

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

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

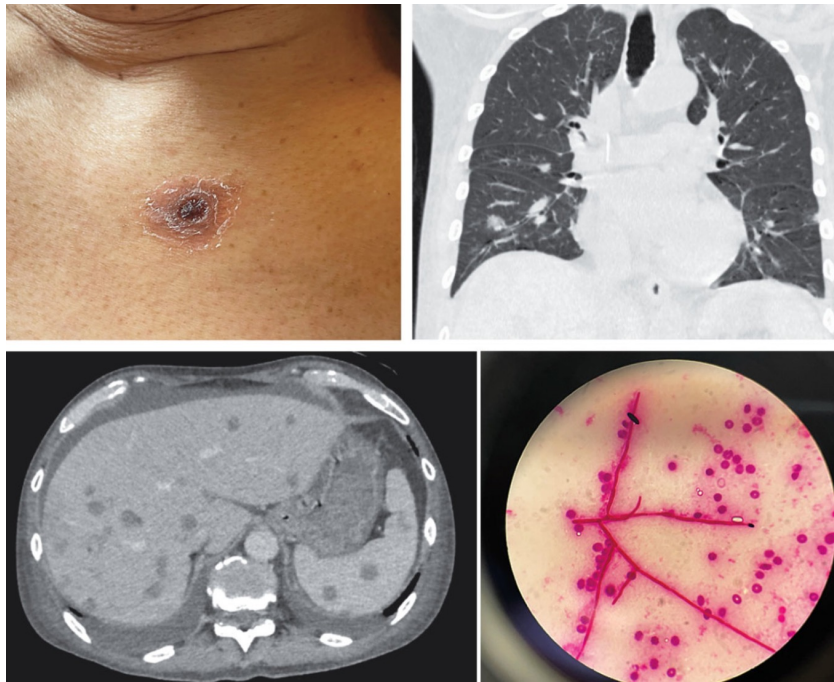
Usually every Wednesday 17:00 - 18:00



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!](#)



Molecular sequencing identified the organism as *Fusarium keratoplasticum*. A diagnosis of disseminated fusariosis was made. Fusariosis is one of the most common invasive mold species in patients with prolonged neutropenia. It is notably associated with fungemia, in contrast to other invasive mold infections. First line treatment is voriconazole and liposomal amphotericin B. Mortality remains high in disseminated infection.

A 61-year-old man with prolonged neutropenia as a result of salvage chemotherapy for **acute myeloid leukemia** was evaluated on hospital day 37 for persistent neutropenic fever despite treatment with broad-spectrum antimicrobial agents. Physical exam was notable for a **lesion with central necrosis on the chest** and a similar lesion on the left palm. A **serum 1,3- β -D-glucan level was elevated**, and a galactomannan was negative. Computed tomography of the chest, abdomen, and pelvis was performed. Gram's staining of blood culture revealed **septate, hyaline hyphae**. Which of the following is the most likely causative organism?

Aspergillus fumigatus

Rhizopus arrhizus

Blastomyces dermatitidis

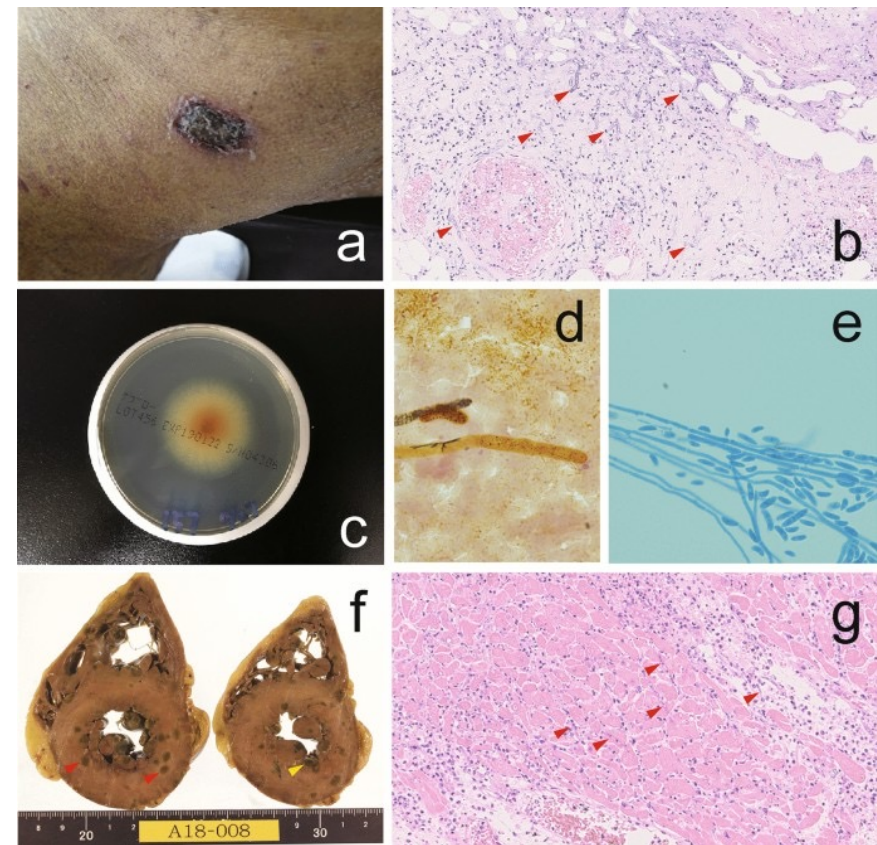
☒ *Fusarium keratoplasticum*

Cryptococcus neoformans

Fusarium keratoplasticum ist ein opportunistischer, filamentöser Schlauchpilz aus dem *Fusarium solani*-Artenkomplex (FSSC). Er ist medizinisch und ökologisch als Krankheitserreger bei Mensch und Tier sowie als Biofilm-Bildner von Bedeutung.

Klinische Relevanz & Eigenschaften

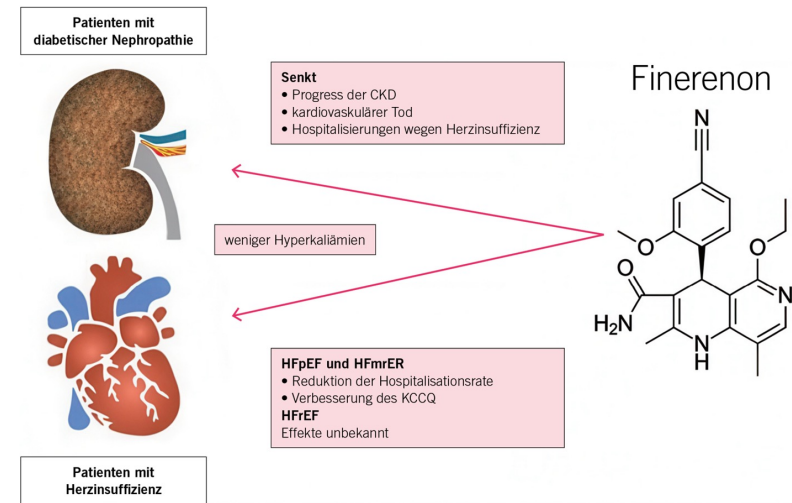
- **Humanpathogen:** Verursacht bei immunkompetenten Menschen lokale Infektionen wie Hornhautentzündungen (Keratitis) oder Nagelpilz.
- **Disseminierte Fusariose:** Bei stark immungeschwächten Patienten (z. B. mit anhaltender Neutropenie) kann er schwere, systemische Infektionen über die Blutbahn auslösen, die oft mit Hautnekrosen einhergehen und eine hohe Sterblichkeit aufweisen.
- **Resistenzen:** Der Pilz ist von Natur aus gegen viele gängige Antimykotika hochgradig resistent, was die Behandlung erschwert. Zur Therapie werden meist **Voriconazol und liposomales Amphotericin B** kombiniert.



Finerenon ist ein nicht-steroidaler, selektiver **Mineralokortikoidrezeptor-Antagonist**. Er schützt Herz und Nieren, indem er Entzündungen und Gewebeverwundung (Fibrose) hemmt. Das Medikament ist für Erwachsene zur Behandlung einer chronischen Nierenerkrankung bei Typ-2-Diabetes sowie bei bestimmter chronischer Herzinsuffizienz zugelassen.

Wirkung und Anwendungsgebiete

- **Nierenschutz:** Verlangsamt das Fortschreiten von Nierenschäden bei Diabetes Typ 2 mit Albuminurie (Eiweiß im Urin).
- **Herzschutz:** Senkt das Risiko für Herzinfarkt, kardiovaskulären Tod und Krankenhauseinweisungen wegen Herzschwäche.
- **Vorteil gegenüber älteren Mitteln:** Anders als ältere Wirkstoffe wie Spironolacton blockiert Finerenon andere Steroidrezeptoren kaum, wodurch typische hormonelle Nebenwirkungen (wie Brustwachstum bei Männern) vermieden werden.



Finerenon ist in Deutschland als Kassenrezept erhältlich. Eine große Packung mit 98 Filmtabletten (10 mg oder 20 mg) kostet laut Apothekendurchschnittspreis (AVP) rund **196,40 €**.

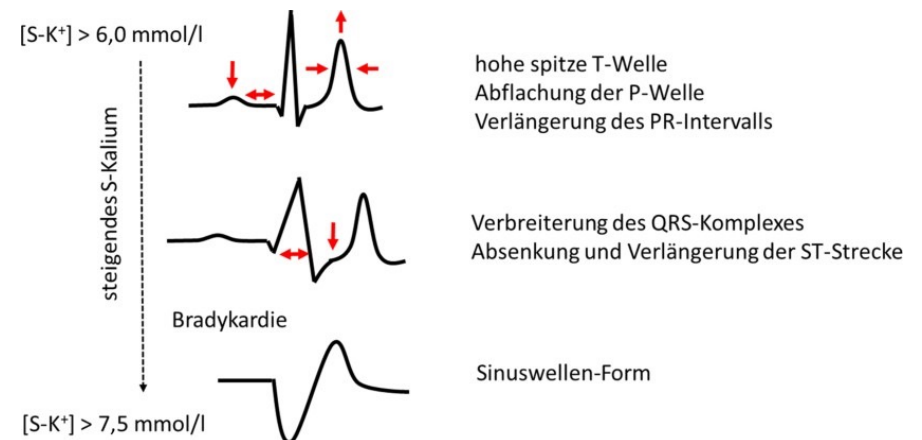
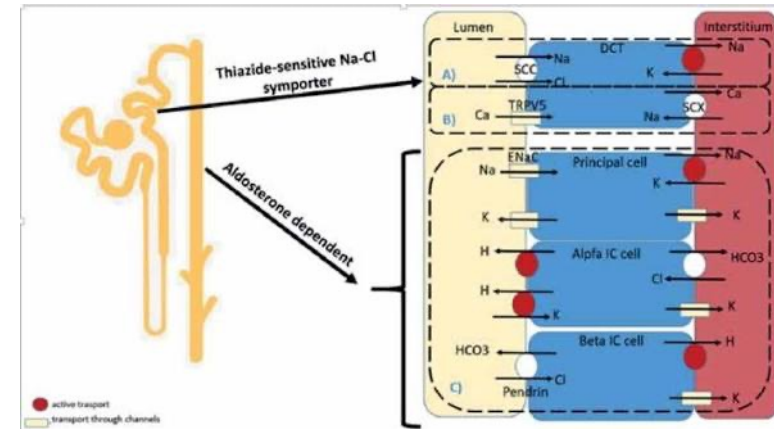
Spironolacton kostet in Deutschland ohne Rezept bzw. als gesetzlicher Festpreis (AVP) je nach Dosierung und Packungsgröße etwa **14 €** für 100 Stück.

The most feared complication of MR blockade

Eine **Hyperkaliämie** bezeichnet eine potenziell lebensbedrohliche Elektrolytstörung, bei der die **Konzentration von Kalium im Blutserum auf über 5,0 mmol/l** (bei Kindern über 5,4 mmol/l) erhöht ist. Da Kalium maßgeblich für die elektrische Erregbarkeit von Herz- und Muskelzellen verantwortlich ist, können schwere Verläufe zu tödlichen Herzrhythmusstörungen führen.

Schweregrade des Kaliumspiegels

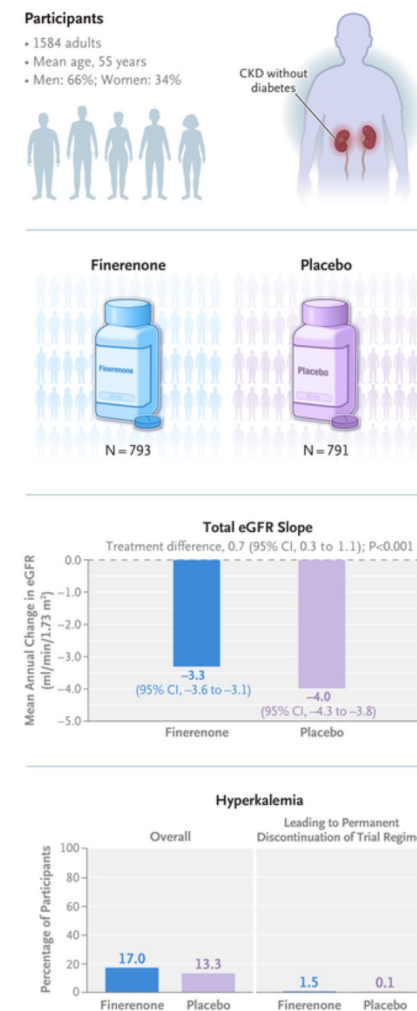
- **Milde Hyperkaliämie:** 5,0 bis 5,4 mmol/l
- **Mittelschwere Hyperkaliämie:** 5,5 bis 5,9 mmol/l
- **Schwere Hyperkaliämie:** 6,0 bis 6,4 mmol/l
- **Lebensbedrohliche Hyperkaliämie:** Über 6,5 mmol/l



Finerenone in Persons with Chronic Kidney Disease without Diabetes

MR Blockade
in non-
diabetic CKD

In randomized trials, **finerenone, a nonsteroidal mineralocorticoid receptor antagonist**, improved kidney and cardiovascular outcomes in patients with type 2 diabetes and chronic kidney disease (CKD). Whether finerenone has similar effects in patients without diabetes who have CKD is unknown. We randomly assigned adults without diabetes who had CKD (estimated glomerular filtration rate [eGFR], 25 to <90 ml per minute per 1.73 m² of body-surface area) and albuminuria (urinary albumin-to-creatinine ratio, 200 to ≤3500, with albumin in milligrams and creatinine in grams) and were using a renin–angiotensin system inhibitor to receive finerenone (10 or 20 mg daily) or placebo. The primary outcome was **the total eGFR slope** (mean annual rate of change in the eGFR from baseline to month 32), assessed with a two-slope linear spline mixed-effects model. Secondary outcomes included a composite of **kidney or cardiovascular events** (reduction from baseline of at least 57% in the eGFR, kidney failure, hospitalization for heart failure, or death from cardiovascular causes), a composite of the two kidney events, and a composite of the two cardiovascular events.



The prevalence of chronic kidney disease (CKD) has more than doubled since 1990, with approximately 800 million adults affected globally in 2023. Although type 2 diabetes is the most common cause of CKD, more than half the cases are in persons without diabetes. Renin–angiotensin system (RAS) inhibitors and sodium–glucose cotransporter 2 (SGLT2) inhibitors reduce the loss of kidney function and risk of kidney failure in adults with CKD, regardless of whether they have diabetes. Despite the use of these guideline-recommended treatments, progressive loss of kidney function and adverse cardiovascular outcomes occur in many persons with CKD, particularly those with severely increased albuminuria levels. Thus, new therapies are needed.

Overactivation of the mineralocorticoid receptor is implicated in the pathophysiology of CKD through increased sodium and fluid retention and activation of proinflammatory and profibrotic processes. Finerenone is a selective nonsteroidal mineralocorticoid receptor antagonist that has been shown to reduce the loss of kidney function and the risk of adverse kidney and cardiovascular outcomes in persons with CKD and type 2 diabetes. The current trial, FIND-CKD (Finerenone in Non-Diabetic CKD), examined the efficacy and safety of finerenone in adults without diabetes who had CKD.

Participants

Eligible participants had a clinical diagnosis of CKD and an estimated glomerular filtration rate (eGFR) of at least 25 but less than 60 ml per minute per 1.73 m² of body-surface area and a urinary albumin-to-creatinine ratio between 200 and 500 (with the albumin level measured in milligrams and the creatinine level measured in grams), or an eGFR of at least 25 but less than 90 ml per minute per 1.73 m² and a urinary albumin-to-creatinine ratio between 500 and 3500. Eligibility criteria included a serum potassium level of 4.8 mmol per liter or less and receipt of a stable dose of an angiotensin-converting enzyme inhibitor or an angiotensin-receptor blocker therapy for at least 4 weeks before screening. Patients were excluded if they had received a diagnosis of type 1 or type 2 diabetes or had a glycated hemoglobin level of at least 6.5%.

Trial Procedures

Participants were randomly assigned in a 1:1 ratio to receive oral finerenone or matching placebo. Randomization was conducted with the use of interactive response technology and included baseline SGLT2 inhibitor use (yes vs. no) and screening urinary albumin-to-creatinine ratio (≤ 1000 vs. >1000) as stratification factors. Finerenone therapy was initiated at a dose of 20 mg per day if the screening eGFR was at least 60 ml per minute per 1.73 m² and at 10 mg per day if the screening eGFR was 25 to less than 60 ml per minute per 1.73 m².

Outcomes

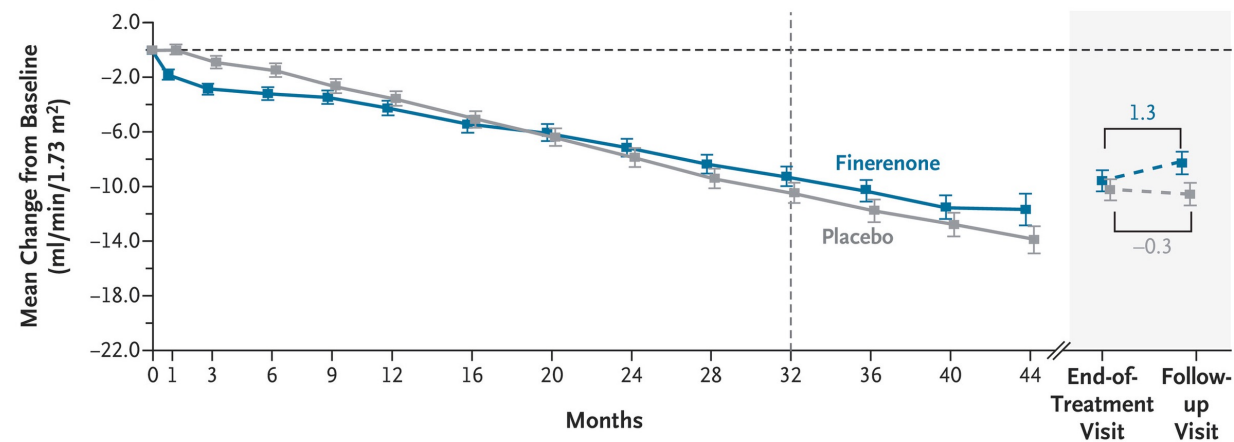
The primary efficacy outcome was the total eGFR slope, defined as the mean annual rate of change in the eGFR from baseline to month 32.

Characteristic	Finerenone (N = 793)	Placebo (N = 791)
Age — yr	54.5±14.2	54.8±14.3
Sex — no. (%)		
Female	275 (34.7)	260 (32.9)
Male	518 (65.3)	531 (67.1)
Race or ethnic group — no. (%)†		
Asian	447 (56.4)	421 (53.2)
Black	22 (2.8)	15 (1.9)
White	308 (38.8)	340 (43.0)
Other	16 (2.0)	15 (1.9)
Medical history		
Atherosclerotic disease	90 (11.3)	105 (13.3)
Hypertension	701 (88.4)	706 (89.3)
Heart failure	16 (2.0)	19 (2.4)
Primary cause of chronic kidney disease		
Hypertensive or ischemic nephropathy	234 (29.5)	225 (28.4)
Chronic glomerulonephritis	446 (56.2)	457 (57.8)
Other‡	29 (3.7)	24 (3.0)
Unknown	84 (10.6)	85 (10.7)
Clinical measurements — mm Hg		
Systolic blood pressure	129.7±13.9	129.3±14.2
Diastolic blood pressure	80.0±9.2	80.1±10.0
Biochemical measurements		
Urinary albumin-to-creatinine ratio§		
Median (IQR)	827.5 (572.0–1257.4)	810.7 (579.6–1234.3)
Distribution — no. (%)		
≤1000	483 (60.9)	509 (64.3)
>1000	310 (39.1)	282 (35.7)
Estimated glomerular filtration rate		
Mean — ml/minute/1.73 m²	46.8±16.2	46.6±16.0
Distribution — no. (%)		
<60 ml/minute/1.73 m²	631 (79.6)	636 (80.4)
≥60 ml/minute/1.73 m²	162 (20.4)	155 (19.6)
Serum potassium level — mmol/liter	4.5±0.4	4.5±0.4
Medication use — no. (%)		
ACE inhibitor	230 (29.0)	205 (25.9)
Angiotensin-receptor blocker	560 (70.6)	585 (74.0)
Diuretic	142 (17.9)	148 (18.7)
SGLT2 inhibitor	135 (17.0)	135 (17.1)

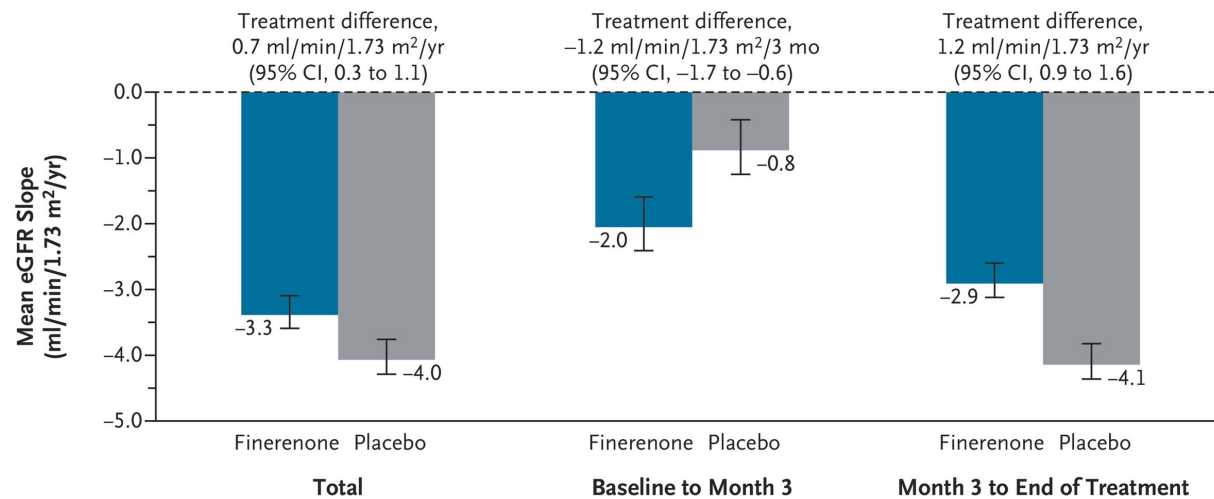
Outcomes and Adverse Events.

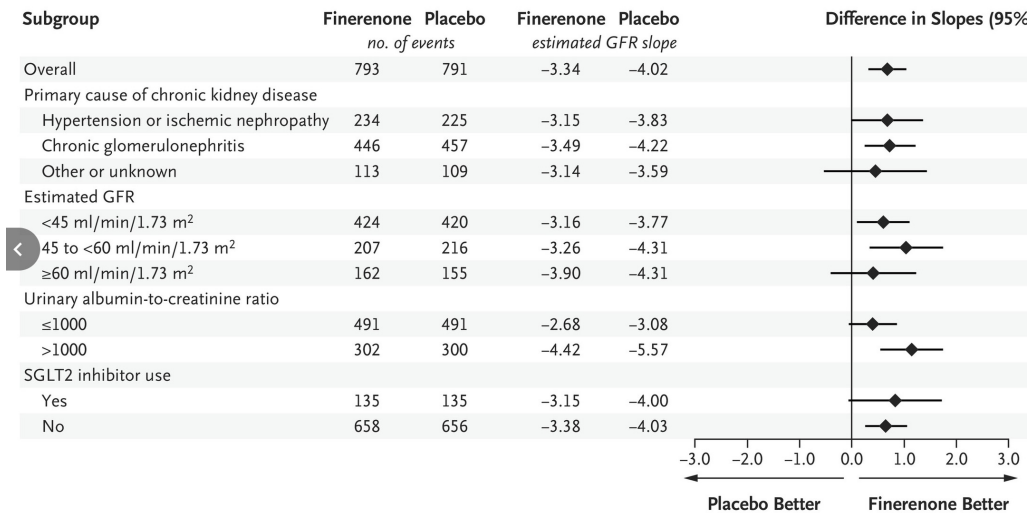
Variable	Finerenone (N = 793)	Placebo (N = 791)	Treatment Effect ^a
Primary outcome			
Mean total eGFR slope (95% CI)	−3.3 (−3.6 to −3.1)	−4.0 (−4.3 to −3.8)	0.7 (0.3 to 1.1)†
Secondary outcomes — no. (%)			
Composite kidney–cardiovascular outcome‡	110 (13.9)	134 (16.9)	0.77 (0.60 to 0.99)§
Composite kidney outcome¶	104 (13.1)	125 (15.8)	0.78 (0.60 to 1.01)
Composite cardiovascular outcome**	10 (1.3)	16 (2.0)	0.60 (0.27 to 1.33)
Adverse events — no. (%)			
Any adverse event			
Overall	542 (68.3)	517 (65.4)	
Related to trial regimen	175 (22.1)	133 (16.8)	
Leading to permanent discontinuation of the trial regimen	17 (2.1)	23 (2.9)	
Any serious adverse event			
Overall	166 (20.9)	168 (21.2)	
Related to trial regimen	9 (1.1)	6 (0.8)	
Leading to permanent discontinuation of trial regimen	1 (0.1)	8 (1.0)	
Leading to hospitalization	159 (20.1)	156 (19.7)	
Life-threatening	4 (0.5)	8 (1.0)	
Leading to death	6 (0.8)	10 (1.3)	
Acute kidney injury			
Overall	23 (2.9)	25 (3.2)	
Leading to permanent discontinuation of the trial regimen	1 (0.1)	1 (0.1)	
Serious adverse event leading to hospitalization	9 (1.1)	8 (1.0)	
Any hyperkalemia††			
Overall	135 (17.0)	105 (13.3)	
Leading to permanent discontinuation of the trial regimen	12 (1.5)	1 (0.1)	
Serious adverse event related to hyperkalemia			
Overall	8 (1.0)	5 (0.6)	
Leading to hospitalization	7 (0.9)	5 (0.6)	
Life-threatening	1 (0.1)‡‡	0	
Leading to death	0	0	

A Total eGFR Slope

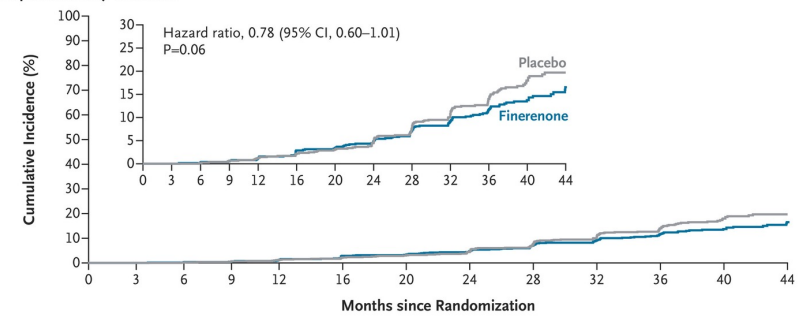


B Mean eGFR Slopes

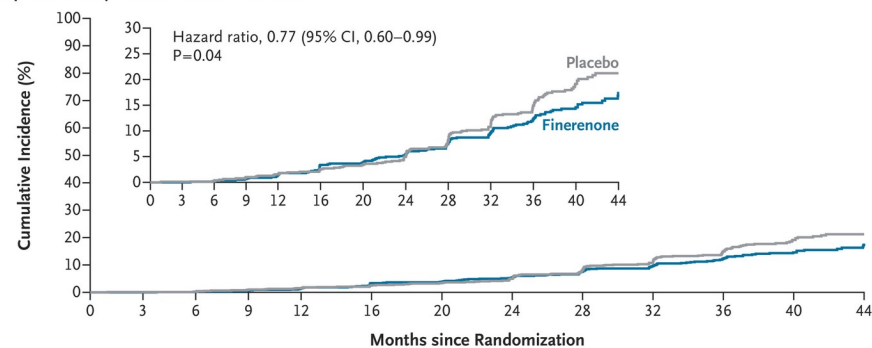




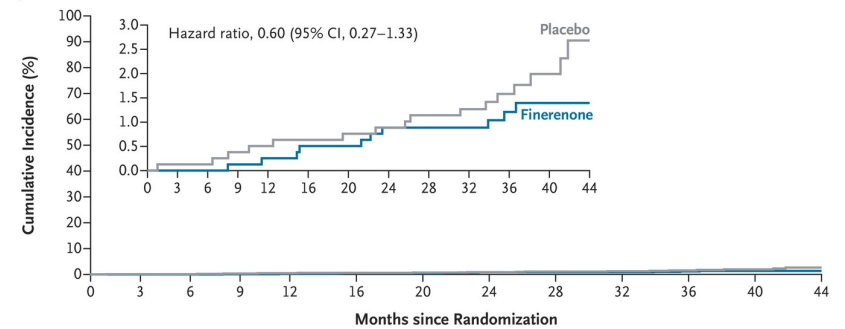
B Composite Kidney Outcome

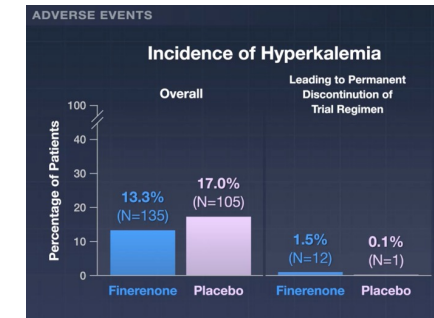
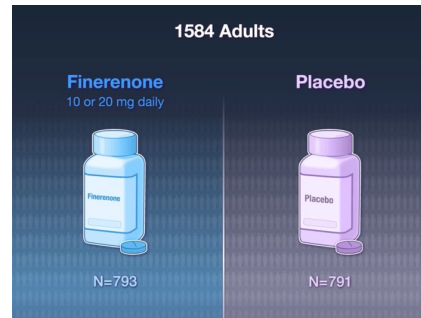
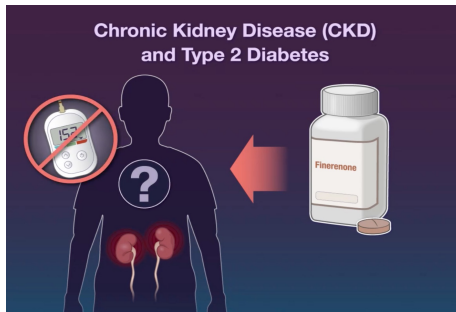
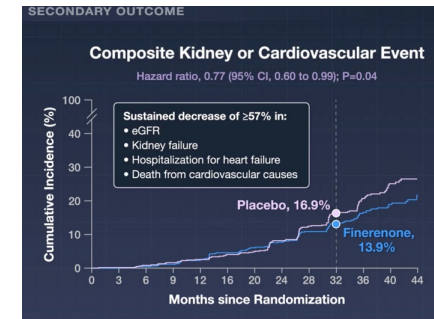
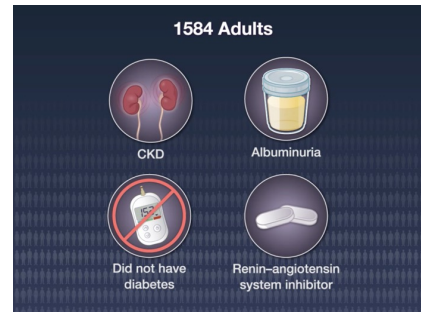
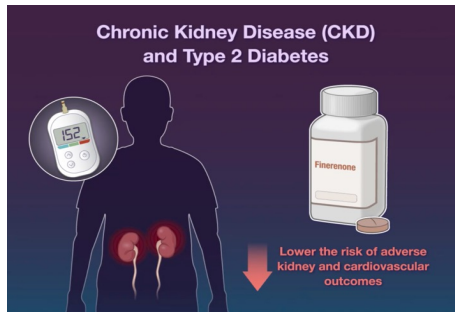


A Composite Kidney–Cardiovascular Outcome

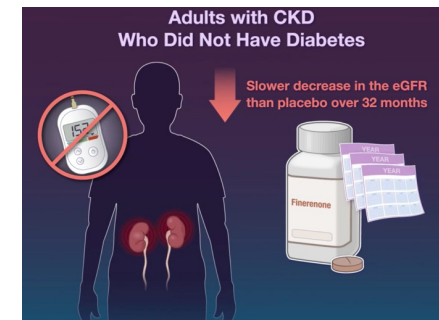
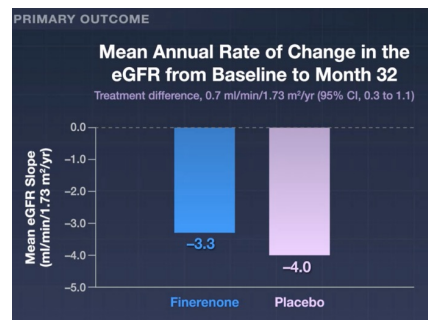
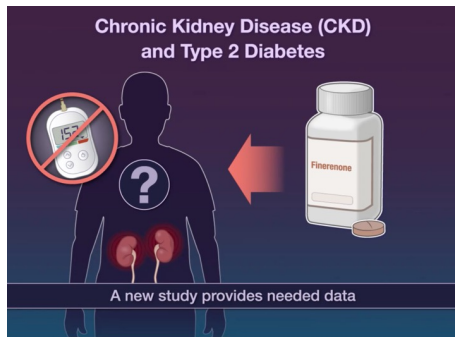


C Composite Cardiovascular Outcome





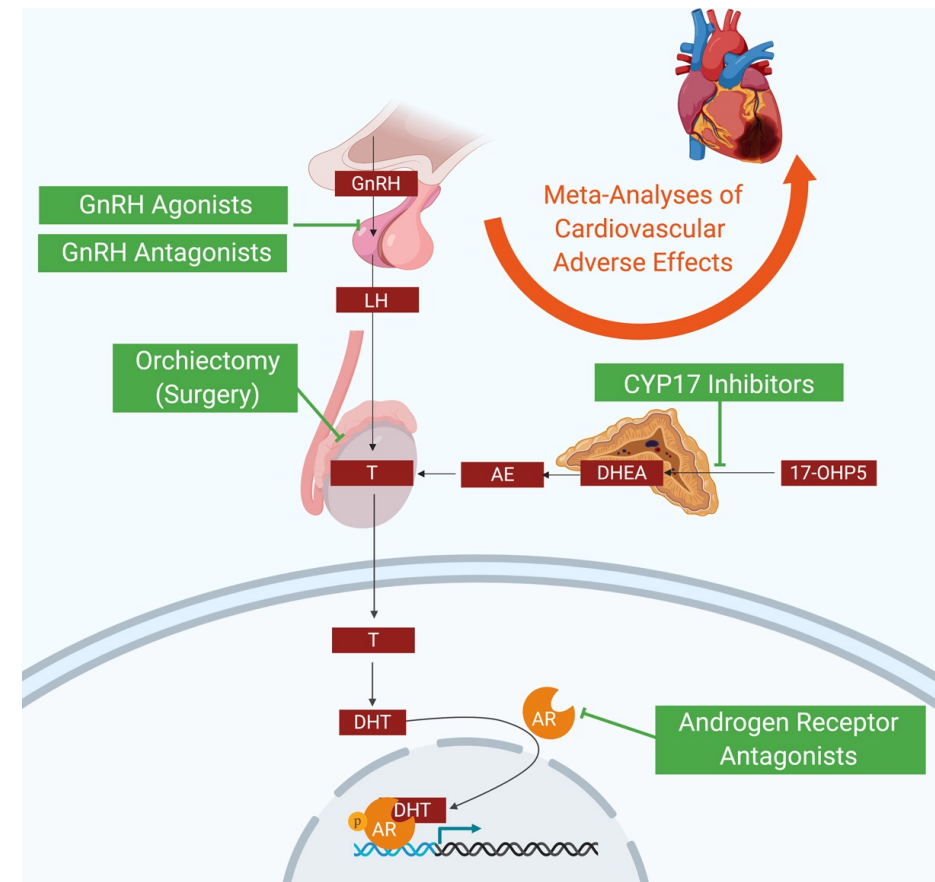
15 times as common but nobody died



Die Androgendeprivations-Therapie (ADT), im Deutschen auch als Hormonentzugstherapie oder Anti-Hormontherapie bekannt, ist eine medizinische Behandlung zur Senkung des Testosteronspiegels. Sie wird vor allem bei Prostatakrebs eingesetzt, um das Wachstum der Krebszellen zu verlangsamen oder zu stoppen, da Testosteron dieses Wachstum anregt.

Arten der Therapie

- **Medikamentöse Senkung:** LH-RH-Analoga oder LH-RH-Antagonisten stoppen die Testosteronproduktion im Hoden.
- **Rezeptorblocker (Antiandrogene):** Tabletten verhindern, dass Testosteron an die Krebszellen andockt.
- **Operative Kastration:** Die chirurgische Entfernung beider Hoden (Orchiektomie).
- **Formen:** Die Behandlung kann dauerhaft (kontinuierlich) oder zeitweise unterbrochen (intermittierend) erfolgen.



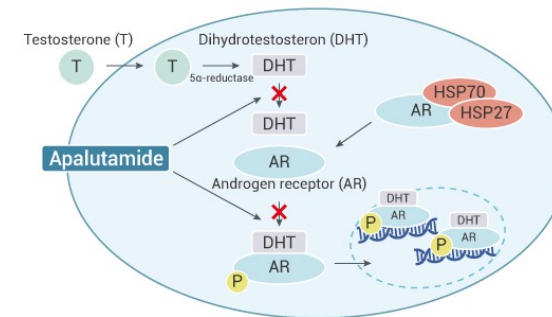
ADT is linked to an increased risk of adverse cardiovascular events, including heart attacks, strokes, and heart failure. This risk is largely driven by metabolic changes like weight gain, insulin resistance, and higher cholesterol.

Apalutamid ist ein verschreibungspflichtiges Mittel zur gezielten Behandlung des **fortgeschrittenen Prostatakarzinoms**. Es gehört zur Medikamentenklasse der **Antiandrogene** (Androgenrezeptor-Antagonisten). Der Wirkstoff blockiert die Bindung von Testosteron an den Tumorzellen, um deren Wachstum effektiv zu bremsen

Anwendungsgebiete

Das Medikament kommt in zwei wesentlichen Stadien zum Einsatz:

- **nmCRPC**: Nicht-metastasiertes, kastrationsresistentes Prostatakarzinom mit hohem Risiko für Metastasen.
- **mHSPC**: Metastasiertes, hormonsensitives Prostatakarzinom in Kombination mit einer Hormonentzugstherapie (ADT).
- Die Standarddosis beträgt **240 mg täglich** (entweder als vier 60 mg Tabletten oder eine 240 mg Tablette).
- Die Einnahme erfolgt als **Einmalgabe** unabhängig von den Mahlzeiten.
- Eine bestehende medizinische Kastration (GnRH-Analoga) muss parallel fortgesetzt werden



Apalutamide (ARN-509)

is a Potent and Competitive AR Antagonist for Prostate Cancer Research

Apalutamid blockiert den Androgenrezeptor (AR) anders als ältere Antiandrogene der 1. Generation (wie Bicalutamid), wirkt aber sehr ähnlich wie andere Inhibitoren der 2. Generation (wie Enzalutamid). Es blockiert die Signalübertragung auf drei Ebenen: **Es verhindert die Bindung des Hormons, stoppt das Wandern des Rezeptors in den Zellkern und blockiert die Bindung an die DNA**

Enzalutamide (Xtandi) and Apalutamide (Erleada) are both second-generation oral non-steroidal anti-androgen medicines used to treat prostate cancer. They differ slightly in their chemical structures, half-lives, receptor binding profiles, and specific side effect management, though both block androgen receptor activity.

Perioperative Apalutamide in High-Risk Localized Prostate Cancer

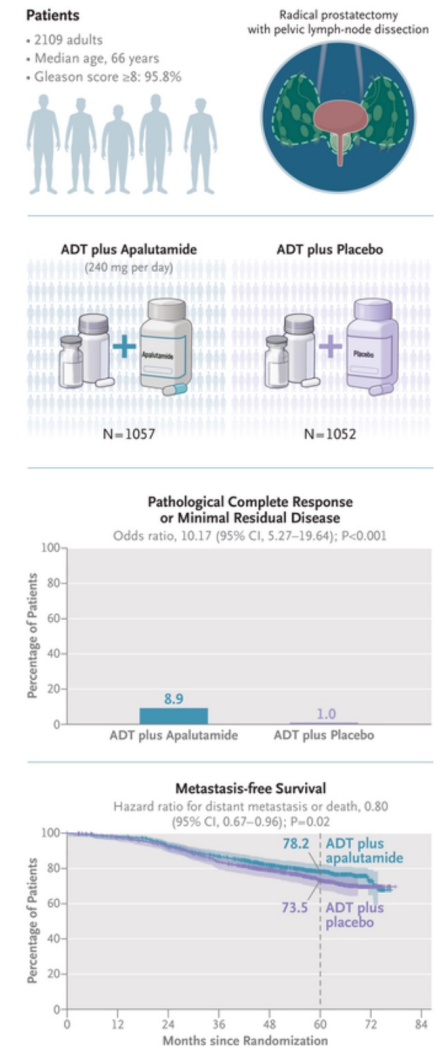
Apalutamide is an AVT

Apalutamide and AVT

Vs.

No apalutamide and AVT

Radical prostatectomy is potentially curative in patients with high-risk localized or locally advanced prostate cancer; however, relapse occurs within 5 years in up to 50% of patients. We conducted a phase 3, double-blind, placebo-controlled trial in which patients with newly diagnosed high-risk localized or locally advanced prostate cancer were randomly assigned in a 1:1 ratio to receive **androgen-deprivation therapy (ADT) plus apalutamide** (240 mg per day) or ADT plus placebo for **6 cycles (28 days each) before and after radical prostatectomy with pelvic lymph-node dissection**. The dual primary end points were a composite of pathological complete response or minimal residual disease (defined as a pathological stage of ypT2 or lower, with a tumor size of ≤5 mm in the greatest dimension) and **metastasis-free survival**, as assessed with conventional imaging or prostate-specific membrane antigen positron-emission tomography. Secondary end points included event-free survival, first subsequent treatment, and distant metastasis (assessed in time-to-event analyses), as well as safety.



Apalutamide is an oral nonsteroidal androgen-receptor inhibitor approved for the treatment of nonmetastatic, castration-resistant prostate cancer (i.e., progressive cancer in the context of very low serum testosterone levels) and metastatic, castration-sensitive prostate cancer on the basis of results from the phase 3 SPARTAN (Selective Prostate Androgen Receptor Targeting with ARN-509) and TITAN (Targeted Investigational Treatment Analysis of Novel Anti-androgen) trials, respectively. In metastatic, castration-sensitive prostate cancer, treatment with ADT plus apalutamide led to rapid, deep, and durable decline in PSA levels and better overall survival than ADT plus placebo. We conducted the PROTEUS (Perioperative Treatment with Enzalutamide United with Surgery) trial to assess the efficacy and safety of 12 cycles of perioperative treatment with ADT plus apalutamide as compared with ADT plus placebo in patients with high-risk localized or locally advanced prostate cancer undergoing radical prostatectomy.

Patients

Eligible patients had histologically confirmed adenocarcinoma, were candidates for radical prostatectomy as assessed by investigators, and had high-risk localized or locally advanced prostate cancer as defined according to a combination of NCCN criteria and additional trial-specific criteria involving the number of positive biopsy cores.

Treatment

Patients were randomly assigned in a 1:1 ratio to receive apalutamide (240 mg) or matched placebo orally once daily, in addition to ADT (gonadotropin-releasing hormone analogue [agonist or antagonist]). Patients received six cycles (28 days each) of neoadjuvant treatment (ADT plus apalutamide or ADT plus placebo), with cessation of apalutamide or placebo during the period from 2 weeks before radical prostatectomy to 4 weeks after prostatectomy, followed by six cycles (28 days each) of adjuvant treatment (ADT plus apalutamide or ADT plus placebo) after prostatectomy. ADT was continuous throughout the treatment phase.

End Points and Assessments

The dual primary end points were pathological complete response or minimal residual disease (a composite end point) and metastasis-free survival.

Characteristic	ADT plus Apalutamide (N = 1057)	ADT plus Placebo (N = 1052)	Overall (N = 2109)
Age			
Median (IQR) — yr	66.0 (62–71)	66.0 (61–70)	66.0 (61–71)
Distribution — no. (%)			
<65 yr	406 (38.4)	442 (42.0)	848 (40.2)
65 to 69 yr	289 (27.3)	300 (28.5)	589 (27.9)
70 to 74 yr	256 (24.2)	216 (20.5)	472 (22.4)
≥75 yr	106 (10.0)	94 (8.9)	200 (9.5)
Race or ethnic group — no. (%)†			
American Indian or Alaska Native	5 (0.5)	1 (0.1)	6 (0.3)
Asian	197 (18.6)	211 (20.1)	408 (19.3)
Black	35 (3.3)	44 (4.2)	79 (3.7)
Native Hawaiian or other Pacific Islander	4 (0.4)	5 (0.5)	9 (0.4)
White	746 (70.6)	717 (68.2)	1463 (69.4)
Multiple	3 (0.3)	3 (0.3)	6 (0.3)
Not reported	67 (6.3)	71 (6.7)	138 (6.5)
Median time from initial diagnosis to randomization (range) — mo‡	2.4 (0.5–192.5)	2.3 (0.5–245.5)	2.3 (0.5–245.5)
PSA level§			
Median (IQR) — ng/ml	14.4 (8.3–29.2)	15.1 (8.1–33.7)	14.8 (8.1–31.5)
Range — ng/ml	1.2–1753.0	0.0–2798.0	0.0–2798.0
Distribution — no./total no. (%)			
<20 ng/ml	630/1025 (61.5)	604/1033 (58.5)	1234/2058 (60.0)
<10 ng/ml	352/1025 (34.3)	344/1033 (33.3)	696/2058 (33.8)
10 to <20 ng/ml	278/1025 (27.1)	260/1033 (25.2)	538/2058 (26.1)
≥20 ng/ml	395/1025 (38.5)	429/1033 (41.5)	824/2058 (40.0)
20 to <40 ng/ml	216/1025 (21.1)	223/1033 (21.6)	439/2058 (21.3)
≥40 ng/ml	179/1025 (17.5)	206/1033 (19.9)	385/2058 (18.7)
Tumor stage at diagnosis — no. (%)			
T1	219 (20.7)	197 (18.7)	416 (19.7)
T2	465 (44.0)	470 (44.7)	935 (44.3)
T3	338 (32.0)	344 (32.7)	682 (32.3)
T4	33 (3.1)	33 (3.1)	66 (3.1)
TX	2 (0.2)	8 (0.8)	10 (0.5)
Regional lymph-node stage at diagnosis — no. (%)			
N0	928 (87.8)	922 (87.6)	1850 (87.7)
N1	129 (12.2)	130 (12.4)	259 (12.3)
Gleason score at diagnosis — no. (%)¶			
7	45 (4.3)	44 (4.2)	89 (4.2)
≥8	1012 (95.7)	1008 (95.8)	2020 (95.8)
8	350 (33.1)	360 (34.2)	710 (33.7)
9	623 (58.9)	596 (56.7)	1219 (57.8)
10	39 (3.7)	52 (4.9)	91 (4.3)
ECOG performance-status score — no./total no. (%)			
0	1019/1057 (96.4)	1017/1051 (96.8)	2036/2108 (96.6)
1	38/1057 (3.6)	34/1051 (3.2)	72/2108 (3.4)
Geographic region — no. (%)			
Europe	557 (52.7)	559 (53.1)	1116 (52.9)
North America	217 (20.5)	214 (20.3)	431 (20.4)
Rest of the world	283 (26.8)	279 (26.5)	562 (26.6)

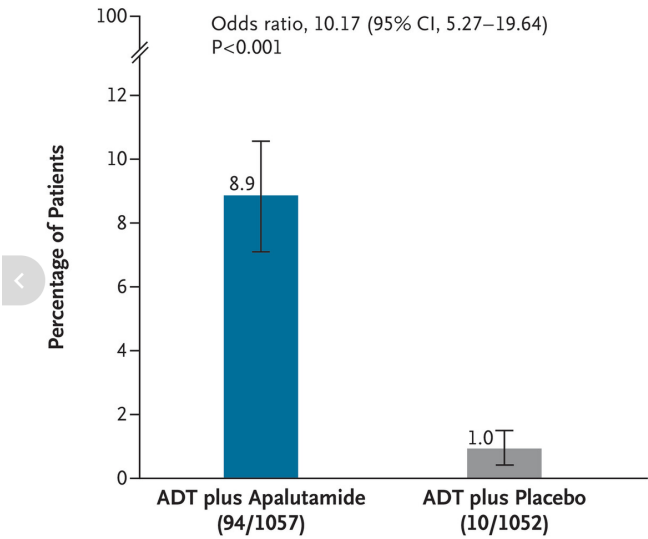
Primary, Secondary, Exploratory, and Post Hoc End Points.

End Point	ADT plus Apalutamide (N = 1057)	ADT plus Placebo (N = 1052)	Hazard Ratio or Odds Ratio (95% CI)†	P Value
Primary end points				
Pathological complete response or MRD‡				
No. of patients (%)	94 (8.9)	10 (1.0)	10.17 (5.27–19.64)§	<0.001¶
95% CI — %	7.2–10.6	0.4–1.5		
Metastasis-free survival — mo	NR	NR	0.80 (0.67–0.96)	0.02**
Secondary end points				
Event-free survival (95% CI) — mo	57.1 (50.9–67.7)	38.4 (35.5–44.3)	0.71 (0.63–0.80)	<0.001**
Time to first subsequent local or systemic therapy (95% CI) — mo††	74.2 (63.8–NE)	41.5 (36.6–47.3)	0.65 (0.57–0.73)	<0.001**
Time to distant metastasis detected on conventional imaging or PSMA PET — mo	NR	NR	0.68 (0.55–0.83)	<0.001**
Freedom from disease (no evidence of disease) at 4 yr				
No. of patients (%)	232 (21.9)	193 (18.3)	1.25 (1.01–1.55)§‡‡	0.04¶
95% CI — %	19.5–24.4	16.0–20.7		
Metastasis-free survival assessed with conventional imaging — mo	NR	NR	0.84 (0.67–1.07)	—
PSA-free survival with testosterone recovery (95% CI) — mo	35.4 (33.4–38.1)	30.3 (28.4–33.0)	0.83 (0.73–0.94)	—
Exploratory end points				
Low residual cancer burden — no. (%)	323 (30.6)	123 (11.7)	3.36 (2.67–4.23)§	—
Time to castration-resistant prostate cancer (95% CI) — mo	NR	NR (71.8–NE)	0.59 (0.46–0.76)	—
Time to testosterone recovery from baseline (95% CI) — mo§§	19.4 (19.0–20.3)	18.7 (18.3–19.1)	0.93 (0.84–1.02)	—
Time to distant metastasis detected on conventional imaging — mo	NR	NR	0.63 (0.46–0.85)	—
Time to distant metastasis detected on PSMA PET — mo	NR	NR	0.72 (0.57–0.89)	—
Time to testosterone recovery from end of 12-mo peri- operative treatment period (95% CI) — mo	8.1 (7.1–8.6)	6.6 (6.3–7.1)	0.92 (0.84–1.01)	—
Post hoc end points				
Investigator-assessed metastasis-free survival (95% CI) — mo	NR	NR (73.6–NE)	0.74 (0.62–0.87)	—
Distant metastasis assessed by blinded independent central review in patients with biochemical fail- ure — no./total no. (%)	134/156 (85.9)	189/221 (85.5)	NA	—

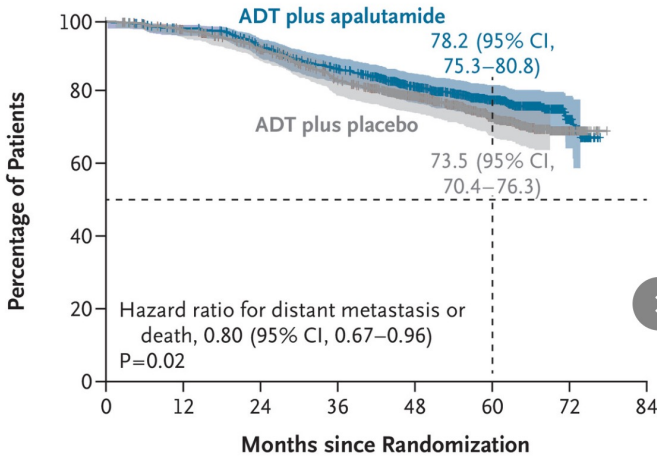
Adverse Events

Adverse Event	ADT plus Apalutamide (N=1050)					ADT plus Placebo (N=1050)				
	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 1	Grade 2	Grade 3	Grade 4	Total
	number of patients (percent)					number of patients (percent)				
Any adverse event	—	—	—	—	1037 (98.8)	—	—	—	—	1027 (97.8)
Grade 3 or 4 adverse event	—	—	—	—	416 (39.6)	—	—	—	—	325 (31.0)
Any serious adverse event	—	—	—	—	203 (19.3)	—	—	—	—	172 (16.4)
Any adverse event leading to discontinuation of apalutamide or placebo	—	—	—	—	78 (7.4)	—	—	—	—	28 (2.7)
Any adverse event leading to dose interruption	—	—	—	—	154 (14.7)	—	—	—	—	81 (7.7)
Any adverse event leading to death	—	—	—	—	14 (1.3)	—	—	—	—	5 (0.5)
Most common adverse events†										
At least 1 adverse event	96 (9.1)	525 (50.0)	393 (37.4)	23 (2.2)	1037 (98.8)	122 (11.6)	580 (55.2)	313 (29.8)	12 (1.1)	1027 (97.8)
Hot flush	550 (52.4)	109 (10.4)	7 (0.7)	0	666 (63.4)	514 (49.0)	79 (7.5)	0	0	593 (56.5)
Urinary incontinence	232 (22.1)	279 (26.6)	16 (1.5)	0	527 (50.2)	248 (23.6)	269 (25.6)	17 (1.6)	0	534 (50.9)
Erectile dysfunction	200 (19.0)	202 (19.2)	35 (3.3)	0	437 (41.6)	192 (18.3)	216 (20.6)	27 (2.6)	0	435 (41.4)
Fatigue	248 (23.6)	39 (3.7)	4 (0.4)	0	291 (27.7)	266 (25.3)	14 (1.3)	1 (0.1)	0	281 (26.8)
Arthralgia	165 (15.7)	68 (6.5)	4 (0.4)	0	237 (22.6)	143 (13.6)	59 (5.6)	2 (0.2)	0	204 (19.4)
Rash	123 (11.7)	69 (6.6)	31 (3.0)	0	223 (21.2)	90 (8.6)	13 (1.2)	2 (0.2)	0	105 (10.0)
Constipation	117 (11.1)	83 (7.9)	0	0	200 (19.0)	98 (9.3)	68 (6.5)	0	0	166 (15.8)
Hypertension	19 (1.8)	70 (6.7)	80 (7.6)	0	169 (16.1)	13 (1.2)	80 (7.6)	91 (8.7)	0	184 (17.5)
Pruritus	114 (10.9)	44 (4.2)	7 (0.7)	0	165 (15.7)	75 (7.1)	15 (1.4)	0	0	90 (8.6)
Procedural pain	35 (3.3)	78 (7.4)	6 (0.6)	0	119 (11.3)	28 (2.7)	112 (10.7)	3 (0.3)	0	143 (13.6)
Urinary tract infection	8 (0.8)	90 (8.6)	18 (1.7)	0	116 (11.0)	5 (0.5)	108 (10.3)	11 (1.0)	0	124 (11.8)
Covid-19	60 (5.7)	35 (3.3)	5 (0.5)	2 (0.2)	102 (9.7)	67 (6.4)	35 (3.3)	2 (0.2)	1 (0.1)	105 (10.0)

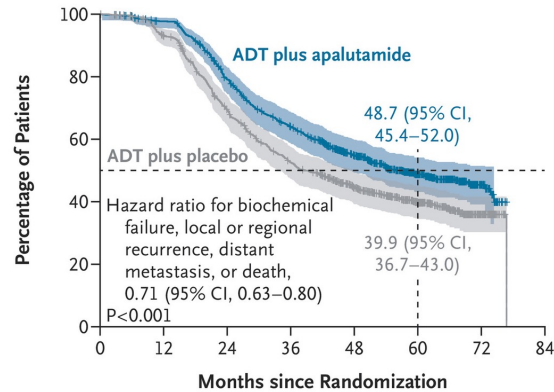
A Pathological Complete Response or Minimum Residual Disease



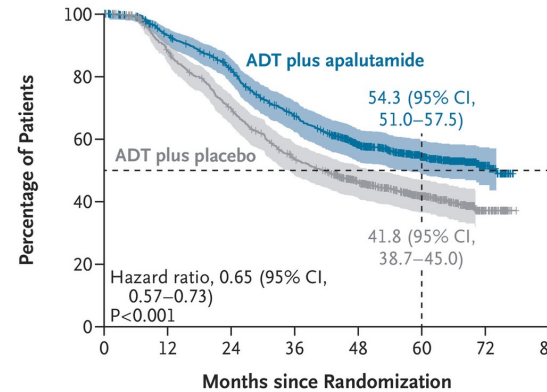
B Metastasis-free Survival



A Event-free Survival



B First Subsequent Local or Systemic Therapy

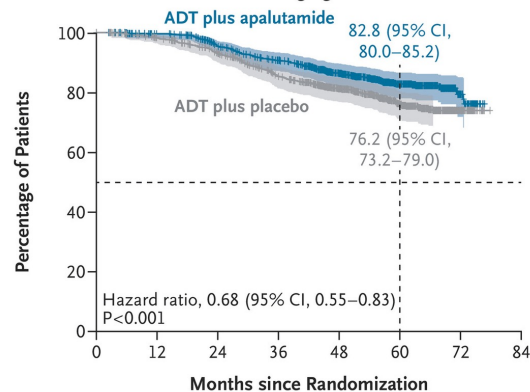


Conclusions:

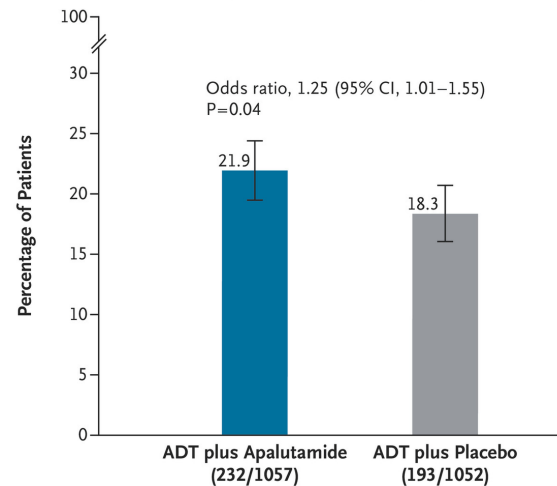
Die Kombination aus einer Androgendeprivationstherapie (ADT) und Apalutamid ist eine wirksame medikamentöse Behandlung für bestimmte Formen von Prostatakrebs. Sie blockiert die Wirkung von männlichen Hormonen (Androgenen) auf die Krebszellen **weitaus stärker als eine alleinige ADT und verlangsamt das Tumorwachstum deutlich.**

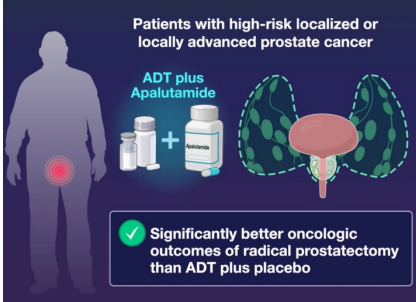
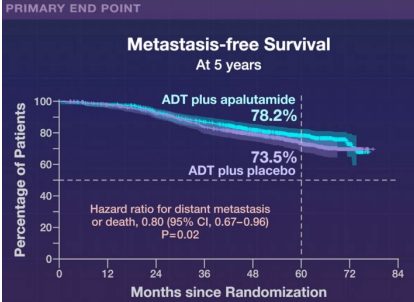
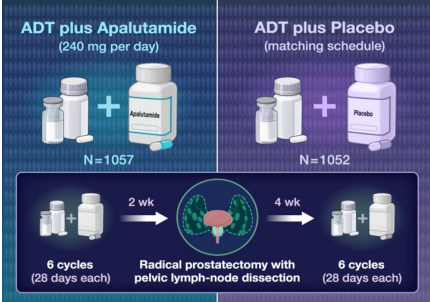
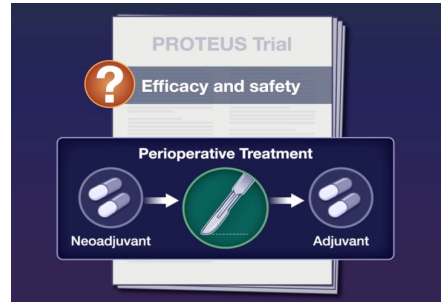
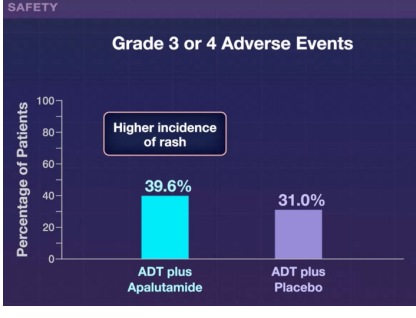
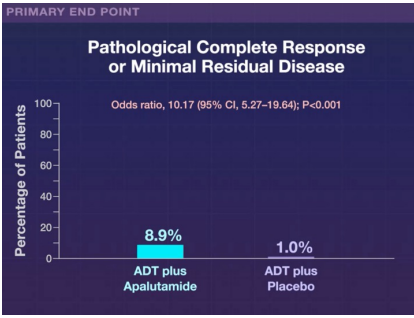
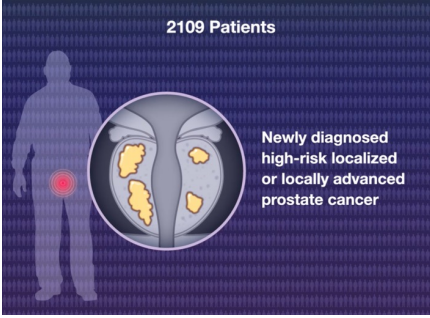
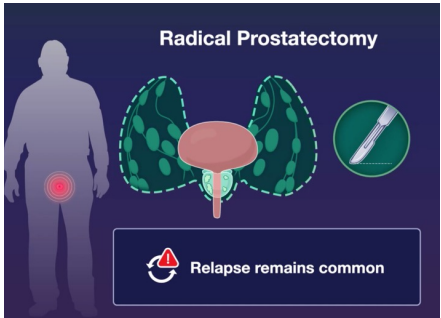
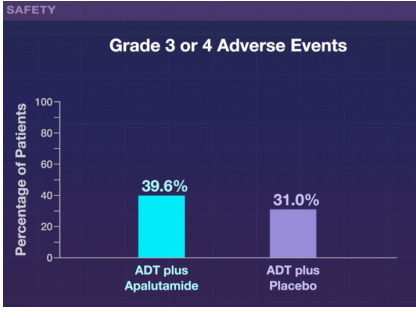
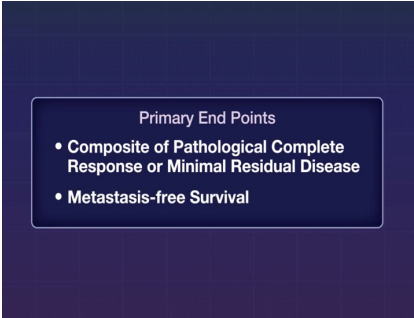
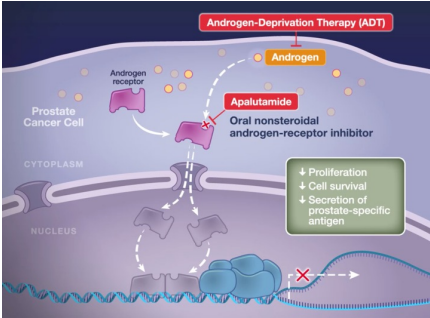
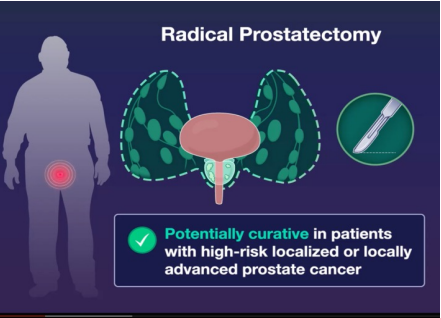
- **Metastasiertes hormonsensitives Prostatakarzinom (mHSPC):** Hier senkt die Kombination das Risiko für ein Voranschreiten der Erkrankung und verbessert nachweislich das Gesamtüberleben.
- **Nicht-metastasiertes kastrationsresistentes Prostatakarzinom (nmCRPC):** Bei dieser Form zögert die Therapie das Auftreten von Fernmetastasen stark heraus.
- **Lokaler Hochrisiko-Prostatakrebs:** Neuere Daten untersuchen den Einsatz im perioperativen (vor/nach operativer Entfernung) Bereich, um das Ansprechen zu verbessern

C Distant Metastasis on Conventional Imaging or PSMA PET



D Freedom from Disease (No Evidence of Disease) at 4 Years

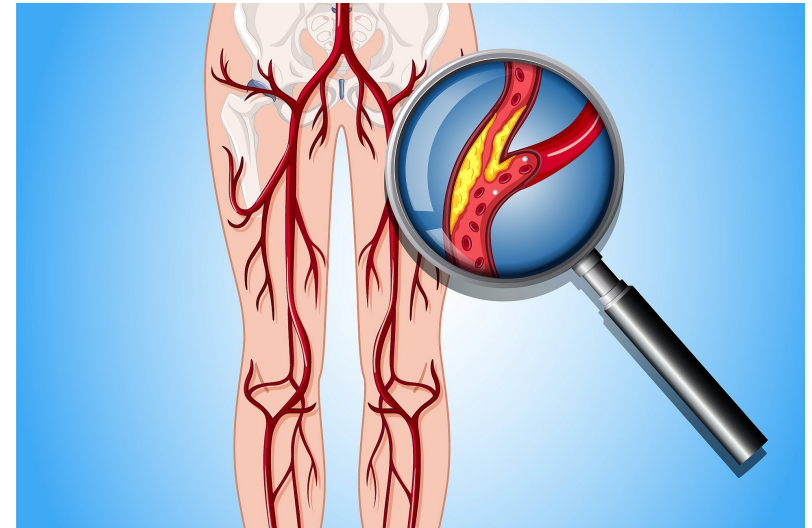




Die **periphere arterielle Verschlusskrankheit (pAVK)**, auch als **Schaufensterkrankheit** bekannt, ist eine chronische Durchblutungsstörung der Extremitäten. Sie wird meistens durch **Arteriosklerose** (Gefäßverkalkung) verursacht, welche zu Verengungen oder Verschlüssen der Arterien führt. Am häufigsten sind die Beine betroffen

Die Erkrankung verläuft typischerweise in vier Stadien (nach Fontaine):

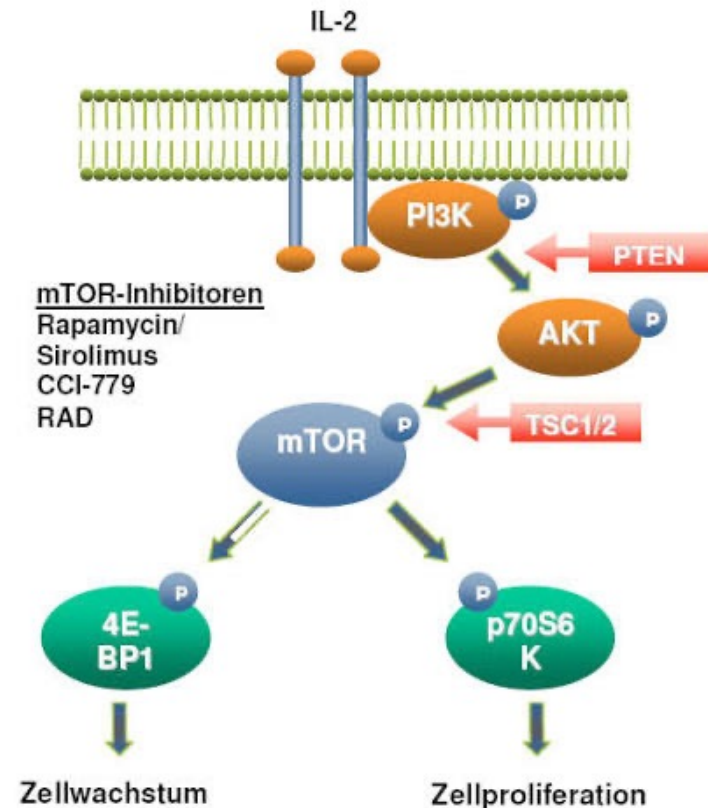
- **Stadium I:** Beschwerdefrei, oft zufällige Diagnose.
- **Stadium II:** Belastungsschmerz beim Gehen, der zum Stehenbleiben zwingt.
- **Stadium III:** Ruheschmerzen, besonders im Liegen.
- **Stadium IV:** Gewebeschäden (Geschwüre, Nekrosen, „Raucherbein“)



Sirolimus (auch bekannt als **Rapamycin**) ist ein starkes **Immunsuppressivum**, das primär zur **Verhinderung von Organabstoßungen nach Nierentransplantationen** eingesetzt wird. Es blockiert das Enzym **mTOR** (mechanistic Target of Rapamycin) und hemmt so die Aktivierung von T-Zellen. Zudem wird es bei der seltenen Lungenerkrankung **Lymphangioleiomyomatose (LAM)**

Wichtige Aspekte der Anwendung

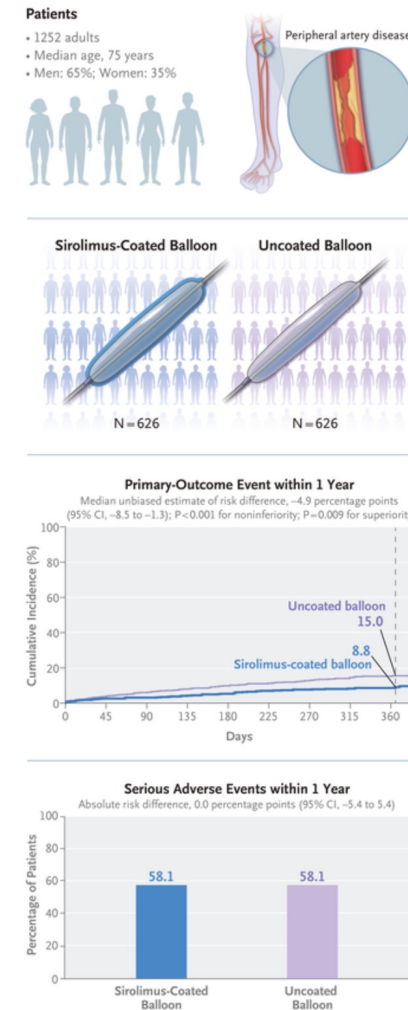
- **Wirkmechanismus:** Gezielte Hemmung des mTOR-Signalwegs zur Unterdrückung der Immunantwort.
- **Wechselwirkungen:** Der Wirkstoff wird über das Enzym CYP3A4 abgebaut. Grapefruitsaft oder Medikamente wie Clarithromycin erhöhen den Blutspiegel massiv.
- **Nebenwirkungen:** Häufig treten Wundheilungsstörungen, Aphten im Mund, Ödeme oder erhöhte Blutfettwerte auf.



Sirolimus-Coated Balloon Angioplasty for Infrainguinal Artery Disease

Sirolimus stent Vs. No-coat stent

Whether sirolimus-coated balloon angioplasty for infrainguinal artery disease reduces the incidence of major adverse limb events remains unknown. In this prospective, open-label, noninferiority trial with a prespecified sequential testing strategy for superiority and blinded outcome adjudication, we randomly assigned patients with infrainguinal artery disease in a 1:1 ratio to undergo angioplasty with a sirolimus-coated balloon or with an uncoated balloon. The primary outcome was a composite of unplanned major amputation affecting the target limb or endovascular or surgical revascularization of the target lesion for critical limb ischemia within 1 year after randomization. The key secondary outcome was a composite of any unplanned amputation affecting the target limb or revascularization of the target lesion for critical or noncritical limb ischemia within 1 year after randomization. The noninferiority margin was 5 percentage points. The primary safety outcome was death from any cause within 1 year after randomization.



Drug-coated balloons were developed to ensure lasting vessel patency after endovascular intervention through local delivery of antiproliferative agents. Drug-coated balloons that deliver paclitaxel, which exerts a local cytotoxic effect, have been shown to delay or prevent restenosis and reduce the need for target-lesion revascularization among patients with femoropopliteal artery disease. However, whether paclitaxel-coated devices are associated with an increased risk of death continues to be debated.

Sirolimus, an inhibitor of mammalian target of rapamycin that exerts a cytostatic effect, has been widely used in drug-eluting coronary stents and may attenuate neointimal hyperplasia in peripheral arteries while potentially minimizing systemic toxic effects. We conducted the SirPAD (Sirolimus-Coated Balloon for Peripheral Artery Disease) trial to assess whether angioplasty with a sirolimus-coated balloon is noninferior and, if the criterion for noninferiority is met, superior to angioplasty with an uncoated balloon with respect to reducing major adverse limb events among patients with symptomatic infrainguinal artery disease.

Eligibility

Eligible patients were at least 18 years of age with symptomatic peripheral artery disease in the femoropopliteal arteries or arteries below the knee that warranted endovascular intervention. Patients were excluded if they were pregnant, breast-feeding, or planned to become pregnant during the trial period; had a known hypersensitivity or allergy to sirolimus; or had participated in another investigational trial in the previous 90 days.

Treatment and Randomization

Eligible patients were randomly assigned in a **1:1 ratio to undergo angioplasty** with **either a sirolimus-coated balloon** or an **uncoated balloon**; trial-group assignments were performed after angiographic screening, identification of the target lesion, and successful passage of the wire through the target lesion. Randomization was computer-generated with permuted blocks and stratified according to trial site and the presence or absence of critical limb ischemia.

Efficacy and Safety Outcomes

The primary **outcome was major adverse limb events** within 1 year after randomization, which was defined as a composite of unplanned major amputation affecting the target limb or endovascular or surgical revascularization of the target lesion for critical limb ischemia.

Demographic features

Variable	Sirolimus-Coated Balloon (N = 626)	Uncoated Balloon (N = 626)
Median age (IQR) — yr	75.5 (67.0–82.0)	75.0 (66.3–83.0)
Female sex — no. (%)	224 (35.8)	215 (34.3)
Median body-mass index (IQR) †	25.2 (22.5–28.2)	25.7 (23.0–29.1)
Cardiovascular risk factors and coexisting conditions		
Diabetes mellitus — no. (%)	275 (43.9)	291 (46.5)
Arterial hypertension — no. (%) ‡	482 (77.0)	483 (77.2)
Dyslipidemia — no. (%)	380 (60.7)	368 (58.8)
History of smoking — no. (%) §	368 (58.8)	371 (59.3)
Renal insufficiency — no. (%) ¶	210 (33.5)	218 (34.8)
Coronary artery disease — no. (%)	257 (41.1)	271 (43.3)
Cerebrovascular disease — no./total (%)	106/626 (16.9)	123/625 (19.7)
History of intervention for peripheral artery disease in the target limb — no. (%)		
Endovascular revascularization	258 (41.2)	245 (39.1)
Surgical thromboendarterectomy	29 (4.6)	27 (4.3)
Peripheral bypass surgery	16 (2.6)	18 (2.9)
Minor amputation	36 (5.8)	35 (5.6)
Major amputation	2 (0.3)	4 (0.6)
Fontaine classification — no./total no. (%)		
Stage I	4/626 (0.6)	8/624 (1.3)
Stage IIa	69/626 (11.0)	60/624 (9.6)
Stage IIb	337/626 (53.8)	344/624 (55.1)
Stage III	57/626 (9.1)	70/624 (11.2)
Stage IV	159/626 (25.4)	142/624 (22.8)
Acute limb ischemia at target limb — no. (%)	64 (10.2)	59 (9.4)
Medications — no. (%)		
Antiplatelet treatment	454 (72.5)	447 (71.4)
Anticoagulant treatment	210 (33.5)	226 (36.1)
Lipid-lowering therapy	416 (66.5)	416 (66.5)

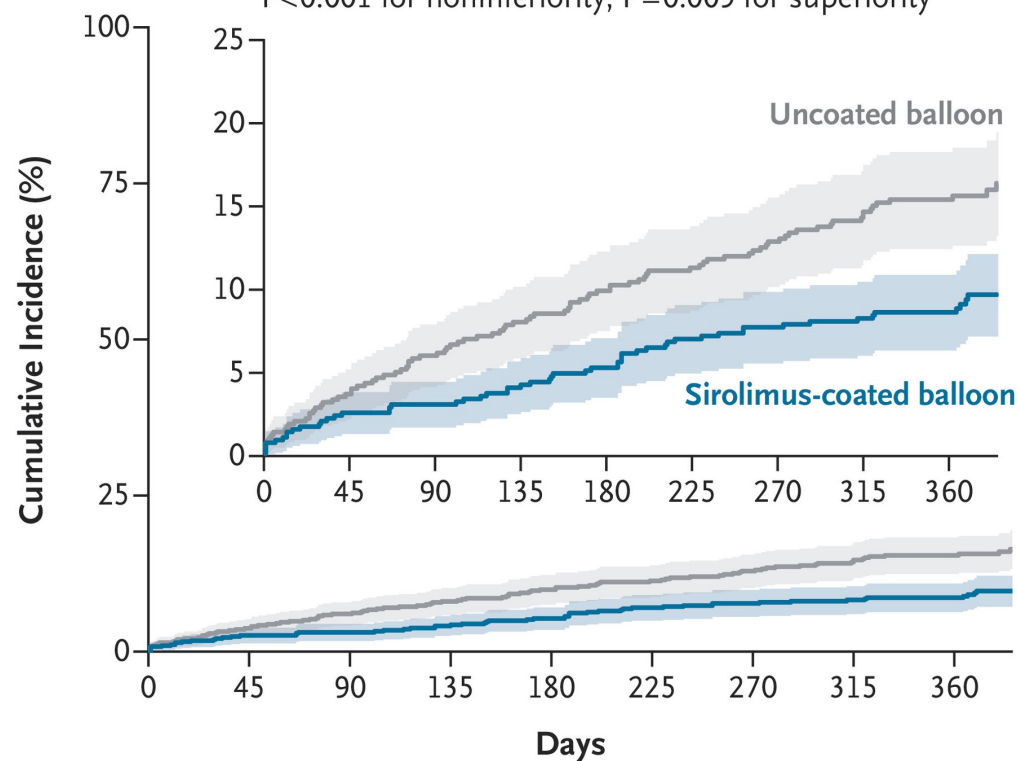
Procedural Data and Characteristics of the Target Lesions.

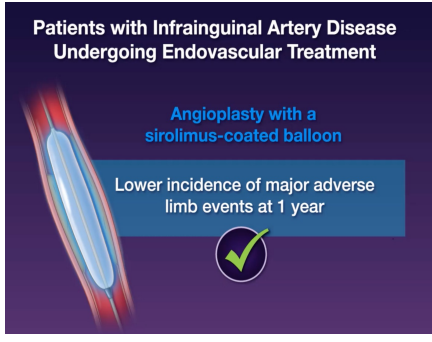
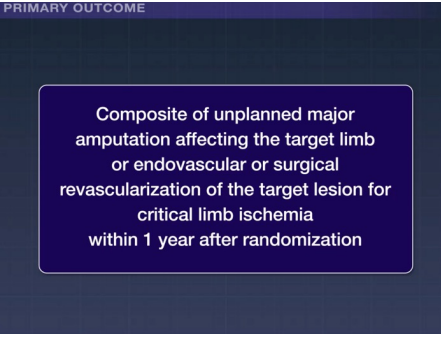
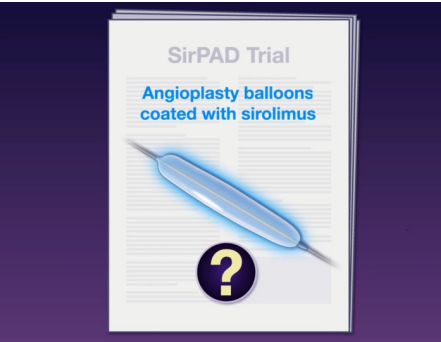
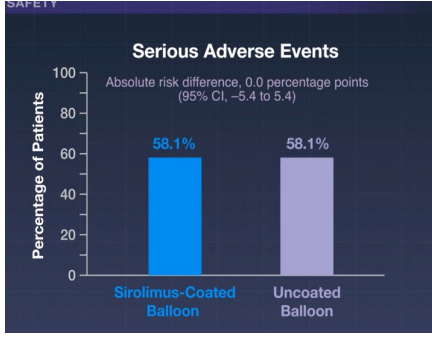
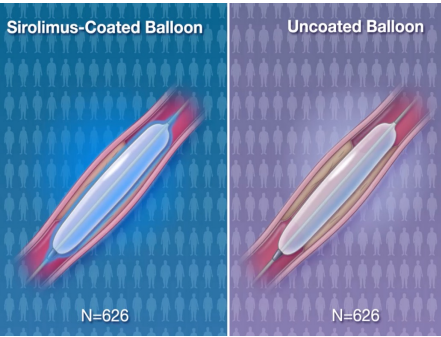
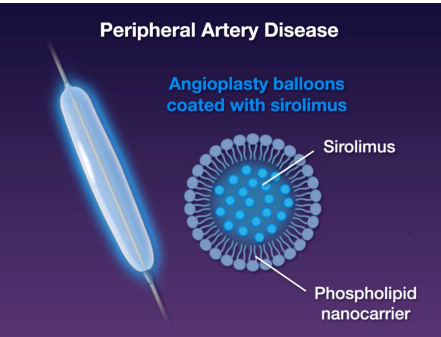
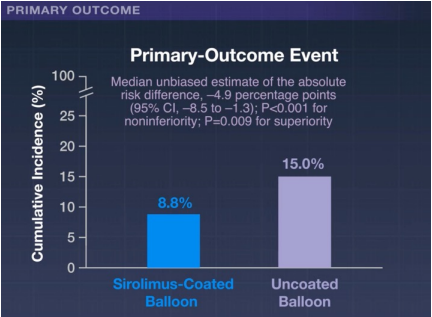
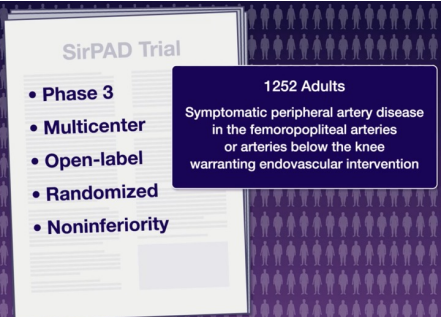
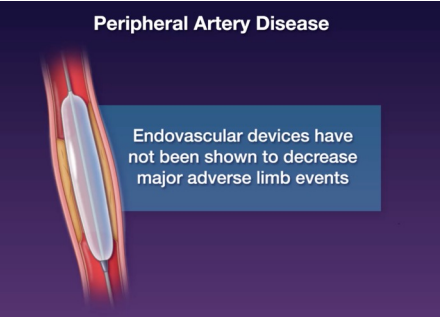
Variable	Sirolimus-Coated Balloon (N = 626)	Uncoated Balloon (N = 626)
Target lesion — no. (%)		
Common femoral artery	34 (5.4)	28 (4.5)
Superficial femoral artery	360 (57.5)	362 (57.8)
Deep femoral artery	2 (0.3)	2 (0.3)
Popliteal artery	219 (35.0)	235 (37.5)
Arteries below the knee	191 (30.5)	188 (30.0)
Tibiofibular trunk	57 (9.1)	66 (10.5)
Peroneal artery	43 (6.9)	50 (8.0)
Anterior tibial artery	79 (12.6)	63 (10.1)
Posterior tibial artery	52 (8.3)	49 (7.8)
Bypass or bypass anastomosis	9 (1.4)	6 (1.0)
Details of the target lesion — no. (%)		
Not previously treated	451 (72.0)	453 (72.4)
Restenosis after previous angioplasty	77 (12.3)	87 (13.9)
Restenosis after previous stent placement	45 (7.2)	35 (5.6)
In-stent occlusion	53 (8.5)	51 (8.1)
Median length of the target lesion (IQR) — mm*	150 (80–200)	143 (60–212)
Total occlusion of the target lesion — no./total no. (%)	350/622 (56.3)	361/623 (57.9)
Lack of technical success of treatment of the index target lesion — no. (%)		
Persistent occlusion	4 (0.6)	3 (0.5)
Persistent lumen stenosis of >50%	5 (0.8)	3 (0.5)
Other reason	2 (0.3)	0
Bailout stent placement — no. (%)	222 (35.5)	250 (39.9)

Primary and Secondary Outcomes.

Outcome	Sirolimus-Coated Balloon (N = 626)	Uncoated Balloon (N = 626)	Absolute Risk Difference (95% CI) percentage points
Primary outcome			
Composite of unplanned major amputation affecting the target limb or endovascular or surgical target-lesion revascularization for critical limb ischemia at 1 yr — no. (%)	55 (8.8)	94 (15.0)	−4.9 (−8.5 to −1.3)†
Secondary efficacy outcomes			
Composite of any unplanned amputation affecting the target limb or target-lesion revascularization for critical or noncritical limb ischemia at 1 yr — no. (%)	144 (23.0)	193 (30.8)	−7.8 (−12.7 to −2.9)‡
Unplanned major amputation affecting the target limb at 1 yr — no. (%)	8 (1.3)	17 (2.7)	−1.4 (−3.1 to 0.2)
Unplanned minor amputation affecting the target limb at 1 yr — no. (%)	34 (5.4)	45 (7.2)	−1.8 (−4.5 to 1.0)
Any unplanned amputation affecting the target limb at 1 yr — no. (%)	37 (5.9)	55 (8.8)	−2.9 (−5.8 to 0.0)
Target-lesion revascularization for critical or noncritical limb ischemia at 1 yr — no. (%)	124 (19.8)	162 (25.9)	−6.1 (−10.7 to −1.4)
Target-lesion revascularization for critical limb ischemia at 1 yr — no. (%)	52 (8.3)	83 (13.3)	−5.0 (−8.4 to −1.5)
Target-lesion revascularization for noncritical limb ischemia at 1 yr — no. (%)	72 (11.5)	79 (12.6)	−1.1 (−4.7 to 2.5)
Any target-limb revascularization at 1 yr — no. (%)	148 (23.6)	177 (28.3)	−4.6 (−9.5 to 0.2)
Clinical improvement of ≥1 Rutherford class at 6 mo — no./total no. (%)§	357/448 (79.7)	354/444 (79.7)	−0.0 (−5.3 to 5.2)
Clinical improvement of ≥1 Rutherford class at 1 yr — no./total no. (%)¶	378/458 (82.5)	362/461 (78.5)	4.0 (−1.1 to 9.1)
Primary safety outcome			
Death from any cause at 1 yr — no. (%)	74 (11.8)	80 (12.8)	−1.0 (−4.6 to 2.7)‖

Median unbiased estimate of the absolute risk difference, −4.9 percentage points (95% CI, −8.5 to −1.3)
P<0.001 for noninferiority; P=0.009 for superiority





Ein Herz-Kreislauf-Stillstand (*cardiac arrest*) ist ein medizinischer Notfall, bei dem das Herz plötzlich aufhört zu schlagen und kein Blut mehr durch den Körper pumpt. Die betroffene Person verliert sofort das Bewusstsein und hört auf zu atmen oder zeigt nur noch Schnappatmung. Ohne sofortige Hilfe führt dies innerhalb weniger Minuten zum Tod.

Sofortmaßnahmen (Erste Hilfe)

- **Notruf wählen:** Sofort die **112** rufen (oder andere Personen dazu auffordern).
- **Prüfen:** Reagiert die Person und atmet sie normal?
- **Herzdruckmassage:** Fest und schnell in die Mitte des Brustkorbs drücken (100-120 Mal pro Minute, ca. 5–6 cm tief).
- **Defibrillator (AED):** Ein automatisierter externer Defibrillator (AED) sollte geholt und nach Anweisung genutzt werden

Overall survival to hospital discharge for out-of-hospital cardiac arrest (OHCA) is low, averaging about 9% to 10% globally.



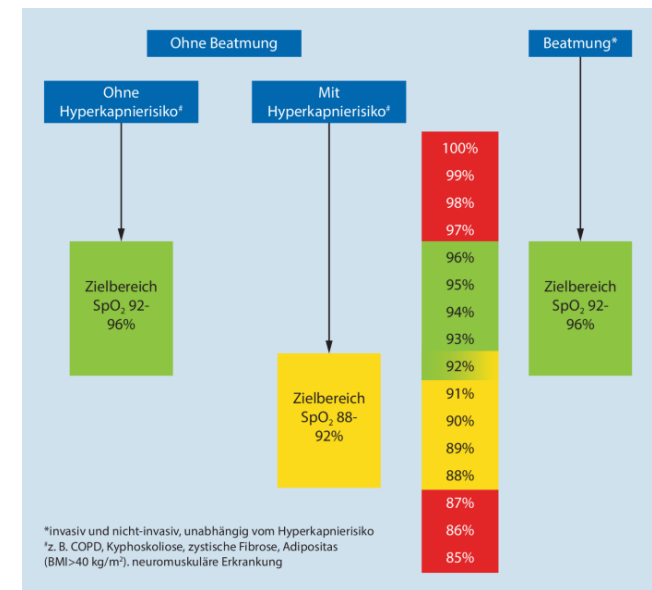
Nach einer erfolgreichen Wiederbelebung (ROSC – Return of Spontaneous Circulation) wird die Sauerstoffgabe jedoch titriert, um eine Sauerstoffsättigung von 94–98 % anzustreben und Hyperoxie (zu viel Sauerstoff) zu vermeiden.

- **Während des Herzstillstands (CPR):**

- **Nach der Wiederbelebung (Post-Resuscitation Care / ROSC):**

- Sobald verlässliche Messwerte (Pulsoxymetrie/BGA) vorliegen, wird der Sauerstoff angepasst.
- **Zielwert der Sättigung:** 94 % bis 98 %.
- Vermeidung von Hyperoxie (extrem hohen Sauerstoffwerten), da freie Sauerstoffradikale und Gefäßverengungen das geimpfte Gehirn und das Herzgewebe zusätzlich schädigen können.

Oxygen



Conservative Oxygen for Unresponsive Patients after Cardiac Arrest

Upper limit
Sat 95%

Vs.

Upper limit:
None

In patients who are unresponsive after resuscitation from cardiac arrest, limiting oxygen exposure to that necessary to achieve acceptable oxygenation may increase the likelihood of survival with a favorable functional outcome. We randomly assigned unresponsive adults receiving mechanical ventilation in the intensive care unit (ICU) after cardiac arrest to conservative or liberal oxygen therapy. In the two groups, the default lower limit of arterial oxygen saturation as measured by pulse oximetry (SpO_2) was 90%. In the conservative-oxygen group, the alarm for the upper limit of the SpO_2 was set at 95%, and the fraction of inspired oxygen (FiO_2) was decreased to 0.21 provided that the SpO_2 was above the lower limit. In the liberal-oxygen group, there were no measures limiting the upper SpO_2 , but the minimum FiO_2 permitted during mechanical ventilation was 0.3. The primary outcome was survival with a favorable functional outcome at 180 days, assessed with the Extended Glasgow Outcome Scale (GOS-E). Levels on the GOS-E range from 1 (death) to 8 ("upper good recovery"). We defined survival with a favorable functional outcome as a GOS-E level of 5 ("lower moderate disability") or higher.

Patients

- 1840 adults
- Mean age, 60 years
- Men: 71%; Women: 29%



Conservative Oxygen

Lower SpO_2 limit: 90%
Upper SpO_2 limit: 95%
 FiO_2 decreased to 0.21 if SpO_2 was above lower limit



N = 882

Liberal Oxygen

Lower SpO_2 limit: 90%
Upper SpO_2 limit: None
 FiO_2 : 0.3 or above

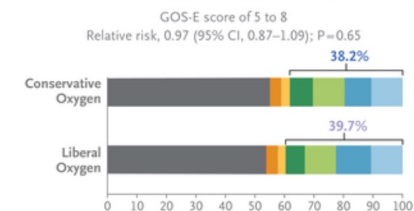


N = 958

GOS-E Scale



Survival with a Favorable Functional Outcome at 180 Days



Brain damage from ischemic encephalopathy is common after a cardiac arrest. Injury results from both oxygen deprivation during the arrest and reperfusion injury after circulation is restored. Studies in animals suggest that high oxygen exposure after reperfusion may overwhelm antioxidant defenses, causing neuronal death. By limiting exposure to hyperoxemia, conservative oxygen therapy may attenuate reperfusion injury and improve outcomes. The Low Oxygen Intervention for Cardiac Arrest Injury Limitation (LOGICAL) trial was designed to test the hypothesis that, in adults in the ICU with suspected ischemic encephalopathy after return of spontaneous circulation, conservative oxygen therapy improves survival with a favorable functional outcome at 180 days as compared with liberal oxygen therapy.

Patients

Adults (≥ 18 years of age) receiving mechanical ventilation in the ICU after a cardiac arrest in whom ischemic encephalopathy was suspected (i.e., those unable to follow verbal commands after return of spontaneous circulation when there was clinical concern about possible brain damage) were eligible for inclusion. Patients who had been enrolled previously and those for whom enrollment was not considered to be in their best interests, including when death was deemed to be imminent and inevitable, were excluded. Enrollment was required within 12 hours after fulfillment of eligibility criteria.

Randomization and Treatment

We randomly assigned patients to conservative or liberal oxygen therapy with the use of a secure, centralized, Internet-based system.

Outcome Measures

The primary outcome was a favorable functional outcome measured with the Extended Glasgow Outcome Scale (GOS-E) at 180 days after randomization,

Characteristics of the Patients at Baseline.

Characteristic	Conservative Oxygen (N = 873)	Liberal Oxygen (N = 948)
Age — yr	60.1±15.1	60.7±15.1
Male sex — no. (%)	629 (72.1)	671 (70.8)
Coexisting conditions — no. (%)		
Hypertension	270 (30.9)	252 (26.6)
Diabetes	192 (22.0)	173 (18.2)
Ischemic heart disease	137 (15.7)	136 (14.3)
Asthma or COPD	135 (15.5)	128 (13.5)
Previous cardiac arrhythmia	128 (14.7)	135 (14.2)
Previous myocardial infarction	79 (9.0)	70 (7.4)
Congestive heart failure	67 (7.7)	80 (8.4)
Percutaneous coronary intervention	60 (6.9)	70 (7.4)
Previous TIA or stroke	48 (5.5)	51 (5.4)
Previous CABG	44 (5.0)	39 (4.1)
Location of cardiac arrest — no. (%)		
Out of hospital	647 (74.1)	698 (73.6)
In hospital	221 (25.3)	243 (25.6)
Unknown	5 (0.6)	7 (0.7)
Witnessed cardiac arrest — no./total no. (%)†	681/864 (78.8)	758/935 (81.1)
Bystander CPR — no./total no. (%)‡	503/643 (78.2)	542/697 (77.8)
First monitored rhythm VF, VT, or AED shockable — no./total no. (%)	423/829 (51.0)	477/903 (52.8)
First monitored rhythm asystole — no./total no. (%)	135/829 (16.3)	127/903 (14.1)
Median response time (IQR) — min	6 (0–10)	6 (0–10)
Time to defibrillation — min	11.2±8.9	11.7±8.8
Time to sustained ROSC — min§	26.0±18.9	25.0±16.7
Cause of cardiac arrest — no. (%)		
Medical	772 (88.4)	823 (86.8)
Other	101 (11.6)	125 (13.2)
Median Pao ₂ (IQR) — mm Hg¶	98 (80–129)	98 (79–131)
Fio ₂	0.52±0.24	0.51±0.23
Median time from ROSC to randomization (IQR) — hr	7.3 (4.9–10.9)	7.0 (4.9–10.9)
Median time from ICU admission to randomization (IQR) — hr	3.0 (1.3–7.1)	3.1 (1.4–6.7)

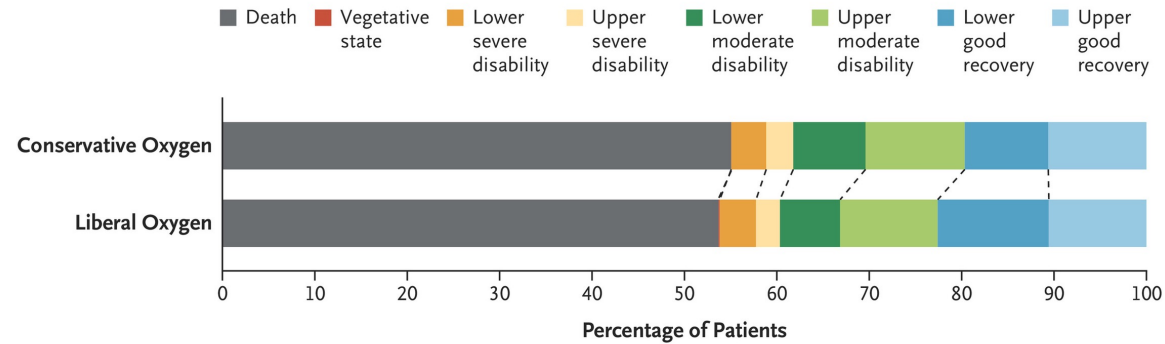
Metrics of Oxygen Exposure.

Variable	Conservative Oxygen (N = 873)	Liberal Oxygen (N = 948)	Between-Group Difference†	Relative Risk (95% CI)‡
Measures of exposure to high arterial oxygen				
Median percentage of hours per patient with Spo ₂ ≥97% (IQR)	21.2 (8.9 to 43.8)	53.0 (29.5 to 75.1)	–31.9 (–35.6 to –28.1)	
Median no. of hours per patient with Spo ₂ ≥97% (IQR)	16 (5 to 34)	37 (16 to 70)	–21.0 (–23.5 to –18.5)	
At least one Pao ₂ recording >100 mm Hg — no. (%)	504 (57.7)	743 (78.4)		0.74 (0.68 to 0.80)
Measures of exposure to low arterial oxygen				
Median percentage of hours per patient with Spo ₂ <88% (IQR)	0 (0 to 1.19)	0 (0 to 0.58)	0 (0 to 0)	
Median no. of hours per patient with Spo ₂ <88% (IQR)	0 (0 to 1)	0 (0 to 1)	0 (0 to 0)	
At least one Pao ₂ recording <60 mm Hg — no. (%)	379 (43.4)	261 (27.5)		1.57 (1.39 to 1.78)
Measures of time spent breathing ambient air				
Median percentage of hours per patient with Fio ₂ =0.21 (IQR)	38.8 (6.8 to 76.1)	0.0 (0 to 4.9)	38.9 (32.5 to 45.2)	
Median no. of hours per patient with Fio ₂ =0.21 (IQR)	23 (5 to 56)	0 (0 to 4)	23.0 (17.9 to 28.1)	

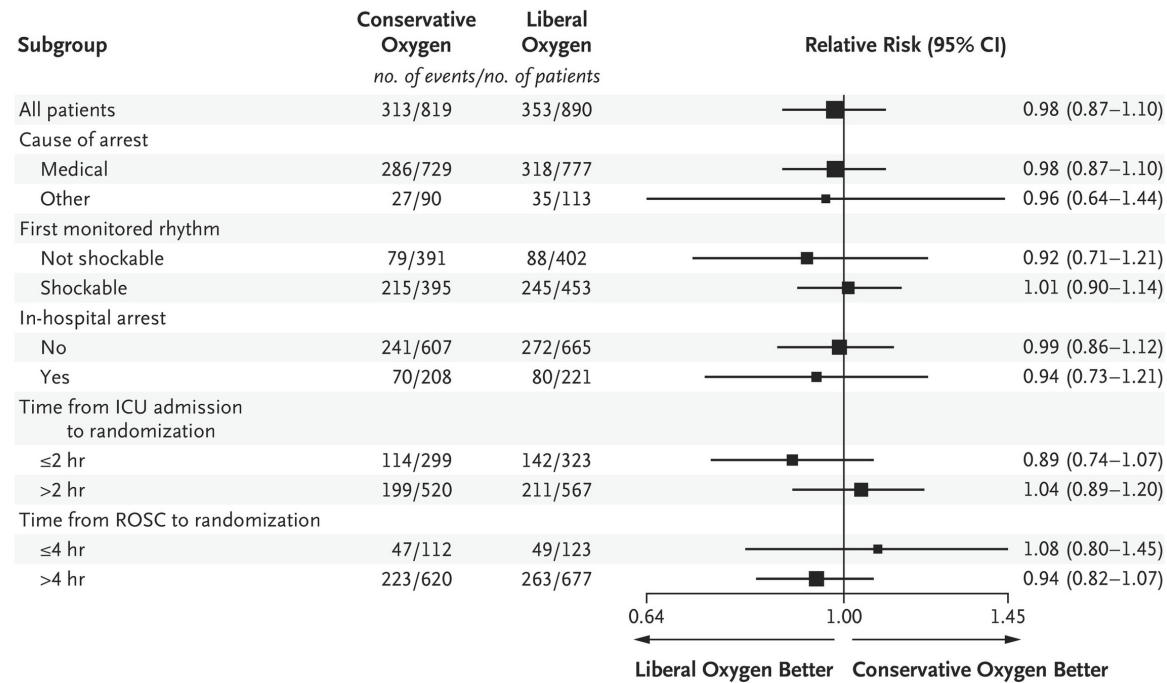
Primary and Secondary Outcomes.

Outcome	Conservative Oxygen (N = 873)	Liberal Oxygen (N = 948)	Between-Group Difference†	Relative Risk (95% CI)‡
Primary outcome				
Favorable functional outcome at day 180 — no./total no. (%)§	313/819 (38.2)	353/890 (39.7)	–0.9 (–5.5 to 3.7)¶	0.97 (0.87 to 1.09)
Secondary outcomes				
Alive at 180 days — no./total no. (%)**	416/866 (48.0)	469/943 (49.7)	–1.4 (–5.9 to 3.1)¶	0.97 (0.88 to 1.06)
Median EQ utility score (IQR)††	0 (0 to 0.91)	0 (0 to 0.92)	0 (0 to 0)	
Survivors only	0.92 (0.80 to 1)	0.92 (0.80 to 1)		
Median score on patient- or proxy-reported health state scale (IQR)‡‡	0 (0 to 70)	0 (0 to 70)	0 (0 to 0)	
Survivors only	75 (50 to 85)	75 (55 to 85)		
Median MoCA-blind score (IQR)§§	0 (0 to 17)	0 (0 to 18)	0 (0 to 0)	
Survivors only	18 (16 to 20)	19 (17 to 20)		
Median hours of mechanical ventilation (IQR)¶¶	65.0 (24.5 to 123.3)	58.4 (22.3 to 121.1)	5.4 (–3.8 to 14.7)	
Median days in ICU (IQR)	4 (2 to 6)	4 (2 to 7)	–0.2 (–0.6 to 0.2)	
Median days in hospital (IQR)	7 (3 to 15)	7 (3 to 15)	0.3 (–0.6 to 1.1)	
Survived and was discharged directly home from hospital — no./total no. (%)	286/871 (32.8)	321/943 (34.0)	0.1 (–4.0 to 4.2)¶	0.98 (0.86 to 1.12)

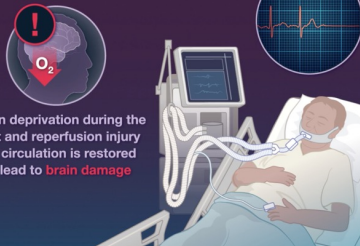
A GOS-E Results



B Subgroup Analysis of Favorable Functional Outcome

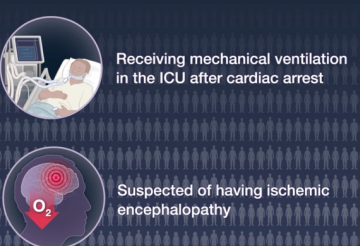


Cardiac Arrest



Oxygen deprivation during the arrest and reperfusion injury after circulation is restored can lead to **brain damage**

1840 Unresponsive Adults

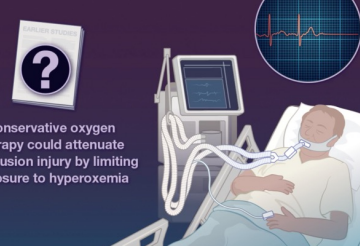


Receiving mechanical ventilation in the ICU after cardiac arrest

Suspected of having ischemic encephalopathy

No adverse events were reported in the trial

Cardiac Arrest



Conservative oxygen therapy could attenuate reperfusion injury by limiting exposure to hyperoxemia

1840 Unresponsive Adults

Conservative Oxygen Therapy



- Lower SpO₂ limit: 90%
- Upper SpO₂ limit: 95%
- FiO₂ decreased to 0.21 if SpO₂ was above lower limit

N=882

Liberal Oxygen Therapy



- Lower SpO₂ limit: 90%
- Upper SpO₂ limit: None
- FiO₂: 0.3 or above

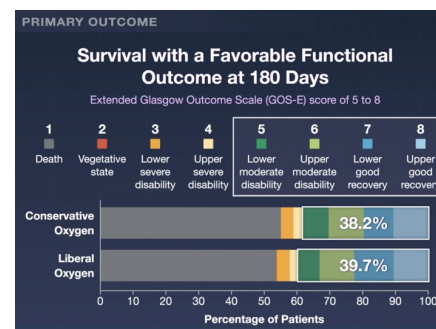
N=958



Did not increase the likelihood of survival with a favorable functional outcome at 180 days

New Trial

Assessed functional outcomes in patients after resuscitation for cardiac arrest whose care involved conservative or liberal oxygen strategies

Syncope

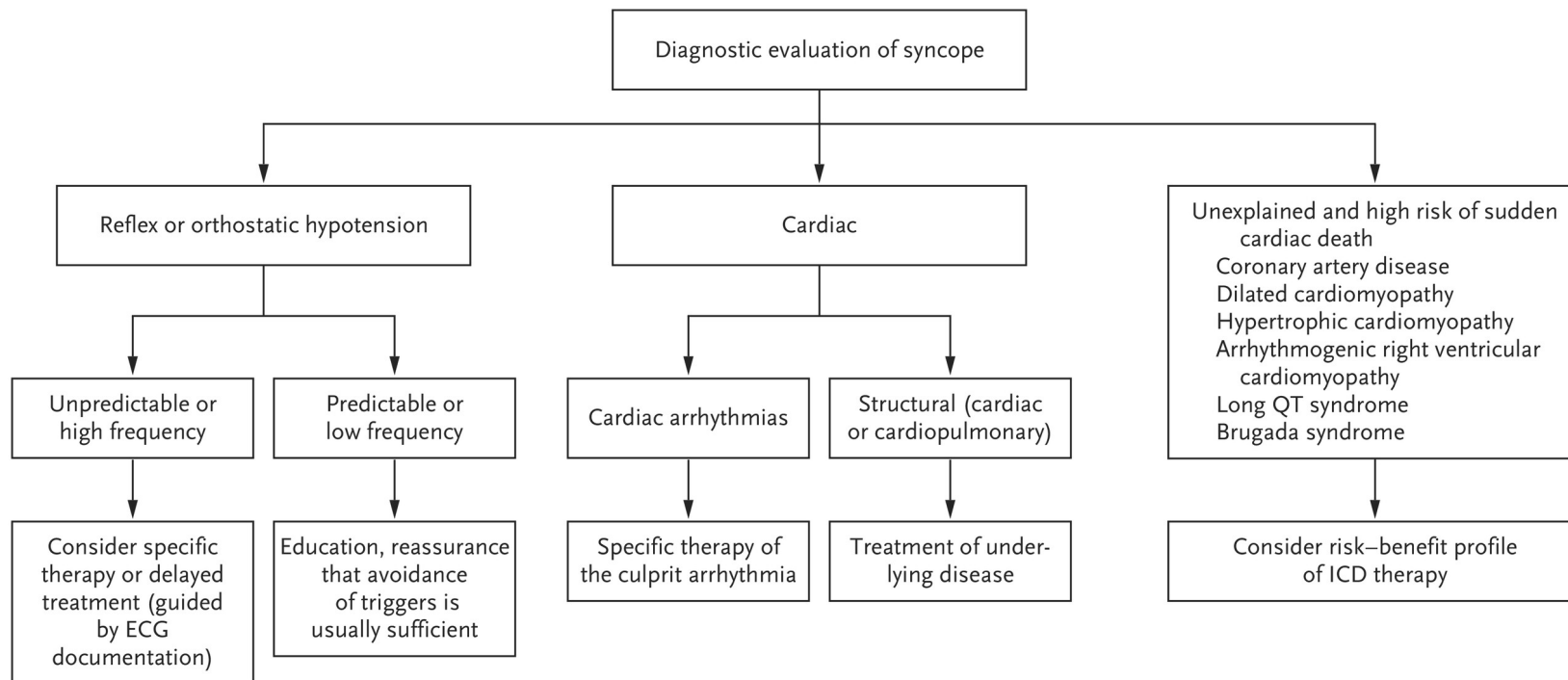
A 75-year-old retired man who lives alone presents to the emergency department with a zygomatic fracture after an unexplained fall. He has a history of hypertension, hyperlipidemia, and depression, for which he is receiving treatment. The incident occurred in the early afternoon while he was walking his dog. It was associated with urinary incontinence, and the patient has no recollection of the event. There were no witnesses. Over the preceding 6 months, he reports having had one similar fall and two episodes of transient loss of consciousness. These episodes occurred after he stood up after eating a meal or sitting for a prolonged period or during nocturnal urination. All events were unwitnessed. How should this case be managed?

KEY POINTS

Syncope

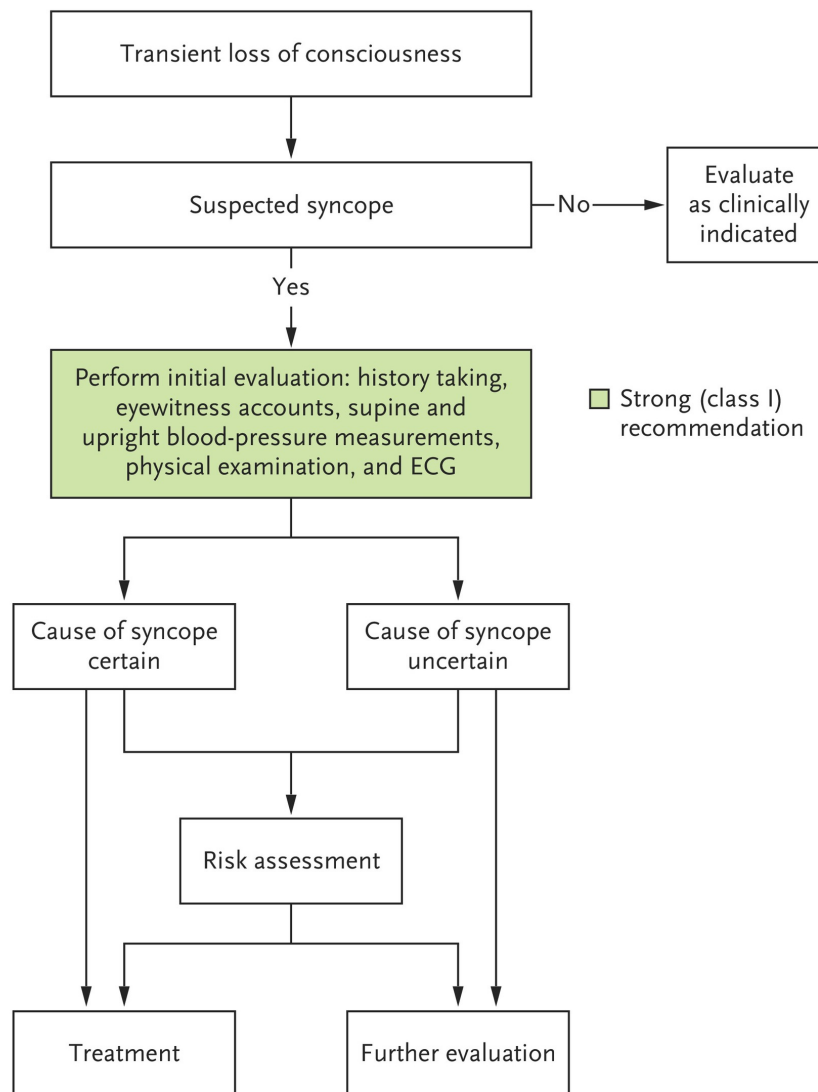
- Syncope is caused by transient cerebral hypoperfusion and is classified as reflex, orthostatic, or cardiac.
- Initial evaluation with history taking, physical examination, electrocardiography, and orthostatic blood-pressure measurement identifies the cause in most patients.
- Risk stratification determines the appropriateness of hospitalization and further testing.
- Management is mechanism-specific and aims to reduce the risks of recurrence and injury.

Eine Synkope ist eine plötzlich auftretende, kurze Ohnmacht mit Verlust der Haltungskontrolle, die durch eine vorübergehende Minderdurchblutung des Gehirns verursacht wird und sich von selbst wieder vollständig erholt.



Treatment of Syncope Based on the Diagnostic Evaluation.

Adapted from Brignole et al. The general framework of treatment is based on risk stratification and the identification of specific mechanisms when possible. ICD denotes implantable cardioverter–defibrillator.



General Principles for Initial Evaluation of All Patients after an Episode of Syncope.

Adapted from the 2017 guidelines from the American College of Cardiology and American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society (ACC–AHA–HRS).⁷ ECG denotes electrocardiography.

Feature

Reflex syncope

Long history of recurrent syncope, in particular occurring before the age of 40 yr

Occurrence after unpleasant sight, sound, smell, or pain

Occurrence with prolonged standing

Occurrence during meal

Occurrence in crowded or hot places

Autonomic activation before syncope: pallor, sweating, nausea, or vomiting

Occurrence with head rotation or pressure on carotid sinus (e.g., due to tumors, shaving, or tight collars)

Absence of heart disease

Syncope due to orthostatic hypotension

Occurrence shortly after standing

Occurrence with prolonged standing

Occurrence with standing after exertion

Postprandial hypotension

Temporal relationship with initiation or changes in dose of vasodepressive drugs or diuretics leading to hypotension

Presence of autonomic neuropathy or parkinsonism

Cardiac syncope

Occurrence during exertion or when supine

Sudden-onset palpitation immediately followed by syncope

Family history of unexplained sudden death at young age

Presence of pulmonary hypertension or structural heart, coronary artery, or pericardial disease

ECG findings suggesting arrhythmic syncope:

Bifascicular block (defined as either left or right bundle-branch block combined with left anterior or left posterior fascicular block)

Other intraventricular conduction abnormalities (QRS duration, ≥ 0.12 sec)

Mobitz type I second-degree atrioventricular block and first-degree atrioventricular block with markedly prolonged PR interval

Asymptomatic mild inappropriate sinus bradycardia (40–50 beats/min) or slow atrial fibrillation (40–50 beats/min) in the absence of negatively chronotropic medications

Nonsustained ventricular tachycardia

Preexcited QRS complexes

Long or short QT intervals

Early repolarization

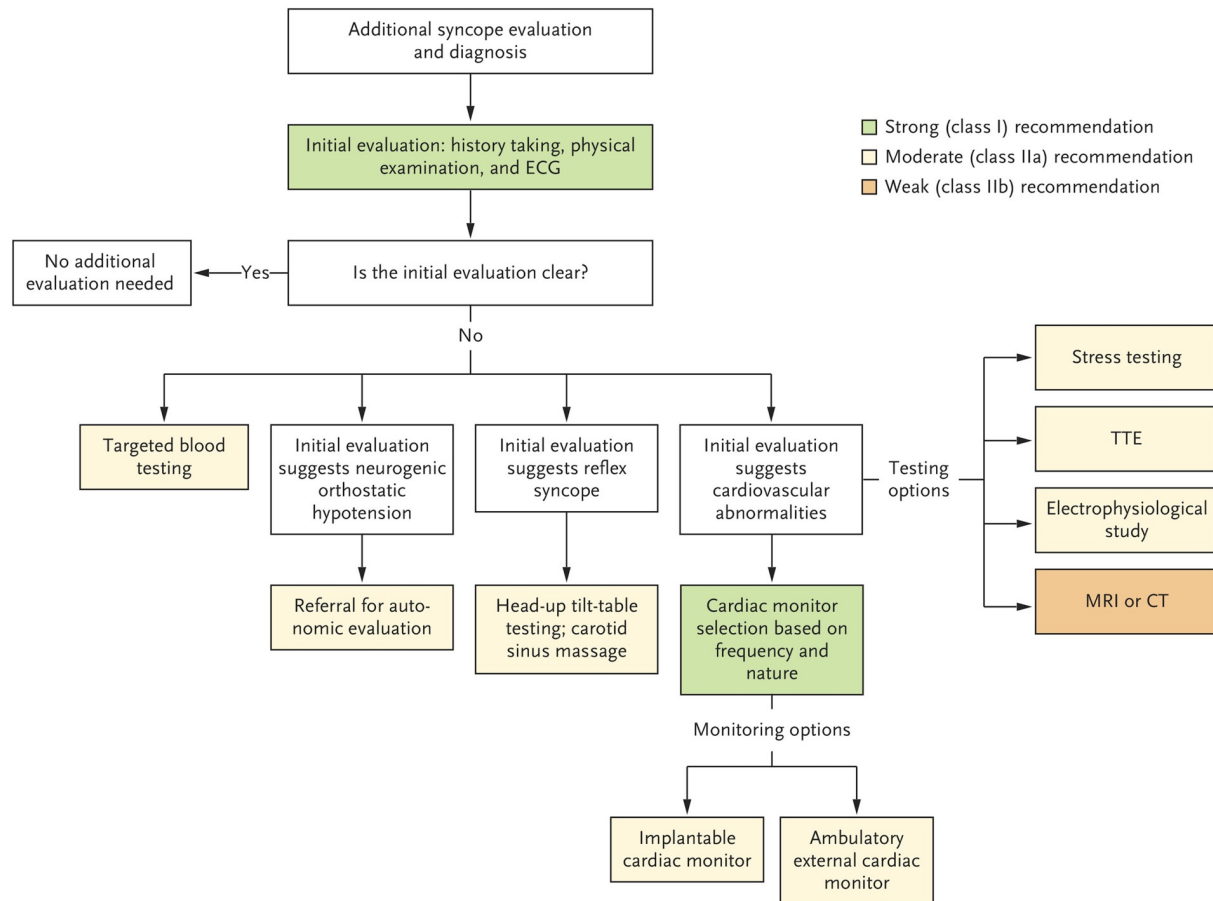
ST-segment elevation with type 1 morphology in leads V1, V2, and V3 (Brugada syndrome)

Negative T waves in right precordial leads, epsilon waves suggestive of arrhythmogenic right ventricular cardiomyopathy

Left ventricular hypertrophy suggesting hypertrophic cardiomyopathy

Disorders That Can Cause Transient Loss of Consciousness and Mimic Syncope.

Condition	Key Features	Distinguishing Points from Syncope
Epileptic seizure	Tonic-clonic movements, tongue biting (lateral), postictal confusion	Longer loss of consciousness, postictal phase, no rapid recovery
Psychogenic pseudosyncope	Apparent loss of consciousness, often prolonged, eyes closed	Normal blood pressure and heart rate during event, no true cerebral hypoperfusion
Hypoglycemia	Sweating, confusion, tremor	Low glucose, gradual onset, not sudden collapse
Vertebrobasilar TIA	Dizziness, ataxia, diplopia	Focal neurologic signs, loss of consciousness uncommon
Drop attacks	Sudden fall without loss of consciousness	Patient remains conscious
Catatlexy	Sudden loss of muscle tone triggered by emotion	Consciousness preserved, associated with narcolepsy
Intoxication with alcohol or drugs	Altered consciousness, unsteadiness	Persistent confusion, not transient
Concussion or head injury	Loss of consciousness after trauma	Trauma is cause, not consequence
Metabolic disturbances	Hypoxemia, electrolyte imbalance	Gradual or fluctuating course
Panic attack or anxiety	Hyperventilation, palpitations	Rarely a true loss of consciousness, situational context
Sleep disorders (e.g., narcolepsy)	Sudden sleep episodes	Occurs in sleep context, not circulatory

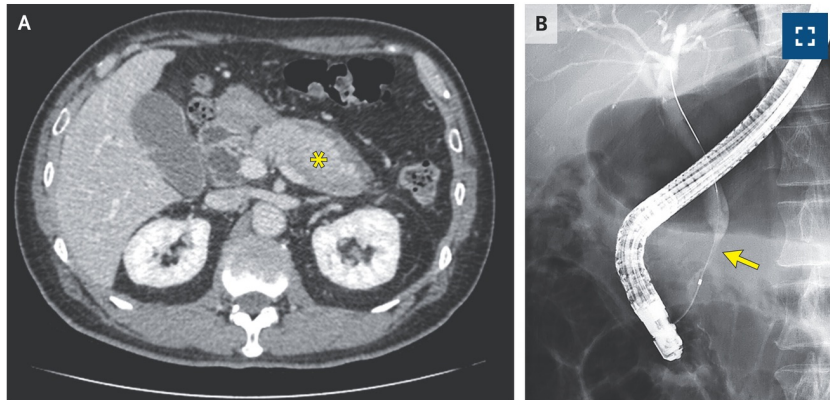


Additional Evaluation and Diagnosis of Syncope According to Current ACC–AHA–HRS Guidelines
 Adapted from the 2017 ACC–AHA–HRS guidelines. CT denotes computed tomography, MRI magnetic resonance imaging, and TTE transthoracic echocardiography.

Conclusion

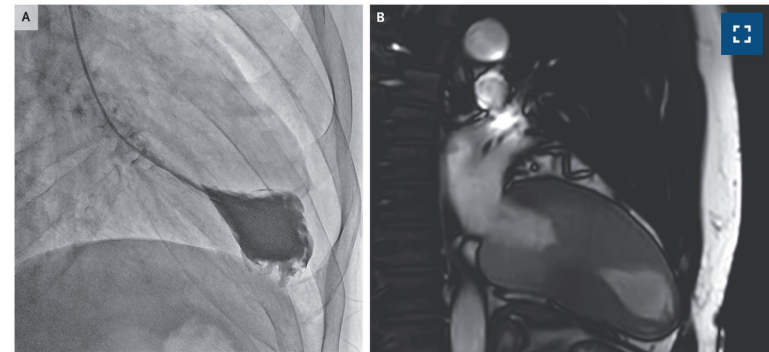
In a patient such as the one described in the vignette, injuries are first managed while emergency causes of syncope are simultaneously ruled out. Because the events were sudden and injurious in an older man, I would deem him to be at intermediate-to-high risk and therefore would recommend monitoring in an emergency department observation unit where he would undergo ECG, echocardiogram, and orthostatic blood-pressure studies. If no arrhythmias or structural heart disease were noted but his blood pressure decreased to 80/55 mm Hg with symptoms of lightheadedness on standing, I would perform carotid sinus massage to evaluate for carotid sinus syndrome. Such a diagnosis would be established with a cardiac pause of at least 3 seconds during upright carotid sinus massage during which the patient would lose consciousness. Although more-prolonged cardiac monitoring, such as an implantable loop recorder, might capture symptom–rhythm correlation, given the patient’s age and injuries, it would be reasonable to proceed directly to implantation of a dual-chamber cardiac pacemaker for syncope attributed to carotid sinus syndrome, coupled with modification of possible culprit medications (antihypertensive and antidepressant medications) to manage orthostatic hypotension. These recommendations align with the most recent U.S. and European guidelines for syncope.

Type 1 Autoimmune Pancreatitis



A 60-year-old man presented to the gastroenterology and hepatology clinic with a 1-month history of postprandial epigastric pain. The physical examination was normal, with no jaundice or abdominal tenderness observed. Laboratory testing showed mild elevations in levels of alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase. Computed tomography of the abdomen with the administration of intravenous contrast material showed a diffusely enlarged, “sausage-like” pancreas with a capsule-like rim of low attenuation (Panel A, asterisk; portal venous phase). The serum IgG4 level was 600 mg per deciliter (reference range, 11 to 121). Endoscopic retrograde cholangiopancreatography identified an intrapancreatic distal bile-duct stricture (Panel B, arrow). Histopathological analysis of a fine-needle aspiration biopsy specimen from the pancreas was limited by crush artifact but showed lymphoplasmacytic infiltration, fibrosis, chronic inflammation, and no cancer. On the basis of the typical imaging findings and an elevated serum IgG4 level, a diagnosis of type 1 autoimmune pancreatitis was made. Type 1 autoimmune pancreatitis is the pancreatic manifestation of IgG4-related disease. It can occur as an isolated disorder (as was the case in this patient) or with the involvement of multiple organs. Treatment with a tapering dose of prednisolone was initiated. At the 2-month follow-up, the pancreatic enlargement and intrapancreatic bile-duct stricture had resolved, as had the patient’s postprandial epigastric pain, and the levels of hepatobiliary enzymes had normalized.

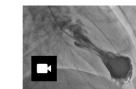
Obstructive Hypertrophic Cardiomyopathy



A 31-year-old man was referred to the cardiology clinic for evaluation of an abnormal electrocardiogram. At 15 years of age, he had received a diagnosis of nonobstructive apical hypertrophic cardiomyopathy but had not received follow-up care since that time. He

reported presyncopal symptoms during emotional distress but no syncope or family history of sudden cardiac death. Physical examination was notable for a grade 3/6 systolic murmur at the left midsternal border. Transthoracic echocardiography revealed marked hypertrophy of the midventricular septum and posterior wall with a maximal wall thickness of 26 mm (reference value, ≤ 10), a systolic intraventricular gradient of 30 mm Hg at rest (reference value, < 5), and a left ventricular ejection fraction (LVEF) of 40%. Beta-blocker therapy was initiated; after 5 months, the LVEF had improved, but the midventricular gradient had increased, which indicated worsening obstruction. Subsequent left ventriculography (Panel A and [Video 1A](#)) and cardiac magnetic resonance imaging (Panel B and [Video 1B](#)) revealed near-complete apposition of the ventricular walls during systole, which resulted in the development of a teardrop-shaped apical pouch. Simultaneous pressure recordings from the left ventricular apex and aorta showed a peak-to-peak gradient of 145 mm Hg, which confirmed a diagnosis of hypertrophic cardiomyopathy with severe obstruction. Myomectomy was performed. Complete heart block developed postoperatively, and a dual-chamber implantable cardioverter-defibrillator was placed. At a 5-month follow-up visit, the patient was asymptomatic.

VIDEO 1



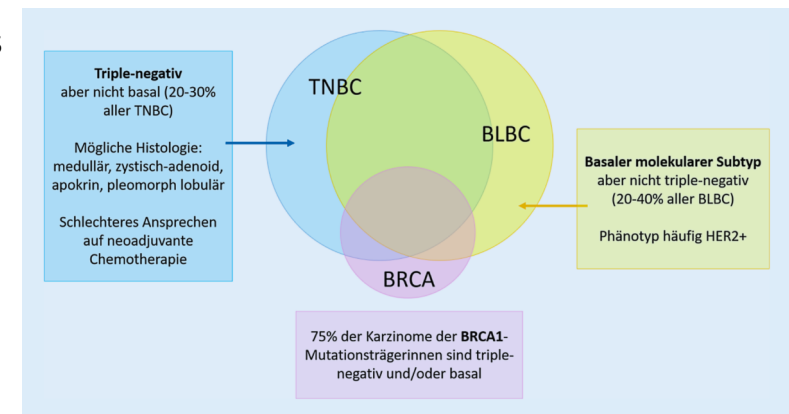
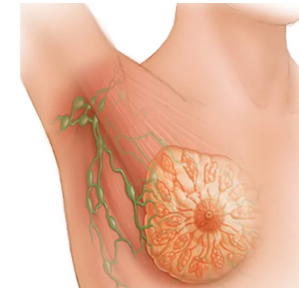
Left Ventriculography and
Cardiac Magnetic Resonance
Imaging 0m 21s

Background for the N Engl J Med mystery case

Ein **triple-negativer Brustkrebs (TNBC)** ist eine besonders **aggressive Form von Brustkrebs**, bei der den Krebszellen drei entscheidende Merkmale auf ihrer Oberfläche fehlen: Rezeptoren für die Hormone **Östrogen, Progesteron** sowie der Wachstumsfaktor-Rezeptor **HER2**. Da diese drei typischen biologischen Andockstellen „negativ“ sind, greifen herkömmliche Antihormon- und klassische HER2-zielgerichtete Therapien hier nicht

- **Chemotherapie:** Da sich die Tumorzellen so schnell teilen, reagieren sie in der Regel sehr empfindlich auf eine Chemotherapie. Oft wird diese als neoadjuvante Therapie (also vor der Operation) eingesetzt, um den Tumor vorab maximal zu verkleinern.
- **Immuntherapie:** Moderne Wirkstoffe (wie z. B. [Pembrolizumab](#)) helfen dem körpereigenen Immunsystem dabei, die wiederzuerkennen und selbstständig zu bekämpfen.
- **Antikörper-Wirkstoff-Konjugate (ADCs):** Neuere zielgerichtete Medikamente wie Sacituzumab Govitecan fungieren als „Trojanische Pferde“, die Chemotherapeutika gezielt direkt in die Krebszellen transportieren.
- **PARP-Inhibitoren:** Bei Patientinnen mit einer nachgewiesenen BRCA1/2-Genmutation können diese Tabletten den Reparaturmechanismus der Tumorzellen blockieren und diese so zerstören.

Triple negative breast cancer



BLBC steht für „basal-like breast cancer“ (basalähnliches Mammakarzinom). Es ist ein sehr aggressiver Untertyp des Brustkrebses, der stark mit dem triple-negativen Brustkrebs (TNBC) übereinstimmt. Den Tumorzellen fehlen die Rezeptoren für Östrogen, Progesteron und HER2, weshalb klassische Hormon- oder Antikörpertherapien nicht wirken

Background for the N Engl J Med mystery case

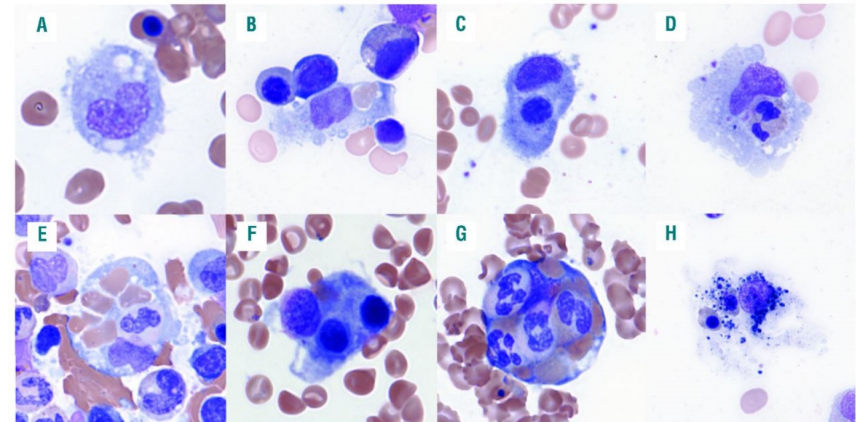
Das nicht bekannte Entzündungssyndrom

Das Krankheitsbild lautet **Hämophagozytische Lymphohistiozytose (HLH)**. Es handelt sich um eine seltene, lebensbedrohliche Erkrankung des Immunsystems, bei der körpereigene Fresszellen (Makrophagen/Monozyten) massiv überaktiviert werden und gesunde Blutzellen sowie Organe angreifen.

Krankheitsmechanismus und Formen

Bei der HLH gerät die Immunregulation außer Kontrolle, was zu einem **sogenannten Zytokinsturm** führt. Fresszellen zerstören fälschlicherweise rote und weiße Blutkörperchen sowie Blutplättchen. Man unterscheidet zwei Hauptformen:

- **Primäre (familiäre) HLH:** Genetisch bedingt, tritt meist schon im Säuglings- oder Kleinkindalter auf.
- **Sekundäre HLH:** Erworben im fortgeschrittenen Alter, ausgelöst durch **schwere Infektionen, Krebserkrankungen oder Autoimmunerkrankungen** (**Makrophagenaktivierungssyndrom**).



Typische Leitsymptome

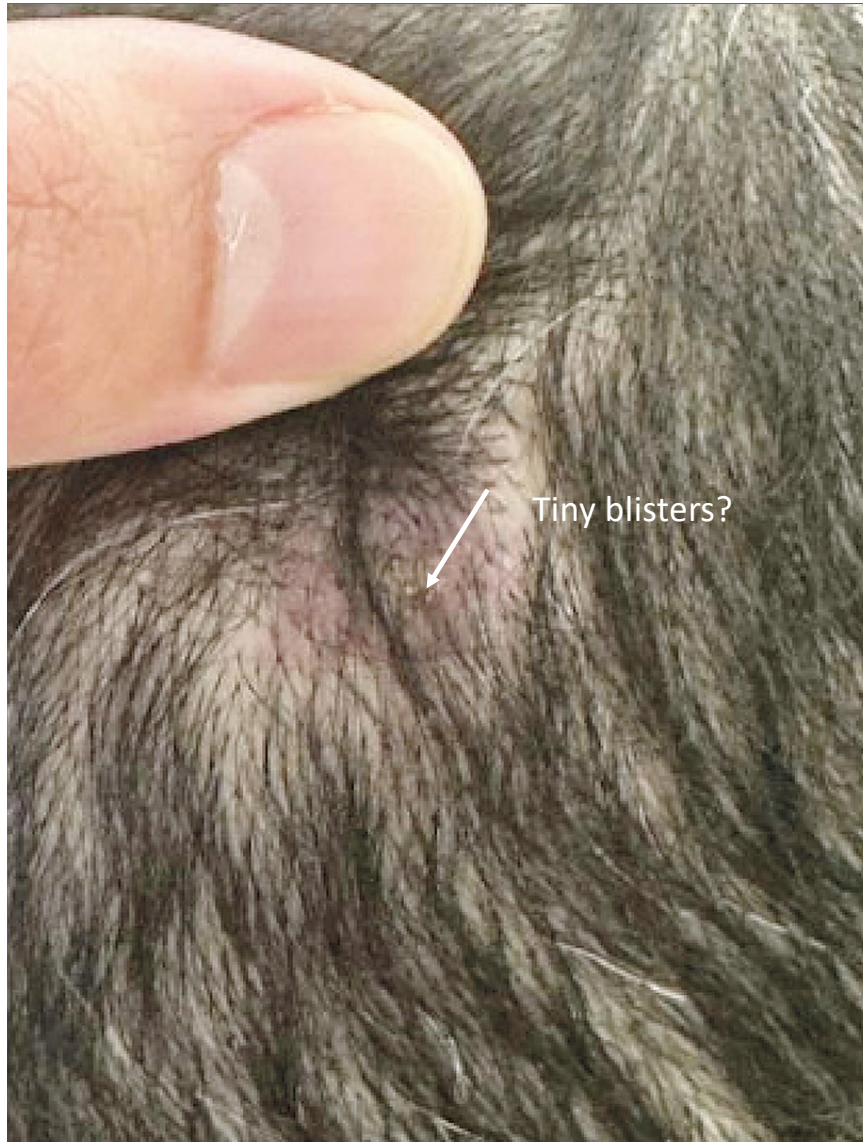
- Anhaltend hohes, therapieresistentes Fieber
- Starke Vergrößerung von Leber und Milz (Hepatosplenomegalie)
- Ausgeprägte Blutbildveränderungen (Mangel an Thrombozyten, Erythrozyten und Leukozyten)
- **Extrem hohe Ferritinwerte im Blut**

Consumed with Inflammation

A 60-year-old woman with stage II triple-negative breast cancer presented to the emergency department with a weeklong history of fevers, rigors, malaise, nonproductive cough, and nausea. She reported intermittent lightheadedness, headaches, and neck pain when febrile but no sore throat, rhinorrhea, shortness of breath, vomiting, abdominal pain, or dysuria. She noted no recent travel or sick contacts. Two months before presentation, she completed neoadjuvant carboplatin, paclitaxel, and doxorubicin and then, 1 month before presentation, underwent lumpectomy of the left breast and sentinel-lymph-node biopsy. She had also been treated as part of a clinical trial with multiple cycles of pembrolizumab (first dose, 6 months before presentation; last dose, 6 days before presentation). Although she had had transient neutropenia from chemotherapy, her white-cell counts had normalized after her last cycle. Postoperatively, mild tenderness and swelling around her left axilla had developed without systemic signs of infection; computed tomographic (CT) imaging was consistent with an uncomplicated seroma. In the days leading up to this presentation, her tenderness in this area had resolved.

The patient was not taking any medications, nor did she have any allergies to medications. She lived in a suburban part of the northeastern United States without any animal exposures. She enjoyed hiking and biking in outdoor areas but reported no recent insect bites. Her son, with whom she lives, had recently traveled to the United Arab Emirates but did not report any infectious symptoms. She had not ingested any raw, unpasteurized, or imported food products but reported recently handling raw goat and lamb meat bought from a local butcher.

On physical examination, the patient appeared comfortable. The oral temperature was 38.9°C, heart rate 120 beats per minute, blood pressure 100/63 mm Hg, and oxygen saturation 99% while she was breathing ambient air. Her neck was supple, and there was no cervical, submandibular, or supraclavicular lymphadenopathy. No oral mucosal lesions were present. A cardiac examination was notable for tachycardia without murmurs, rubs, or gallops. The lungs were clear to auscultation. The abdomen was soft, nondistended, and nontender to palpation without hepatosplenomegaly. She was alert and oriented and had no focal neurologic deficits. A skin examination was notable for a small, erythematous, tender but nonfluctuant papule on her scalp and a well-healing incision in the left axilla at her lumpectomy site without overlying erythema, fluctuance, or tenderness to palpation.

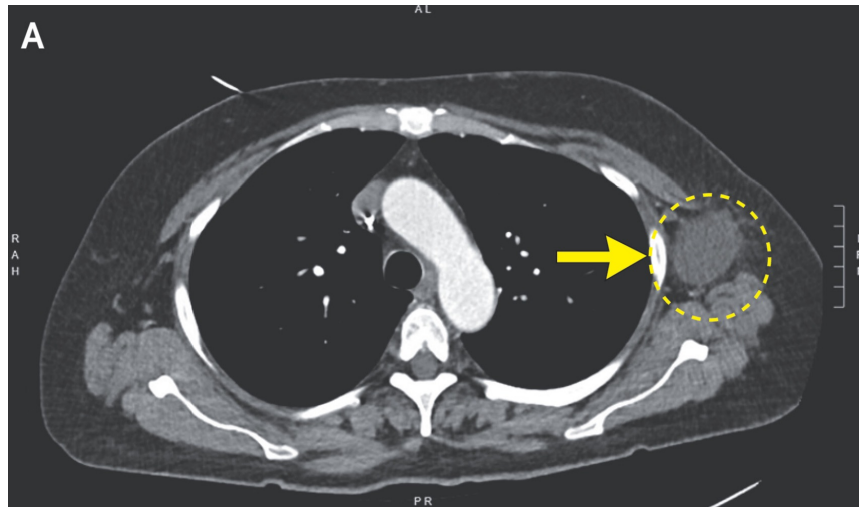


Scalp Lesion.

A small (<1 cm in diameter), mildly erythematous, and tender but nonfluctuant papule was present on the scalp and had been present for 4 days. The patient was not aware of this lesion until it was identified on the presenting physical examination.

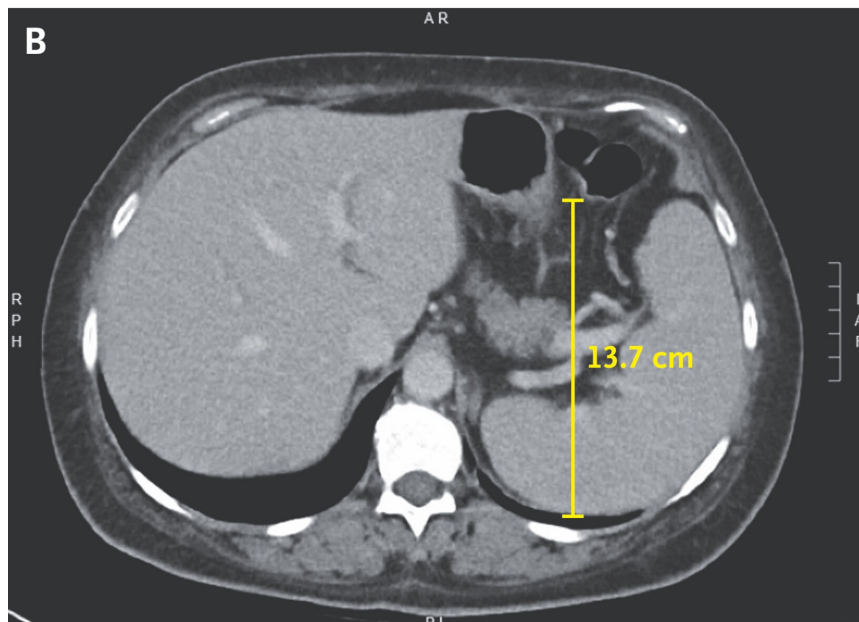
In this patient with chemotherapy-related immunocompromise, I am most concerned about an infection causing the fever and associated symptoms. Her cough suggests the possibility of upper or lower respiratory tract infection. Given her residual axillary seroma, a superimposed soft-tissue infection could also be driving her fevers, although the absence of worsening tenderness in this area makes this less likely. **Pembrolizumab-associated inflammatory conditions, including cytokine release syndrome or hemophagocytic lymphohistiocytosis (HLH), should also be considered.** Cancers can also cause fever, but this is unlikely with breast cancer.

The white-cell count was 1860 per microliter, hemoglobin level 9.2 g per deciliter, and platelet count 66,000 per microliter. (These values were 4670 per microliter, 11.2 g per deciliter, and 162,000 per microliter, respectively, 1 month earlier.) The neutrophil count was 1390 per microliter (normal range, 1920 to 7600), lymphocyte count 350 per microliter (normal range, 720 to 4100), and monocyte count 100 per microliter (normal range, 160 to 1100). A comprehensive metabolic panel; coagulation studies, including prothrombin time (expressed in the international normalized ratio), partial-thromboplastin time, and fibrinogen level; and lactate level were unremarkable. Nasopharyngeal polymerase-chain-reaction (PCR) testing for Covid-19, influenza, parainfluenza, adenovirus, and respiratory syncytial virus was negative. Sputum and throat cultures were negative. Blood cultures were obtained. The C-reactive protein level was 248.9 mg per liter (normal value, <3.0), and the erythrocyte sedimentation rate was 34 mm per hour (normal value, <30). Testing for antibodies against *Bordetella pertussis* and *Mycoplasma pneumoniae* was negative. Serologic testing for brucella and toxoplasma was negative. Serum PCR studies for Epstein–Barr virus, parvovirus, cytomegalovirus, and toxoplasma were also negative, as were tests for beta-D-glucan and galactomannan. Urinalysis showed trace bacteria without red or white cells; urine culture grew less than 10,000 colony-forming units (CFU) per milliliter of corynebacterium species and 10,000 to 50,000 CFU per milliliter of lactobacillus species.



Computed Tomography of the Chest, Abdomen, and Pelvis with Intravenous Contrast.

Panel A shows a fluid collection measuring 4 cm by 3 cm (arrow) in the left axillary space where the patient had undergone her lumpectomy and axillary lymph-node biopsy. There was no thickening of the wall around the fluid, enhancement with contrast, internal gas loculations, or fat stranding to suggest a superimposed infection. Panel B shows that the spleen was enlarged at 13.7 cm (abnormal, >13.0 cm in the craniocaudal dimension); in previous imaging a month earlier, the size of the spleen was less than 11.5 cm.



The combination of fever, splenomegaly, cytopenias, hypertriglyceridemia, hyperferritinemia, and elevated level of soluble CD25 (a soluble form of the interleukin-2 receptor alpha chain) is consistent with a diagnosis of HLH. Whether the CD25 level meets diagnostic criteria is uncertain, because established criteria relied on a different functional assay, and there is no accepted conversion factor. Nonetheless, in this clinical context with the other features present, the diagnosis of HLH appears certain.

.

Intravenous antibiotic therapy with vancomycin and cefepime was initiated on admission.

The patient remained febrile, and on day 3 of admission, she was switched from cefepime to piperacillin–tazobactam for improved anaerobic coverage, and doxycycline was added for empirical treatment of tickborne illnesses. Despite broad-spectrum antibiotics, the patient continued to have fevers, and on hospital day 4, symptomatic hypotension developed.

The patient's hypotension resolved with intravenous fluid boluses. Her white-cell count and hemoglobin level continued to decrease, with lows of 1010 per microliter and 7.0 g per deciliter, respectively. Additional laboratory testing showed a ferritin level of 37,956 micrograms per liter (normal range, 13 to 150), a triglyceride level of 296 mg per deciliter (3.3 mmol per liter; normal range, 35 to 150 mg per deciliter [0.4 to 1.7 mmol per liter]), a fibrinogen level of 222 mg per deciliter (normal range, 200 to 400), a soluble CD25 level of 4268.1 pg per milliliter (normal range, 175.3 to 858.2) by enzyme-linked immunosorbent assay, and an interleukin-6 level of 56.2 pg per milliliter (normal value, <7.1). Flow cytometry and molecular testing did not show evidence of a hematologic cancer.

On day 5, intravenous methylprednisolone (1 mg per kilogram of body weight daily) was initiated and resulted in immediate resolution of the patient's fevers, easing of her cytopenias, and reduction in the ferritin level. By day 8, blood cultures remained negative, and doxycycline was stopped after PCR tests for babesia, borrelia, ehrlichia, and anaplasma were negative. On day 9, she was transitioned to oral prednisone (100 mg daily) and discharged on hospital day 11 with a plan to slowly taper her dose of prednisone by 10 mg weekly. She continued to do well clinically, and the decision was made to discontinue pembrolizumab. Additional scalp lesions developed after discharge that were biopsied and consistent with shingles, for which she was treated with valacyclovir.

Commentary

This patient presented with fever and neutropenia that persisted despite broad-spectrum antibiotics without evidence of active infection. In the context of recent treatment with pembrolizumab, splenomegaly, and other serologic markers, she ultimately received a diagnosis of pembrolizumab-associated HLH, which responded rapidly to glucocorticoid therapy.

Pembrolizumab (ein Immuncheckpoint-Inhibitor) **kann sehr selten eine Hämophagozytische Lymphohistiozytose (HLH) als schwerwiegende immunvermittelte Nebenwirkung auslösen.**

Dies ist eine lebensgefährliche Überaktivierung des Immunsystems mit hohem Fieber, Organschäden und stark veränderten Blutwerten.

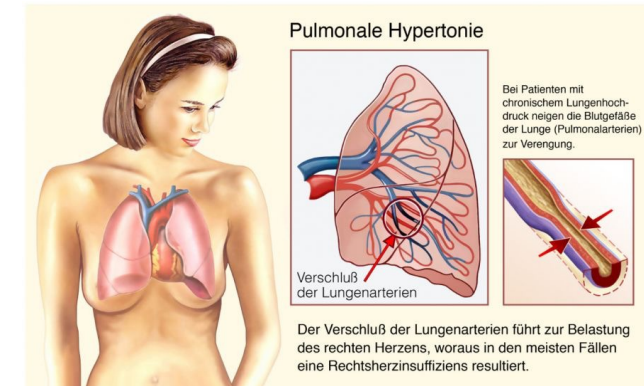
Was Sie über Pembrolizumab und HLH wissen sollten

- **Häufigkeit:** **Extrem selten**, aber in der klinischen Literatur dokumentiert.
- **Zeitpunkt:** Tritt meist wenige Wochen **nach Beginn der Therapie** oder kurz nach einer Infusion auf, kann aber auch verzögert einsetzen.
- **Symptome:** Anhaltendes hohes **Fieber, starke Schwäche, Gelbsucht, Atemnot oder Hautausschlag.**
- **Laborwerte:** Extrem hoher **Ferritinwert**, niedrige Blutzellen (Panzytopenie) und gestörte Leberwerte.
- **Behandlung:** **Sofortiger Stopp** von Pembrolizumab und hochdosierte Gabe von Cortison (z. B. Prednisolon/Dexamethason) oder speziellen Immunhemmern (wie Anakinra).

Die **pulmonale Hypertonie (PH)** – im Volksmund als **Lungenhochdruck** bezeichnet – ist eine chronische und fortschreitende Erkrankung, die durch einen **dauerhaft erhöhten Blutdruck im Lungenkreislauf** (mittlerer pulmonalarterieller Druck > 20 mmHg) definiert ist. Durch verengte oder steife Gefäße muss die rechte Herzkammer das Blut mit deutlich erhöhtem Kraftaufwand in die Lunge pumpen, was langfristig zu einer Überlastung des Herzens (Rechtsherzinsuffizienz) führen kann.

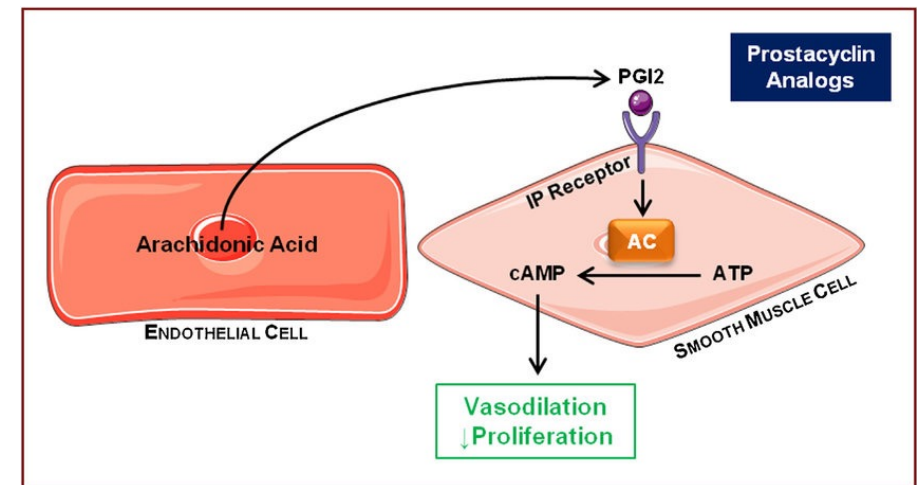
Die Europäische Gesellschaft für Kardiologie (ESC) unterteilt den Lungenhochdruck je nach Auslöser in fünf Kategorien:

- **Gruppe 1: Pulmonalarterielle Hypertonie (PAH)** – Seltene Form, ausgelöst durch direkte Gefäßveränderungen; kann idiopathisch (ohne erkennbare Ursache), vererbt oder durch Bindegewbserkrankungen bedingt sein.
- **Gruppe 2: PH bei Linksherzerkrankungen** – Die häufigste Form; entsteht durch einen Blutrückstau infolge einer Herzschwäche der linken Herzhälfte.
- **Gruppe 3: PH bei Lungenerkrankungen** – Ausgelöst durch chronischen Sauerstoffmangel bei Erkrankungen wie COPD oder Lungenfibrose.
- **Gruppe 4: Chronisch-thromboembolische pulmonale Hypertonie (CTEPH)** – Verursacht durch nicht aufgelöste, chronische Blutgerinnsel (nach Lungenembolien).
- **Gruppe 5: PH mit unklaren Mechanismen** – Entsteht im Zuge anderer Grunderkrankungen wie Stoffwechsel- oder Bluterkrankungen.

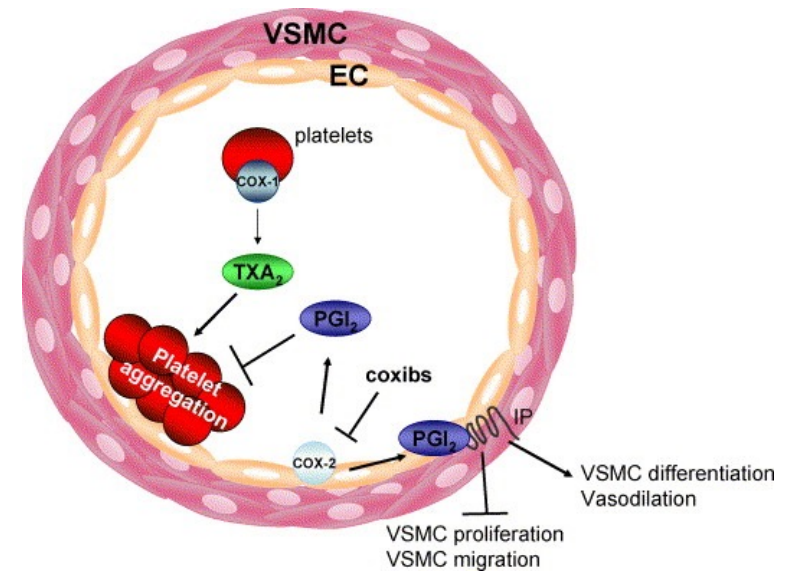


- **PDE-5-Hemmer** (z. B. Sildenafil, Tadalafil): Erweitern die Blutgefäße in der Lunge über den Stickstoffmonoxid-Weg.
- **Endothelin-Rezeptor-Antagonisten / ERA** (z. B. Bosentan, Ambrisentan, Macitentan): Blockieren den Botenstoff Endothelin, der die Gefäße verengt.
- **sGC-Stimulatoren** (z. B. Riociguat): Stimulieren die lösliche Guanylatcyclase und verstärken die gefäßerweiternde Wirkung von Stickstoffmonoxid.
- ➔ **Prostazyklin-Analoga & IP-Rezeptor-Agonisten** (z. B. Iloprost, Treprostinil, Epoprostenol, Selexipag): Ersetzen das körpereigene, gefäßerweiternde Prostazyklin.
- **Aktivin-Signalweg-Inhibitoren** (z. B. Sotatercept): Ein neuerer Ansatz, der direkt an den zellulären Umbauprozessen der Gefäßwände ansetzt.

Prostacyclin (auch Prostaglandin I₂, kurz PGI₂) ist ein körpereigenes Gewebshormon aus der Gruppe der Eicosanoide. Es wirkt stark **gefäßerweiternd (vasodilatatorisch)** und **hemmt die Verklumpung der Blutplättchen (Thrombozytenaggregation)**. Als Arzneistoff wird es primär zur Behandlung von pulmonaler Hypertonie (Lungenhochdruck) eingesetzt.



Ralinepag ist ein potenter, oral einzunehmender und hochselektiver Prostacyclin-Rezeptor-Agonist, der zur Behandlung der **pulmonalen arteriellen Hypertonie (PAH)** entwickelt wird. Das Medikament senkt den Blutdruck in den Lungenarterien und wird als Tablette mit verlängerter Freisetzung einmal täglich eingenommen.



Ralinepag for the treatment of pulmonary arterial hypertension (ADVANCE OUTCOMES): a randomised, double-blind, placebo-controlled phase 3 study

Does
ralinepag
protect
PAH from
„getting
worse“?

Summary

Background Pulmonary arterial hypertension (PAH) is a rare, progressive disease characterised by elevated pulmonary vascular resistance that can lead to right ventricular failure and premature death. Ralinepag is an oral, once-daily, selective prostacyclin IP receptor agonist developed to treat PAH. We aimed to evaluate the efficacy and safety of ralinepag in patients with PAH.

Methods ADVANCE OUTCOMES was a randomised, double-blind, placebo-controlled, event-driven, phase 3 trial of ralinepag in patients with PAH. Eligible patients were aged 18 years or older and PAH was diagnosed on the basis of the 2022 European Society of Cardiology and European Respiratory Society guidelines (mean pulmonary artery pressure >20 mm Hg, pulmonary artery wedge pressure ≤15 mm Hg, and pulmonary vascular resistance of >2 Wood units). Patients were randomly assigned (1:1) to ralinepag or placebo, initiated at a dose of 50 µg once daily and titrated weekly until the highest tolerated individualised dose was reached. Randomisation was stratified by baseline 6-minute walk distance (6MWD), PAH aetiology, and oral background therapy. A block size of four was used within each combination of stratification factors. The sponsor, patients, and all personnel directly involved with the conduct of the study were masked to study drug identity and randomisation assignments. The primary outcome was time to first clinical worsening event, a composite of death from any cause, admission to hospital due to worsening PAH or right heart failure, initiation of parenteral or inhaled prostacyclin-pathway therapy, disease progression, or unsatisfactory long-term clinical response. Efficacy analyses were done in the full analysis set and safety analyses in the safety set; both sets comprised 687 patients after exclusion of 41 randomly assigned and treated patients from sites in China (exclusions due to regulatory challenges and data integrity concerns). This study is registered with ClinicalTrials.gov (NCT03626688) and euclinicaltrials.eu (2023-509304-16-00) and is complete.

Findings Patients were enrolled between Jan 24, 2019, and June 20, 2025. Of 1037 patients screened for eligibility, 728 were randomly assigned and received at least one dose of ralinepag or placebo; 687 were included in the full analysis and safety sets, of whom 350 received ralinepag and 337 received placebo. Median follow-up from randomisation to clinical worsening event, censoring, or study closure was 85·0 weeks (IQR 27·6–160·9) in the ralinepag group and 78·4 weeks (34·6–137) in the placebo group. At baseline, patients had a mean 6MWD of 438·9 m (SD 104·8) and 548 (80%) of 687 patients were receiving dual background PAH therapy. Overall, 64 (18%) of 350 patients in the ralinepag group and 121 (36%) of 337 patients in the placebo group had a first clinical worsening event (hazard ratio 0·45 [95% CI 0·33–0·62]; $p < 0·0001$). The largest numerical between-group differences in components of the composite outcome were observed for disease progression, initiation of parenteral or inhaled prostacyclin-pathway therapy, and unsatisfactory long-term clinical response. Adverse event was the primary reason for treatment discontinuation in 65 (19%) of 350 patients in the ralinepag group and ten (3%) of 337 patients in the placebo group. Serious adverse events occurred in 98 (28%) patients in the ralinepag group and 104 (31%) patients in the placebo group. Adverse events leading to death occurred in 15 (4%) and 14 (4%) patients, respectively.

Interpretation In patients with PAH receiving contemporary background therapy, ralinepag significantly reduced the risk of first clinical worsening compared with placebo, but was associated with more adverse-event-related treatment discontinuations. These results support the use of ralinepag as an oral, once-daily prostacyclin-pathway treatment option for PAH.

Introduction

Pulmonary arterial hypertension (PAH) is a rare, progressive disease characterised by elevated pulmonary vascular resistance that leads to right ventricular failure and ultimately death. Despite available treatments, long-term survival for patients with PAH remains poor; in a French registry cohort, 5-year survival was 52%.¹ PAH is commonly idiopathic, but can also be heritable or occur in relation to exposure to drugs or toxins such as methamphetamine, or conditions such as connective tissue disease, HIV infection, or congenital heart disease.² Currently, 16 approved therapies target the nitric oxide, endothelin, prostacyclin, and activin signalling pathways to improve haemodynamics and exercise capacity and delay disease progression, but morbidity and mortality remain very high and underscore the need for additional efficacious therapies.³

Ralinepag is an oral, highly selective, non-prostanoid, prostacyclin IP receptor agonist developed to treat PAH. Ralinepag has a longer half-life than selexipag, an oral prostacyclin IP receptor agonist approved for the treatment of PAH. In non-clinical studies, ralinepag was shown to be more potent than selexipag's active metabolite at increasing cellular cyclic adenosine monophosphate concentrations.⁴⁻⁸ As a prostacyclin IP receptor agonist, ralinepag is intended to activate prostacyclin signalling, which can promote vasodilation and might counter the proliferative and inflammatory mechanisms implicated in pulmonary vascular disease.⁹ In a previous phase 2 trial, ralinepag reduced pulmonary vascular resistance compared with placebo.¹⁰ Ralinepag's pharmacokinetic profile also supports less frequent dosing than selexipag.¹¹ In an open-label extension study, improvements in haemodynamic parameters, exercise capacity, and WHO functional class were observed during up to 24 months of treatment with ralinepag.¹² These findings supported further evaluation of ralinepag in patients with PAH in the phase 3 ADVANCE OUTCOMES trial, the results of which we report here.

	Ralinepag group (n=350)	Placebo group (n=337)
Sex		
Male	94 (27%)	73 (22%)
Female	256 (73%)	264 (78%)
Age, years	54 (42-65)	52 (40-63)
Age category		
<65 years	260 (74%)	262 (78%)
≥65 years	90 (26%)	75 (22%)
Race		
White	283 (81%)	268 (80%)
Black or African American	10 (3%)	12 (4%)
American Indian or Alaska Native	1 (<1%)	0
Native Hawaiian or other Pacific Islander	2 (1%)	1 (<1%)
Asian	21 (6%)	38 (11%)
Multiple	2 (1%)	4 (1%)
Other	18 (5%)	11 (3%)
Not reported	13 (4%)	3 (1%)
Ethnicity		
Hispanic or Latino	95 (27%)	100 (30%)
Not Hispanic or Latino	235 (67%)	222 (66%)
Not reported	9 (3%)	13 (4%)
Unknown	11 (3%)	2 (1%)
Time since diagnosis, years*	2.1 (0.8-5.4)	2.6 (0.9-5.9)
Aetiology of PAH		
Idiopathic	198 (57%)	194 (58%)
Heritable	21 (6%)	12 (4%)
Drug-induced or toxin-induced	10 (3%)	11 (3%)
Connective tissue disease	100 (29%)	94 (28%)
HIV infection	9 (3%)	9 (3%)
Congenital systemic-to-pulmonary shunt	11 (3%)	13 (4%)
Congenital heart disease	1 (<1%)	3 (1%)
Missing	0	1 (<1%)
WHO functional class		
II	261 (75%)	223 (66%)
III	89 (25%)	113 (34%)
IV	0	1 (<1%)
6MWD, m	441.3 (106.9)	436.5 (102.7)
NT-proBNP, pg/mL†	233.5 (95.0-582.0)	192.0 (78.0-508.0)
Mean pulmonary artery pressure, mm Hg‡	45.5 (14.2)	45.2 (14.2)
Use of medications for PAH		
None	8 (2%)	6 (2%)
Monotherapy with ERA	14 (4%)	17 (5%)
Monotherapy with PDE5 inhibitor or sGC stimulator	45 (13%)	49 (15%)
Dual therapy with ERA and PDE5 inhibitor	257 (73%)	248 (74%)
Dual therapy with ERA and sGC stimulator	26 (7%)	17 (5%)
REVEAL Lite 2 risk category†		
Low risk	244 (71%)	246 (73%)
Intermediate risk	59 (17%)	50 (15%)
High risk	43 (12%)	39 (12%)

(Table 1 continues on next page)

	Ralinepag group (n=350)	Placebo group (n=337)
(Continued from previous page)		
COMPERA 2.0 risk category†		
Low risk	186 (54%)	160 (48%)
Intermediate-to-low risk	118 (34%)	139 (41%)
Intermediate-to-high risk	41 (12%)	33 (10%)
High risk	1 (<1%)	3 (1%)
Comorbidities		
Diabetes	9 (3%)	14 (4%)
Hypertension	97 (28%)	84 (25%)
Obesity	42 (12%)	40 (12%)
Data are n (%), mean (SD), or median (IQR). COMPERA=Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension. ERA=endothelin receptor antagonist. NT-proBNP=N-terminal pro-B-type natriuretic peptide. PAH=pulmonary arterial hypertension. PDE5=phosphodiesterase type 5. REVEAL=Registry to Evaluate Early and Long-term PAH Disease Management. sGC=soluble guanylate cyclase. 6MWD=6-minute walk distance. *Data from 350 patients in the ralinepag group and 336 patients in the placebo group. †Data from 346 patients in the ralinepag group and 335 patients in the placebo group. ‡Data from 349 patients in the ralinepag group and 337 patients in the placebo group.		
Table 1: Baseline characteristics of treatment groups		

	Ralinepag group (n=350)	Placebo group (n=337)	Treatment effect (95% CI); p value
Primary outcome: occurrence of first clinical worsening event	..	..	HR 0.45 (0.33 to 0.62)*; p<0.0001
Any event	64 (18%)	121 (36%)	..
Death from any cause	11 (3%)	10 (3%)	..
Hospitalisation due to worsening PAH or right heart failure, or both	19 (5%)	20 (6%)	..
Initiation of parenteral or inhaled prostacyclin-pathway therapy	10 (3%)	22 (7%)	..
Disease progression	10 (3%)	36 (11%)	..
Unsatisfactory long-term clinical response	14 (4%)	33 (10%)	..
Secondary outcome: NT-proBNP (pg/mL) from baseline to week 28†	..	..	Percentage change relative to placebo -24.3 (-36.1 to -10.3); p=0.0013
Mean (SD)	-33.2 (789.25)	97.4 (654.58)	..
Percentage change relative to baseline (SE)	-4.3 (6.28)	26.4 (7.87)	..
Secondary outcome: 6MWD (m) from baseline to week 28†	..	..	Least-squares mean difference 20.41 (6.81 to 34.02); p=0.0033
Least-squares mean (SE)	8.24 (5.15)	-12.17 (4.95)	..
Secondary outcome: WHO functional class improvement at week 28‡	..	..	Common OR 1.34 (0.89 to 2.01); p=0.16
Improved	67 (19%)	57 (17%)	..
Not improved	283 (81%)	280 (83%)	..
Secondary outcome: clinical improvement at week 28§	..	..	Common OR 1.47 (1.08 to 2.02); p=0.015
Improved	154/346 (45%)	116/335 (35%)	..
Not improved	192/346 (55%)	219/335 (65%)	..

Data are n (%), mean (SD), or n/N (%) unless otherwise specified. Primary outcome components are first clinical worsening events. Efficacy analyses were conducted on the full analysis set, which comprised 687 patients: 350 assigned to and treated with ralinepag and 337 assigned to and treated with placebo. Patients from sites in China were excluded from the primary efficacy and safety analyses. HR=hazard ratio. NT-proBNP=N-terminal pro-B-type natriuretic peptide. OR=odds ratio. PAH=pulmonary arterial hypertension. 6MWD=6-minute walk distance. *HR, 95% CI, and p value were calculated with Cox proportional hazards model with treatment and randomisation stratification factors in the model, in which 6MWD is included as a continuous covariate instead of as a factor. †Results were obtained using a mixed model for repeated measures with change from baseline as the dependent variable (log-transformed for NT-proBNP). Fixed effects included treatment group, visit, treatment-by-visit interaction, and randomisation stratification factors (except baseline 6MWD category). Baseline 6MWD was included as a covariate, and baseline log-transformed NT-proBNP was additionally included as a covariate for the NT-proBNP outcome. ‡Missing shift imputed as non-responder. The p value was obtained from a stratified Cochran-Mantel-Haenszel test with baseline WHO functional class (II vs III or IV) as the strata and modified ridit scores (appendix p 103, 166-67). §Missing shift imputed as non-responder. Patients were included in the analysis only if all three criteria for clinical improvement were observed (ie, not missing) at baseline. The p value was obtained from a stratified Cochran-Mantel-Haenszel test with baseline number of non-invasive low-risk criteria (none or one vs two or three) as the strata and using modified ridit scores. The 95% CI and p value are nominal without adjusting for multiplicity.

Table 2: Primary and secondary outcomes in treatment groups

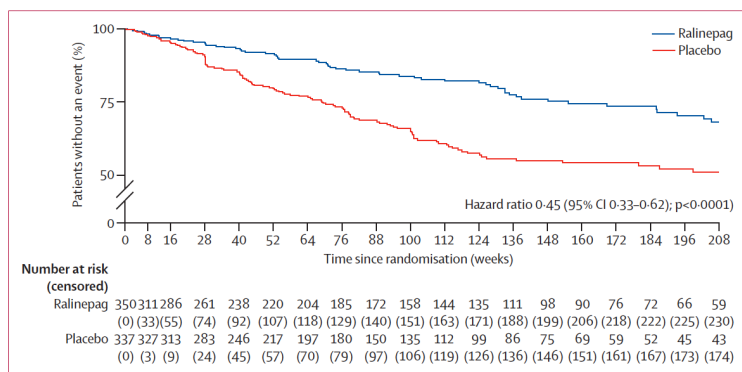


Figure 2: Primary composite outcome
Kaplan-Meier curves for time to first clinical worsening event, a composite of death from any cause; admission to hospital for worsening PAH, right heart failure, or both; initiation of parenteral or inhaled prostacyclin-pathway therapy; disease progression; or unsatisfactory long-term clinical response. The analysis used all available data, whereas the Kaplan-Meier curve is truncated at 4 years (208 weeks).

	Ralinepag group (n=350)	Placebo (n=337)
Total number of adverse events	6574	3512
Number of patients with at least one adverse event	346 (99%)	320 (95%)
Total number of serious adverse events	178	194
Number of patients with at least one serious adverse event	98 (28%)	104 (31%)
Total number of adverse events leading to withdrawal of study drug	110	39
Number of patients with adverse event as primary reason for treatment discontinuation*	65 (19%)	10 (3%)
Number of patients with adverse events leading to death	15 (4%)	14 (4%)
Most frequently occurring adverse events)†		
Headache	284 (81%)	140 (42%)
Diarrhoea	204 (58%)	95 (28%)
Nausea	158 (45%)	86 (26%)
Myalgia	126 (36%)	36 (11%)
Jaw pain	125 (36%)	30 (9%)
Extremity pain	114 (33%)	27 (8%)
Vomiting	104 (30%)	38 (11%)
Flushing	76 (22%)	22 (7%)
Arthralgia	68 (19%)	38 (11%)
COVID-19	59 (17%)	65 (19%)
Fatigue	59 (17%)	55 (16%)
Dizziness	54 (15%)	64 (19%)
Dyspnoea	54 (15%)	44 (13%)
Oedema peripheral	52 (15%)	33 (10%)
Upper respiratory tract infection	52 (15%)	52 (15%)
Cough	38 (11%)	48 (14%)
Decreased appetite	37 (11%)	5 (1%)
Back pain	35 (10%)	27 (8%)
Palpitations	35 (10%)	26 (8%)
Pain	34 (10%)	10 (3%)
Nasopharyngitis	31 (9%)	51 (15%)
Abdominal pain	28 (8%)	22 (7%)

(Table 3 continues in next column)

	Ralinepag group (n=350)	Placebo (n=337)
(Continued from previous column)		
Insomnia	28 (8%)	23 (7%)
Urinary tract infection	27 (8%)	35 (10%)
Abdominal pain upper	25 (7%)	24 (7%)
Hypokalaemia	25 (7%)	17 (5%)
Influenza	25 (7%)	23 (7%)
Anaemia	24 (7%)	14 (4%)
Gastro-oesophageal reflux disease	23 (7%)	21 (6%)
Hypotension	23 (7%)	20 (6%)
Chest pain	22 (6%)	25 (7%)
Pneumonia	22 (6%)	21 (6%)
Sinusitis	22 (6%)	20 (6%)
Asthenia	21 (6%)	9 (3%)
Increased NT-proBNP	20 (6%)	23 (7%)
Rash	20 (6%)	18 (5%)
Iron deficiency	19 (5%)	9 (3%)
Muscle spasms	19 (5%)	18 (5%)
Dyspepsia	16 (5%)	24 (7%)
Epistaxis	16 (5%)	17 (5%)
Oropharyngeal pain	16 (5%)	19 (6%)
Worsening of PAH	16 (5%)	27 (8%)
Pyrexia	16 (5%)	18 (5%)
Constipation	13 (4%)	20 (6%)
Syncope	13 (4%)	26 (8%)
Anxiety	11 (3%)	17 (5%)

Data are number of events or n (%). NT-proBNP=N-terminal-pro B-type natriuretic peptide. PAH=pulmonary arterial hypertension. *Excludes one patient in the ralinepag group whose originally recorded primary reason for treatment discontinuation was adverse event but who was classified as having discontinued because of an investigator-reported clinical worsening event. †Adverse events occurred in at least 5% of patients in either the ralinepag or placebo group.

Table 3: Summary of adverse events in treatment groups

Research in context

Evidence before this study

Pulmonary arterial hypertension (PAH) is a rare, progressive disease characterised by elevated mean pulmonary vascular resistance that can lead to right ventricular failure and premature death. Although treatment options have improved over the past three decades, long-term survival remains poor and additional treatment options are needed. Prostacyclin-pathway therapies are established treatments for PAH, but their use can be limited by route of administration, dosing frequency, titration requirements, and tolerability. Ralinepag is an oral, once-daily, selective prostacyclin IP receptor agonist developed to treat PAH. In a previous double-blind, multicentre, phase 2 trial, ralinepag reduced pulmonary vascular resistance compared with placebo, and an open-label extension study suggested sustained improvements in haemodynamic and functional measures with an adverse-event profile consistent with prostacyclin-pathway therapy. We searched The PubMed database from January to August, 2018, when the ADVANCE Outcomes study was initiated, for all published reports in English of clinical trials in patients with PAH treated with prostacyclin pathway agents by combining the search terms “pulmonary arterial hypertension” and “prostacyclin” and “prostacyclin agonist” with “randomised clinical trial”.

Added value of this study

To our knowledge, the ADVANCE OUTCOMES study is one of only two randomised controlled trials to have evaluated a

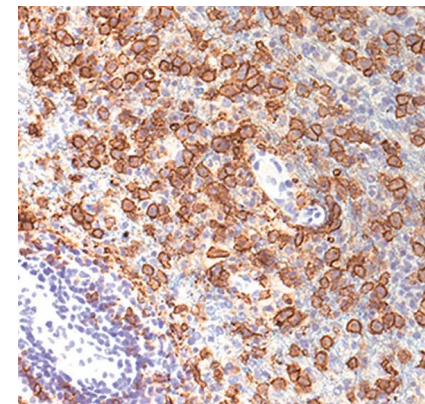
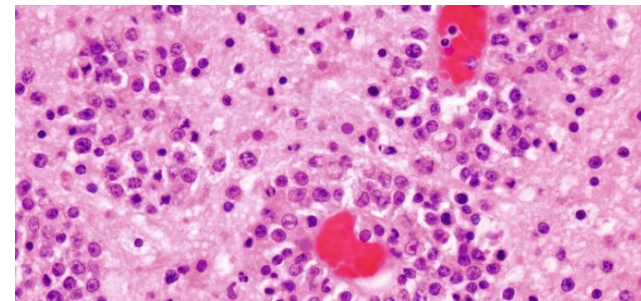
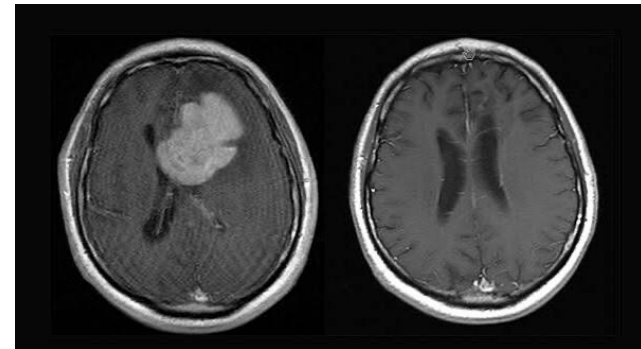
prostacyclin IP receptor agonist in patients with PAH, and it is the first to incorporate contemporary haemodynamic eligibility criteria aligned with the 2022 European Society of Cardiology and European Respiratory Society guidelines. In a pretreated population in which most patients were at low or intermediate-to-low risk and were receiving dual background PAH therapy, ralinepag reduced the risk of first clinical worsening compared with placebo. The direction of the effect was consistent across subgroups and results were accompanied by reductions in N-terminal proB-type natriuretic peptide and improvements in exercise capacity.

Implications of all the available evidence

These findings support ralinepag as an oral, once-daily prostacyclin-pathway treatment option for patients with PAH receiving contemporary background therapy. The results suggest that further prostacyclin-pathway intensification can reduce clinical worsening even in a largely pretreated population with relatively preserved baseline functional capacity. However, the trial does not establish comparative efficacy or tolerability versus other approved prostacyclin-pathway therapies, and the primary composite outcome was not driven by differences in death or admission to hospital. Further research should clarify how ralinepag is best positioned among available PAH therapies, how tolerability during titration can be optimised, and whether longer-term treatment affects harder clinical outcomes.

Das **Primäre ZNS-Lymphom (PZNSL)** ist laut der [Onkopedia-Leitlinie](#) ein seltenes, aggressives Non-Hodgkin-Lymphom (meist ein diffuses großzelliges B-Zell-Lymphom), das ausschließlich im Zentralnervensystem auftritt. Der Therapieansatz bei fitten Patienten ist **kurativ** und basiert auf einer Hochdosis-Methotrexat-Induktion mit Rituximab sowie einer anschließenden Hochdosisschemotherapie mit autologer Stammzelltransplantation.

- **Diagnostik:** Bestätigung zwingend mittels stereotaktischer Biopsie (Gewebeprobe) vor einer Kortisontherapie.
- **Therapie:** Chemotherapie mit ZNS-gängigen Substanzen und Antikörpern; Vermeidung einer primären Ganzhirnbestrahlung zur Reduktion von Neurotoxizität.
- **Rezidiv:** Behandlung erfolgt individuell mit modernen Wirkstoffen oder im Rahmen klinischer Studien



Primary CNS lymphoma
PCNSL

MATRix
Rituximab
Cytarabine
Thiotepa
Methotrexate

R-DeVIC
Rituximab
Dexamethazone
Etoposide
Ifosfamide
Carboplatin

HCT-ASCT
High-dose chemotherapy
Autologous stem-cell
transplantation

High-dose chemotherapy followed by autologous stem-cell transplantation versus non-myeloablative consolidation in primary CNS lymphoma (MATRix/IELSG43): a randomised phase 3 trial

Summary

Background Consolidation therapy for primary CNS lymphoma (PCNSL) includes high-dose chemotherapy with autologous stem-cell transplantation (HCT-ASCT), yet its efficacy compared with non-myeloablative chemoimmunotherapy remains uncertain. This study aimed to provide randomised comparative evidence on the efficacy and safety of thiotepa-based HCT-ASCT versus non-myeloablative R-DeVIC consolidation after uniform MATRix induction in newly diagnosed PCNSL.

Methods This open-label, randomised, phase 3 trial was conducted across 56 university and academic non-university hospitals with established transplantation facilities in five European countries. Eligible for inclusion were untreated, immunocompetent patients with B-cell PCNSL, aged 18–65 years regardless of Eastern Cooperative Oncology Group (ECOG) performance status, or 66–70 years with ECOG performance status 0–2. Pretreatment corticosteroids were permitted. Exclusion criteria included lymphoma manifestation outside the CNS, and congenital or acquired immunodeficiency. Patients received four cycles of MATRix induction (comprising rituximab, high-dose cytarabine, and thiotepa, in addition to high-dose methotrexate). Patients reaching at least partial response were randomly assigned (1:1) to two cycles of R-DeVIC (rituximab plus dexamethasone, etoposide, ifosfamide, and carboplatin) or HCT-ASCT with carmustine and thiotepa. The primary endpoint was progression-free survival, assessed in the full analysis set (excluding patients with major violations of entry criteria). The safety analysis set contained all randomised patients who initiated therapy. This study is registered with ClinicalTrials.gov (NCT02531841) and the EU Clinical Trials Register (EudraCT number 2012-000620-17). The study is completed.

Findings Between July 16, 2014, and Aug 31, 2019, 368 patients were enrolled. 346 (94%) patients started induction treatment, and 230 were randomly assigned; 229 patients were analysed (R-DeVIC group, n=115; HCT-ASCT group, n=114). After a median follow-up of 45·3 months, 3-year progression-free survival was significantly superior in the HCT-ASCT group (hazard ratio 0·43 [95% CI 0·27–0·68]; p=0·0003). The 3-year progression-free survival was 78% (95% CI 69–85) in the HCT-ASCT group compared with 51% (41–60) in the R-DeVIC group. The mean number of adverse events per patient was 9·3 (SD 4·4) in the R-DeVIC group and 14·6 (5·8) in the HCT-ASCT group. Fatal serious adverse events following consolidation treatment occurred in two patients in the R-DeVIC group (both acute myeloid leukaemia) and in five patients in the HCT-ASCT group (infections and infestations [n=4], pulmonary embolism [n=1]); all of these events apart from the pulmonary embolism were judged to be possibly related to treatment.

Interpretation In the largest randomised trial in untreated PCNSL to date, HCT-ASCT significantly improved progression-free and overall survival compared with non-myeloablative consolidation in patients who had completed induction treatment, establishing it as the preferred consolidation strategy in fit patients.

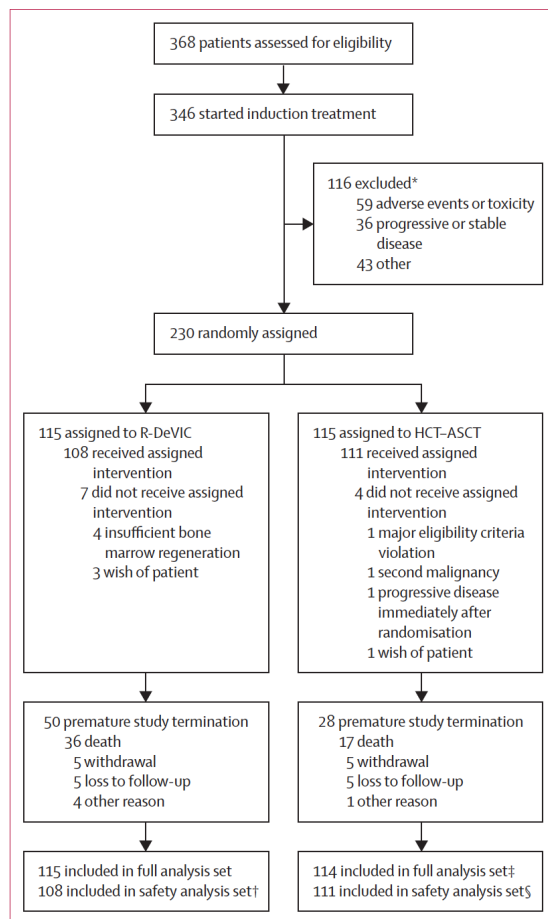


Figure 1: Trial profile

R-DeVIC=rituximab plus dexamethasone, etoposide, ifosfamide, and carboplatin. HCT-ASCT=high-dose chemotherapy followed by autologous stem-cell transplantation. *Multiple reasons can apply. Most frequent among other reasons were insufficient stem-cell harvest (n=11), wish of patient (n=7), and screening failure (n=7). †Seven patients who did not start the assigned treatment were excluded. ‡One patient with a major eligibility criteria violation was excluded. §Three patients who did not start the assigned treatment were excluded.

	R-DeVIC group (n=115)	HCT-ASCT group (n=114)
Age, years		
Median (IQR)	60 (54–64)	58 (51–64)
≥65 years	28 (24%)	23 (20%)
<65 years	87 (76%)	91 (80%)
Sex at birth		
Female	53 (46%)	49 (43%)
Male	62 (54%)	65 (57%)
ECOG performance status		
0	18 (16%)	25 (22%)
1	70 (61%)	56 (49%)
2	16 (14%)	29 (25%)
3	7 (6%)	3 (3%)
4	3 (3%)	0
Missing	1 (1%)	1 (1%)
Serum LDH concentration		
Increased	72 (63%)	79 (69%)
Not increased	43 (37%)	35 (31%)
Presence of neurological symptoms at initial diagnosis	106 (92%)	105 (92%)
Histological result		
Total valid	113 (100%)	114 (100%)
DLBCL	111 (98%)	111 (97%)
Low-grade B-NHL	0	2 (2%)
Other*	2 (2%)	1 (1%)
CD20 positivity		
Total valid	114 (100%)	114 (100%)
Yes	113 (99%)	114 (100%)
No	1 (1%)	0
Missing	1 (1%)	0
Imaging		
Number of lesions		
Singular lesion	41 (36%)	49 (43%)
Multiple lesions	72 (64%)	65 (57%)
Missing	2 (2%)	0
Location		
Infratentorial manifestation	8 (7%)	5 (4%)
Supratentorial manifestation	83 (74%)	81 (72%)
Both	21 (19%)	27 (24%)
Missing	3 (3%)	1 (1%)
Meningeal involvement	5 (4%)	5 (4%)
Signs of leukoencephalopathy	4 (4%)	4 (4%)

(Table 1 continues in next column)

	R-DeVIC group (n=115)	HCT-ASCT group (n=114)
(Continued from previous column)		
Slit lamp result		
No signs of ocular infiltration	92 (80%)	90 (80%)
Ocular infiltration possible	4 (3%)	11 (10%)
Not analysed	19 (17%)	13 (11%)
CSF examination		
Cytology		
Positive	11 (10%)	5 (4%)
Suspicious	7 (6%)	12 (11%)
Negative	67 (58%)	75 (66%)
Other result	5 (4%)	1 (1%)
Not analysed	25 (22%)	21 (18%)
Protein concentration		
Increased	41 (35%)	43 (38%)
Not increased	35 (30%)	44 (38%)
Not analysed	39 (34%)	27 (23%)
Cumulative dexamethasone dose before treatment start, mg; median (IQR)	152.0 (84.0–240.0)	156.0 (72.0–272.0)

Data are n (%) unless otherwise indicated. There were no imbalances in potential confounders noted that could be due to chance or inconsistencies in randomisation. R-DeVIC=rituximab plus dexamethasone, etoposide, ifosfamide, and carboplatin. HCT-ASCT=high-dose chemotherapy followed by autologous stem-cell transplantation. ECOG=Eastern Cooperative Oncology Group. LDH=lactate dehydrogenase. DLBCL=diffuse large B-cell lymphoma. B-NHL=B-cell non-Hodgkin lymphoma. CSF=cerebrospinal fluid. *Other: R-DeVIC group: high-grade B-NHL, meningeosis lymphomatosa; HCT-ASCT group: Burkitt lymphoma.

Table 1: Baseline patient characteristics

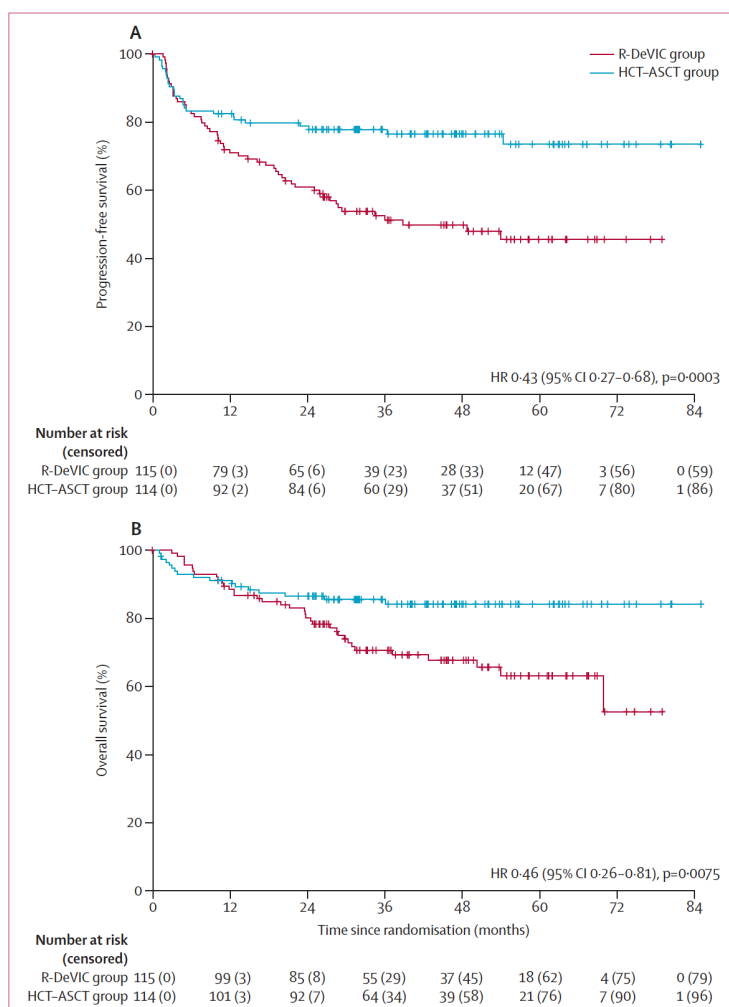


Figure 2: Kaplan-Meier analysis of progression-free survival (A) and overall survival (B) over time for the full analysis set

HRs were determined by Cox regression models adjusted for response status. HR=hazard ratio. R-DeVIC=rituximab plus dexamethasone, etoposide, ifosfamide, and carboplatin. HCT-ASCT=high-dose chemotherapy followed by autologous stem-cell transplantation.

	R-DeVIC group (n=115)	HCT-ASCT group (n=114)	Effect size (95% CI)
Rate of complete responses on day 60, n/N (% [95% CI])	75/115 (65% [56-74])	79/114 (69% [60-78])	OR 1.22 (0.68-2.18)
Overall survival			
Median (range), months	54 (44-not reached)	Not reached	..
3-year overall survival (95% CI)	71% (61-78)	86% (78-91)	HR 0.46 (0.26-0.81)
3-year cumulative incidence rate of relapse (95% CI)	45% (35-54)	19% (12-26)	SHR 0.40 (0.24-0.66)
EORTC QLQ-C30 median change in points (IQR)*			
Baseline to end of treatment	16.7 (-8.3 to 33.3)	8.3 (-16.7 to 25.0)	..
Baseline to 1-year follow-up	8.3 (-8.3 to 25.0)	16.7 (0 to 25.0)	..

Effect sizes are shown for the HCT-ASCT group compared with the R-DeVIC group. R-DeVIC=rituximab plus dexamethasone, etoposide, ifosfamide, and carboplatin. HCT-ASCT=high-dose chemotherapy followed by autologous stem-cell transplantation. OR=odds ratio. HR=hazard ratio. SHR=subdistribution hazard ratio. EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire. *Median change from baseline to end of treatment is reported for the 35/52 (67%) patients in the R-DeVIC group and 43/63 (68%) patients in the HCT-ASCT group, and from baseline to 1-year follow-up for the 23/52 (44%) patients in the R-DeVIC group and 27/63 (43%) patients in the HCT-ASCT group, who had available quality-of-life data at the respective timepoints (the denominators 52 [R-DeVIC group] and 63 [HCT-ASCT group] are the numbers of patients who had at least one baseline assessment at screening and did not experience progressive disease, relapse, or death).

Table 2: Secondary efficacy endpoints for the full analysis set

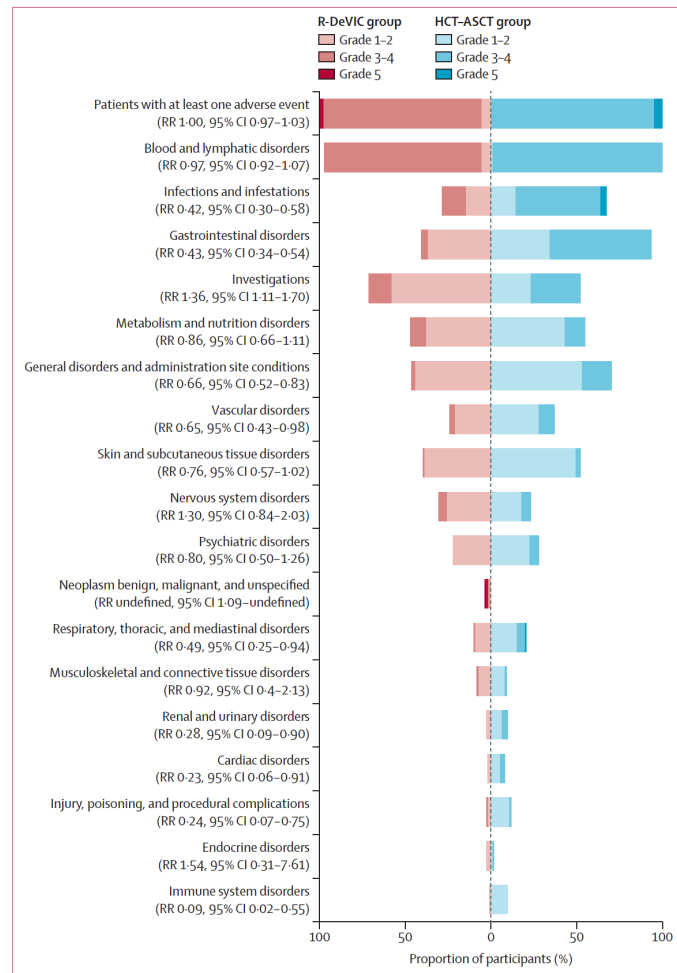


Figure 3: Adverse events in the safety analysis set (n=219)

Adverse events are grouped by MedDRA system organ class and graded according to Common Terminology Criteria for Adverse Events version 4.0. MedDRA system organ class totals are shown if the sum incidence of adverse events within one group was at least 10% (all grades) or if the sum incidence of adverse events being at least severe (grade ≥ 3) was at least 5%, or at least one fatal adverse event was reported within the group. MedDRA=Medical Dictionary for Regulatory Activities. RR=relative risk. R-DeVIC=rituximab plus dexamethasone, etoposide, ifosfamide, and carboplatin. HCT-ASCT=high-dose chemotherapy followed by autologous stem-cell transplantation.

	Induction (n=346)			Consolidation					
	All grades	Grade ≥ 3	Grade 5	R-DeVIC group (n=108)			HCT-ASCT group (n=111)		
				All grades	Grade ≥ 3	Grade 5	All grades	Grade ≥ 3	Grade 5
Patients with at least one adverse event	344 (99%)	340 (98%)	18 (5%)	108 (100%)	102 (94%)	2 (2%)	111 (100%)	111 (100%)	5 (5%)
Blood and lymphatic disorders	337 (97%)	332 (96%)	1 (<1%)	105 (97%)	99 (92%)	0	111 (100%)	110 (99%)	0
Thrombocytopenia	331 (96%)	328 (95%)	1 (<1%)	101 (94%)	90 (83%)	0	108 (97%)	106 (95%)	0
Anaemia	330 (95%)	299 (86%)	0	102 (94%)	75 (69%)	0	103 (93%)	82 (74%)	0
Leukopenia	313 (90%)	310 (90%)	0	89 (82%)	74 (69%)	0	101 (91%)	99 (89%)	0
Neutropenia	261 (75%)	252 (73%)	0	74 (69%)	61 (56%)	0	85 (77%)	82 (74%)	0
Febrile neutropenia	187 (54%)	185 (53%)	0	15 (14%)	15 (14%)	0	68 (61%)	67 (60%)	0
Infections and infestations	233 (67%)	179 (52%)	13 (4%)	31 (29%)	15 (14%)	0	75 (68%)	59 (53%)	4 (4%)
Device-related infection	55 (16%)	43 (12%)	0	3 (3%)	2 (2%)	0	23 (21%)	14 (13%)	0
Urinary tract infection	52 (15%)	32 (9%)	0	9 (8%)	7 (6%)	0	15 (14%)	11 (10%)	0
Pneumonia	49 (14%)	42 (12%)	4 (1%)	2 (2%)	2 (2%)	0	8 (7%)	8 (7%)	2 (2%)
Mucosal infection	42 (12%)	14 (4%)	0	2 (2%)	0	0	23 (21%)	13 (12%)	0
Skin infection	38 (11%)	15 (4%)	0	5 (5%)	0	0	4 (4%)	2 (2%)	0
Bronchitis	30 (9%)	22 (6%)	0	6 (6%)	1 (1%)	0	4 (4%)	4 (4%)	0
Sepsis	18 (5%)	18 (5%)	3 (1%)	0	0	0	3 (3%)	3 (3%)	1 (1%)
Abdominal infection	13 (4%)	13 (4%)	0	1 (1%)	1 (1%)	0	8 (7%)	8 (7%)	0
Neutropenic sepsis	7 (2%)	7 (2%)	1 (<1%)	0	0	0	3 (3%)	3 (3%)	1 (1%)
Pneumonia fungal	2 (1%)	1 (<1%)	0	0	0	0	1 (1%)	1 (1%)	1 (1%)
Septic shock	8 (2%)	8 (2%)	3 (1%)	0	0	0	3 (3%)	3 (3%)	0
Candida sepsis	1 (<1%)	1 (<1%)	1 (<1%)	0	0	0	0	0	0
Endocarditis staphylococcal	1 (<1%)	1 (<1%)	1 (<1%)	0	0	0	0	0	0
H1N1 influenza	1 (<1%)	1 (<1%)	1 (<1%)	0	0	0	0	0	0
Pseudomonal sepsis	2 (1%)	2 (1%)	1 (<1%)	0	0	0	0	0	0
Pulmonary sepsis	3 (1%)	3 (1%)	1 (<1%)	0	0	0	0	0	0
Gastrointestinal disorders	250 (72%)	50 (14%)	1 (<1%)	44 (41%)	4 (4%)	0	104 (94%)	66 (59%)	0
Stomatitis	117 (34%)	23 (7%)	0	10 (9%)	0	0	88 (79%)	60 (54%)	0
Nausea	113 (33%)	4 (1%)	0	23 (21%)	0	0	63 (57%)	13 (12%)	0
Constipation	74 (21%)	1 (<1%)	0	12 (11%)	0	0	9 (8%)	0	0
Diarrhoea	67 (19%)	11 (3%)	0	7 (7%)	3 (3%)	0	65 (59%)	12 (11%)	0
Abdominal pain	54 (16%)	7 (2%)	0	6 (6%)	0	0	23 (21%)	4 (4%)	0
Vomiting	50 (15%)	2 (1%)	0	9 (8%)	0	0	44 (40%)	1 (1%)	0
Investigations	313 (90%)	176 (51%)	0	77 (71%)	14 (13%)	0	58 (52%)	32 (29%)	0
Alanine aminotransferase increased	280 (81%)	143 (41%)	0	47 (44%)	2 (2%)	0	50 (45%)	5 (5%)	0
Gamma-glutamyltransferase increased	230 (66%)	62 (18%)	0	51 (48%)	11 (10%)	0	71 (64%)	27 (24%)	0
Aspartate aminotransferase increased	230 (66%)	67 (19%)	0	26 (24%)	0	0	48 (43%)	2 (2%)	0
Blood creatinine increased	134 (39%)	10 (3%)	0	21 (19%)	0	0	24 (22%)	2 (2%)	0
Blood bilirubin increased	119 (34%)	8 (2%)	0	8 (7%)	1 (1%)	0	18 (16%)	0	0

(Table 3 continues on next page)

MICR

	Induction (n=346)			Consolidation			HCT-ASCT group (n=111)		
	All grades	Grade ≥3	Grade 5	R-DeVIC group (n=108)			All grades	Grade ≥3	Grade 5
				All grades	Grade ≥3	Grade 5			
(Continued from previous page)									
Metabolism and nutrition disorders	236 (68%)	64 (18%)	0	51 (47%)	10 (9%)	0	61 (55%)	13 (12%)	0
Hyperglycaemia	152 (44%)	29 (8%)	0	29 (27%)	4 (4%)	0	25 (23%)	7 (6%)	0
Hyponatraemia	121 (35%)	20 (6%)	0	20 (19%)	4 (4%)	0	29 (26%)	0	0
Hyperkalaemia	72 (21%)	8 (2%)	0	11 (10%)	1 (1%)	0	10 (9%)	0	0
General disorders and administration site conditions	260 (75%)	59 (17%)	1 (<1%)	50 (46%)	2 (2%)	0	78 (70%)	19 (17%)	0
Pyrexia	165 (48%)	24 (7%)	1 (<1%)	10 (9%)	0	0	50 (45%)	4 (4%)	0
Pain	120 (35%)	19 (5%)	0	14 (13%)	0	0	25 (23%)	5 (5%)	0
Fatigue	110 (32%)	12 (3%)	0	25 (23%)	1 (1%)	0	37 (33%)	9 (8%)	0
Peripheral oedema	106 (31%)	4 (1%)	0	19 (18%)	1 (1%)	0	21 (19%)	1 (1%)	0
Vascular disorders	153 (44%)	55 (16%)	0	26 (24%)	3 (3%)	0	41 (37%)	10 (9%)	0
Hypertension	94 (27%)	31 (9%)	0	17 (16%)	2 (2%)	0	28 (25%)	8 (7%)	0
Hypotension	48 (14%)	13 (4%)	0	7 (6%)	0	0	15 (14%)	1 (1%)	0
Skin and subcutaneous tissue disorders	176 (51%)	3 (1%)	0	43 (40%)	1 (1%)	0	58 (52%)	3 (3%)	0
Alopecia	144 (42%)	0	0	38 (35%)	0	0	49 (44%)	0	0
Nervous system disorders	172 (50%)	42 (12%)	1 (<1%)	33 (31%)	5 (5%)	0	26 (23%)	6 (5%)	0
Headache	100 (29%)	5 (1%)	0	14 (13%)	0	0	14 (13%)	0	0
Psychiatric disorders	121 (35%)	35 (10%)	0	24 (22%)	0	0	31 (28%)	6 (5%)	0
Confusion state	83 (24%)	26 (8%)	0	9 (8%)	0	0	17 (15%)	4 (4%)	0
Depression	45 (13%)	5 (1%)	0	13 (12%)	0	0	10 (9%)	3 (3%)	0
Neoplasm benign, malignant, and unspecified	1 (<1%)	0	0	4 (4%)	3 (3%)	2 (2%)	0	0	0
Acute myeloid leukaemia	0	0	0	2 (2%)	2 (2%)	2 (2%)	0	0	0
Respiratory, thoracic, and mediastinal disorders	127 (37%)	31 (9%)	3 (1%)	11 (10%)	1 (1%)	0	23 (21%)	6 (5%)	1 (1%)
Epistaxis	68 (20%)	6 (2%)	0	6 (6%)	0	0	10 (9%)	0	0
Dyspnoea	55 (16%)	5 (1%)	0	4 (4%)	0	0	8 (7%)	2 (2%)	0
Pulmonary embolism	1 (<1%)	1 (<1%)	0	0	0	0	1 (1%)	1 (1%)	1 (1%)
Musculoskeletal and connective tissue disorders	119 (34%)	19 (5%)	0	9 (8%)	1 (1%)	0	10 (9%)	1 (1%)	0
Bone pain	85 (25%)	9 (3%)	0	4 (4%)	1 (1%)	0	5 (5%)	0	0
Muscular weakness	25 (7%)	7 (2%)	0	5 (5%)	0	0	4 (4%)	1 (1%)	0
Renal and urinary disorders	49 (14%)	8 (2%)	0	3 (3%)	0	0	11 (10%)	4 (4%)	0
Cardiac disorders	35 (10%)	13 (4%)	1 (<1%)	2 (2%)	0	0	9 (8%)	3 (3%)	0
Injury, poisoning, and procedural complications	35 (10%)	5 (1%)	0	3 (3%)	1 (1%)	0	13 (12%)	1 (1%)	0
Infusion-related reaction	16 (5%)	0	0	1 (1%)	0	0	12 (11%)	0	0
Endocrine disorders	33 (10%)	1 (<1%)	0	3 (3%)	0	0	2 (2%)	1 (1%)	0
Immune system disorder	32 (9%)	1 (<1%)	0	1 (1%)	0	0	11 (10%)	0	0
Hypersensitivity	32 (9%)	1 (<1%)	0	1 (1%)	0	0	11 (10%)	0	0
Data are n (%). Adverse events are shown if their incidence was at least 10% (all grades) or in case of being at least severe (grade ≥3) if their incidence was at least 5%. Fatal events were listed irrespective of frequency. System organ class totals are shown if their sum incidence was at least 10% (all grades) or in case of being at least severe (grade ≥3) was at least 5%, but no single adverse event's incidence was at least 10% or 5%. R-DeVIC=rituximab plus dexamethasone, etoposide, ifosfamide, and carboplatin. HCT-ASCT=high-dose chemotherapy followed by autologous stem-cell transplantation.									
Table 3: Adverse events									

Implications of all the available evidence

Taken together with previous trials, our findings support thiotepa-based HCT-ASCT as the preferred consolidation for fit PCNSL patients who respond to intensive high-dose methotrexate-based induction, where transplantation expertise is available. Non-myeloablative multi-agent chemotherapy, such as R-DeVIC, could be a therapeutic option for patients who are not candidates for HCT-ASCT, but should be further evaluated within clinical trials.

At the same time, approximately one-third of patients in MATRix/IELSG43 did not reach randomisation due to induction toxicity or early progression, underscoring that optimisation of induction regimens is urgently needed. Ongoing phase 3 studies exploring modified high-dose methotrexate based induction treatment and trials integrating novel agents such as Bruton's tyrosine kinase inhibitors, immunomodulatory drugs, and chimeric antigen receptor T-cell therapy are likely to redefine treatment strategies, particularly for older or frailer patients. Until such data mature, international guidelines and clinical practice should consider MATRix followed by thiotepa-based HCT-ASCT as a standard first-line approach for eligible patients with newly diagnosed PCNSL.

Auf Deutsch heißt „community-acquired pneumonia in children“ **ambulant erworbene Pneumonie im Kindesalter** (oft abgekürzt als **pCAP**). Es ist eine Lungenentzündung, die ein Kind zu Hause oder im Alltag bekommt – und nicht erst im Krankenhaus. Die Behandlung richtet sich nach den offiziellen Empfehlungen der [AWMF Leitlinienregister](#) für Deutschland, Österreich und die Schweiz.

- **Viren:** Sie sind bei Babys und kleinen Kindern oft der Auslöser.
- **Bakterien:** Am häufigsten sind Pneumokokken (*Streptococcus pneumoniae*).
- **Atypische Erreger:** Zum Beispiel *Mycoplasma pneumoniae*, die oft bei größeren Kindern und Schulkindern auftreten.



(Better not „step down“)

Oral step-down, optimal drug, and total duration of antibiotic treatment in African children hospitalised with severe community-acquired pneumonia (PediCAP): a factorial randomised controlled trial

Summary

Background WHO recommends 5 days of intravenous antibiotics for children hospitalised with severe community-acquired pneumonia (CAP). We aimed to investigate the safety of a step-down to different oral antibiotics and the shortest effective duration.

Methods PediCAP was an open-label, parallel group, 2×5 factorial randomised controlled trial of children aged 2 months to 6 years hospitalised with severe CAP without complicating factors in 13 hospitals across five sub-Saharan African countries. Children weighing 3–30 kg and with point-of-care C-reactive protein of more than 10 mg/L were randomly assigned (5:5:1) to either a step-down from intravenous antibiotics to oral amoxicillin (250 mg) or amoxicillin–clavulanate (co-amoxiclav; 200 mg amoxicillin to 28.5 mg clavulanate) via dispersible tablets twice daily (superiority comparison) for five total (intravenous plus oral) durations (4–8 days; non-inferiority comparison), or a 5-day, fixed-duration, intravenous-only treatment (non-inferiority comparison). Children were stepped down when clinically improved and able to take oral antibiotics. Clinicians could change antibiotics if clinically indicated. The primary outcome was the proportion of readmission or death at day 28 (non-inferiority margin vs intravenous only: +10%). The study was registered with the ISRCTN registry (ISRCTN63115131) and is complete.

Findings Between Dec 7, 2020, and Aug 14, 2023, 2248 children were screened for eligibility and 1101 were randomly allocated (480 [43.6%] girls and 621 [56.4%] boys). The primary outcome was available in 1055 (95.8%) children. For children in the step-down groups, the mean total antibiotic exposure was 6.0 days (SD 3.5) in the 4-day group, 6.8 days (4.2) in the 5-day group, 7.4 (3.6) in the 6-day group, 8.3 days (3.4) in the 7-day group, and 9.2 days (2.9) in the 8-day group ($p<0.0001$), with 140 (68.6%) of 204, 151 (76.3%) of 198, 167 (85.2%) of 196, 179 (89.5%) of 200, and 186 (91.6%) of 203, respectively, stepping down within their randomised duration ($p<0.0001$). Primary outcomes occurred in 33 (6.9%) of 475 in the co-amoxiclav group, 27 (5.6%) of 484 in the amoxicillin group, and six (6.3%) of 96 in the intravenous-only group, with both oral step-down strategies non-inferior to the intravenous-only strategy (upper 95% CIs of 6.0 for co-amoxiclav and 5.7 for amoxicillin) and no evidence of superiority for co-amoxiclav over amoxicillin (adjusted risk difference 1.3% [95% CI –1.8 to 4.4]; $p=0.40$). Primary outcomes occurred in eight (4.1%) of 194 in the 4-day group, ten (5.3%) of 190 in the 5-day group, 16 (8.5%) of 188 in the 6-day group, 16 (8.3%) of 193 in the 7-day group, and ten (5.2%) of 194 in the 8-day group; all durations were non-inferior to the 8-day group (all upper 95% CIs $\leq 6.0\%$). There was no evidence of consistent differences in adverse events for oral antibiotic or duration comparisons. For antibiotic-related or serious adverse events, there was one (1.0%) in the intravenous-only group and 12 (2.5%) in the amoxicillin group (adjusted risk difference –2.3% [95% CI –4.2 to –0.3]; $p=0.025$), and 16 (3.4%) in the co-amoxiclav group (+0.8% [–1.2 to 2.8]; $p=0.42$); rates increased with randomised duration (slope estimate +0.9% [0.1 to 1.7]; $p=0.032$).

Interpretation For sub-Saharan African children hospitalised with severe CAP without complicating factors, a strategy of stepping down upon clinical improvement to oral amoxicillin after initial intravenous antibiotics, with a total treatment duration of 4–5 days, is non-inferior to WHO-recommended 5-day intravenous treatment.

Oral step-down

Clinical Judgment
Against Guidelines

	Overall (N=1101)	Amoxicillin (n=502)	Co-amoxiclav (n=499)	Intravenous only (n=100)	4 days (n=204)	5 days (n=198)	6 days (n=196)	7 days (n=200)	8 days (n=203)
Country									
Mozambique	204 (18.5%)	95 (18.9%)	90 (18.0%)	19 (19.0%)	37 (18.1%)	37 (18.7%)	36 (18.4%)	36 (18.0%)	39 (19.2%)
South Africa	280 (25.4%)	128 (25.5%)	127 (25.5%)	25 (25.0%)	53 (26.0%)	51 (25.8%)	50 (25.5%)	50 (25.0%)	51 (25.1%)
Uganda	287 (26.1%)	131 (26.1%)	131 (26.3%)	25 (25.0%)	53 (26.0%)	52 (26.3%)	51 (26.0%)	54 (27.0%)	52 (25.6%)
Zambia	183 (16.6%)	83 (16.5%)	83 (16.6%)	17 (17.0%)	34 (16.7%)	32 (16.2%)	32 (16.3%)	34 (17.0%)	34 (16.7%)
Zimbabwe	147 (13.4%)	65 (12.9%)	68 (13.6%)	14 (14.0%)	27 (13.2%)	26 (13.1%)	27 (13.8%)	26 (13.0%)	27 (13.3%)
Median age, months	13 (6–25)	13 (6–24)	13 (7–26)	14 (7–22)	14 (7–25)	13 (7–23)	13 (6–29)	13 (6–27)	13 (7–24)
Sex									
Female	480 (43.6%)	212 (42.2%)	217 (43.5%)	51 (51.0%)	90 (44.1%)	78 (39.4%)	82 (41.8%)	99 (49.5%)	80 (39.4%)
Male	621 (56.4%)	290 (57.8%)	282 (56.5%)	49 (49.0%)	114 (55.9%)	120 (60.6%)	114 (58.2%)	101 (50.5%)	123 (60.6%)
Weight band									
≥3 kg to <6 kg	162 (14.7%)	78 (15.5%)	73 (14.6%)	11 (11.0%)	17 (8.3%)	29 (14.6%)	37 (18.9%)	32 (16.0%)	36 (17.7%)
≥6 kg to <10 kg	535 (48.6%)	248 (49.4%)	240 (48.1%)	47 (47.0%)	115 (56.4%)	102 (51.5%)	81 (41.3%)	98 (49.0%)	92 (45.3%)
≥10 kg to <14 kg	274 (24.9%)	124 (24.7%)	119 (23.8%)	31 (31.0%)	48 (23.5%)	48 (24.2%)	48 (24.5%)	46 (23.0%)	53 (26.1%)
≥14 kg to <20 kg	115 (10.4%)	46 (9.2%)	60 (12.0%)	9 (9.0%)	21 (10.3%)	18 (9.1%)	27 (13.8%)	20 (10.0%)	20 (9.9%)
≥20 kg to <25 kg	15 (1.4%)	6 (1.2%)	7 (1.4%)	2 (2.0%)	3 (1.5%)	1 (0.5%)	3 (1.5%)	4 (2.0%)	2 (1.0%)
Weight-for-age Z score									
–3 or less	96 (8.7%)	47 (9.4%)	44 (8.8%)	5 (5.0%)	10 (4.9%)	21 (10.6%)	23 (11.7%)	16 (8.0%)	21 (10.3%)
–3 to –2 or less	139 (12.6%)	65 (12.9%)	61 (12.2%)	13 (13.0%)	30 (14.7%)	22 (11.1%)	20 (10.2%)	34 (17.0%)	20 (9.9%)
–2 to <2	831 (75.5%)	374 (74.5%)	383 (76.8%)	74 (74.0%)	162 (79.4%)	146 (73.7%)	150 (76.5%)	141 (70.5%)	158 (77.8%)
2 to <3	24 (2.2%)	12 (2.4%)	8 (1.6%)	4 (4.0%)	2 (1.0%)	7 (3.5%)	2 (1.0%)	7 (3.5%)	2 (1.0%)
≥3	11 (1.0%)	4 (0.8%)	3 (0.6%)	4 (4.0%)	0	2 (1.0%)	1 (0.5%)	2 (1.0%)	2 (1.0%)
Height-for-age Z score									
–3 or less	173 (15.7%)	87 (17.3%)	79 (15.8%)	7 (7.0%)	34 (16.7%)	32 (16.2%)	29 (14.8%)	33 (16.5%)	38 (18.7%)
–3 to –2 or less	152 (13.8%)	81 (16.1%)	57 (11.4%)	14 (14.0%)	25 (12.3%)	26 (13.1%)	26 (13.0%)	26 (13.0%)	33 (16.3%)
–2 to <2	713 (64.8%)	311 (62.0%)	333 (66.7%)	69 (69.0%)	139 (68.1%)	122 (61.6%)	131 (66.8%)	131 (65.5%)	121 (59.6%)
2 to <3	24 (2.2%)	8 (1.6%)	12 (2.4%)	4 (4.0%)	2 (1.0%)	6 (3.0%)	4 (2.0%)	5 (2.5%)	3 (1.5%)
≥3	37 (3.4%)	14 (2.8%)	17 (3.4%)	6 (6.0%)	3 (1.5%)	12 (6.1%)	4 (2.0%)	4 (2.0%)	8 (3.9%)
Unknown	2 (0.2%)	1 (0.2%)	1 (0.2%)	0	1 (0.5%)	0	0	1 (0.5%)	0
HIV status									
Infected	9 (0.8%)	7 (1.4%)	2 (0.4%)	0	1 (0.5%)	3 (1.5%)	3 (1.5%)	1 (0.5%)	1 (0.5%)
Exposed, uninfected	73 (6.6%)	29 (5.8%)	39 (7.8%)	5 (5.0%)	10 (4.9%)	20 (10.1%)	13 (6.6%)	12 (6.0%)	13 (6.4%)
Uninfected	586 (53.2%)	262 (52.2%)	267 (53.5%)	57 (57.0%)	107 (52.5%)	98 (49.5%)	99 (50.5%)	113 (56.5%)	112 (55.2%)
Mother negative, assumed uninfected	270 (24.5%)	122 (24.3%)	126 (25.3%)	22 (22.0%)	51 (25.0%)	45 (22.7%)	53 (27.0%)	50 (25.0%)	49 (24.1%)
Unknown	163 (14.8%)	82 (16.3%)	65 (13.0%)	16 (16.0%)	35 (17.2%)	32 (16.2%)	28 (14.3%)	24 (12.0%)	28 (13.8%)
Any pneumococcal conjugate vaccine dose									
Yes	1002 (91.0%)	450 (89.6%)	463 (92.8%)	89 (89.0%)	187 (91.7%)	178 (89.9%)	179 (91.3%)	189 (94.5%)	180 (88.7%)
No	61 (5.5%)	30 (6.0%)	24 (4.8%)	7 (7.0%)	15 (7.4%)	10 (5.1%)	6 (3.1%)	8 (4.0%)	15 (7.4%)
Not known	38 (3.5%)	22 (4.4%)	12 (2.4%)	4 (4.0%)	2 (1.0%)	10 (5.1%)	11 (5.6%)	3 (1.5%)	8 (3.9%)
CRP result									
10–40 mg/L	208 (18.9%)	101 (20.1%)	89 (17.8%)	18 (18.0%)	31 (15.2%)	34 (17.2%)	34 (17.3%)	54 (27.0%)	37 (18.2%)
40–80 mg/L	402 (36.5%)	179 (35.7%)	183 (36.7%)	40 (40.0%)	72 (35.3%)	67 (33.8%)	84 (42.9%)	63 (31.5%)	76 (37.4%)
>80 mg/L	491 (44.6%)	222 (44.2%)	227 (45.5%)	42 (42.0%)	101 (49.5%)	97 (49.0%)	78 (39.8%)	83 (41.5%)	90 (44.3%)

(Table 1 continues on next page)

	Overall (N=1101)	Amoxicillin (n=502)	Co-amoxiclav (n=499)	Intravenous only (n=100)	4 days (n=204)	5 days (n=198)	6 days (n=196)	7 days (n=200)	8 days (n=203)
(Continued from previous page)									
Mean heart rate, bpm	140 (19)	140 (19)	141 (18)	139 (21)	139 (20)	141 (18)	140 (19)	142 (17)	140 (20)
Mean respiratory rate, bpm	51 (12)	50 (12)	52 (12)	51 (12)	51 (12)	51 (12)	51 (13)	51 (12)	50 (12)
Mean oxygen saturation, SaO ₂	92 (7)	92 (8)	92 (7)	93 (7)	93 (6)	92 (8)	92 (8)	92 (8)	92 (8)
Oxygen saturation <90%	343 (31.2%)	156 (31.1%)	157 (31.5%)	30 (30.0%)	66 (32.4%)	62 (31.3%)	58 (29.6%)	67 (33.5%)	60 (29.6%)
Mean temperature, °C	37.0 (0.9)	37.0 (0.9)	37.0 (0.8)	37.0 (0.9)	37.0 (0.8)	37 (1)	37.0 (0.9)	37.0 (0.9)	37.0 (0.9)

Data are n (%), median (IQR), or mean (SD). Children assigned to oral step-down groups appear twice in the table: once in randomised drug columns (ie, amoxicillin or co-amoxiclav) and once in the randomised duration columns (ie, 4, 5, 6, 7, or 8 days). See the appendix for additional baseline characteristics (pp 23–28); these characteristics are across the 11 factorially randomised individual arms (pp 29–31), community-acquired pneumonia signs (p 16), and parent-reported symptoms (p 16). bpm=beats per min. bpm=breaths per min. CRP=C-reactive protein. SaO₂=transcutaneous oxygen saturation.

Table 1: Participant characteristics

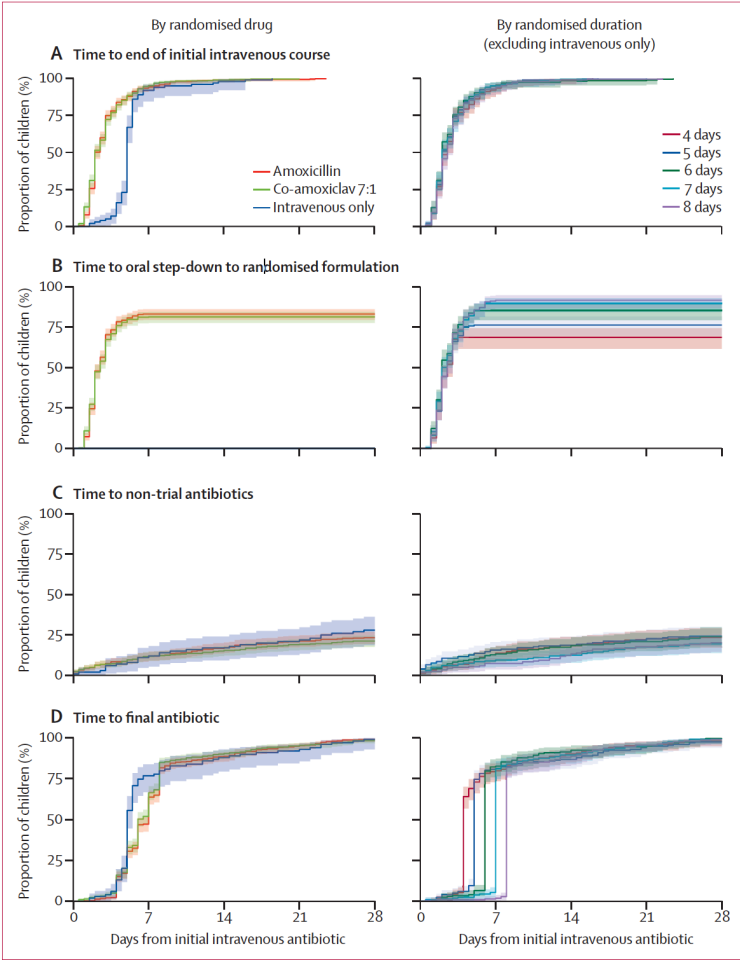


Figure 2: Antibiotic treatment over time by randomised drug and by randomised duration in the oral step-down groups only
The shaded areas represent 95% CIs. Times are measured from the initiation of intravenous treatment because treatment duration within randomised groups was based on the total duration of intravenous and oral antibiotics. Randomisation was within 24 h of initiation of intravenous antibiotics for all participants, with very similar durations across all groups (appendix pp 23–28). The time to oral step-down per oral antibiotic and per duration are available in the appendix (p 19).

	Amoxicillin	Co-amoxiclav	Intravenous only	Difference co-amoxiclav vs amoxicillin: average adjusted marginal effects (95% CI)	p value (co-amoxiclav vs amoxicillin)	Difference amoxicillin vs intravenous only: mean adjusted marginal effects (95% CI)	p value (amoxicillin vs intravenous only)
Readmission to hospital or death	27/484 (5.6%)	33/475 (6.9%)	6/96 (6.3%)	+1.3% (-1.8 to 4.4)	0.40	-2.3% (-10.2 to 5.7)	0.58
Death	11/484 (2.3%)	12/473 (2.5%)	2/96 (2.1%)	+0.3% (-1.6 to 2.1)	0.79	-2.4% (-10.3 to 5.5)	0.55
Length of stay during index hospitalisation, days	5.5 (4.1; n=502)	5.2 (3.6; n=499)	6.5 (3.0; n=100)	-0.3 (-0.7 to 0.2)	0.22	-0.9 (-1.8 to -0.0)	0.049
Total length of stay up to 28 days, days	5.7 (4.3; n=484)	5.4 (3.8; n=475)	6.9 (3.6; n=96)	-0.2 (-0.7 to 0.3)	0.36	-1.1 (-2.1 to -0.1)	0.025
Days of supplemental oxygen during index hospitalisation	2.4 (3.7; n=502)	2.1 (3.3; n=499)	2.2 (2.7; n=100)	-0.3 (-0.7 to 0.1)	0.14	+0.4 (-0.4 to 1.1)	0.34
Days on antibiotics up to 28 days	7.8 (4.0; n=484)	7.4 (3.4; n=473)	7.3 (5.2; n=96)	-0.5 (-0.9 to 0.0)	0.050	+2.2 (1.3 to 3.1)	<0.0001
Modification of randomised antibiotics for any reason other than early stopping, or requiring a subsequent course of antibiotics for any reason up to 28 days	117/485 (24.1%)	111/479 (23.2%)	30/97 (30.9%)	-0.9% (-6.2 to 4.5)	0.74	-10.2% (-22.3 to 2.0)	0.10
Modification of randomised antibiotics for inadequate response, or additional courses in the index hospitalisation for CAP relapse	22/485 (4.5%)	18/473 (3.8%)	6/96 (6.3%)	-0.7% (-3.2 to 1.8)	0.57	-4.5% (-12.7 to 3.7)	0.28
Grade 3 or 4 adverse events or serious adverse events	44/484 (9.1%; 59 events)	45/474 (9.5%; 56 events)	9/96 (9.4%; 12 events)	+0.3% (-3.3 to 3.9)	0.86	-1.0% (-8.7 to 6.8)	0.81
Antibiotic-related adverse events or serious adverse events	12/484 (2.5%; 14 events)	16/475 (3.4%; 21 events)	1/96 (1.0%; 1 events)	+0.8% (-1.2 to 2.8)	0.42	+2.3% (0.3 to 4.2)	0.025
Line complications	21/484 (4.3%)	26/475 (5.5%)	11/96 (11.5%)	+1.3% (-1.7 to 4.4)	0.39	-12.9% (-24.8 to -0.1)	0.048

Data are n/N (%), n/N (%; n events) for adverse events, or mean (SD; n). The n/N data for adverse events represent the number of children who had at least one adverse event per the total number of children with available data. Estimates of differences between drugs are outputs from models with fixed effects of drug, duration, and site. Estimates of linear effect of duration are outputs from models including only children in oral step-down arms with fixed effects of drug, duration, and site. See the appendix for other secondary outcomes including key solicited events and specific complications (pp 44–45), details of serious adverse events and reactions (p 51), and more analyses of mortality (pp 13, 21, 48–50). CAP=community-acquired pneumonia.

Table 2: Effect of randomised drug on primary and key secondary and safety outcomes

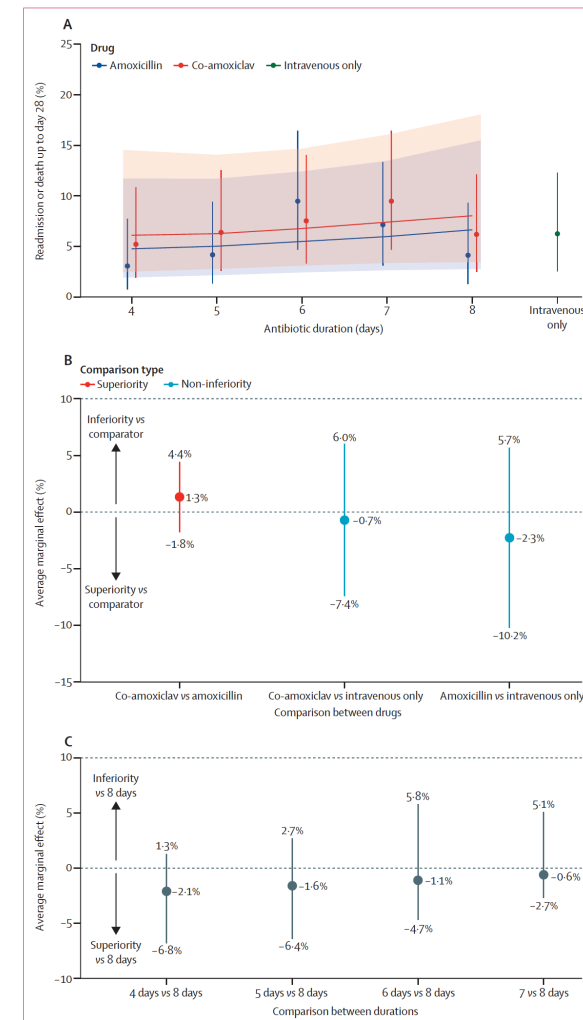


Figure 3: Readmission or death by day 28 (primary outcome)
(A) By antibiotic duration, showing fitted lines. Vertical lines show 95% CIs. Shaded areas show the 95% CIs for the fitted lines. Higher values correspond to worse outcomes. (B) By drug comparisons. Vertical lines show 95% CIs. The dotted horizontal line at 10% represents the non-inferiority margin. (C) By duration comparisons for oral step-down groups only. Vertical lines show 95% CIs. The dotted horizontal line at 10% represents the non-inferiority margin.

	4 days	5 days	6 days	7 days	8 days	Mean adjusted marginal linear effect per additional day (95% CI)	p value
Readmission to hospital or death	8/194 (4.1%)	10/190 (5.3%)	16/188 (8.5%)	16/193 (8.3%)	10/194 (5.2%)	+0.5% (−0.6 to 1.6)	0.34
Death	1/194 (0.5%)	3/190 (1.6%)	9/188 (4.8%)	8/193 (4.1%)	2/192 (1.0%)	+0.3% (−0.3 to 1.0)	0.33
Length of stay during index hospitalisation, days	5.0 (2.8; n=204)	5.6 (4.7; n=198)	5.2 (4.0; n=196)	5.4 (3.9; n=200)	5.4 (3.8; n=203)	+0.1 (−0.1 to 0.2)	0.42
Total length of stay up to 28 days, days	5.1 (3.0; n=194)	5.8 (4.7; n=190)	5.4 (4.1; n=188)	5.8 (4.4; n=193)	5.6 (4.0; n=194)	+0.1 (−0.1 to 0.3)	0.34
Days of supplemental oxygen during index hospitalisation	2.0 (2.3; n=204)	2.5 (4.3; n=198)	2.2 (2.9; n=196)	2.3 (3.6; n=200)	2.4 (4.0; n=203)	+0.1 (−0.1 to 0.2)	0.43
Days on antibiotics up to 28 days	6.0 (3.5; n=194)	6.8 (4.2; n=190)	7.4 (3.6; n=188)	8.3 (3.4; n=193)	9.2 (2.9; n=192)	+0.8 (0.6 to 0.9)	<0.0001
Modification of randomised antibiotics for any reason other than early stopping, or requiring a subsequent course of antibiotics for any reason up to 28 days	46/194 (23.7%)	47/192 (24.5%)	47/188 (25.0%)	46/194 (23.7%)	42/196 (21.4%)	−0.6% (−2.4 to 1.3)	0.54
Modification of randomised antibiotics for inadequate response, or additional courses in the index hospitalisation for CAP relapse	7/194 (3.6%)	7/190 (3.7%)	12/188 (6.4%)	9/194 (4.6%)	5/192 (2.6%)	−0.2% (−1.0 to 0.7)	0.71
Grade 3 or 4 adverse events or serious adverse events	12/194 (6.2%; n=15 events)	16/190 (8.4%; n=20 events)	20/188 (10.6%; n=28 events)	24/193 (12.4%; n=30 events)	17/193 (8.8%; n=22 events)	+1.0% (−0.3 to 2.2)	0.14
Antibiotic-related adverse events or serious adverse events	1/194 (0.5%; n=1 events)	5/190 (2.6%; n=6 events)	7/189 (3.7%; n=11 events)	6/193 (3.1%; n=6 events)	9/193 (4.7%; n=11 events)	+0.9% (0.1 to 1.7)	0.032
Line complications	10/194 (5.2%)	13/190 (6.8%)	8/189 (4.2%)	10/193 (5.2%)	6/193 (3.1%)	−0.6% (−1.6 to 0.4)	0.22

Data are n/N (%), n/N (%; n events) for adverse events, or mean (SD; n). The n/N data for adverse events represent the number of children who had at least one adverse event per the total number of children with available data. Estimates of differences between drugs are outputs from models with fixed effects of drug, duration, and site. Estimates of linear effect of duration are outputs from models including only children in oral step-down groups with fixed effects of drug, duration, and site. See the appendix for other secondary outcomes including key solicited events and specific complications (pp 46–47), details of serious adverse events and reactions (p 52), and more analyses of mortality (pp 13, 21, 48–50). CAP=community-acquired pneumonia.

Table 3: Effect of randomised duration on primary and key secondary and safety outcomes

Implications of all the available evidence

Taken together with existing evidence on antibiotic duration in mild and moderate pneumonia, PediCAP shows that shorter courses and an early switch to oral treatment are also safe and effective for children hospitalised with severe or very severe pneumonia, including in resource-constrained settings. Implementing an intravenous-to-oral step-down strategy with amoxicillin, for a total duration of 4–5 days, would allow earlier discharge, reduce the risk of hospital-acquired infections and antimicrobial resistance, and lessen the financial burden of hospitalisation on families. Furthermore, this strategy reduces unnecessary parenteral antibiotic exposure and supports reliance on amoxicillin as the preferred oral antibiotic given its availability, affordability, and alignment with WHO recommendations. These findings support a revision of WHO guidelines for severe childhood pneumonia and provide a pragmatic, scalable strategy for improving outcomes and reducing costs in low-income and middle-income countries where pneumonia remains a leading cause of child mortality.



[The Clinical Trial Is Open. The Elderly Need Not Apply.](#)
- The New York Times



Age Diversity In Clinical Trials: Why It Matters

**Older adults
major users of
medications**

Clinical evidence in
frail older adults

- Limited for effectiveness
- Increased risk of severe adverse drug effects

**Translatable pre-
clinical data
needed**

- Exposures: duration, polypharmacy, deprescribing
- Models: type, age, disease
- Outcomes: healthspan, frailty

**Application to
geriatric
pharmacotherapy**

- Informed decisions to proceed to clinical trials in older adults
- Bio-informatics using pre-clinical and clinical data to inform personalised medicine for geriatric patients



Advancing the relevance of clinical trials for older patients

Older patients represent the fastest growing patient group in clinical care. They are a heterogeneous group, for whom evidence for making treatment decisions is often scarce. Important domains for advancing the relevance of clinical trials for older patients are selection and inclusion of representative patients, choosing appropriate therapeutic interventions, and studying relevant outcomes. In the last decade, a myriad of publications has recommended multiple solutions that improve the relevance of trials for older people. Although uptake of these recommendations has been slow, there are now some excellent and successful implementation approaches that show that it is possible to design and execute trials that are inclusive of older patients, address relevant outcomes, and allow for real-world comparisons of intervention effectiveness. Observational studies based on different data sources add useful complementary information. This narrative review aims to synthesise best practices and successful strategies to improve the relevance of clinical trials for older patients.

Panel: Consequences of current trial design for clinical decision making and trial inclusion in a real patient

Case

Mrs A is aged 78 years, with newly diagnosed stage III breast cancer, and chemotherapy is considered. She lives with her husband; he has heart failure and she helps him with bathing and his medications. She values her independence, enjoys working in her garden, and spending time with her family. She is discussing treatment options and potential trial participation with her treating physician and would like to know more about the benefits and risks.

Findings from geriatric assessment

- Mild frailty (slowed gait, reduced stamina, but independent in daily activities)
- Mild forgetfulness affecting planning and organisation
- Social support: weekly visits from children and grandchildren; neighbour assists with transport as she does not have a driver's licence
- Comorbidities: type 2 diabetes, chronic kidney disease stage III

Dilemmas in decision making with currently available evidence

Patient characteristics

Evidence from selected trial populations regarding treatment benefit might not apply to real-world patient populations who did not fulfil eligibility criteria, making it difficult to adequately inform this patient.

Intervention

Mrs A is concerned that treatment side-effects will affect her ability to take care of her husband; it is unknown what the treatment tolerability is in older patients with comorbidities.

Outcomes

Mrs A prioritises maintaining her independence and cognitive function; evidence generated by conventional trial endpoints does not provide information about these outcomes.

Potential barriers to trial inclusion

Patient characteristics

Age, comorbidities (such as diabetes and chronic kidney disease), and mild cognitive impairment might lead to exclusion under strict trial criteria.

Intervention

Mrs A prefers the treatment arm that involves the least treatment burden and number of hospital visits, so she does not need to ask her neighbour for transportation or leave her husband alone at home, but randomisation means it is uncertain which treatment arm she will be placed in.

Outcomes

Competing risk makes outcomes harder to specify; collecting outcomes other than mortality (eg, functional decline or maintenance of independence) is more complicated

Data sources	Internal validity (risk of bias)		External validity (generalisability)		Examples
RCTs	High comparability between groups through randomisation		Explanatory: strict inclusion criteria, intervention control, and intensive monitoring	Pragmatic: inclusion criteria and intervention closer to usual-care conditions Hybrid (types 1–3): simultaneously test intervention effectiveness and implementation strategies	Pembrolizumab for early triple-negative breast cancer: KEYNOTE-522 (explanatory RCT); ⁹¹ invasive treatment strategy for older patients with myocardial infarction ⁵⁴
Claims databases	Few or some frailty, multimorbidity, or functional parameters		Near-exhaustivity of population coverage (county, region, or country)		Study on denosumab vs oral bisphosphonates among female patients who are dialysis dependent (used the Consolidated Renal Operations in a Web-Enabled Network database from Medicare and Medicaid Services) ⁹²
CDRs (eg, electronic health records)	Few or some frailty, multimorbidity, or functional parameters through medical notes		Monocentre	Multicentre	Study on nirmatrelvir or ritonavir vs molnupiravir in patients with COVID-19 who have comorbidities (used the Taipei Medical University Clinical Research Database; multicentre CDR) ⁹³
Epidemiological population registries (eg, cancer or stroke)	Scarce or no information on frailty, multimorbidity, or functional parameters		Near-exhaustivity of population coverage (county, region, or country)		Study on risk of stroke or systemic embolism and major bleeding associated with the use of oral anticoagulants in elderly patients with atrial fibrillation (used the Norwegian Patient Registry and the Norwegian Prescription Database) ⁹⁴
Clinical cohorts	Retrospective: scarce or no information on few frailty, multimorbidity, or functional parameters	Prospective: numerous frailty, multimorbidity, or functional parameters; residual confounding	Monocentre	Multicentre	Direct oral anticoagulants for atrial fibrillation in older adults and extremely older adults ⁹⁵ (prospective monocentre clinical cohort study); immune checkpoint inhibition and chemotherapy in older adults with non-small cell lung cancer ⁹⁶ (retrospective multicentre clinical cohort study)

Figure: Validity framework for research in older adults

Green represents a low risk of bias (internal validity) or high generalisability. Yellow represents some concerns with internal validity (mainly confounding bias) or generalisability. Red represents a high risk of bias (mainly confounding bias) or low generalisability. RCT=randomised controlled trial. CDR=clinical data repository.

Successful trial example		Strengths of study design
Patient inclusion, selection, and characterisation		
Exclusion of older patients based on age or strict inclusion criteria ¹⁴	IST-3 ³¹ showed that thrombolysis within 6 h improved overall survival in patients with ischaemic stroke	Wide inclusion criteria; included 53% of patients aged >80 years
Adopt broad inclusion criteria and critically assess the necessity of each potential exclusion criterion ^{2,23,35}	GAP70+ ³⁶ showed that a geriatric assessment with targeted management recommendations significantly reduced grade 3–5 chemotherapy toxicity within 3 months among patients >70 years with advanced cancer, compared with usual care	Patients required at inclusion to have at least one impaired geriatric domain, such as poor physical performance, comorbidities, malnutrition, or functional or cognitive deficits—effectively targeting older adults who are vulnerable or frail
Develop trials specifically for older, frail, or multimorbid patients by tailoring exclusion criteria ^{30,35}		
Exclusion from trial based on concerns or lack of clarity regarding cognitive ability to consent	MAP ³⁷ is an ongoing trial that investigates the effect of metformin to prevent cognitive decline in patients with mild cognitive impairment without diabetes	Tool for assessing capacity to consent
Implement procedures to deal with concerns and issues regarding cognition and consent during the inclusion phase ^{2,37}	In a trial with rivastigmine, it was shown that this drug led to moderate improvement in dementia associated with Parkinson's disease ³⁸	Allowed for consent by a family member when cognitive impairment affected capacity to consent
Consider consent by proxy when capacity to consent is lacking		
Failure to sufficiently recruit older patients, especially those living with frailty, resulting in an unrepresentative study population or not achieving target accrual or primary endpoint	TrACER ³⁹ is an ongoing pragmatic trial assessing the effectiveness of a guideline-based colony stimulating factor standing order intervention in patients receiving chemotherapy	External stakeholder advisory group with patients, payors, pharmacists, guideline experts, providers, and an ethicist, which informs and engages in trial design, dissemination, and implementation
Integrate active stakeholder (eg, health-care providers, patients, caregivers, and public) engagement and co-design ^{3,10,35}	SPRINT ^{32,33} showed that a systolic blood pressure 120 mm Hg compared with 140 mm Hg resulted in lower rates of fatal and non-fatal major cardiovascular events	Protocol for targeted enrolment of specific subgroups, including patients aged ≥75 years; met recruitment goals within 28 months; included a frailty index at baseline
Develop a protocol for targeted recruitment of older or frail patients ^{27,33}	MTOPS ³⁴ showed that finasteride treatment compared with placebo led to an increase in the percentage of patients who did not have progression of benign prostatic hyperplasia	Used several recruitment strategies including emails, newspapers, medical sources, and radio advertisements; also published the most effective recruitment strategies (newspaper and mail)
Use multiple channels of communication to recruit; target caregivers in addition to patients ²		
Little (time for) patient education to motivate them for trial participation and address concerns	Video-assisted education in informed consent procedures resulted in greater comprehension in patients who underwent percutaneous nephrolithotomy ³⁵	Used video-assisted education in providing informed consent for the procedure, and patients were randomly assigned to this procedure or written consent only
Integrate additional patient education strategies in the trial protocol	EnTraP ⁴⁰ showed that an education and support programme targeted at surgical trainee principal investigators was effective in increasing recruitment of a clinical trial	Patients randomly assigned to the educational programme or standard practice to show approach effectiveness in a large clinical trial
No physician education or limited motivation for including older patients in trials ⁴⁰	GO2 ³⁸ showed that upfront dose-reduced chemotherapy resulted in similar overall survival in older patients with advanced upper-gastrointestinal cancer	Patients stratified by frailty, those considered unfit for full-dose treatment were randomly assigned (60% chemotherapy vs best supportive care) in a separate randomisation arm
Allow training of research staff into the trial protocol and trial budget ^{1,35}		
Allow for stratification in subgroups based on physician-assessment or frailty, thereby adapting randomisation levels of treatment intensity to frailty ³⁰	PREVENTABLE ³⁹ is an ongoing trial investigating the effect of a preventive statin on survival free of new dementia or persistent disability in older community-dwelling adults ≥75 years	A pragmatic design with flexible inclusion and follow-up regimens
Trial-related procedures required from the patient or caregivers are too burdensome or too complex to understand ^{30,33}	IEMO 80-plus ⁴² showed that treatment with levothyroxine in patients ≥80 years with subclinical hypothyroidism did not improve hypothyroid symptoms or fatigue	Offered to perform all study related procedures at the place of residence of the participants
Use short, simple consent forms and limit trial-related burden as much as possible; offer alternatives to full clinic visits (such as telephone consultations) ^{3,10,29}		
Design pragmatic, flexible, and decentralised trials (eg, by integrating home visits) to decrease trial burden for the patient and their caregivers ^{2,10,32}		
Little or no available data to allow for comparison with real-life population	HYVET ⁴³ showed that antihypertensive treatment in older patients (>80 years) resulted in lower blood pressure and a reduction in stroke and cardiovascular events	Used core geriatric dataset at baseline to characterise the population
Use a core (geriatric) dataset to characterise the full trial population or embed this in a companion study specifically for older patients ^{2,10,32,33}	The GERONTE trial ³⁵ evaluates the benefit of a new care pathway for older patients with multimorbidity and cancer	Only standardises which geriatric domains are assessed and how frailty results are reported, while leaving the choice of assessment methods to the investigator
Allow for pragmatic execution of geriatric or frailty assessment to facilitate alignment with existing care		
Insufficient input of geriatricians in study design	FAST-MAG ³ showed that paramedic infusion initiation with magnesium in patients with acute stroke did not improve clinical outcome	Geriatricians were included in the research team and assisted in study procedures and interpretation; included 550 patients aged >80 years of whom 60 were aged >90 years
Integrate geriatricians in the study design and conduct		
(Table continues on next page)		

	Successful trial example	Strengths of study design	
(Continued from previous page)			
Intervention			
Treatment burden of the trial (or one of the trial arms) is too intense for older patients to tolerate ^{30,32,37}	Use adapted treatment intensity in the experimental arm, or in both arms (in a trial specific for older patients) ³⁰	MRC FOCUS ²⁸ was a 2 × 2 factorial trial comparing 5-fluorouracil vs capecitabine chemotherapy, with or without oxaliplatin; the trial showed that a combination with oxaliplatin was preferable, although the primary endpoint was not met	Targeted frail patients and used adapted chemotherapy regimens with reduced doses of all regimens in all arms, which made the trial feasible for frail patients who could not tolerate full-dose treatment
Have an adapted intervention with a run-in (ie, test) period in a small number of patients to assess safety before enrolling a larger cohort of patients	TRADE-hypo ³⁸ investigated safety and efficacy of durvalumab with either hypothoracic or conventionally fractionated thoracic radiotherapy	Had a run-in period to assess safety; after inclusion of 38 older patients, two major adverse events occurred in the intervention arm, after which a recruitment stop in this arm was performed (per-protocol); inclusion in the control arm continues	Patients were randomly assigned to standard treatment or a lower starting dose with stepwise increase in dose
Gradual dose up-titration of potentially toxic drugs to avoid excessive toxicity at the start	DESIREE ³⁹ showed that stepwise dose escalation of everolimus resulted in a reduced incidence of stomatitis in patients with metastatic hormone receptor-positive breast cancer		Patients were randomly assigned to standard treatment or a lower starting dose with stepwise increase in dose
Design a parallel trial for patients unfit for the primary trial	FOXTR0T2 and FOXTR0T3 ^{44,45} are ongoing trials in patients with locally advanced colon cancer testing different neoadjuvant regimens		Patients who are unfit for the most intensive neoadjuvant treatment (in FOXTR0T3) can be enrolled in FOXTR0T2, which uses a milder regimen
Include an observational arm for patients unfit to be randomly assigned ^{28,38}	DOSAGE ⁴⁴ is an ongoing trial investigating dose-reduced chemotherapy in older patients with metastasised colorectal cancer		Includes patients who do not want to be randomly assigned (or are deemed unfit for random assignment by their clinician) in an observational study arm
Optimise treatment, support, and management of comorbidities and geriatric impairments to increase trial feasibility	PERFORM-TAVR ⁴⁴ is an ongoing trial in patients who will undergo transcatheter aortic valve replacement; the trial will investigate a programme including nutritional and exercise interventions		Examines the synergistic effects of exercise and protein supplementation to counteract frailty and improve patient-centred outcomes following transcatheter aortic valve replacement
Outcome			
Relevant outcomes for older patients are not included or not reported ⁴⁶			
Choose endpoints that are meaningful to older people, such as functional autonomy, cognition, depression, and nutrition ⁴⁶	DANTON ⁴⁷ showed that discontinuing antihypertensive treatment in nursing-home residents with dementia resulted in a non-significant increase in serious adverse events		Used the Neuropsychiatric Inventory Nursing Home Scale and quality of life as co-primary endpoints
Use patient-reported outcomes, such as health-related quality of life, patient's symptoms, or satisfaction as primary endpoints	TRUST ⁴⁸ showed that treatment with levothyroxine did not result in clinical benefit in older patients with subclinical hypothyroidism		Used two primary endpoints that were relevant for patients in this context (change in hypothyroid symptoms score and tiredness score)
Assess benefit of interventions by combining patient-reported outcomes with other endpoints to form co-primary or composite endpoints	ASPRE ⁴⁹ assessed the effect of aspirin on disability-free survival		Used a primary composite endpoint of death, dementia, or persistent physical disability
Analyse composite endpoints with generalised pairwise comparisons, allowing for simultaneous assessment of multiple endpoints and prioritisation	SHAPERS ⁵⁰ is an ongoing trial investigating whether neoadjuvant short-course radiotherapy is a better trade-off between safety and efficacy than total neoadjuvant therapy in patients with locally advanced rectal cancer		Uses a multicomponent measure of treatment effect based on generalised pairwise comparisons as a primary endpoint; this measure includes overall survival at 3 years, progression-free survival, neuropathy, and grade ≥3 toxicity
Use hierarchical endpoints (ie, first confirm non-inferiority of lower intensity treatment, and if confirmed evaluate patient-reported outcomes to establish the best treatment approach)	EMPULSE ⁵¹ showed that empagliflozin in patients hospitalised with heart failure improved clinical benefit		Used the hierarchical endpoint clinical benefit, defined as death from any cause, number of heart failure events, and time to first heart failure event, or a 5-point or greater difference in change from baseline in the Kansas City Cardiomyopathy Questionnaire Total Symptom Score at 90 days
Competing risks are insufficiently considered in the trial design			
Incorporate competing risk in the trial design and report appropriate statistical analyses ⁵²	MOSCA-FRAIL ⁵³ showed that an invasive treatment strategy did not improve clinical outcomes in older, frail patients with non-ST-segment elevation acute myocardial infarction		Used a competing risk event analysis for cardiac death with non-cardiac death as a competing event as a co-primary composite endpoint
No age-specific analyses or consideration for heterogeneity in the study cohort			
Routinely plan and execute analyses for subgroups based on age, functioning, and comorbidity	SENIOR-RITA ⁵⁴ showed that an invasive treatment with revascularisation in older patients with non-ST-segment elevation acute myocardial infarction did not improve clinical outcome		The trial included prespecified subgroup analyses including different levels of physical frailty, comorbidity, and cognitive impairment
Insufficient number of older people available for subgroup analyses			
Perform pooled analyses or meta-analyses of different trials in a similar population	A pooled analysis of five adjuvant chemotherapy trials in older patients with breast cancer showed that taxane-based adjuvant chemotherapy was superior to alternative regimens, although with higher toxicity ⁴⁸		Pooled patient-level data from older patients who were enrolled in five previous phase 3 trials

Table: Barriers and strategies to improve clinical trial relevance for older adults

Conclusions

The older population continues to expand rapidly, forming a very large, diverse population with little trial evidence due to persistent obstacles to participation. Priorities for elevating trial applicability include recruiting a representative sample of older patients, selecting age-adapted interventions, and prioritising meaningful endpoints. Some all-age trials now better characterise the included population or include stratified interventions enabling real-world transposition. In older-age specific trials, there are now some excellent successful examples of trials that address relevant outcomes and interventions and are relevant to all older patients, including those with frailty. These trials can be complemented by alternative data sources and designs, such as various forms of observational studies based on different data sources including claims data and CDRs, which have their own advantages and limitations. However, although observational studies can complement the findings of randomised trials they should not be seen as an alternative to RCTs.

Regulatory agencies recognise the limited generalisability of registrational trials to older populations and have developed guidance for investigators in academia and industry. Both the European Medicines Agency and the FDA have requested sponsors to consider older people explicitly in trial design, provide data from subgroup analyses in older patients, remove restrictive eligibility criteria, and integrate geriatric-relevant endpoints.^{108,109} For most agencies, the guidance is non-binding, which limits uptake. Much information on older people can also be retrieved from registrational trials on new drugs that are increasingly coordinated by the pharmaceutical industry. Age subanalyses can provide important information for drug efficacy as well as toxicity according to age and frailty status but are not systematically performed or are suboptimally performed. It is important that registrational trial data are shared with academic researchers,¹¹⁰ allowing more accurate identification of the population who benefits or does not benefit from new treatments, since this benefit can be different for older versus younger people.

Artificial intelligence is up to the challenge of reducing human suffering, experts say. Are we?





Global advances in health artificial intelligence: a workforce imperative

[The global health workforce is approaching a breaking point, driven by administrative overload, inefficient workflows, burnout, and accelerating retirements, with a projected global shortfall of 11 million health professionals by 2030. This urgency coincides with the rapid emergence of clinical artificial intelligence (AI) tools, especially generative systems now embedded in documentation, triage, and workflow support. Therefore, AI should be framed less as a substitute for clinicians than as a retention strategy that preserves careers, expertise, and the human core of care. High-impact uses include ambient documentation, coding support, scheduling and demand prediction, claims and billing support, and inbox triage—tools that can reduce clerical burden and return time to caring, teaching, and leadership. Workforce shortages also create an ethical and geopolitical dilemma; reliance on international recruitment can deepen global inequities, whereas responsible AI deployment might ease competition for scarce talent and expand capacity in lower-resource settings. Yet, AI will not fix dysfunctional systems by default; poorly designed implementation can shift burdens, erode confidence, and widen gaps in health-care quality, access, and clinician wellbeing. Practice must remain clinician-led, patient-centred, and grounded in shared decision making. The policy priority is expertise amplification, not workforce replacement.

AI applications:

Documentation, Triage, Work-flow, Coding, Scheduling, Billing

Ambient note transcription

Ambient AI scribes are being rapidly adopted; early-adopter health systems report improved clinician experience and reductions in self-reported burnout relative to pre-deployment baseline. In a 6-week pilot survey, Mass General Brigham (Boston, MA, USA) reported a 40% relative reduction in self-reported burnout (n=223) and less time outside work completing notes (from ≥ 90 min to < 30 min; n=124).⁴

Coding and billing

Translating clinical notes into billing codes is a time-consuming, error-prone task.⁵ AI systems now outperform manual entry in speed and consistency. In one study, natural language processing applied to more than 120 000 free-text chief complaints from a statewide health information exchange extracted clinical concepts and assigned 88% of them to the correct ICD-10-Clinical Modification category. However, only 42% of concepts were assigned the exact code, illustrating both the promise and the current limits of automated coding in front-line care.⁶ Another system analysed entire clinical notes to assign disease-specific ICD codes, achieving an area under the receiver operating characteristic curve of 0.91–0.92 across two electronic health record systems.⁷ Such tools could ease documentation burdens and reduce clerical strain on clinicians.

Insurance claim filing and adjudication

Risk adjustment models are employed to prevent adverse selection (the disproportionate enrolment of individuals at high-risk of insurance claims into a single plan), anticipate budgetary reserve needs, and offer care management services to individuals at high risk of costly outcomes (eg, hospitalisation, complications, and prolonged stays in care). An AI model trained on 1 million US patients reduced misestimation of cost by US\$3.5 million per 10 000 insured people in one study compared with linear regression.⁸

Hospital occupancy and staffing prediction

AI helps match staff to real-world demand. Models that consider prescription and procedure data identify what clinicians actually do in practice, as their specialty designation can be ambiguous, giving planners a clearer picture of workforce supply. For example, a family physician may focus on women's health rather than broad spectrum general medicine.⁹ At the same time, AI models support reliable next-day bed and staffing calls.¹⁰ The outcome is fewer last-minute changes, less overtime, and a workforce that feels planned for, rather than perpetually reactive.

Smart cost risk prediction

Health systems aim to identify patients at risk for costly outcomes (prolonged stays, readmissions, etc) and intervene early. One study found that deep learning-derived predictions of patient outcomes far outperformed traditional risk scores.¹³ AI models can even predict diagnosis-related group codes (and associated costs) early during hospital stays with high accuracy.¹⁴

Effectively deploying these tools means more time for clinicians to care, teach, and lead. What is happening without these tools is more sobering—clinicians burning out so severely they abandon the profession altogether. In 2024, hospitals in the USA reported nurse turnover of 16%, and 42% of hospitals operated with nurse vacancy rates above 10%, citing unsustainable workloads.¹⁵ In the 2022 national nursing workforce survey, a majority of nurses said they would not recommend the profession to younger generations.¹⁶ If this trend continues, we face a future in which no number of medical or nursing school slots will compensate for what we have lost: not just labour, but vocation.

AI as a geopolitical and ethical workforce strategy

We face an ethical emergency—if health-care systems in high-income countries rely on importing foreign clinicians to fill staffing gaps, they deepen global inequality. WHO has already named 55 countries vulnerable to outbound health worker migration.¹⁷ These nations, which often have fragile health systems, cannot afford to lose talent.

Here, AI is more than a technical tool; it becomes a geopolitical strategy. A US hospital using AI to double radiology throughput might be able to avoid hiring an overseas radiologist. A National Health Service chatbot resolving patient queries at scale in the UK can potentially spare the need to recruit a nurse from Ghana. In this framing, AI is not just about efficiency. It is about avoiding futile competition for scarce human capital.

Conclusions and outlook

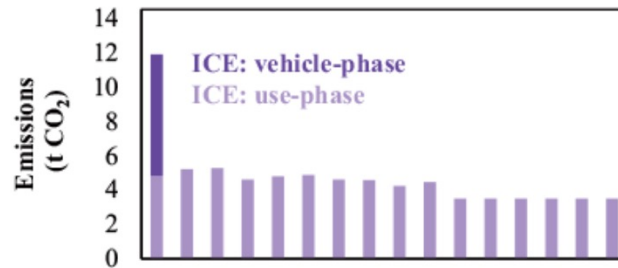
Health AI is no longer a futuristic promise; it is a strategic imperative. But the most powerful argument for health AI is not cost savings or diagnostic speed; it is workforce survival. The coming decade demands that we stop asking whether AI can replace clinicians and start asking how it can help us keep them. In that reframed question lies the path to global equity, sustainable systems, and care that endures. To do anything less is to accept a future where care is rationed not by policy but by the limits of human exhaustion.



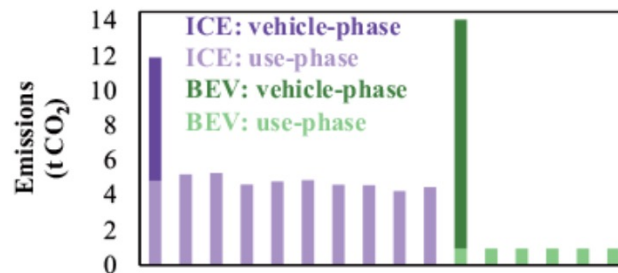
The climate benefits of retiring a fully operational internal combustion engine vehicle

Internal combustion engine (ICE) vehicles represent the single largest source of carbon dioxide emissions for most US households. Although battery electric vehicles (BEVs) considerably reduce use-phase emissions, the transition poses a fundamental life cycle optimization challenge: **Is there a net climate benefit to retiring a functional ICE vehicle before its end of life?** Retiring a functioning ICE vehicle incurs a **fundamental trade-off between BEV manufacturing emissions and decreased vehicle operation emissions**. In this study, We evaluated this trade off across a comprehensive range of retirement scenarios and found that scrappage-and-replacement yields **consistent emissions reductions across most contexts, including the retirement of new ICE vehicles**. **Although scrapping a functional asset remains economically prohibitive under current market conditions**, these results demonstrate a major mitigation potential for policy interventions, such as enhanced scrappage subsidies, to address the emissions of an increasingly durable ICE fleet.

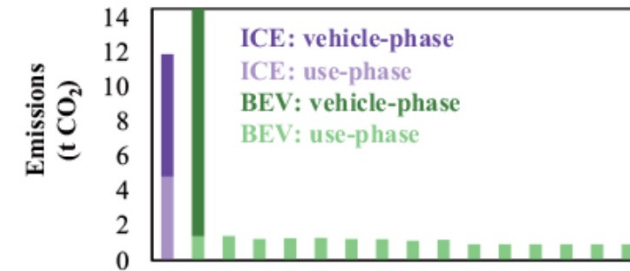
A Scenario 1: Continuous ICE Vehicle



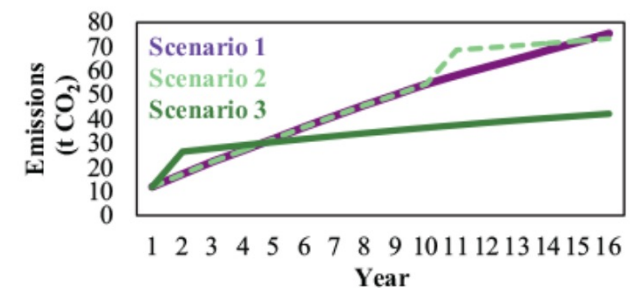
B Scenario 2: Retire ICE Vehicle Year 11



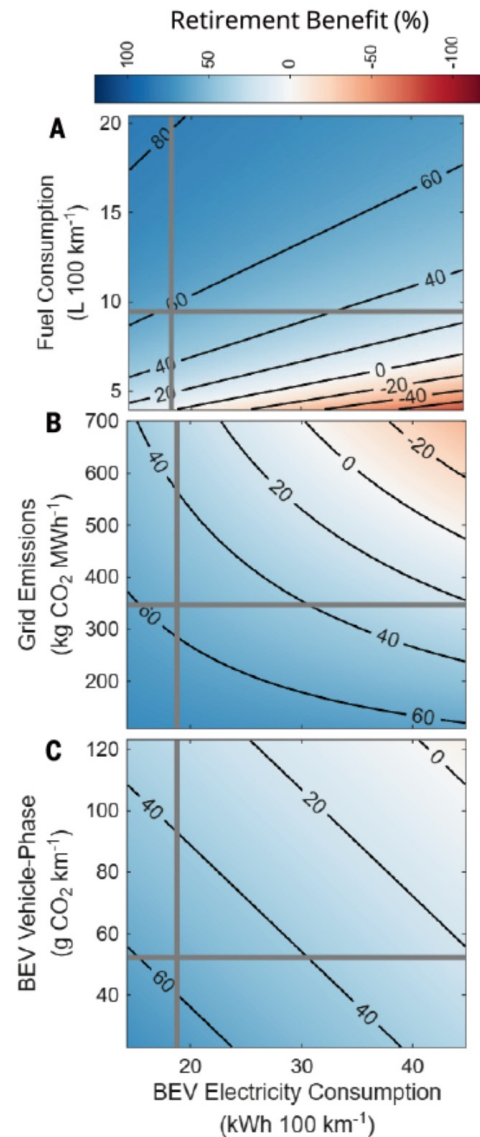
C Scenario 3: Retire ICE Vehicle Year 2



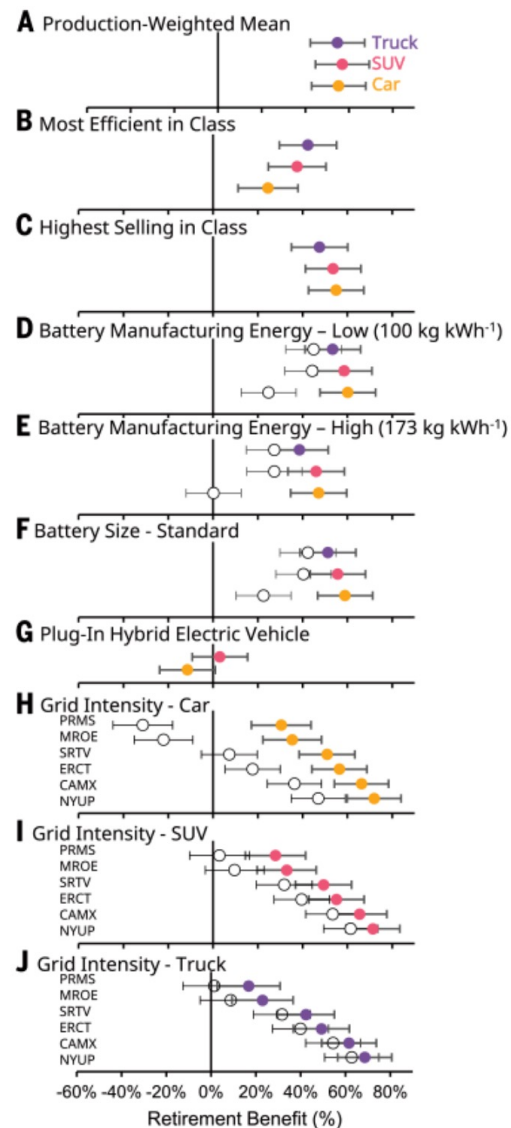
D Cumulative Emissions



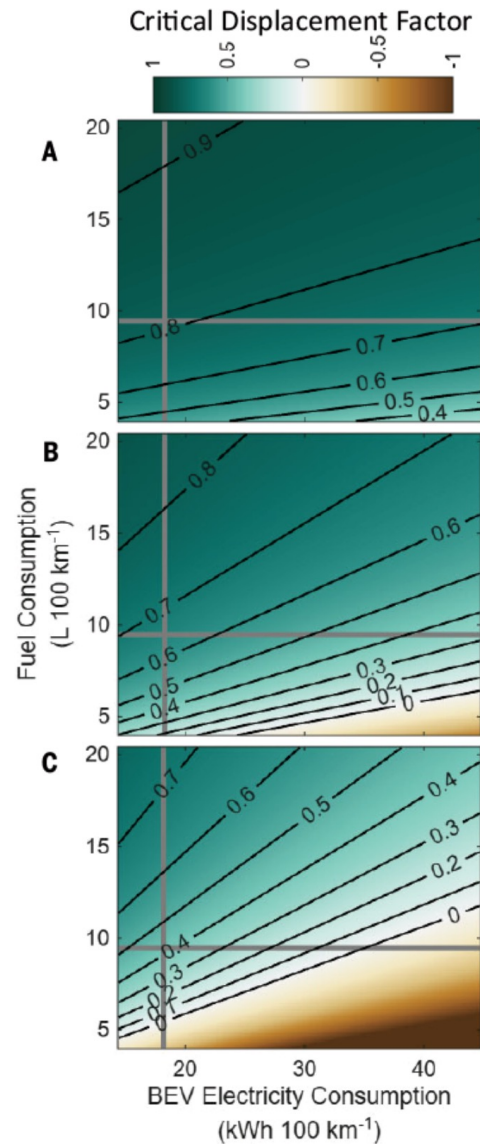
Life cycle emission comparisons between baseline (continued ICE vehicle operation) and retirement scenarios. Emissions include use phase (tailpipe and fuel cycle for ICE vehicle; electricity generation for BEV) and vehicle phase (manufacturing and mining). **(A)** Scenario 1: The ICE vehicle is operated for its full design life. **(B)** Scenario 2: The ICE vehicle is scrapped at year 11 and replaced with a BEV. **(C)** Scenario 3: The ICE vehicle is scrapped at year 2 and replaced with a BEV. **(D)** Cumulative use and vehicle-phase emissions. The ICE vehicle production emissions are sunk costs because they are common to both the baseline and retirement pathways. Values reflect a sales-weighted average SUV, US average grid mix, and time-varying annual mileage. Comprehensive sensitivity analyses for all parameters are provided in the subsequent figures.



Cumulative emission benefit of retirement relative to a comprehensive range of vehicle efficiency, grid carbon intensity, and manufacturing emissions. The benefit represents the difference between cumulative emissions in continuous petroleum-fueled scenarios (inclusive of ICE vehicles and HEVs) and retirement scenarios occurring at year 1 (normalized by use-phase emissions). Emissions include the operational phase (tailpipe and refining and upstream for petroleum-fueled vehicles; power plant and upstream for BEVs) and the BEV production phase (manufacturing and material acquisition). Parameter ranges incorporate the full spectrum of efficiencies **(A)** reported by the US EPA, specifically using high-efficiency hybrid electric vehicle (HEV) benchmarks for the minimum consumption bound, as well as the range of grid emissions **(B)** and BEV production emissions associated with varying battery sizes and manufacturing intensities **(C)**. The retirement benefit is independent of ICE vehicle and HEV manufacturing, which is mathematically a sunk cost. Gray lines indicate US sales-weighted mean parameter values.



Sensitivity of the retirement benefit (B) to discrete parameter settings. The cumulative emissions benefit over the vehicle lifetime when retirement occurs at year 1, incorporating all production-and use-phase impacts (truck, purple; SUV, pink; car, yellow). **(A to C)** Efficiency variants: Sensitivity is evaluated for production-weighted class averages (A), class-leading efficient vehicles (B), and the highest-selling vehicles (C). The latter highlights the climate impact of current consumer behavior, in which a small number of high-volume models dominate the market share. **(D to G)** Vehicle and technology variants: Sensitivities for low (D) and high (E) battery production intensities, baseline battery capacity (F), and the retirement of plug-in hybrid electric vehicles [PHEVs; (G)]. **(H to J)** Infrastructure variants: Impact of regional grid intensities across the range of US subgrids (see supplementary materials for more details). All results are invariant to production emissions of the petroleum-fueled vehicles, which function as mathematically sunk costs that cancel out in all comparative calculations. Where applicable [(D) to (J)], open markers indicate the retirement of class-leading HEVs, while closed markers represent retirement cases for the highest-selling ICE vehicles. Error bars represent 95% confidence intervals derived from the propagation of error.



Critical displacement thresholds for transportation modal shift.

If the ICE vehicle is resold rather than retired, a decrease in used-vehicle prices may induce a modal shift from low-emission transit to personal vehicle use. **The critical displacement factor D** represents the threshold at which induced emissions from this modal shift completely offset the net BEV adoption benefit. (A to C) Grid intensity scenarios: Variability in the displacement threshold is explored across three grid intensities—110 (A), 347 (B), and 699 g CO₂ eq kWh⁻¹ (C)—as a function of BEV efficiency (x axis) and ICE vehicle/HEV efficiency (y axis). These scenarios assume a shift from zero-emissions modes (e.g., active transport); sensitivity to higher intensity modes (e.g., mass transit) is provided in the supplementary materials. In regions where the BEV life cycle intensity exceeds that of the ICE vehicle, the critical displacement factor is negative (brown shading), representing an undefined with respect to the modal shift effect. Gray lines denote production-weighted averages for the current US fleet.

Discussion

In this study, we found that retirement of a functional ICE vehicle for a BEV, even when the ICE vehicle is brand new, provides large carbon mitigation benefits across a wide range of scenarios. Given these results and the outsized impact of transportation emissions on the US carbon budget, policy-makers could achieve substantial GHG mitigation through investments in vehicle scrap-and-replace programs. Optimization of such policies would require design to account for both vehicle efficiency and regional electric grid emissions. Moreover, the consistent GHG advantage of BEVs demonstrated here suggests that further innovation should not only prioritize BEV sustainability but also overcoming operational challenges, such as charger network reliability and equitable access.

Current scrap-and-replace rebates are insufficient to make the retirement of newer ICE vehicles financially desirable. Nevertheless, we examined the full range of scrappage scenarios (including new ICE vehicles) to demonstrate the theoretical upper-boundary conditions for emissions benefits when an ICE vehicle is scrapped with a BEV replacement. Newer vehicle scrappage is economically prohibitive with existing scrap-and-replace subsidies, necessitating the use of these limited resources for only the least-efficient ICE vehicles in the fleet. However, as climate impacts accelerate and the ICE vehicle fleet becomes more durable, a major shift in policy to support vehicle retirement may become necessary. The results presented here demonstrate that such a policy shift would result in emissions reductions across most contexts.

After years of unexplained fainting, a 'tilt table test' pinpointed the cause



43 year-old woman

As a child, Janet Mercel was prone to fainting. She remembers passing out in her Upstate New York home, at school and at the grocery store.

But her parents weren't too worried, she said, because she was an otherwise healthy child. The only medical intervention she recalls is a doctor suggesting iron supplements for anemia.

Then, in her 20s, living in New York and working in the fashion and design industry, Mercel began collapsing more frequently: on the subway at Union Square; on a mall escalator into the arms of two teenage boys; in a movie theater. She'd wake up surrounded by concerned onlookers or leaning on someone's shoulder.

Mercel's episodes generally occurred when she was tired, dehydrated, stressed or sick. During a bout of mononucleosis, Mercel drove from a friend's house to her parent's in Red Hook and fainted behind the wheel, hitting a tree. The car was totaled, but Mercel was not hurt.

She grew to recognize the warning signs. Her head and face would get hot, and then she might break into a cold sweat. Her hands and fingers tingled. Her vision would begin to cloud while her ears rang. Sometimes, all the color would drain from her face. If she got out into the air and walked around, she said, she could sometimes stop an episode from escalating. Often, though, there was nothing she could do.

Panic attacks? Epilepsy? Years pass ...

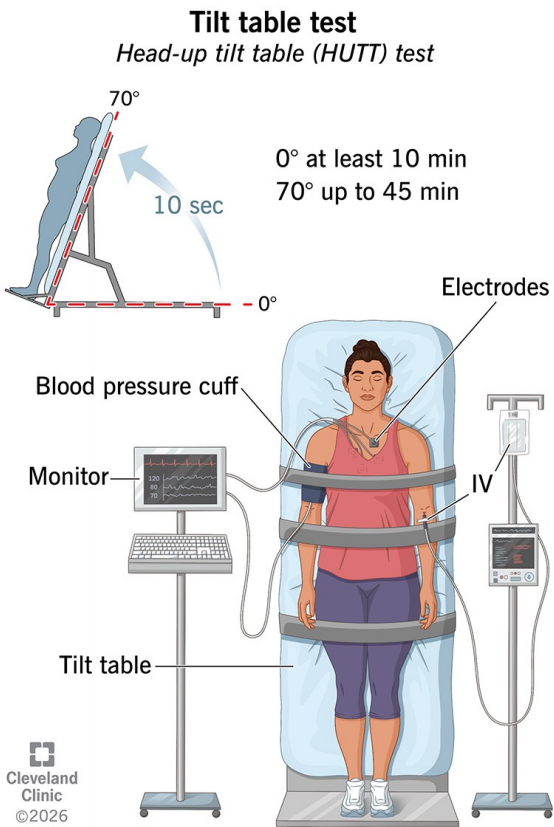
One confounding factor was that many of Mercel's symptoms looked as though she was having a panic attack. Sometimes, she said, it was difficult to determine whether panic led to her fainting or whether the physical symptoms before fainting triggered panic. Doctors diagnosed her with an anxiety disorder and over the years prescribed Klonopin, Valium, Lorazepam and several other medications. Early on, a doctor said she was "an overstimulated, high-strung 20-year-old girl," she recalled: "The feedback was, I needed to calm down."

For epilepsy, she was prescribed Levetiracetam, commonly known as Keppra. She remembers being at a work meeting, sitting on a sofa, drooling and barely able to function. She decided to stop that medication: "I said, 'No, I can't do this. Even if I do have epilepsy, I can't be on this drug.'" After researching the condition, she suspected the diagnosis might be wrong.

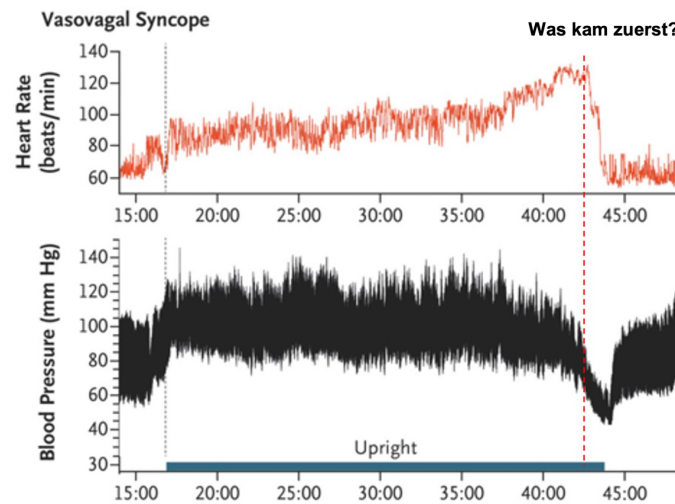
In June 2014, Mercel was scheduled for three days of testing at a New York University Langone Health location. Doctors tried to induce an epileptic reaction, she said, but nothing worked. She remembers the hospital as particularly crowded, and she shared a room with a combative patient. This, Mercel said, led to a panic attack and fainting.

The battery of tests included Mercel wearing a Holter monitor, a device that records the heart's rhythm over time. When her heart rate and blood pressure dropped precipitously, Mercel said, a cardiologist was called in for a consultation. But she said routine testing by NYU Langone Health cardiologist Stuart Dickerman showed her pulse and other vital signs to be in the normal range.

Later that summer, Dickerman and other physicians conducted what's known as a "tilt table test," which can help pinpoint the cause of fainting and other symptoms. During the test, Marcel felt dizzy and faint when placed upright at 70 degrees, records show, and then she lost consciousness. While she was being brought back down to a supine position, things got worse. "A pause of 21 seconds was noted in her heart rhythm followed by two beats (measuring 30 bpm) followed by an additional pause of five seconds," records show. "Chest compressions were performed for about 8 seconds. Her heart rate afterwards was 50 bpm. ... It was about 2 minutes before the patient was able to open her eyes and verbally respond to her name being called."

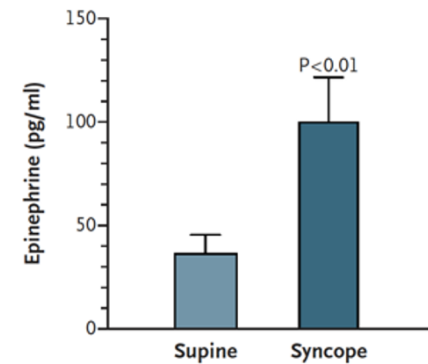
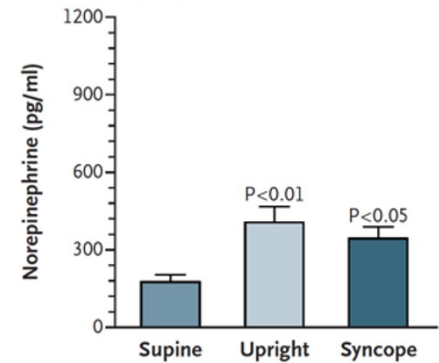


Not the Washington Post patient



Heart rate slowly increases over 20 min.
Then it suddenly crashes to 40 bpm. BP
is stable at 129/80, then crashes to
60/40. BP fall comes first.

Vasovagal Syncope

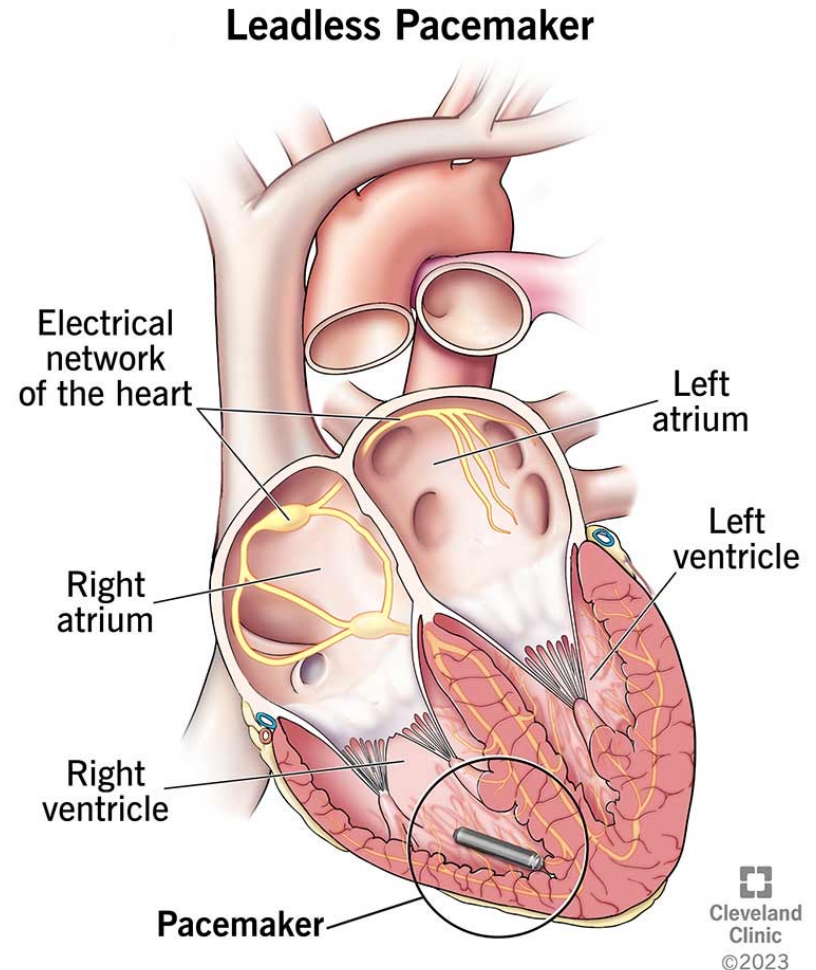


Hormonal
responses
are normal

The most common reason that people faint is “vasovagal episodes, also known as neurocardiogenic syncope,” Chinitz said. “There’s a specific reflex, the Bezold-Jarisch reflex, that causes a lowering of heart rate and blood pressure. It’s very common.” This reflex can cause lightheadedness in some people and fainting in others. Mercel had “a malignant form of neurocardiogenic syncope,” Chinitz said, “... a severe version of a common condition that caused repeated loss of consciousness.”

Mercel was given the option to enter a clinical trial for what was then a device not yet approved by the Food and Drug Administration: a cashew-size, “leadless” pacemaker.

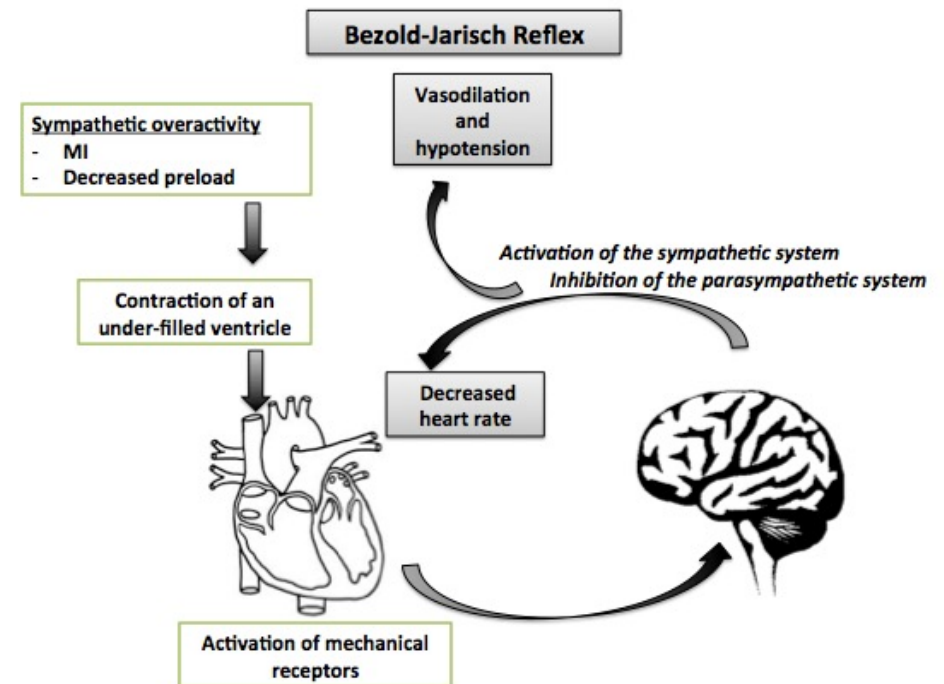
Unlike a traditional pacemaker, which requires an incision in the chest and wires that run from a battery under the skin into the heart, Chinitz said the leadless pacemaker is a small capsule-like device that’s inserted through a vein in the groin and placed directly into the heart. Because the procedure is less invasive, he said, the complication rate is lower compared with that of traditional pacemakers. This device, later approved by the FDA in 2016, produces electrical impulses that prevent the heart rate from dropping below a set point, thereby treating irregular or stalled heart beats.



Bezold-Jarisch-Reflex ist ein kardiovaskulärer Schutz- und Schonreflex des Herzens. Er führt zu einer klassischen Trias aus **Bradykardie** (verlangsamter Herzschlag), **Hypotonie** (blutdruckabfall) und **Vasodilatation** (weitere Gefäße), um den Sauerstoffbedarf des Herzmuskels in Notlagen zu senken.

Der Reflexbogen im Detail

- **Sensoren:** Chemo- und Mechanorezeptoren (sogenannte C-Faser-Endigungen) vor allem in der inferoposterioren Wand des linken Ventrikels.
- **Afferenter Schenkel:** Unmyelinisierte Vagusnerv-Fasern (C-Fasern) leiten das Signal zum Hirnstamm (zum *Nucleus tractus solitarius* in der Medulla oblongata).
- **Zentrale Verarbeitung:** Im Gehirn wird die sympathische Aktivität drastisch gedrosselt und der Parasympathikus (Vagustonus) stark hochgefahren.
- **Efferenter Schenkel:**
 - Verstärkte Vagus-Aktivität am Herzen → Abfall der Herzfrequenz (Bradykardie).
 - Hemmung des Sympathikus in der Peripherie → Erschlaffung der Blutgefäße (Vasodilatation) und Blutdruckabfall (Hypotonie)



Also, unlike a traditional dual-chamber pacemaker, which senses and paces both the heart's atrium and ventricle, the device Mercel has “only paces the ventricle,” Chinitz said. “It detects when her heart pauses, kicks in immediately and then turns off when her natural rhythm returns. It's very specific in function, but for some patients, that's all they need.”

Mercel said her decision was simple: By this time, she had lost weight and felt so sick that she was willing to try pretty much anything. Chinitz implanted the new pacemaker in a procedure that took less than an hour, he said.

However, “it was not a bumpless recovery,” Mercel said. She fainted the night of the procedure when a nurse got her out of bed; her sutures popped, and she was bleeding. She also developed deep vein thrombosis at the procedure site a few months later.

Still, she eventually stabilized, fainting far less frequently than before having the pacemaker — but not never. Two years after the device was implanted, Mercel set out for South and Central America to train for a marathon. She contracted Zika in Nicaragua and fainted while training. On the second of two flights home, she fainted on the plane, and she recalls a passenger, possibly a doctor, saying, “She has no pulse.”

Upon her return, her cardiologist suggested she not push the marathon running quite so hard — while the pacemaker kicks in to stabilize her heart rate, it doesn't prevent her blood pressure from dropping.

A balancing act

At that point, Mercel was considering having children, but her cardiologist said that the stress of childbirth was too risky. Several years later, she got a second opinion from a female OB/GYN, who believed Mercel's heart could withstand a vaginal delivery. Mercel gave birth to a daughter in 2022. [✦ Dive deeper](#)

Mercel has offered testimonials and spoken at two summits hosted by Medtronic, the manufacturer of her pacemaker. She has not been paid by the company, she said, except to cover travel costs.

These days, Mercel, a writer and executive editor of Avenue Magazine, doesn't run as much, instead varying her activities with yoga and biking.

“I was an adrenaline junkie for a long time,” the 43-year-old said. “That has subsided. ... I'm much better at managing myself before I tip over.”

Physiological Phenomenology of Neurally-Mediated Syncope with Management Implications

Background

Due to lack of efficacy in recent trials, current guidelines for the treatment of neurally-mediated (vasovagal) syncope do not promote cardiac pacemaker implantation. However, the finding of asystole during head-up tilt –induced (pre)syncope may lead to excessive cardioinhibitory syncope diagnosis and treatment with cardiac pacemakers as blood pressure is often discontinuously measured. Furthermore, physicians may be more inclined to implant cardiac pacemakers in older patients. We hypothesized that true cardioinhibitory syncope in which the decrease in heart rate precedes the fall in blood pressure is a very rare finding which might explain the lack of efficacy of pacemakers in neurally-mediated syncope.

Conclusions

Hypotension precedes bradycardia onset during head-up tilt-induced (pre)syncope in the vast majority of patients, even in those classified as cardioinhibitory syncope according to the modified VASIS classification. Furthermore, cardioinhibitory syncope becomes less frequent with increasing age.

Schroeder et al. PLoS one 2011

