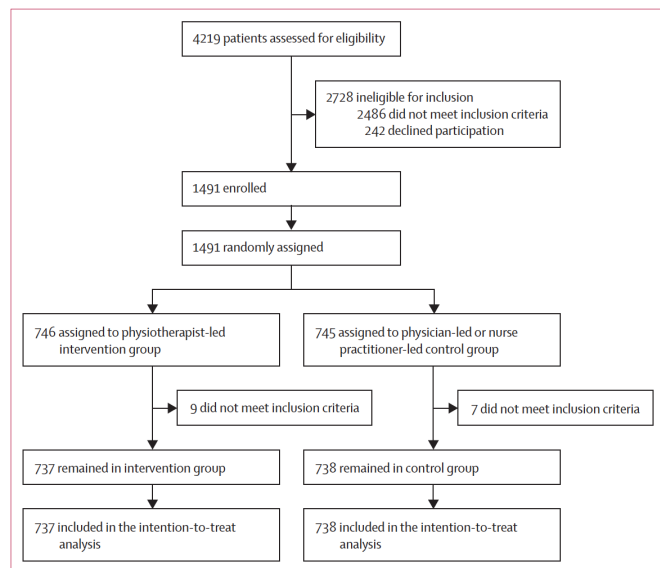


Figure 1: Trial profile

	Intervention (n=737)	Control (n=738)	Overall (n=1475)
Age, years	40.0 (16.2)	40.3 (16.8)	40.1 (16.5)
Sex			
Male	362 (49.1%)	357 (48.4%)	719 (48.7%)
Female	374 (50.7%)	381 (51.6%)	755 (51.2%)
Not reported	1 (0.1%)	0	1 (0.1%)
Country of birth			
Australia	494 (67.0%)	502 (68.0%)	996 (67.5%)
Overseas	242 (32.8%)	236 (32.0%)	478 (32.4%)
Not reported	1 (0.1%)	0	1 (0.1%)
Language spoken at home			
English	693 (94.0%)	699 (94.7%)	1392 (94.4%)
Non-English	43 (5.8%)	37 (5.0%)	80 (5.4%)
Not reported	1 (0.1%)	2 (0.3%)	3 (0.2%)
Need for interpreter			
No	729 (98.9%)	731 (99.1%)	1460 (99.0%)
Yes	7 (0.9%)	6 (0.8%)	13 (0.9%)
Not reported	1 (0.1%)	1 (0.1%)	2 (0.1%)
Socio-economic status*			
Low socio-economic status	109 (14.8%)	113 (15.3%)	222 (15.1%)
High socio-economic status	563 (76.4%)	556 (75.3%)	1119 (75.9%)
Not reported	65 (8.8%)	69 (9.3%)	134 (9.1%)
Arrival time			
Outside working hours	341 (46.3%)	348 (47.2%)	689 (46.7%)
Working hours	396 (53.7%)	390 (52.8%)	786 (53.3%)
Triage category†			
2: emergency	3 (0.4%)	1 (0.1%)	4 (0.3%)
3: urgent	49 (6.6%)	40 (5.4%)	89 (6.0%)
4: semi-urgent	586 (79.5%)	577 (78.2%)	1163 (78.8%)
5: non-urgent	99 (13.4%)	120 (16.3%)	219 (14.8%)
Mode of arrival			
Ambulance	24 (3.3%)	27 (3.7%)	51 (3.5%)
Self-presented	707 (95.9%)	707 (95.8%)	1414 (95.9%)
Other	3 (0.4%)	2 (0.3%)	5 (0.3%)
Not reported	3 (0.4%)	2 (0.3%)	5 (0.3%)
Principal emergency department diagnosis			
Fractures or dislocations	309 (41.9%)	288 (39.0%)	597 (40.5%)
Soft-tissue conditions	428 (58.1%)	450 (61.0%)	878 (59.5%)

Data are mean (SD) or n (%). SEIFA=Socio-Economic Indexes for Areas. *SEIFA categories were used to measure socio-economic status (based on postcode of residence); SEIFA categories 1–5 indicate low socio-economic status and 6–10 indicate high socio-economic status. †Triage category according to the Australasian Triage Scale.

Table 1: Baseline characteristics

	Intervention (n=737)	Control (n=738)	Effect size (95% CI)	p value
Primary outcome				
Emergency department length of stay (h), unadjusted	2.4 (2.0)	3.4 (1.9)	Mean difference –1.0 (–1.2 to –0.8)	<0.0001
Emergency department length of stay (h), adjusted	2.4 (2.0)	3.4 (1.9)	Mean difference –1.0 (–1.2 to –0.8)	<0.0001
Emergency department length of stay (h), sensitivity*	2.4 (2.0)	3.4 (1.9)	Mean difference –1.1 (–1.3 to –0.9)	<0.0001
Secondary outcomes				
Time to initial assessment (min)	47.6 (31.4)	86.1 (62.0)	Mean difference –38.6 (–43.6 to –33.6)	<0.0001
Duration of clinical care (min)	96.9 (113.3)	116.4 (101.3)	Mean difference –19.5 (–30.7 to –8.4)	0.0006
Emergency department length of stay ≤4 h	661 (89.7%)	561 (76.0%)	OR 2.8 (2.1 to 3.8)	<0.0001
Seen on time†	525/709 (74.0%)	339/711 (47.7%)	OR 3.2 (2.6 to 4.0)	<0.0001
Short stay admission	10 (1.4%)	14 (1.9%)	OR 0.7 (0.3 to 1.6)	0.41
Inpatient admission	23 (3.1%)	24 (3.3%)	OR 1.0 (0.5 to 1.7)	0.89
Emergency department re-presentation‡	9 (1.2%)	9 (1.2%)	OR 1.0 (0.4 to 2.5)	1.0
Readmission§	3 (0.4%)	2 (0.3%)	OR 1.5 (0.3 to 9.0)	0.66
Imaging	553 (75.0%)	578 (78.3%)	OR 0.8 (0.7 to 1.1)	0.13
Opioids	111 (15.1%)	119 (16.1%)	OR 0.9 (0.7 to 1.2)	0.57
Gabapentinoids	1 (0.1%)	0	..	..
Benzodiazepines	2 (0.3%)	0	..	..

Data are mean (SD), n (%), or n/N (%), unless otherwise specified. Data available for time to initial assessment, duration of clinical care, and seen on time: intervention n=709, control n=711. Model estimates obtained using a generalised linear mixed model with a fixed effect indicating the group allocation, a random hospital effect with binomial distribution, and logit link function. p values are nominal (unadjusted). Multiplicity across secondary outcomes was controlled using the Holm–Sidak procedure (adjusted significance thresholds 0.013–0.050). All secondary outcomes remained statistically significant after adjustment. OR=odds ratio. *Means and 95% CIs were obtained using Duan's smearing estimator applied to marginal predictions from a log10-scale mixed-effects model.²⁴ †Seen on time refers to proportion of presentations for which the waiting time to commencement of clinical care was within the time specified in the definition of the triage category: emergency (within 10 min), urgent (within 30 min), semi-urgent (within 60 min), and non-urgent (within 120 min). ‡Re-presentation to the emergency department for the same chief complaint within 72 h. §Readmitted as hospital inpatient within 30 days.

Table 2: Primary and secondary health service outcomes by trial groups

	Intervention (n=684)*	Control (n=665)*	Mean difference (95% CI)	p value
Quality-of-life†				
Day 1	593; 63.8 (20.1)	550; 64.0 (20.1)	-0.1 (-2.3 to 2.1)	0.93
Day 7	554; 69.9 (18.8)	512; 68.9 (18.6)	1.1 (-1.2 to 3.3)	0.35
Day 42	500; 75.9 (18.3)	437; 74.9 (17.7)	0.8 (-1.6 to 3.1)	0.53
Pain intensity‡				
Day 1	599; 4.5 (2.2)	561; 4.7 (2.3)	-0.2 (-0.5 to 0.0)	0.066
Day 7	556; 3.2 (2.1)	518; 3.3 (2.3)	-0.2 (-0.4 to 0.1)	0.19
Day 42	506; 1.8 (1.9)	442; 1.8 (1.9)	0.1 (-0.2 to 0.3)	0.67
Satisfaction§				
Day 1	594; 8.7 (1.5)	555; 7.6 (2.1)	1.1 (0.9 to 1.3)	<0.0001

Data are n with mean (SD) unless otherwise specified. *Number of patients with at least one completed follow-up. †Quality of life assessed using the EQ-5D-5L visual analogue scale, ranging from 0 (worst imaginable health) to 100 (best imaginable health). ‡Pain intensity measured on a 0–10 numeric rating scale (where 10 indicates worst pain). §Satisfaction with emergency department care measured on a 0–10 numeric rating scale (where 10 indicates the highest level of satisfaction).

Table 3: Patient-reported outcomes by trial groups and timepoints

	Intervention (n=591)	Control (n=555)	Overall (n=1146)	p value*
Adverse events (any)	39 (6.6%)	33 (5.9%)	72 (6.3%)	0.72
Causal relationship†				
Unrelated	15/39 (38.5%)	6/33 (18.2%)	21/72 (29.2%)	0.11
Related	23/39 (59.0%)	26/33 (78.8%)	49/72 (68.1%)	..
Unknown	1/39 (2.6%)	1/33 (3.0%)	2/72 (2.8%)	..
Severity				
Mild	37/39 (94.9%)	32/33 (97.0%)	69/72 (95.8%)	1.0
Moderate	1/39 (2.6%)	0	1/72 (1.4%)	..
Unknown	1/39 (2.6%)	1/33 (3.0%)	2/72 (2.8%)	..
Expectedness				
Unexpected	20/39 (51.3%)	13/33 (39.4%)	33/72 (45.8%)	0.67
Expected	18/39 (46.2%)	19/33 (57.6%)	37/72 (51.4%)	
Unknown	1/39 (2.6%)	1/33 (3.0%)	2/72 (2.8%)	
Serious adverse events	0	1/555 (0.2%)	1/1146 (0.1%)	0.48

Data are n (%) unless otherwise specified. Data completeness for adverse events at day 1 was 591 (80%) of 737 in the intervention group and 555 (75%) of 738 in the control group; 1146 (78%) of 1475 overall. Adverse and serious adverse events are summarised as the number and percentage of patients experiencing at least one event. No patient reported experiencing more than one adverse event. The denominators for percentages are all randomly assigned patients for whom data are available. *Fisher's exact test. †Causal relationship to the therapies administered during the emergency department visit and not to the study intervention.

Table 4: Adverse events by trial groups

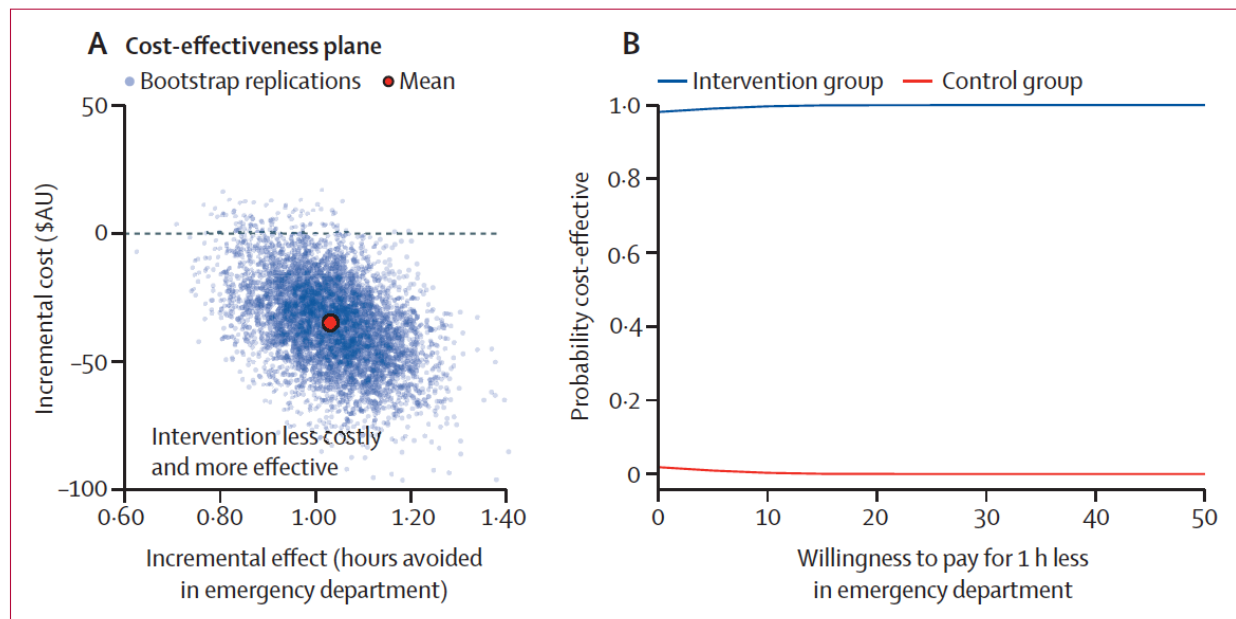


Figure 2: Cost-effectiveness plane (A) and cost-effectiveness acceptability curve (B) for base case analysis

Research in context

Evidence before this study

We searched MEDLINE (via Ovid) and Embase (via Ovid) from database inception to March 6, 2026, for randomised trials and systematic reviews evaluating physiotherapist-led, allied health, or nursing models of care for musculoskeletal conditions in emergency departments. Search terms included "emergency department", "allied health", "physiotherapy", "primary-contact", and "musculoskeletal", with related synonyms. We also screened reference lists of relevant systematic reviews and eligible studies. No language restrictions were applied. We identified two relevant reviews. A 2018 scoping review did not identify any randomised controlled trials evaluating efficiency outcomes such as waiting time, duration of clinical care, or emergency department length of stay. A 2024 systematic review identified five randomised trials, but they primarily focused on patient-reported outcomes, with limited evaluation of emergency department flow, system performance, and cost-effectiveness. One small study (n=260) assessed patient-flow outcomes and reported very low-certainty evidence that a greater proportion of patients were seen within 20 min when assessed by a physician compared with a nurse practitioner or physiotherapist. High-quality randomised evidence evaluating these models of care remains limited.

Added value of this study

This multicentre randomised trial provides the largest and most comprehensive randomised evaluation to date of a physiotherapist-led model of care for patients presenting to

emergency departments with uncomplicated musculoskeletal conditions and incorporates a prospective economic evaluation to inform implementation. Compared with usual physician-led or nurse practitioner-led care, physiotherapist-led care reduced emergency department length of stay and improved measures of care timeliness. Patients receiving physiotherapist-led care reported higher satisfaction with care. Pain intensity, quality of life, imaging use, and use of high-risk medications were similar between groups. Adverse events, hospital admissions, and emergency department re-presentations were also similar between groups. The trial included a large sample (n=1475) and achieved complete follow-up for the primary outcome. A prospective economic evaluation showed that the intervention was cost-effective, with lower costs and improved outcomes, indicating a high probability of cost savings.

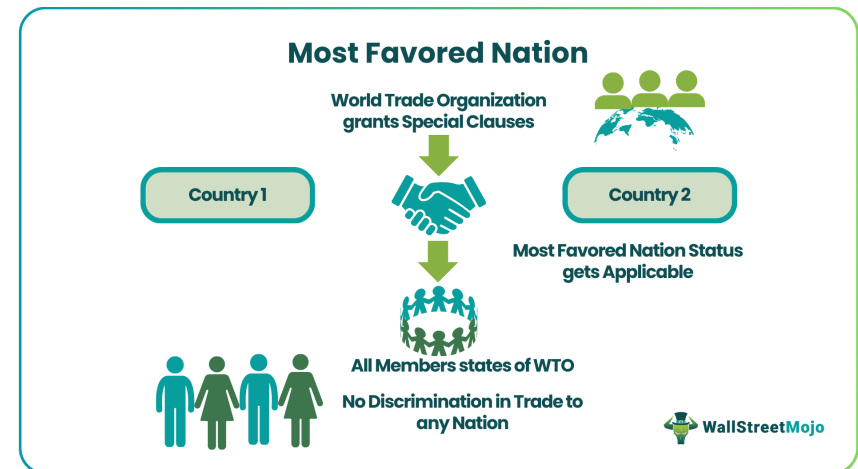
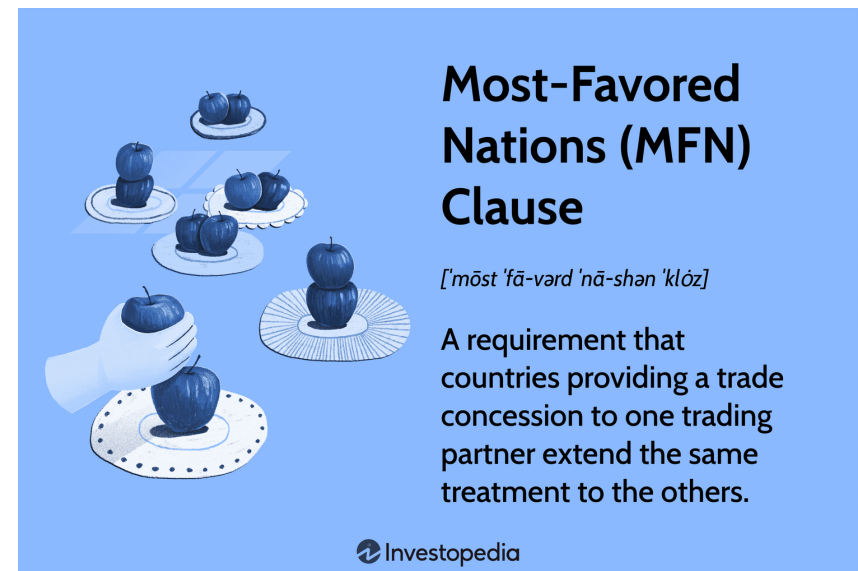
Implications of all the available evidence

This trial provides high-quality evidence that a physiotherapist-led model of care in emergency departments can reduce length of stay and improve timeliness of care for patients presenting with uncomplicated musculoskeletal conditions without evidence of harm or worse clinical outcomes. The economic findings indicate that these improvements can be achieved while reducing costs, supporting this model as a high-value approach to emergency department care. These findings provide decision-relevant evidence for workforce redesign strategies in emergency departments. Further research is needed to evaluate scalability across different health systems.

Most-Favored-Nation (MFN) pricing is a policy or contractual arrangement where a seller agrees to give a buyer the absolute lowest price that they offer to any other customer or market.

Context & Mechanics

- **International Drug Benchmarking:** Most prominently discussed in U.S. healthcare policy, MFN pricing ties domestic prescription drug costs to the lowest or second-lowest net prices found in comparable high-income peer nations (such as OECD countries with similar GDP per capita).
- **Commercial & Contractual Clauses:** In general business and B2B contracts, an MFN clause (or most-favored-customer clause) guarantees that a client will automatically receive any future price discounts given to a competitor if the seller drops prices elsewhere.
- **Core Rationale:** It prevents price discrimination, aiming to eliminate situations where domestic or specific buyers pay significantly higher rates than other groups for the identical good or service



Trump's plan to lower drug prices will fail because of manufacturers' behavior

Most-favoured-nation pricing for prescription drugs in US Medicare: a cohort study

Summary

Background The prices of new medicines in the USA are among the highest in the world. The Centers for Medicare and Medicaid Services released mandatory most-favoured-nation payment models for prescription drugs covered under Medicare part B (GLOBE) and part D (GUARD). Under these payment models, manufacturers would be required to pay Medicare additional rebates for net drug prices exceeding the lowest international list price in a basket of 19 reference countries adjusted by gross domestic product per capita on purchasing power parity basis. In this study, we aimed to model the impact of the GLOBE and GUARD models for Medicare spending.

Methods In this cohort study of the GLOBE and GUARD payment models in US Medicare, we linked Medicare spending and prices with estimated current rebates, ex-manufacturer prices, and international sales data using Medicare data and commercial databases of sales and pricing from 19 model-specified reference countries (ie, Australia, Austria, Belgium, Canada, Czechia, Denmark, France, Germany, Ireland, Israel, Italy, Japan, Netherlands, Norway, South Korea, Spain, Sweden, Switzerland, and the UK) for all potential model-eligible brand-name drugs. The primary outcomes were estimated reductions in net Medicare spending under the GLOBE and GUARD payment models and median ratio of estimated reductions in Medicare spending to annual sales in the referenced country. In scenario analyses, we estimated changes in potential savings if the reference basket was narrowed to G7 countries and if manufacturers with separate agreements with the Department of Health and Human Services were exempt from model inclusion.

Findings The study included 195 brand-name drugs accounting for Medicare spending of US\$87.9 billion. The estimated reductions in net Medicare spending were \$5.2 billion (16.1%) under GLOBE and \$6.4 billion (17.6%) under GUARD. In scenario analyses, potential savings would be reduced by 12.2% if the reference basket was narrowed to G7 countries and 71.3% if manufacturers with separate agreements were exempt from model participation. The median ratio of estimated reductions in Medicare net spending under GLOBE and GUARD to annual sales in the binding lowest referenced country was 3.8 (IQR 1.0–22.8). For 101 (73.2%) of 138 drugs, estimated reductions in Medicare spending would exceed annual sales in the binding referenced country.

Interpretation Most-favoured-nation pricing for brand-name medicines in Medicare was projected to decrease net spending. Potential reductions in net Medicare spending would be substantially greater than sales in the reference countries, suggesting that shifts in manufacturer behaviour with model implementation could reduce possible savings.

Introduction

In December, 2025, the Centers for Medicare and Medicaid Services released mandatory most-favoured-nation payment models for prescription drugs in Medicare.¹ Prices for medicines in the USA are among the highest in the world,² and the Trump administration has sought most-favoured-nation pricing to not only reduce US prices to those paid by peer countries but also to pressure other countries to increase pharmaceutical spending outside the USA.^{3,4} For example, in April, 2026, the UK announced details of an agreement on pharmaceutical trade with the USA, under which the share of the National Health Service budget spent on medicines would increase from 10% to 12% by 2036 and

the UK would increase the net price paid by the National Health Service for new launched medicines by 25%, implemented in part by raising the National Institute for Health and Care Excellence's cost-effectiveness thresholds from £20 000–30 000 to £25 000–35 000 per quality-adjusted life year. In June, 2026, the US Trade Representative initiated an investigation into whether pharmaceutical pricing policies in Germany were resulting in persistent underpayment for new medicines and thereby unfairly burdening US commerce. Although most-favoured-nation (or international reference pricing) is widely used in Europe and elsewhere to control prescription drug spending, it has not been previously used in the USA.^{5,6}

	GLOBE	GUARD
Model population	25% of Medicare part B fee-for-service beneficiaries	25% of Medicare part D beneficiaries
Inclusion criteria		
Minimum annual spending	US\$100 million (adjusted for inflation after first year)	\$69 million (adjusted for inflation after first year)
Drug classes*	Seven drug classes: antineoplastics, immunological drugs; haematological drugs; central nervous system agents; metabolic bone disease agents; ophthalmic agents; and antigout agents	17 drug classes: analgesics; anticonvulsants; antidepressants; antimigraine agents; antineoplastics; antipsychotics; antivirals; bipolar agents; blood glucose regulators; cardiovascular agents; central nervous system agents; gastrointestinal agents; genetic, enzyme, or protein disorders; replacements, modifiers, or treatments; immunological agents; metabolic bone disease agents; ophthalmic agents; and respiratory tract and pulmonary agents
Price adjustment		
GDP-PPP adjustment	Reference prices multiplied by GDP-PPP adjustment factor†	Reference prices multiplied by GDP-PPP adjustment factor†
Threshold percentage	GDP-PPP adjusted benchmark price multiplied by 102% (or 105% if net prices voluntarily submitted)	GDP-PPP adjusted benchmark price multiplied by 102% (or 105% if net prices voluntarily submitted)
Add-on payment amount	Dollar value of part B statutory add-on payment applied to benchmark	Not applicable
Reference basket		
Included countries	Australia, Austria, Belgium, Canada, Czechia, Denmark, France, Germany, Ireland, Israel, Italy, Japan, Netherlands, Norway, South Korea, Spain, Sweden, Switzerland, and the UK	Same as GLOBE
Medicare's most-favoured-nation payment models span part B (the GLOBE model), which primarily covers clinician-administered medicines, and part D (the GUARD model), which covers outpatient retail drugs. GDP-PPP=gross domestic product per capita (purchasing power parity basis). GLOBE=Global Benchmark for Efficient Drug Pricing. GUARD=Guarding US Medicare Against Rising Drug Costs. *The Centers for Medicare and Medicaid Services defines these drug classes using the US Pharmacopeia classification. †See the appendix for GDP-PPP adjustment factors (p 5).		
Table 1: Key features of GLOBE and GUARD payment models		

	n (%) or n/N (%)	GLOBE net spending (\$Bn)	GUARD net spending (\$Bn)
Study cohort	195 (100%)	32.7	36.2
Primarily covered by			
Medicare part B	47 (24.1%)	32.7	..
Medicare part D	148 (75.9%)	..	36.2
Manufacturer			
Participating	131 (67.2%)	27.5	23.1
Non-participating	64 (32.8%)	5.1	13.1
Protected class, part D only*			
Protected class drugs	73/148 (49.3%)	..	18.3
Non-protected class	75/148 (50.7%)	..	17.9
Oncology			
Cancer medicines	67 (34.4%)	17.7	11.3
Non-cancer medicines	128 (65.6%)	15.0	24.9
Orphan Drug Act designation			
Rare disease-only products†	59 (30.3%)	4.0	17.5
Other products	136 (69.7%)	28.7	18.7
Therapeutic area (Anatomical Therapeutic Chemical classification)			
A (alimentary tract and metabolism)	14 (7.2%)	..	2.0
B (blood and blood-forming organs)	8 (4.1%)	1.5	1.1
C (cardiovascular)	9 (4.6%)	..	2.5
J (anti-infectives)	17 (8.7%)	..	3.5
L (antineoplastic and immunomodulating agents)	106 (54.4%)	23.4	18.0
M (musculoskeletal)	4 (2.1%)	3.1	0.2
N (neurological)	20 (10.3%)	..	5.4
R (respiratory)	8 (4.1%)	0.4	1.2
S (sensory)	6 (3.1%)	4.3	0.8
Other	3 (1.5%)	..	1.5

GLOBE=Global Benchmark for Efficient Drug Pricing. GUARD=Guarding US Medicare Against Rising Drug Costs.

*The protected class policy applies to Medicare part D and requires that plans cover essentially all approved drugs within six classes: antineoplastics, anticonvulsants, antidepressants, antipsychotics, antiretrovirals, and immunosuppressants for preventing transplant rejection. †Indicates drugs approved for only rare diseases under the Orphan Drug Act and therefore exempt from Medicare price negotiation.

Table 2: Characteristics of medicines included in the study cohort

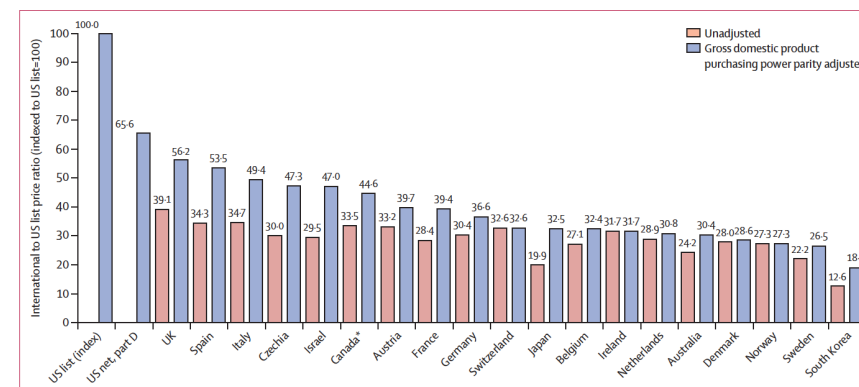


Figure 1: Comparison of price ratios of list and net Medicare drug prices to international reference prices
Price ratios indexed to US list prices (reference=100) for the 19 countries included in the international price reference basket are shown. Reference country price ratios are based on ex-manufacturer prices and adjusted (baseline) versus unadjusted by gross domestic product purchasing power parity adjustment factors (appendix p 5). *Canadian prices from lower of provincial or federal prices, see Methods for further details.

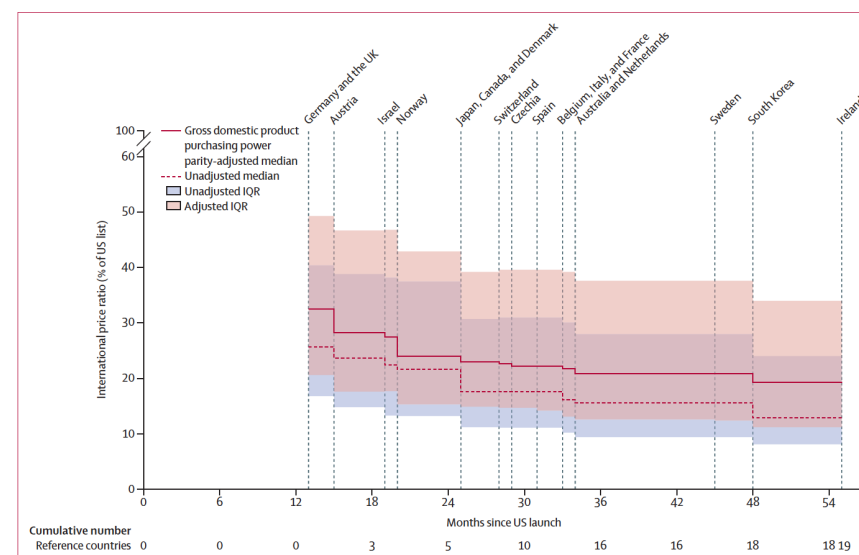


Figure 2: Evolution of median international price ratios from time of US launch
The changes in ratios of unadjusted and gross domestic product purchasing power parity-adjusted (baseline) median international prices to US list prices are shown over time from the time of US product launch. The cumulative number reference countries shows the number of reference countries in the study cohort with available international prices. The earliest available international price is at 13 months from US launch with German price availability.

	Estimated reduction in annual Medicare net spending	% change in Medicare net spending	% change relative to baseline most-favoured-nation model*
Scenario			
Baseline most-favoured-nation models	GLOBE \$5.2 billion; GUARD \$6.4 billion	GLOBE 16.1%; GUARD 17.6%	..
Baseline, adjusted for inflation-linked rebates	GLOBE \$5.2 billion; GUARD \$6.2 billion	GLOBE 16.0%; GUARD 17.2%	GLOBE -0.5%; GUARD -2.4%
Scenario analyses			
Expanding most-favoured-nation to 100% Medicare population†	GLOBE \$21.0 billion; GUARD \$25.5 billion	GLOBE 64.2%; GUARD 70.3%	GLOBE +300%; GUARD +300%
Exclusion of companies with agreements‡	GLOBE \$0.9 billion; GUARD \$2.4 billion	GLOBE 2.8%; GUARD 6.7%	GLOBE -82.8%; GUARD -61.8%; total -71.3%
Narrowing reference basket to G7 countries only	GLOBE \$4.7 billion; GUARD \$5.5 billion	GLOBE 14.5%; GUARD 15.1%	GLOBE -9.8%; GUARD -14.3%; total -12.2%
Matched formulation, route, and strength	GLOBE \$5.1 billion; GUARD \$6.1 billion	GLOBE 15.5%; GUARD 16.9%	GLOBE -3.7%; GUARD -3.9%; total -3.8%
Table shows estimated reductions in annual Medicare net spending based on actual 2024 Medicare part B and part D utilisation and estimates of net Medicare prices (see Methods for further details). Dollars are in USD. GLOBE=Global Benchmark for Efficient Drug Pricing. GUARD=Guarding US Medicare Against Rising Drug Costs. *Relative to baseline most-favoured-nation scenario. †The scenario assumes expansion to 100% of part B fee-for-service beneficiaries and 100% of part D beneficiaries. ‡The scenario assumes exclusion of products by 17 pharmaceutical companies with agreements announced with the Trump administration as of June, 2026 (appendix p 4).			
Table 3: Estimated reductions in Medicare spending under GLOBE and GUARD most-favoured-nation payment models			

Research in context

Evidence before this study

We searched PubMed, Scopus, and Embase for studies published from database inception until June 1, 2026, using the terms “most-favored-nation”, “external reference pricing”, “international reference pricing”, “GLOBE model”, “GUARD model”, and “pharmaceutical pricing model” without language restrictions. Most-favoured-nation pricing, which would anchor the prices of medicines to those in a basket of comparator countries, was first announced as a policy goal by the Trump administration under an executive order in May, 2025. This goal was followed by specific payment models announced in December, 2025, to implement most-favoured-nation pricing for medicines in the US Medicare programme. There is evidence that US prices for medicines are substantially higher than those in comparator countries, even after accounting for rebates and discounts. However, no previous study has assessed the potential effect of the most-favoured-nation payment models or the relative differences between model savings with referenced country markets.

Added value of this study

This retrospective cohort study represents, to the best of our knowledge, the first evaluation of the Trump administration’s most-favoured-nation pricing models in US Medicare. Using linked data on Medicare spending, net prices, global pricing, and international sales data in 19 reference countries for all potential model-eligible medicines, we modelled the impacts of novel payment models on Medicare spending. Most-favoured-nation

pricing for medicines was associated with decreased net Medicare spending, with the greatest savings coming from drugs that are shielded from price competition or Medicare negotiations. We also showed possible future impacts on referenced countries: for most medicines, estimated reductions in Medicare spending would exceed annual sales in referenced countries.

Implications of all the available evidence

The Trump administration’s push to implement most-favoured-nation pricing for medicines in Medicare represents the first time that such policies have been proposed at this scale in the USA. Concerns about the implications of these payments models in the USA have been reported by countries around the world and by the European Commission. Because of the disparity in size of Medicare compared with markets in other countries, our results suggest that this policy change could have unintended effects on prices and access to medicines in referenced countries. To minimise reductions in Medicare revenue, pharmaceutical companies might be incentivised to delay market launch or pursue other strategies to prevent the establishment of a reference price in the lowest-priced reference countries. In addition to these possible shifts in manufacturer behaviour that would erode potential savings, implementation of these payment models could be challenged by changes in scope due to confidential separate agreements negotiated between the Trump administration and individual pharmaceutical companies.



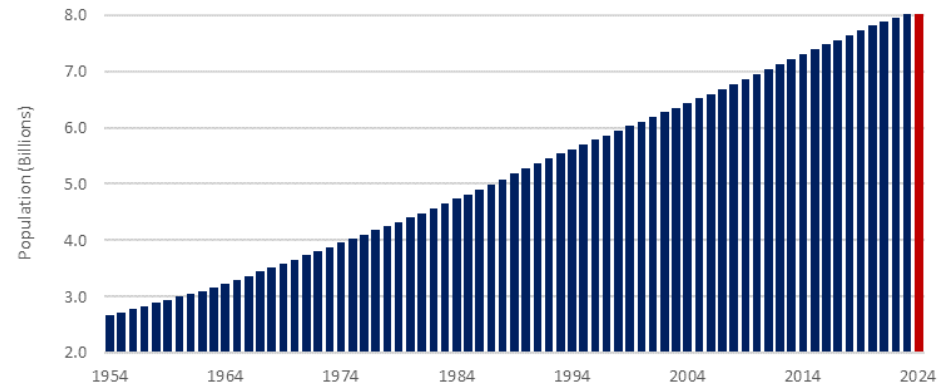
Die United States Agency for International Development (USAID) war bis zu ihrer offiziellen Auflösung im Juli 2025 die weltgrößte Behörde für staatliche Entwicklungszusammenarbeit.

Hintergrund und Ende der Behörde

- **Gründung:** Die unabhängige US-Behörde wurde 1961 ins Leben gerufen, um globale Armut zu bekämpfen und humanitäre Hilfe zu koordinieren.
- **Auflösung:** Unter US-Präsident Donald Trump wurden die Hilfgelder Anfang 2025 zunächst eingefroren und die Behörde im Juli 2025 von Außenminister Marco Rubio offiziell aufgelöst.
- **Umstrukturierung:** Verbleibende und kompatible Aufgaben wurden daraufhin in das US-Außenministerium eingegliedert, während über 80 % der ursprünglichen Projekte gestrichen wurden.

Has the world's population really grown from 3bn in the 1960's to 8bn?

Source: United Nations Population Prospects Database



Wichtigste Instrumente zur Umverteilung und Gesundheitsförderung

- **Vermögenssteuer für Höchstvermögen**

- *Ansatz:* 3%-Steuer auf Milliardärsvermögen.
- *Gesundheitseffekt:* Kann bis zu 29,5 Mio. Todesfälle in ärmeren Staaten abwenden.

- **Mindeststeuer für Konzerne**

- *Ansatz:* Globale Mindestbesteuerung multinationaler Unternehmen.
- *Gesundheitseffekt:* Schätzungsweise 20 Mio. vermiedene Todesfälle durch finanzierte Gesundheitsprogramme.

- **Finanztransaktionssteuern**

- *Ansatz:* Kleine Abgaben auf globale Finanzströme.
- *Gesundheitseffekt:* Etwa 24 Mio. vermiedene Todesfälle durch stabile Entwicklungsbudgets.

- **Bedingungslose Cash-Transfers & Basisrenten**

- *Ansatz:* Direkte finanzielle Unterstützung für einkommensschwache Haushalte.
- *Gesundheitseffekt:* Verbessert Ernährungssicherheit und Mütter-/Kindergesundheit direkt.

Soaking the rich
is an old idea
that they will
surely resist

Wealth redistribution policies to mitigate the impact of development assistance defunding: a retrospective evaluation and forecasting analysis up to 2030

Summary

Background The ongoing decline in funding for humanitarian and development assistance stands in stark contrast to the global rise in wealth concentration and widening socioeconomic inequalities. This study aimed to assess whether the implementation of wealth redistribution policies—proposed in recent high-level international agreements to support development—could mitigate the health impact of the current official development assistance (ODA) defunding crisis.

Methods We conducted an integrated retrospective impact evaluation and forecasting analysis using longitudinal panel data from 59 low-income and lower-middle-income countries. First, we estimated the association between per-capita ODA and mortality outcomes from 2002 to 2021 using two-way fixed-effects multivariable Poisson regression models with robust standard errors, adjusting for key demographic, socioeconomic, and health-system covariates. We did extensive sensitivity and triangulation analyses to assess the robustness and plausibility of the findings. We then evaluated ten wealth redistribution policies with validated country-level microsimulation models to forecast mortality outcomes under alternative wealth redistribution scenarios versus the current defunding scenario from 2026 to 2030.

Findings In comparison with the baseline ODA category, high ODA funding was associated with a 24% reduction in age-standardised all-cause mortality (rate ratio [RR] 0.76; 95% CI 0.67–0.87) and a 33% reduction in under-5 mortality (0.67; 0.50–0.89). Forecasting analyses showed that, in comparison with the current ODA funding reductions in the 59 selected low-income and lower-middle-income countries, all ten wealth redistribution policies were associated with millions of averted deaths by 2030: overall, the lowest number of averted deaths was 6 591 984 (95% uncertainty interval 4 884 075–8 374 138) for a 3% crypto tax applied to the top 10 000 holders, while the highest number of averted deaths was 29 509 934 (20 273 842–38 603 961) for a 3% wealth tax on ultra-high-net-worth individuals; in children younger than 5 years, the corresponding numbers of averted deaths were 1 312 912 (802 926–1 785 121) for a 3% crypto tax applied to the top 10 000 holders and 3 464 607 (1 235 930–5 609 331) for a 3% wealth tax on ultra-high-net-worth individuals.

Interpretation The implementation of wealth redistribution policies proposed in recent high-level international agreements could mitigate the health consequences of the current ODA defunding crisis, avert millions of deaths, and support the achievement of the UN Sustainable Development Goals, particularly those related to health.

Introduction

The world is experiencing extreme levels of inequality, which is manifested across multiple dimensions and has worsened in the aftermath of the COVID-19 pandemic.¹ Today, the top 10% of the global population owns approximately 75% of global wealth, while the bottom 50% holds only 2%, with absolute income inequality steadily increasing over the past three decades.² Moreover, the wealthiest 0.002% of the global population—corresponding to 92140 centi-millionaires—controls an estimated US\$37.1 trillion in global wealth, surpassing the gross domestic product (GDP) of the world's largest

economy—the USA (\$31.1 trillion). In parallel, the world's 3028 billionaires collectively hold \$16.1 trillion in wealth, and this extreme concentration of wealth is continuing to accelerate.^{1,3} In stark contrast, the world's poorest populations are facing one of the most challenging periods in recent decades. Poverty rates have increased after the COVID-19 pandemic, with an estimated 808 million people living in extreme poverty (below \$3 per day) and 3.5 billion people living in poverty (below \$6.85 per day) in 2025.⁴ Recent estimates show that a quarter of low-income and middle-income countries (LMICs) still have per-capita incomes below 2019 levels, with the worst stagnation in low-income countries, where the COVID-19 pandemic erased all previous development gains.⁵

Official development
assistance = ODA

Age standardized
mortality rate =
ASMR

Under 5 mortality
rate = U5MR

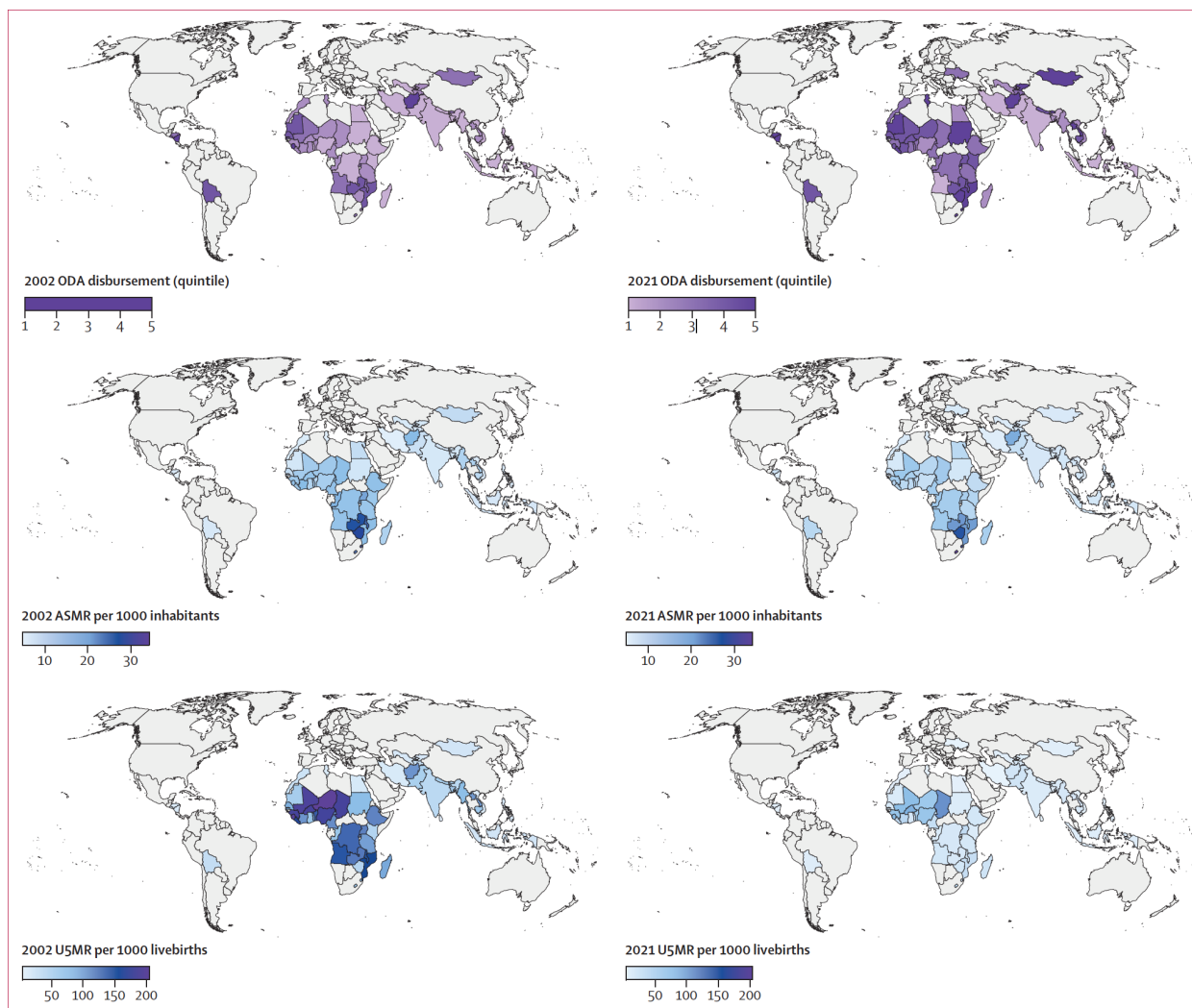


Figure: ODA funding per capita by quartiles across the selected 59 low-income and lower-middle-income countries in 2002 and 2021, age-standardised mortality rates per 1000 inhabitants in 2002 and 2021, and under-5 mortality rates per 1000 livebirths in 2002 and 2021
ASMR=age-standardised mortality rate. ODA=official development assistance. U5MR=under-5 child mortality rate.

	2002	2011	2021	Change from 2002 to 2021
Mortality rate				
Overall ASMR per 1000 population	12.80 (3.45)	11.01 (2.36)	11.95 (2.74)	-6.64
Children aged <5 years per 1000 livebirths	89.68 (42.92)	68.50 (33.27)	44.92 (25.27)	-49.91
ODA or funding				
ODA per capita (constant US\$)	20.94 (17.84)	41.29 (37.75)	43.68 (28.05)	108.60
Average funding per country (in millions of US\$)	323.74 (339.57)	814.82 (943.92)	1099.55 (979.86)	239.64
Population size				
All 59 countries	2 726 214 458	3 295 823 882	3 897 063 090	42.95%
Other covariates				
Economic growth (%)	4.8% (6.39)	4.92% (4.23)	4.39% (4.94)	-8.54%
GDP per capita PPP (constant US\$)	3761.46 (2423.56)	5220.56 (3673.93)	6237.61 (4218.8)	65.83
Conflict or wars index ξ	0.09 (0.2)	0.05 (0.13)	0.05 (0.12)	-44.44
Fertility rate (births per woman)	4.6 (1.59)	4.09 (1.53)	3.54 (1.31)	-23.04
Urban population (% population)	35.9% (15.22)	40.06% (16.36)	44.23% (16.85)	23.20%
Primary education (% population)	49.86% (25.09)	54.39% (24.84)	60.79% (25.73)	21.92%
Basic drinking water (% population)	62.00% (19.81)	69.69% (17.47)	77.25% (15.77)	24.60%
Health expenditure per capita (PPP)	114.93 (98.08)	206.5 (195.74)	321.45 (262.93)	179.69
Social protection coverage (% population)	20.47% (19.6)	27.6% (24.31)	31.54% (27)	54.08%
Data are presented as mean (SD), percentage, or absolute number. Mortality (all ages) is expressed per 1000 population, and mortality for children younger than 5 years is expressed per 1000 livebirths. Economic growth is based on GDP in constant US dollars. ASMR=age-standardised mortality rate. GDP=gross domestic product. ODA=official development assistance. PPP=purchasing power parity.				
Table 1: Descriptive statistics of mortality rates, ODA funding, and demographic, socioeconomic, and health-care-related variables in the selected countries (n=59) from 2002 to 2021				

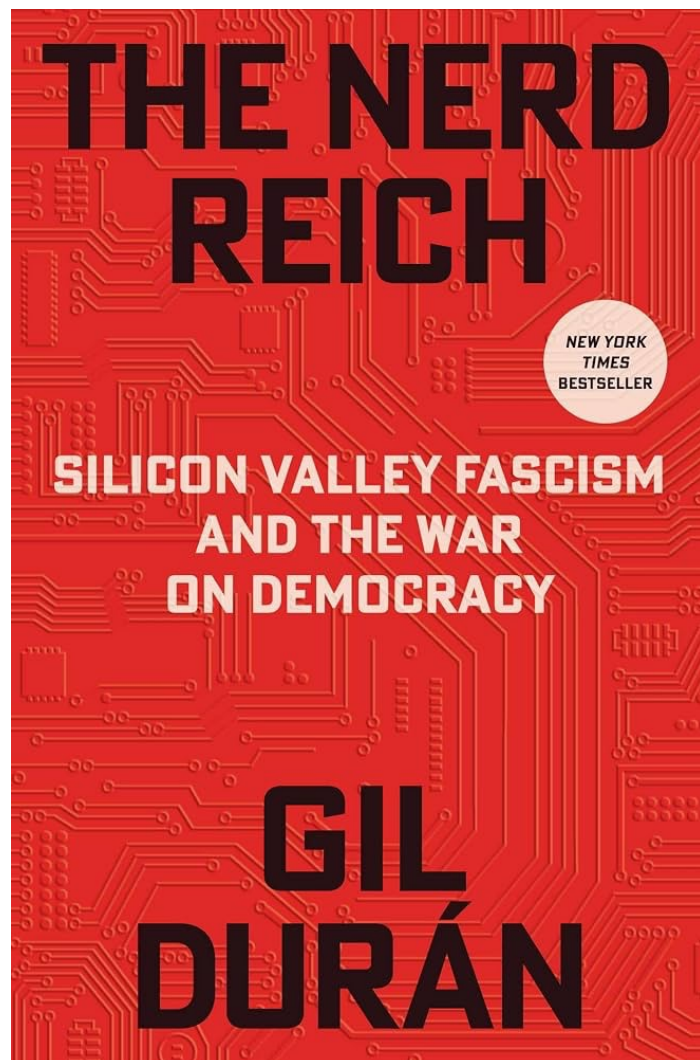
	Overall (ASMR)	Childhood mortality rates			
		Infancy (0–1 year)	Preschool (2–4 years)	Child (<5 years)	School age (5–9 years)
ODA quintiles					
Baseline (mean 6.38; range 0–12.34)	1	1	1	1	1
Low (mean 18.68; range 12.35–24.40)	0.92 (0.89–0.96; p<0.0001)	0.93 (0.87–0.99; p=0.031)	0.91 (0.80–1.03; p=0.14)	0.92 (0.85–1.00; p=0.045)	0.92 (0.87–0.97; p=0.004)
Lower-intermediate (mean 30.21; range 24.41–35.97)	0.85 (0.78–0.93; p=0.001)	0.80 (0.71–0.91; p=0.0005)	0.72 (0.57–0.91; p=0.006)	0.77 (0.66–0.90; p=0.001)	0.80 (0.70–0.92; p=0.001)
Upper-intermediate (mean 42.81; range 35.98–52.12)	0.79 (0.72–0.88; p<0.0001)	0.76 (0.66–0.88; p=0.0002)	0.65 (0.51–0.83; p=0.0005)	0.72 (0.61–0.86; p=0.0002)	0.75 (0.65–0.88; p=0.0003)
High (mean 83.03; range 52.13 or more)	0.76 (0.67–0.87; p<0.0001)	0.72 (0.57–0.92; p=0.010)	0.57 (0.39–0.83; p=0.03)	0.67 (0.50–0.89; p=0.006)	0.73 (0.58–0.92; p=0.008)
Control variables					
Economic downturn	1.00 (0.96–1.04; p=0.90)	0.98 (0.91–1.05; p=0.56)	0.95 (0.84–1.08; p=0.48)	0.97 (0.89–1.06; p=0.53)	0.94 (0.85–1.04; p=0.24)
GDP per capita	0.95 (0.91–0.98; p=0.003)	0.95 (0.90–1.01; p=0.08)	0.87 (0.77–0.99; p=0.031)	0.93 (0.88–1.00; p=0.053)	0.82 (0.78–0.87; p<0.0001)
Conflict or wars index	1.20 (1.05–1.36; p=0.006)	1.35 (1.15–1.59; p=0.0002)	1.51 (1.17–1.97; p=0.002)	1.41 (1.16–1.71; p=0.0004)	1.53 (1.24–1.89; p=0.0001)
Fertility rate	1.03 (0.99–1.07; p=0.20)	0.99 (0.89–1.09; p=0.79)	1.03 (0.82–1.28; p=0.81)	0.99 (0.87–1.13; p=0.86)	0.93 (0.81–1.06; p=0.26)
Urban population	0.94 (0.88–0.97; p=0.039)	0.89 (0.78–1.02; p=0.09)	0.91 (0.74–1.11; p=0.35)	0.87 (0.76–1.00; p=0.06)	0.98 (0.83–1.17; p=0.86)
Primary education	0.95 (0.92–0.98; p=0.004)	0.84 (0.76–0.93; p=0.001)	0.82 (0.71–0.94; p=0.006)	0.84 (0.76–0.93; p=0.001)	0.88 (0.81–0.96; p=0.005)
Basic drinking water	0.97 (0.93–1.02; p=0.23)	0.94 (0.87–1.01; p=0.14)	0.89 (0.78–1.00; p=0.06)	0.91 (0.84–0.99; p=0.032)	0.98 (0.88–1.09; p=0.67)
Health expenditure	0.94 (0.91–0.98; p=0.002)	0.84 (0.80–0.90; p=0.001)	0.72 (0.61–0.85; p=0.0001)	0.82 (0.76–0.88; p<0.0001)	0.74 (0.64–0.86; p<0.0001)
Social protection coverage	0.95 (0.89–1.01; p=0.10)	0.96 (0.88–1.04; p=0.32)	0.90 (0.78–1.05; p=0.19)	0.94 (0.85–1.04; p=0.25)	0.98 (0.88–1.10; p=0.76)
Number of observations	1177	1177	1177	1177	1177
Number of countries	59	59	59	59	59
Data are rate ratio coefficients (95% CI), unless otherwise stated. ASMR=age-standardised mortality rate. ODA=official development assistance. GDP=gross domestic product.					
Table 2: Adjusted rate ratios from multivariable fixed-effects Poisson models with robust standard errors for the association between mortality rates and annual ODA per capita in the selected countries (n=59) from 2002 to 2021					

Scenarios, not reality

	Rationale	Strengths	Limitations
Tax on ultra-high-net-worth individuals			
(1) \$90 billion (1% tax on billionaires); ²² (2) \$217.5 billion (2% tax on billionaires); ²³ and (3) \$343.5 billion (3% tax on billionaires) ²²	A simple, presumptive tax scheme that sets a minimum tax rate for billionaires as a percentage of their wealth (should they already pay that percentage in taxes, no extra amount would be charged; should they pay less, only the difference would be charged)	Addresses tax avoidance of the extremely rich and reinstates some form of progressivity, albeit moderate (at 2% taxation, billionaires would pay an overall tax rate similar to the ordinary citizen)	Wealth evaluation might be difficult for some assets; risk of wealth concealment; need for global cooperation
Global minimum tax for large corporations (revenues >€750 million): eg, corporate tax			
\$173.5 billion ⁴⁶	Aims to reduce the amount of global profit of large multinational enterprises, which is subject to low taxation (below a 15% effective tax rate)	Strongly demanded, as 36.1% of global profit is currently taxed below a 15% effective tax rate due to extensive use of tax incentives worldwide; addressing low-taxed profits would yield a more level playing field across multinational enterprises as well as governments, promoting healthy market competition rather than rentier capitalism	Wide implementation across jurisdictions might be difficult and corporations could attempt to shift profits to tax havens; yet, 45 countries are taking steps towards implementing this tax
Carbon tax			
\$102.2 billion ⁴⁷	Tax imposed on polluters to partially compensate for the negative externality associated with the production of greenhouse gas emissions	Raises funds to mitigate pollution and disincentivises the excessive use of natural resources; positive reinforcing is effective in the fight against poverty, especially considering the disproportionately negative effects of climate change in many LMICs	Opposition from powerful lobbies; potentially regressive effects if not duly implemented; revenues are likely to decrease in the long run
Crypto tax			
(1) \$32.6 billion (3% tax on top 10 000 holders; own calculations based on Makarov and Schoar's 2021 and 2025 estimates ⁴⁸); and (2) \$100 billion ⁴⁹	Fiscal levy imposed on economic activities related to cryptocurrencies (eg, buying, selling, trading, mining, staking, or receiving); it might be based on capital gains, volumes, or transaction values; applicable to a set of increasingly popular digital assets not considered here (eg, non-fungible tokens)	Taxing cryptocurrencies is now recognised as a priority for governments across the world given the substantial amount of untaxed economic activity related to them, leading to loss of revenues, biased investment incentives, and potential illegal activities	Difficulties in setting precise tax regimes, because cryptocurrencies can be seen and used as investments or means of payment, or both. Difficulties regarding compliance; key hurdles are pseudonymity (identities appearing as nicknames on the blockchain ledger) and disintermediation (operations carried out without the need for intermediaries); yet, major progress is under way as 60 countries have committed to the Crypto Asset Reporting Framework
Tobin tax			
\$234 billion ⁴⁰	Originally envisaged as a tax on short-term foreign exchange trades and then often intended more broadly as a tax on financial transactions; typically consists of a low-rate tax, but able to lead to substantial revenues given the high volume of transactions	Instrument offering a double dividend: first, a tool to calm speculation, reduce instability due to market volatility, and strengthen countries' monetary policy autonomy; and second, as a means to generate revenues that could finance global public goods, world welfare, and hold off the decline of development aid	Objections due to possible financial implications of the measure such as reduction of liquidity, decrease in market trading volumes and increased transaction costs; risk of substitution and relocation of operations to more tax-friendly jurisdictions if not widely applied
Tax on interest earnings from LMICs' debt			
(1) \$74 billion (100% of interest payments by LMICs to official creditors); ⁴¹ and (2) \$120 billion (50% of interest payments by LMICs to official creditors plus 25% of interest payments by LMICs to private lenders) ⁴¹	Decisions taken by national governments, international organisations, and other creditors to reduce to various degrees or restructure, or both, LMICs' external debt obligations; the aim is to reach debt sustainability and free up resources for health, education, and infrastructure to foster economic growth and poverty reduction	Particularly appealing considering that external debt servicing costs—the combination of debt repayments and payments of interest on existing debt—have doubled over the past decade for LMICs, due to a combination of high and rising debt stocks, rising interest rates and depreciating currencies; the poorest countries have been hit the hardest	Debt relief could: undermine confidence in a country's creditworthiness, making future borrowing more costly; increase the risk of moral hazard attitudes, whereby countries would contract unsustainable debts in the future in the hope of further relief; undermine the financial stability of multilateral institutions and their ability to offer affordable financing to poor countries
LMICs=low-income and middle-income countries.			
Table 3: Summary of wealth redistribution scenarios, including sources, amounts (US\$ billions), rationale, strengths, and limitations			

„What could be done“

Table 4: Averted deaths under the various wealth redistribution scenarios, compared to the current defunding scenario and business-as-usual scenarios in the 59 selected countries, 2026–30



Research in context

Evidence before this study

We searched PubMed for reports examining the effects of official development assistance (ODA) on mortality worldwide, from database inception to Dec 31, 2025. The search was conducted in two streams: one broadly addressed ODA and the other explicitly focused on humanitarian assistance, to capture studies that might not have used ODA-specific descriptors. The ODA search string comprised the following descriptors: “(“international cooperation” OR “international funding” OR “international investment*” OR “foreign investment*” OR “global health investment*” OR “global health funding” OR “international aid” OR “official development assistance” OR “foreign aid” OR “foreign assistance” OR “development aid” OR “ODA” OR “development assistance for health”) AND (“mortality” OR “life expectancy” OR “death*” OR “fatal*”) AND (“program evaluation” OR “outcome assessment” OR “impact evaluation” OR “health effect” OR “causal effect” OR “effectiveness” OR “evaluation” OR “modelling”)”. An analogous search strategy was applied for humanitarian assistance. Searches were conducted in titles, abstracts, and keywords. Of 399 records retrieved, 74 met the inclusion criteria, and after abstract screening, 12 were identified as directly relevant to the research question. Across the reviewed literature, the effectiveness and impact of international cooperation and ODA on mortality have been evaluated through various modelling studies, primarily programme-specific models of US President’s Emergency Plan for AIDS Relief funding disruptions that show substantial excess deaths among children, mothers, and those with HIV when funding is halted or frozen. Country-level longitudinal research further links child-health ODA to lower infant and under-5 mortality rates, while effects on maternal and neonatal outcomes are mixed and seem to depend on subsector composition, funding stability, and coordination. Overall, the evidence suggests that targeted, stable ODA contributes to mortality reduction, whereas sudden cuts or aid sanctions are associated with increased deaths and service coverage losses. Despite this evidence, most studies have concentrated on models or US-funded programmes, leaving the effects of overall ODA, including differences among other donors, on mortality less understood. There is a need for research that combines retrospective data and projections across a broader set of countries, especially those most vulnerable to ODA shocks, to fully understand the effects of funding fluctuations on mortality. Regarding wealth redistribution policies, we searched PubMed for reports examining the effects of wealth

redistribution policies on mortality worldwide, from database inception to Dec 31, 2025. The search string comprised the following descriptors: “(“wealth” OR “assets” OR “net worth” OR “capital” OR “property”) AND (“tax*” OR “redistribution” OR “fiscal policy” OR “fiscal policy” OR “levy”) AND (“mortality” OR “life expectancy” OR “death”)”. Of 117 records retrieved, 12 met the inclusion criteria, and after abstract screening, two were identified as directly relevant to the research question. Although there is a substantial literature on the relationship between wealth levels and mortality, evidence on the effects of wealth redistribution policies remains scarce. To date, only one recent study has evaluated these policies, showing that—when applied to the US context—they could substantially reduce survival inequities and increase population longevity.

Added value of this study

This study combines retrospective analyses with near-term projections to 2030 across a broad set of countries, with a particular focus on low-income and lower-middle-income countries, which are most vulnerable to fluctuations in international assistance. This approach allows us to comprehensively assess the effects of international cooperation—and its potential contraction—on mortality in the context of the ongoing ODA crisis. Our models estimate that higher ODA funding levels over the past two decades were associated with a 24% reduction in age-standardised all-cause mortality and a 33% reduction in under-5 mortality. We further project that, if current ODA defunding trends continue, more than 7.9 million additional deaths could occur in low-income and lower-middle-income countries by 2030. Crucially, our study provides the first evidence that implementing wealth redistribution policies proposed in recent high-level international agreements to support development could mitigate these health impacts, potentially saving between 6.6 million and 29.5 million lives by 2030, depending on policy type, target population, and taxation level.

Implications of all the available evidence

The current sudden and severe reductions in ODA funding could have serious consequences for population health. However, our findings demonstrate the substantial potential of alternative wealth redistribution policies—such as those already proposed in recent high-level international agreements on global development—to mitigate the health benefits lost due to ODA defunding. If implemented, such policies could save millions of lives and substantially accelerate progress towards achieving the health-related UN Sustainable Development Goals by 2030.

Peripheral Arterial Disease 1

Understanding peripheral arterial disease in the current era

Atherosclerotic cardiovascular disease is the primary driver of premature death in global populations in recent decades. Mortality statistics, most publications, and guidelines in the atherosclerotic cardiovascular disease field have traditionally focused on cardiac and cerebrovascular adverse events and causes of death. However, given the increasing prevalence of lower extremity peripheral arterial disease and its expanding burden on global health systems, such an emphasis might represent a skewed perception of vascular risk within the broader atherosclerotic spectrum. Although common risk factors appear similar in all atherosclerotic cardiovascular disease subgroups, several crucial differences exist, including pathophysiological details and lesion patterns, as well as adherence to guideline-based recommendations. Individuals with peripheral arterial disease frequently remain asymptomatic for many years, often decades, and are typically diagnosed only at an advanced stage of the condition. By this time, however, the expected long-term outcomes are already extremely poor. When diagnosed at this point, the overall 5-year mortality is between 30% and 50%, thus even surpassing outcomes of severe cancer and acute myocardial infarction. Compared with cardiac and cerebrovascular disease, peripheral arterial disease receives lower priority in research and clinical practice, which is compounded by poor patient adherence to preventive care, lifestyle modification, and pharmacological therapy. This clinical Series of three papers aims to improve this distressing situation. For this purpose, it is important to recognise the underacknowledgment, underdiagnosis, and undertreatment of peripheral arterial disease and to understand the complex inter-relationships behind it before suitable interdisciplinary measures can be initiated. In this Series paper, we want to reach the broad interdisciplinary community, and above all, those who see these patients every day in general practice and internal medicine. The focus is primarily on the global importance of peripheral atherosclerosis and its drivers. In paper 2 of this Series, readers are introduced to modern complementary therapy, ranging from the optimisation of risk factors and optimal pharmacological therapies to innovative endovascular procedures and traditional surgical treatments. In the sense of integrated care and a stepwise approach, the described therapy alternatives can be combined individually for each patient. Paper 3 of this Series provides readers with a deep insight into the global significance and burden of peripheral arterial disease. Since this disease is primarily characterised by its long-term, chronically progressive course, improving long-term outcomes represents a central aspect of this paper. It aims to further illuminate striking disparities between geographical regions, sexes, and socioeconomic groups. With strong recommendations, this clinical Series can help to guide both clinicians and policy makers towards effective preventive measures.

Key messages

- Lower extremity peripheral arterial disease (PAD) is a global health burden with more than 113 million people aged 40 years and older affected worldwide and a rising global prevalence of 1.5%
- Due to the chronic progressive nature of cardiovascular disease, PAD remains asymptomatic and undiagnosed over decades; preventive measures should be initiated as early as possible to improve deleterious outcomes
- Although the underlying arterial pathophysiology differs to some degree from coronary artery disease and cerebrovascular artery disease, the most common risk factors and recommendations on best medical therapies are similar; however, the adherence to guideline-based recommendations is known to be worse in patients with PAD
- As of today, there is a lack of level 1A evidence on both screening measures and multifaceted health interventions to improve this situation; however, risk-based screening may be considered by health-care specialists
- A step-by-step diagnosis approach to validly diagnose PAD should be applied before forwarding patients into a stepwise care system with vascular specialists (eg, vascular surgery, angiology, and interventional radiology)

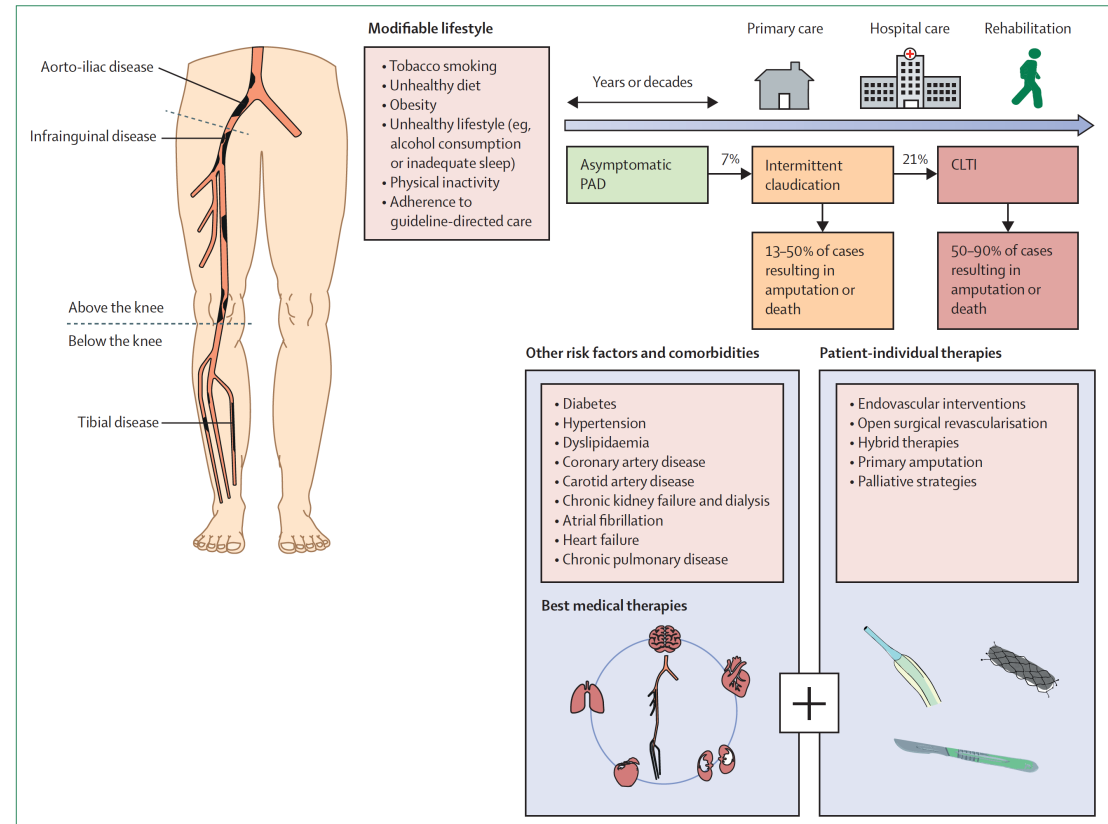


Figure 1: Typical regions of vessel involvement in people with PAD and illustration of the life course of affected people from asymptomatic PAD through intermittent claudication to CLTI, with reported progression rates and major amputation risk as well as death rates at the symptomatic disease stage. Although modification of risk factors and best medical therapies for the treatment of common comorbidities are fundamental for people with asymptomatic PAD and intermittent claudication, several invasive strategies (both catheter-based and open surgical) also exist to treat CLTI. CLTI=chronic limb-threatening ischaemia. PAD=peripheral arterial disease.

Step-by-step guide to diagnosis of PAD

Diagnostic pathway

Suspected lower limb PAD

History: risk factor profile with any history of classical or atypical limb symptoms during exercise, ischaemic rest pain, wound healing disorders, ulcer, or gangrene.



Comprehensive physical examination including pulse palpation and ABI at rest

Non-invasive bedside testing (ABI)

Aims: quantifiable and objective testing of lower limb blood flow. Calculation of ABI: use lowest ankle pressure for screening and highest for treatment decisions.

Post-exercise ABI measurement

Complementary bedside testing (eg, toe pressure, Doppler waveform, and transcutaneous oxygen pressure)

Pre-procedural planning

Additional diagnostic investigation and non-invasive and invasive imaging (pre-procedural steps only if revascularisation is deemed necessary)

Aims: assessment of macroperfusion, especially in complex multi-level disease.

Figure 2: Step-by-step guide to diagnosis of PAD

PAD=peripheral arterial disease. ABI=ankle-brachial index.

Always consider anamnesis and relevant cardiovascular comorbidities

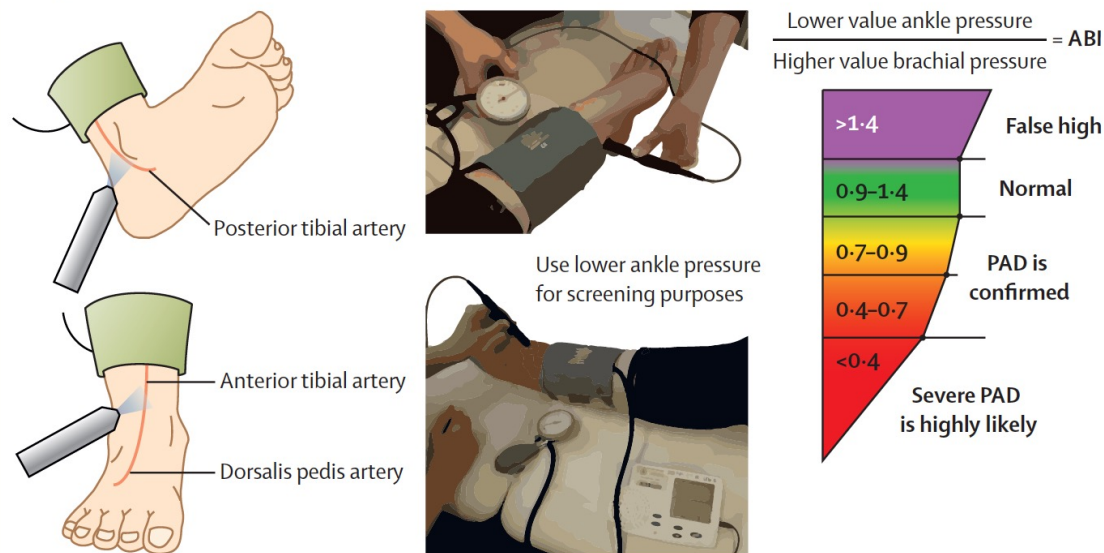


Figure 3: The measurement of ABI for the detection of lower extremity PAD

The measurement is conducted in a supine position following a resting period. The Doppler probe is positioned behind the medial malleolus and between the malleoli at a 45-degree angle to the course of the vessel, to provide two different measures. The blood pressure cuff should be wrapped tightly around the lower leg as close to the measurement site as possible. To calculate the ABI, the lower value ankle systolic pressure is divided by the higher value brachial pressure. An ABI of 0.9 or less is considered as conclusive evidence of PAD. ABI=ankle-brachial index. PAD=peripheral arterial disease.

Peripheral Arterial Disease 2

Current advancements in the care of peripheral arterial disease: modern approaches to medical, endovascular, and surgical treatment

People with peripheral arterial disease (PAD) of the lower limbs are at very high risk of cardiovascular events and therefore the cornerstone of their management is medical therapy and behaviour modification to reduce that risk. The risk of limb loss (through major amputation) is low in people with asymptomatic PAD or intermittent claudication with only a few patients progressing to the most severe form of PAD: chronic limb threatening ischaemia. Supervised exercise therapy is effective in patients with intermittent claudication to improve their walking capacity and avoids the risks associated with revascularisation procedures to improve blood flow to the limb. Although some people with intermittent claudication might need revascularisation, it is overused in this group. Revascularisation of stenosed or occluded arteries can be done by open or endovascular surgery and is generally reserved for people with chronic limb threatening ischaemia who are at highest risk of limb loss because these interventions carry substantial peri-procedural risks and often have minimal durability. Innovative therapies to treat PAD focus on improving health-related quality of life, reducing limb loss, and improving survival but the disease remains challenging due to its impact on multiple arterial levels and in different organ systems (polyvascular disease).

Key messages

- In people with peripheral arterial disease (PAD) the risk of cardiovascular events is high, but the risk of limb loss is low, which highlights the importance of medical therapy and behaviour modification in risk reduction
- The innovative therapies to treat PAD focus on improving health-related quality of life, reducing limb loss, and improving survival but the impact of PAD on multiple arterial levels can make therapies challenging
- There is regional variability in the use of endovascular or open surgical revascularisation procedures
- Although supervised exercise therapy is effective in people with PAD and intermittent claudication, revascularisation therapies are overused
- In people with chronic limb threatening ischaemia (the more severe form of PAD) endovascular interventions are more commonly used than surgical revascularisation despite weak evidence of their superior outcomes
- The advancements in the care of PAD have been driven by improvements in technology, mainly minimally invasive technics, diagnostic methods, and intensified pharmacological preventive therapy but their unequal distribution continues to be a major concern
- Studies showing a rapid increase in PAD (particularly in low-income countries) call for global health initiatives, technology transfer, and investment in health-care infrastructure to ensure availability of medical therapy and to improve education on existing risk factors

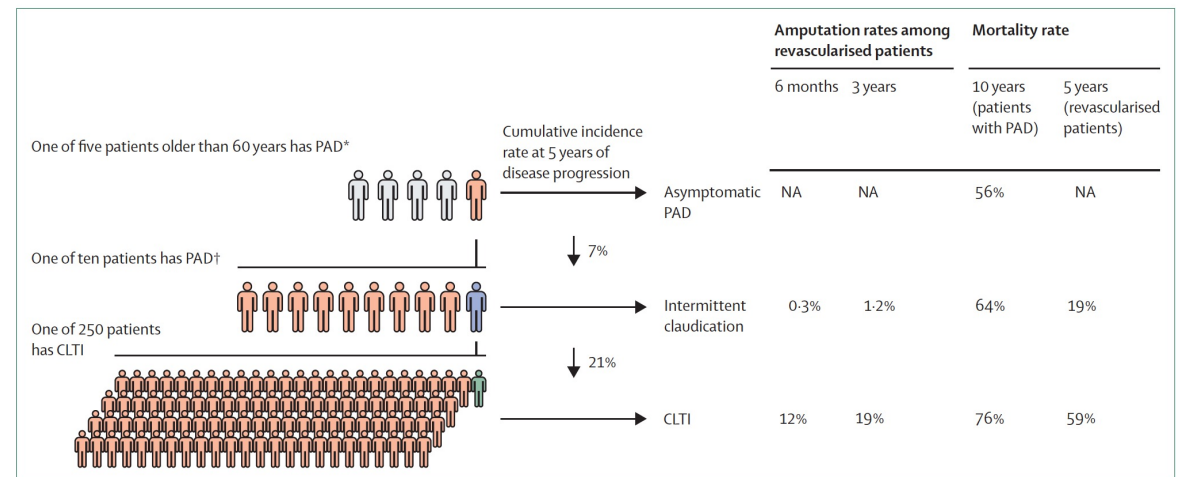


Figure 1: Population-based prevalence and natural course for different stages of PAD in the general population and among revascularised patients^{11,24-27}
 PAD=peripheral arterial disease. CLTI=chronic limb threatening ischaemia. NA=not available. *Ankle-brachial index value of less than 0.9. †Intermittent claudication or CLTI.

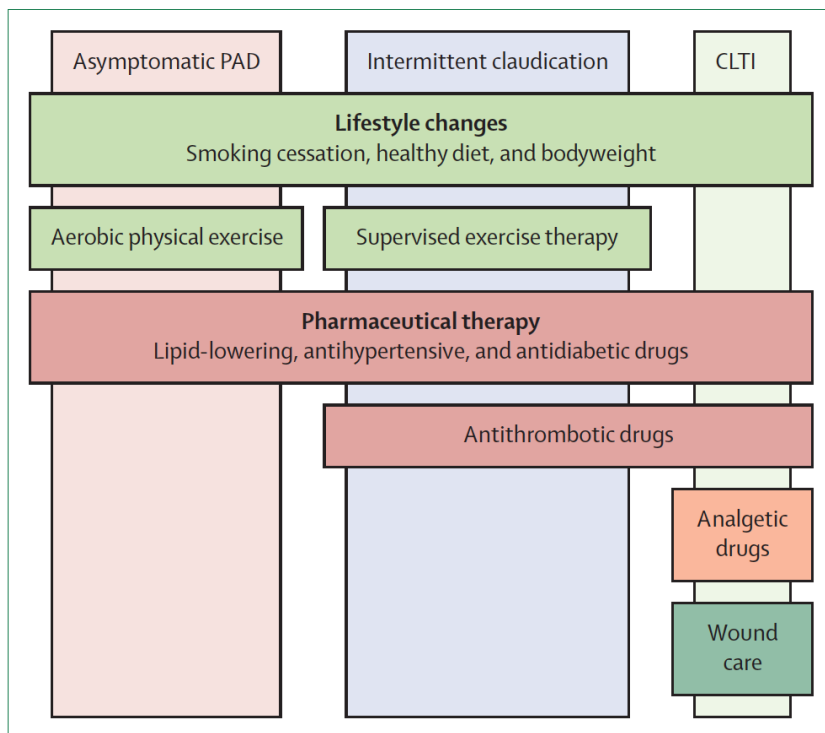


Figure 2: Non-invasive treatment for different stages of PAD
 PAD=peripheral arterial disease. CLTI=chronic limb threatening ischaemia.

	Treatment target	Suggested therapeutic agents
Smoking ^{32,33}	Total abstinence	Nicotine replacement therapy, varenicline, bupropion, and smoking-cessation support programmes
LDL cholesterol ³²⁻³⁹	<1.4 mmol/L (55 mg/dL) and reduction >50% from baseline and dietary changes	Statins (first line), ezetimibe (second line), and PCSK9 inhibitors (third line)
Arterial hypertension ⁴⁰⁻⁴³	<130/80 mm Hg for those younger than 80 years and <140/80 mm Hg for those 80 years or older	ACE inhibitor or ARB, CCB, and thiazide diuretics
Platelet and coagulation activity (symptomatic PAD only) ^{10,13,32,44-49}	Treatment compliance	Single antiplatelet therapy with clopidogrel or aspirin; alternatively, intensified antithrombotic strategies such as combination of aspirin and low-dose rivaroxaban
Type 2 diabetes ⁵⁰⁻⁵²	HbA _{1c} <7.0% (<53 mmol/mol)	GLP-1 receptor agonists and SGLT2 inhibitors

ACE=angiotensin-converting enzyme. ARB=angiotensin receptor blocker. CCB=calcium channel blocker. HbA_{1c}=glycated haemoglobin A_{1c}. PAD=peripheral arterial disease.

Table 1: Summary of recommendations on medical treatment of risk factors in patients with PAD

Pros		Cons
Aortoiliac		
Open surgical approach (aortofemoral bypass [unilateral or bilateral])	Good long-term patency	Risks associated with open surgery and infection of prosthetic graft material and risk of re-occlusions
Endovascular (iliac or aortoiliac stent or stent graft)	Less invasive than open surgery and generally good long-term patency	Technically challenging to re-open long occlusions of the aorta and iliac arteries and risk of re-occlusions
Common femoral artery		
Open surgical approach (endarterectomy)	Good long-term patency	Risks associated with open surgery and wound infection and risk of re-occlusions
Endovascular	Option for older adults and frail patients or those with clinically significant comorbidities or for patients with increased surgical site infection risks (or other surgical adverse risk profiles) such as scarred groin from previous procedures; alternative to open surgery if occlusion above femoral bifurcation	Few long-term data and risk of occlusion and stent fractures
Superficial femoral and popliteal artery		
Open surgical approach (bypass*)	Better patency than endovascular surgery	Risk of graft stenosis and following occlusion; follow-up preferred
Endovascular†	Less invasive than open surgery; good for short segment occlusions	Risk of re-occlusions
Below the knee arteries (crural and pedal arteries)		
Open surgical approach (bypass*)	Better patency than endovascular surgery	Risk of graft stenosis and following occlusion; follow-up preferred
Endovascular‡	Less invasive than open surgery	Difficult to open long occlusions and may compromise ability to perform subsequent bypass surgery; poor long-term patency
For most situations, although open revascularisation is believed to carry a higher perioperative morbidity and mortality rate, it offers a higher long-term patency, but studies have shown variable outcomes due to heterogeneous patient populations and different defined outcomes. *Autologous vein graft preferred over synthetic graft. †Can be considered for drug-eluting or plain balloon angioplasty or stent. ‡Plain balloon angioplasty preferred.		
Table 2: The available revascularisation modalities for patients with peripheral arterial disease of lower limbs at different anatomical locations		

	Asymptomatic PAD	Intermittent claudication	CLTI	Unsalvageable PAD
General practitioner	To do: • Lifestyle changes including physical activity • Best medical treatment	To do: • Life-style changes • Exercise therapy • Best medical treatment	To do: • Treat risk factors • Manage pain • Manage infection	To do: • Treat risk factors • Manage pain • Manage infection
Specialist clinic		To do: Revascularisation can be considered for patients with continued disabling limb symptoms	To do: • Flow-revascularisation • Wound care • Podiatric care • Infection care	To do: Palliative amputation and symptom and infection care

Figure 3: Management of different stages of PAD
PAD=peripheral arterial disease. CLTI=chronic limb threatening ischaemia.

	Study phase	Target population	Interventions	Patients (N)	Country
NCT06777901	Phase 4	Patients with PAD (Rutherford categories 4 or 5) and target lesion in de novo intrapopliteal artery	Auryon atherectomy system vs balloon angioplasty alone	200	USA
NCT06480760	Phase 1/2	Patients with PAD	Carnosine supplementation vs placebo	144	USA
NCT06473740	Phase 4	Patients with severe lower-limb ischaemia (Rutherford categories 4 and 5)	Combined endovascular treatment and gene therapy with deoxyribonucleic acid supercoiled plasmid pCMV-VEGF165 (neovascugen) vs isolated endovascular treatment	386	Russia
NCT04228978	NA	Patients with PAD and BMI >25 kg/m ²	Weight loss and exercise vs exercise alone	212	USA
NCT05009862	Phase 4	Patients with PAD	Rivaroxaban 2.5 mg twice daily and aspirin 81 mg daily vs placebo and aspirin 81 mg daily	75	USA
NCT05756491	NA	Patients with PAD (Rutherford categories 1–5) requiring endovascular revascularisation that can be performed on an outpatient basis	Accompanied patients in conventional outpatient care vs unaccompanied patients with remote surveillance	2000	France
NCT06112171	NA	Patients with PAD (Rutherford categories 2–5) with de novo or restenotic lesion in the superficial femoral artery or proximal popliteal artery with ≥70% stenosis documented angiographically	Treatment with lithotripsy system followed by supra stent implantation in lesion segments with severe calcification vs treatment with balloon angioplasty with a conventional or high-pressure balloon angioplasty followed by supra stent implantation in lesion segments with severe calcification	120	Germany
NCT06071429	NA	Patients with symptomatic chronic limb threatening ischaemia (Rutherford categories 4 or 5) with infrapopliteal target lesions	Treatment with MAGNITUDE bioresorbable scaffold device vs percutaneous transluminal angioplasty	276	USA
NCT05406622	NA	Patients with symptomatic chronic limb threatening ischaemia (Rutherford categories 4 or 5) with infrapopliteal target lesions	Treatment with MOTIV sirolimus-eluting bioresorbable scaffold device vs percutaneous transluminal angioplasty	292	USA
All studies are currently recruiting. NA=not available. PAD=peripheral arterial disease.					
Table 3: Selected ongoing interventional randomised controlled clinical trials related to the treatment of PAD					

Peripheral Arterial Disease 3

Peripheral arterial disease: adverse impacts, disparities in outcomes, and the path ahead

This is the third paper in the peripheral arterial disease (PAD) Series. The first and second papers in this Series outline that PAD affects over 300 million people worldwide and can be diagnosed by non-invasive tests, as well as that treatment requires medications to reduce modifiable risk factors and that exercise therapy and revascularisation are required in selected patients. In this paper, the devastating effects of PAD at the individual level are described, including chronic pain, functional limitation, loss of independence, impaired physical and mental quality of life, unemployment, and financial instability. Individuals with PAD are also at high risk of major adverse events, including major amputation, myocardial infarction, stroke, and death. The burden of PAD falls heavily on underserved groups, including women, First Nations Peoples globally, other non-White individuals, patients with financial insecurities, and those living in remote areas. Recommendations to advance PAD management are presented and include short-term changes, such as improving disease awareness and introducing multidisciplinary models of care that deliver more holistic medical and rehabilitation care, as well as long-term changes, such as testing whether screening and initiation of early medical management can reduce the burden of PAD. Furthermore, modification of health-care services is needed to provide better access for underserved, rural and remote, First Nations, and low-income populations.

Key messages

- Peripheral arterial disease (PAD) affects over 300 million people worldwide and represents a major global public health burden
- PAD can be diagnosed through clinical evaluation and non-invasive testing; although population-wide screening is not currently recommended, targeted screening of individuals at high-risk and underserved groups might be warranted
- Optimal management of PAD requires pharmacological therapy, exercise therapy, and revascularisation in selected patients; revascularisation strategies should be led by guidelines, available expertise, and shared decision making with the patient
- Effective control of modifiable risk factors can reduce the risk of cardiovascular complications and limb loss, which require multifaceted interventions, such as modifications to care delivery systems to improve appropriate prescribing and long-term adherence
- Delayed diagnosis and inappropriate management can result in devastating complications that severely affect quality of life, including reduced walking ability, intractable pain, chronic non-healing foot wounds, revascularisation procedures, minor and major amputations, mental health problems, and recurrent hospitalisations; furthermore, 5-year mortality in patients with advanced PAD exceeds that of most cancers and even acute myocardial infarction
- Substantial disparities in access to care and outcomes of PAD persist across sex, race, socioeconomic groups, and geographical regions, addressing these inequities will require increased investment in PAD management, including public awareness campaigns, targeted screening to support early-stage diagnosis linked with co-developed community-acceptable multidisciplinary care programmes that incorporate education, medical, and psychological management and rehabilitation.
- In the long-term, prevention of PAD and other cardiovascular diseases should be prioritised through adoption of healthier lifestyles, including improved diet, smoking cessation, and exercise

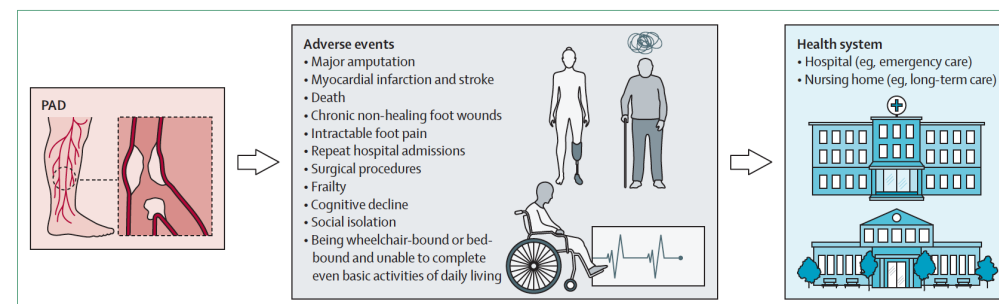


Figure 1: Effects of PAD on the individual and health systems
PAD=peripheral arterial disease.

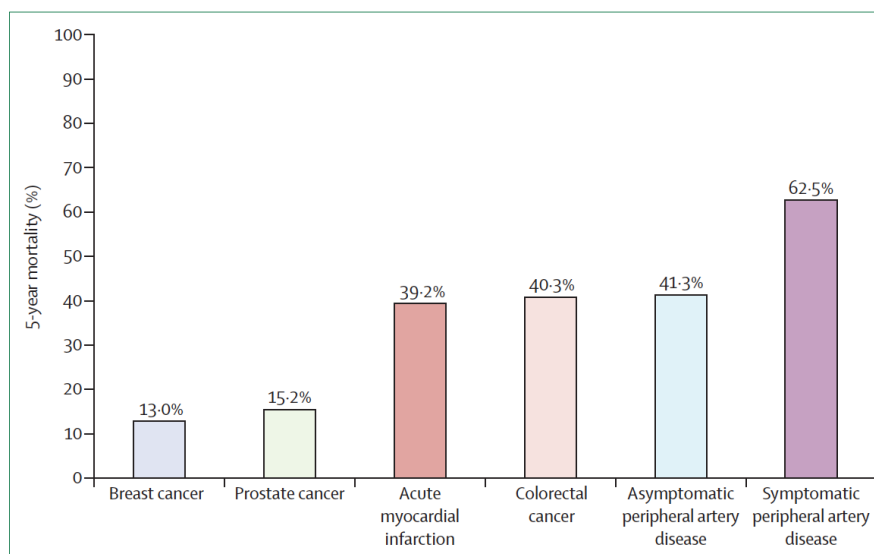


Figure 2: 5-year all-cause mortality for common conditions in the UK

Data from multiple populations. Reproduced with permission from Popplewell and colleagues.* PAD=peripheral arterial disease.

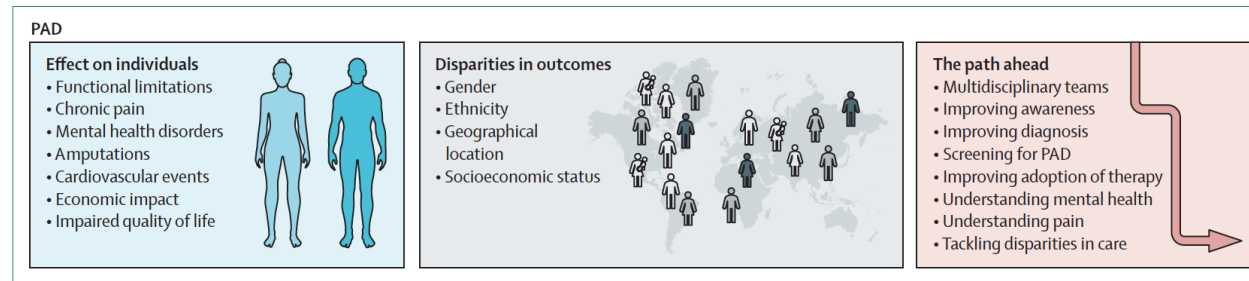


Figure 3: Effect, disparities, and the path ahead for managing PAD
 PAD=peripheral arterial disease.

	Quality of life impairment	Functional limitation or decline	Depression	Anxiety and stress	Opiate use disorder
Presentation	Symptomatic vs asymptomatic PAD; ²⁴ tissue loss vs other PAD presentations; ²⁴ symptom duration more than 6 months vs less than 6 months ²⁵	More severe limb ischaemia vs less severe limb ischaemia ²⁶	CLTI vs no CLTI or severe vs less severe limb ischaemia ^{27,28}	More severe limb ischaemia vs less severe limb ischaemia and more severe pain vs less severe pain ²⁸	CLTI ²⁹ vs no CLTI
Age, sex, and race	Younger vs older age; ³⁰ non-White compared with White race ³¹	Older vs younger age; ³² male compared with female sex ³²	Younger vs older age; ^{27,33} male compared with female sex; ^{8,9,27,33} White compared with Black and Asian race ⁹	Male compared with female sex; ⁹ White compared with Black and Asian race ⁹	Male compared with female sex ²⁹
Comorbidities	Hypertension, ^{30,31,35} chronic lung disease, ^{31,35} and past DVT ³¹ vs absence of these risk factors	Hypertension, ²⁶ diabetes, ³⁵ chronic airways disease, ³⁵ greater weight or weight gain, ³² and smoking ³² vs absence of these risk factors	CHD, ³² dyslipidaemia, ³³ CKD, ^{27,33} heart failure, ^{27,33} chronic lung disease, ^{9,27} hypothyroidism, ⁹ obesity, ⁹ and diabetes ^{27,34} vs absence of these risk factors	Chronic lung disease, ⁹ hypothyroidism, ⁹ and obesity ⁹ vs absence of these risk factors	Diabetes ²⁹ vs absence of diabetes
Function	Non-ambulatory vs walking; ³⁰ shorter vs longer walking distance ³⁵	Shorter vs longer walking distance when first diagnosed ³²	Low vs high physical activity; decreasing vs stable physical activity ^{3,36}	Low vs high physical activity; decreasing vs stable physical activity ³⁶	Not reported
Mental health and social factors	Depression, ²⁵ higher patient health questionnaire-8 depression score, ²⁵ higher generalised anxiety disorder-2 anxiety score vs lower score, ²⁵ absence of private insurance, ²⁵ and insufficient social support ^{25,37}	Worse vs better quality of life scores; ²⁵ depression vs no depression ⁸	Insufficient social support ³⁷ and past drug misuse ⁹ vs absence of these risk factors	Past drug misuse ⁹ vs no past drug misuse	Past drug misuse vs no past drug misuse; ²⁹ absence vs presence of private insurance ²⁹
Treatment	Not receiving exercise therapy or revascularisation vs having these treatments ^{25,38}	Not receiving exercise therapy vs having this treatment ³⁸	Past revascularisation or amputation ²⁸ vs no past revascularisation or amputation	Past amputation ²⁸ vs no past amputation	Not reported

CHD=coronary heart disease. CKD=chronic kidney disease. CLTI=chronic limb-threatening ischaemia. DVT=deep vein thrombosis. PAD=peripheral arterial disease.

Table 1: Risk factors for worse quality of life impairment, functional limitation or decline, depression, anxiety, stress, and opiate use disorder in patients with PAD

	Major amputation	MACE	Death
Age ≥80 years or per year of age ^{62,63}	NR	1.02 (1.01–1.03)	2.52 (1.93–3.29)
Male sex ^{59,60}	1.05 (1.00–1.11)	1.10 (1.06–1.14)	1.13 (1.10–1.16)
Race (compared with White individuals) ^{60,64,65}			
African American	2.02 (1.81–2.26)	NR	NR
Native American	1.22 (1.04–1.45)	NR	NR
Asian, native Hawaiian, or Pacific Islander	1.15 (1.00–1.33)	NR	NR
Hispanic	1.36 (1.22–1.52)	NR	NR
CLTI ^{52–54}	14.05 (5.98–33.00)*	2.18 (1.44–3.31)*	3.21 (2.00–5.14)
Diabetes ^{51,63,66}	1.31 (1.14–1.50)	1.31 (1.04–1.66)	1.87 (1.14–3.06)
Smoking ^{57,58}	2.26 (1.07–4.77)	NR	1.50 (1.00–2.20)
CHD ^{57,63,67}	2.49 (1.12–5.51)	1.85 (1.49–2.31)	2.07 (1.19–3.62)
Stroke ⁶⁸	NR	NR	5.13 (1.79–14.7)
COPD ⁶⁷	NR	NR	2.92 (1.63–5.23)
CKD† ^{69,70}	1.81 (1.04–3.18)	2.36 (1.26–4.40)	NR
ESRF ^{58,70}	2.11 (1.27–3.53)	2.40 (1.40–4.00)	5.19 (1.25–21.5)
Frailty ⁵⁶	NR	NR	1.86 (1.25–2.76)
Depression ^{77,73,44}	1.68 (1.19–2.37)	NR	1.24 (1.07–1.25)
No health insurance ⁶⁰	1.41 (1.02–1.95)	NR	NR
Not receiving statins ^{63,71}	1.54 (1.22–1.92)	2.50 (1.96–3.23)	1.64 (1.47–1.85)
Worse vs better quality of life (EuroQol-5D) ⁷²	1.10 (1.02–1.18)	1.04 (1.02–1.08)	NR
Not improved vs improved quality of life over 12 months (EuroQol-5D) ⁷²	NR	1.11 (1.06–1.15)	NR

Presented are odds ratios, hazard ratios, or relative risks (95% CI) from meta-analyses, clinical trials, and large studies mainly published since 2020. As data are from different cohorts with varying levels of adjustment for other risk factors the ratios are not directly comparable between risk factors. Some ratios have been inverted to report adverse compared with less adverse risk factor. MACE is usually defined as the combined incidence of non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death. CHD=coronary heart disease. CKD=chronic kidney disease. CLTI=chronic limb-threatening ischaemia. COPD=chronic obstruction pulmonary disease. ESRF=end-stage renal failure requiring dialysis. MACE=major adverse cardiovascular event. NR=not reported to be significantly associated with outcome. * Odds ratio calculated from reported data. † Estimated glomerular filtration rate less than 60 mL or 30 mL per min.

Table 2: Examples of risk factors for major adverse events in patients with peripheral arterial disease

Panel 1: Summary of recommendations to address peripheral arterial disease burden

Insufficient awareness and knowledge

- Awareness campaigns using social media and other platforms
- Education of doctors, other health professionals, patients, and public
- Establishment of peripheral arterial disease (PAD) self-help groups and PAD foundations

Ineffective treatment of early-stage PAD

- Better reimbursement for simple tests to diagnose PAD such as the ankle brachial index
- Incentivising medical treatment of early-stage PAD

Ineffective uptake of medical and exercise management

- Integrated multidisciplinary care models incorporating non-surgeon specialists to improve evidence-based management
- Better reimbursement of medical and rehabilitation treatment of PAD

Underdiagnosis and treatment of mental health issues and pain

- Inclusion of more holistic care at diagnosis including counselling, psychosocial, treatment of pain and mental health disorder, and support to address socioeconomic challenges

Female sex and underserved racial, geographical, and socioeconomic groups

- Campaigns to raise awareness about PAD in underserved groups

- Increase workforce diversity
- Increase enrolment of underserved groups in clinical trials
- Community consultation and engagement in PAD treatments
- Models of care designed to be culturally appropriate, easy to access (eg, telehealth-delivered), free at source, and integrated in overall care

Research

- Prioritising funding for PAD-specific international clinical trials that address key evidence gaps in care, such as:
 - Population screening and early treatment PAD in at-risk groups
 - New assessment of foot perfusion
 - Patient-centred co-developed multidisciplinary models of care to control modifiable risk factors
 - Interventions to reduces inequality in PAD
 - New PAD-specific drugs to treat walking impairment, pain, anxiety, depression, and poor quality of life
 - Best approaches to revascularisation
 - Optimal wound management approaches
 - Optimal patient rehabilitation
- Establish centre of excellence for PAD and provide funding to build research networks that engage patients in setting the agenda

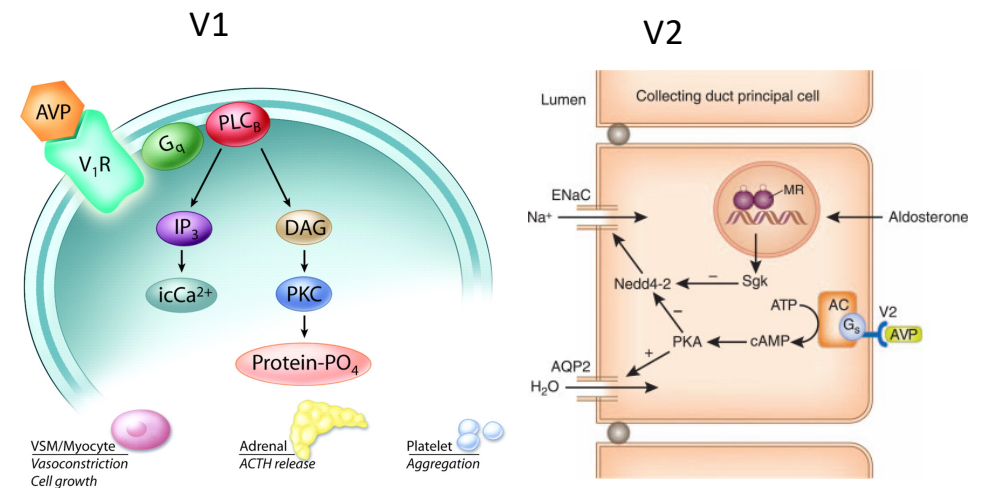
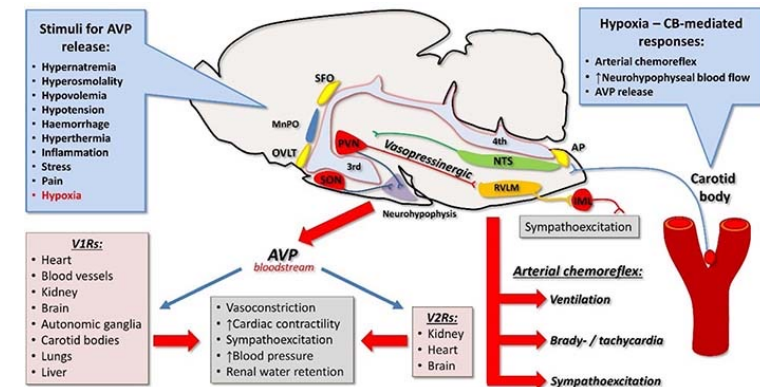
Panel 2: Priorities to address peripheral arterial disease burden

- System change to focus on treatment of early stage as well as advanced peripheral artery disease through better reimbursement models, allocated specialists to deliver holistic care, and incentives to control modifiable risk factors optimally
- Increased awareness and knowledge of the public, patients, and health professional through media campaigns, revised health professional training programmes, and patient education resources
- Research expansion on peripheral artery disease focused on testing screening, new treatments and models of care, and approaches to reduce inequality, and to develop collaborative centres of excellence globally with patient-centred agenda driving discovery, training, and education (panel 1)

Plasma arginine vasopressin (AVP) levels are frequently elevated or show altered regulation in certain experimental and human forms of hypertension, such as essential hypertension, though the exact relationship remains complex and somewhat controversial.

Role of AVP in Hypertension

- **Elevated Levels:** Clinical and population-based studies often find higher circulating AVP (or its surrogate marker, copeptin) in patients with essential hypertension compared to normotensive controls. Levels can scale with hypertension severity or stage.
- **Mechanisms:** AVP contributes to blood pressure elevation through V2-receptor-mediated water retention in the kidneys (expanding blood volume) and V1-receptor-mediated vasoconstriction, as well as potential central nervous system effects on autonomic pathways.
- **Permissive Role:** Long-term high blood pressure is rarely driven by AVP alone; instead, AVP often acts in a permissive or contributory way alongside fluid and sodium imbalance.



Übersicht der AVP-Rezeptoren

Rezeptor-Subtyp	Hauptsächliche Lokalisation	G-Protein & Signalweg	Primäre physiologische Funktion
V1a (AVPR1A)	Gefäßmuskelzellen, Leber, Gehirn, Blutplättchen	G_{q/11} Aktiviert Phospholipase C, erhöht intrazelluläres Calcium (Ca ²⁺)	Vasokonstriktion (Gefäßverengung), Glykogenolyse in der Leber, Thrombozytenaggregation, Steuerung von Sozialverhalten
V1b / V3 (AVPR1B)	Hypophysenvorderlappen, Gehirn (insb. Hippocampus)	G_{q/11} Aktiviert Phospholipase C, erhöht intrazelluläres Calcium (Ca ²⁺)	Stimulation der ACTH-Freisetzung (Stressregulation über die HPA-Achse)
V2 (AVPR2)	Hauptzellen der renalen Sammelrohre, Gefäßendothel	G_s Aktiviert die Adenylatzyklase, erhöht zyklisches AMP (cAMP)	Wasserretention (Einbau von Aquaporin-2 -Kanälen zur Rückresorption von freiem Wasser), endotheliale Vasodilatation



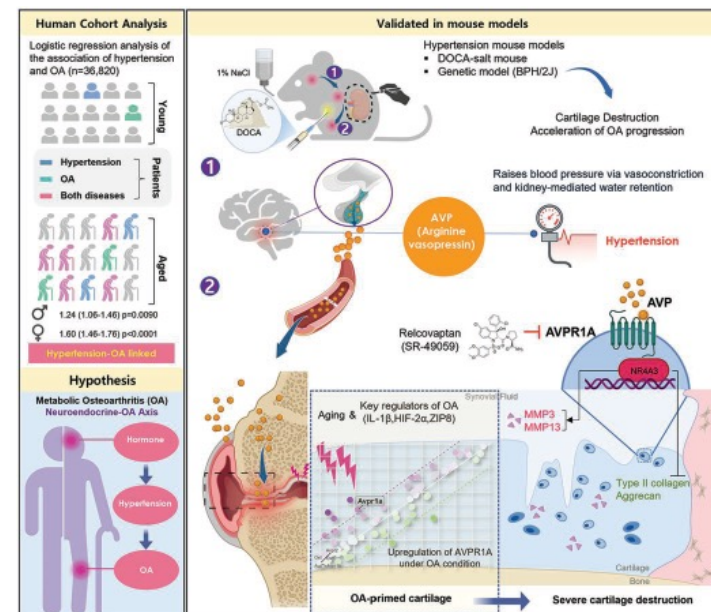
Hypertension fuels osteoarthritis through neuroendocrine signaling

INTRODUCTION: Osteoarthritis (OA), the leading cause of disability among older adults, has long been considered a disease driven primarily by mechanical wear and tear. However, accumulating evidence indicates that OA is also influenced by systemic metabolic, endocrine, and vascular factors. Hypertension, which is highly prevalent in aging populations, is associated with an increased OA risk and greater severity. However, the mechanisms linking elevated blood pressure to impaired cartilage homeostasis remain undefined.

RATIONALE: Transcriptomic analyses in mice identified *Avpr1a*, which encodes the **receptor for the neuroendocrine hormone arginine vasopressin (AVP)**, as one of the **most strongly upregulated genes in OA chondrocytes**. Further screening revealed that *Avpr1a* is the only AVP receptor gene that is **up-regulated in articular cartilage**. Because the AVP-AVPR1A axis plays a central role in blood pressure regulation, its dysregulation within cartilage suggests a **direct molecular link between hypertension and OA**. Given that circulating AVP concentration increases under hypertensive conditions, we hypothesized that **hypertension-induced elevations in AVP act on OA-primed chondrocytes**—sensitized through mechanical injury or aging—that up-regulate AVPR1A, thereby activating catabolic signaling pathways.

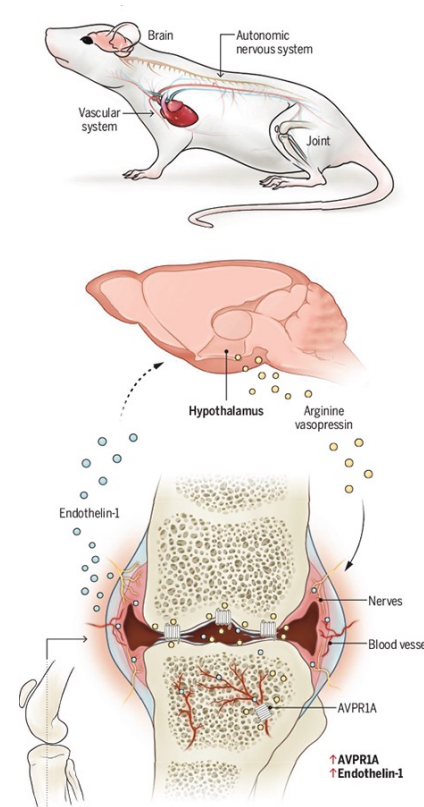
RESULTS: We combined **human cohort analyses** with two hypertensive mouse models to define the mechanistic **relationship between hypertension and OA**. Logistic regression of population-scale data demonstrated that hypertension was independently associated with OA prevalence, with progressively stronger associations observed in advanced structural disease. **In both mouse models, hypertension markedly exacerbated experimental OA**, increasing cartilage erosion and subchondral bone plate thickening without affecting synovitis or osteophyte maturity. We further demonstrated that **AVP** is not synthesized locally within joint tissues but instead reaches the synovial fluid through the **systemic circulation**. **AVPR1A expression was increased in OA cartilage** but remained low in healthy, young cartilage. Both mechanical wear and tear and natural aging acted as priming factors by up-regulating basal AVPR1A expression.

Consequently, this priming, rather than hypertension alone, was required to activate the AVP-AVPR1A signaling axis. Activation of this pathway promoted catabolic signaling while suppressing anabolic signaling without inducing cellular senescence. **Cartilage destruction required concurrent elevation of both AVP and AVPR1A.** Genetic deletion or local intra-articular pharmacological antagonism of AVPR1A prevented hypertension-induced cartilage degeneration, demonstrating that hypertension-driven OA progression depends specifically on AVP-AVPR1A signaling. Finally, **transcriptomic and functional analyses identified NR4A3** as the principal transcriptional effector **linking hypertensive endocrine signaling to chondrocyte catabolism**, independent of the renin-angiotensin-aldosterone system or oxytocin receptors.



Hypertension accelerates OA through AVP-AVPR1A signaling. Elevated circulating AVP in hypertension exacerbates cartilage degeneration in mechanically injured or aged joints. Under OA conditions, chondrocytes selectively up-regulate AVP receptor AVPR1A, rendering articular cartilage highly responsive to systemic AVP. Activation of this signaling axis drives downstream NR4A3 transcription, increasing catabolic enzyme expression while suppressing anabolic cartilage matrix synthesis to promote disease progression. DOCA, deoxycorticosterone acetate; HIF-2 α , hypoxia-inducible factor 2 α ; IL-1 β , interleukin-1 β ; ZIP8, zinc importer ZIP8.

CONCLUSION: These findings establish the **AVP-AVPR1A axis as an endocrine-skeletal signaling pathway through which systemic hypertension accelerates OA progression.** Hypertension elevates circulating AVP, OA primes chondrocytes to express AVPR1A, and their combined activation drives cartilage matrix breakdown and subchondral bone remodeling. **Targeting AVPR1A or its downstream mediators offers a therapeutic strategy to slow OA progression in hypertensive individuals experiencing joint injury or advanced age.**



NR4A3 (also known as *NOR1* or neuron-derived orphan receptor 1) is a human gene that encodes an intracellular transcription factor and orphan nuclear receptor involved in cell growth, metabolism, and programmed cell death.

A whole-body view of osteoarthritis

Osteoarthritis is not exclusively caused by localized inflammation in bone joints that leads to cartilage damage. It is also driven by metabolic dysfunction across the body. Both vascular and neural signaling pathways can affect joint health. The hormones endothelin-1 and arginine vasopressin, which is produced by the hypothalamus and binds to AVP receptor 1A (AVPR1A), have a dual role: They increase blood pressure, which can lead to hypertension, and also joint inflammation, which promotes osteoarthritis.

Trump announces plan to send \$90 payments to millions of seniors



President Donald Trump announced plans to send \$90 payments to more than 20 million older Americans, with Trump tying the initiative to his broader push to lower health care costs.

The money would be drawn from about \$2 billion set aside to improve Medicare's hospital and medical insurance programs, which has not been used for that purpose since the initiative's inception in 2008, administration officials said Saturday. Both parties have used the money, held in the Medicare Improvement Fund, in congressional budget maneuvers.

"Under our leadership, we're finally going to use the Medicare Improvement Fund to do what it was designed and intended to do: Help America's seniors," Trump said in a video released by the White House on Saturday.