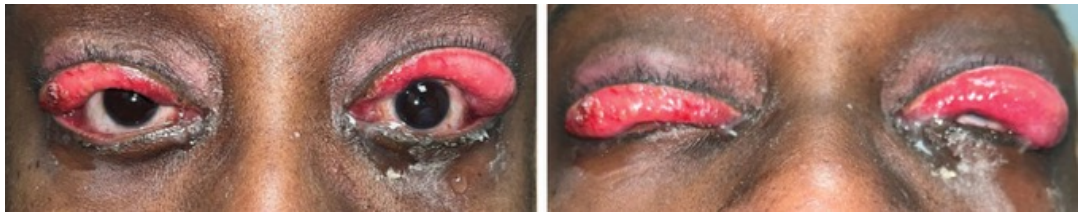
https://www.mdc-berlin.de/de/veroeffentlichungstypen/clinical-journal-club

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



Examination showed upper-eyelid eversion with conjunctival hyperemia and incomplete eyelid apposition on attempted closure of both eyes. Manual retraction of the upper eyelids while the patient was looking down showed marked laxity with complete eyelid eversion. A diagnosis of floppy eyelid syndrome was made. This syndrome is characterized by excessive laxity of the upper eyelids and results in eyelid malposition and chronic irritation of the ocular surface. It is associated with obstructive sleep apnea. The patient was referred for polysomnographic testing, which showed moderate obstructive sleep apnea. The patient was started on nocturnal continuous positive airway pressure, ophthalmic lubricants, and eye patches while sleeping. The eyelid changes subsequently improved.

39-year-old woman with obesity presented to an ophthalmology clinic with a 6-week history of a foreign-body sensation and tearing in both eyes. Symptoms were worse upon awakening. She also reported daytime fatigue, snoring, and difficulty sleeping at night. Ophthalmologic examination and findings with attempted closure of both eyes are shown. What is the most appropriate next step?

Blepharoplasty

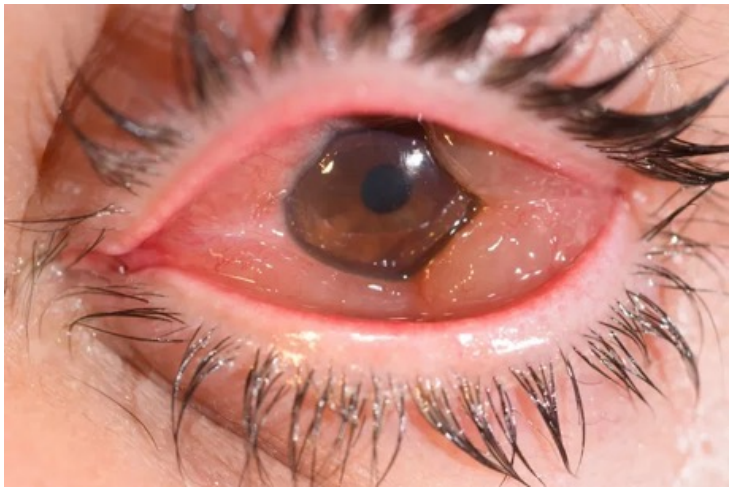
Computed tomography of the chest to look for a superior sulcus tumor

Ice pack test

● Referral for a sleep study

Topical antimicrobials

Chemosis (Bindehautödem) ist eine glasige, wulstartige Schwellung der Augenbindehaut, die durch Flüssigkeitsansammlung (Exsudat) bei Entzündungen oder Allergien entsteht. Die Bindehaut hebt sich dabei von der Lederhaut ab und kann aus der Lidspalte hervortreten. Symptome sind Juckreiz, Fremdkörpergefühl oder Schmerzen, oft ausgelöst durch Heuschnupfen, Infektionen oder Kontaktlinsenunverträglichkeit. Die Behandlung erfolgt ursachengerecht mit antiallergischen/entzündungshemmenden Tropfen oder kalten Kompressen.



Possible causes

The main causes of conjunctival chemosis are:

- Allergy to substances such as pollen, dust, animal dander, foods, or medications;
- Viral or bacterial conjunctivitis;
- Eye surgery, such as blepharoplasty;
- Angioedema;
- Hyperthyroidism.

Other causes of chemosis include autoimmune diseases, eye injuries, exposure to chemicals, or simply rubbing the eyes.

Das **Floppy-Eyelid-Syndrom (FES „Schlappaugenlid“)** ist eine häufig unterdiagnostizierte Erkrankung der Augenlider, die durch eine extreme Schlaffheit und Dehnbarkeit der Oberlider gekennzeichnet ist. Das Lidgewebe verliert seine Elastizität (oft durch Elastinabbau), wodurch es sich nachts im Schlaf leicht nach außen umstülpen kann, wenn es Kontakt mit dem Kopfkissen hat.

Symptome und Warnzeichen

- **Morgendliche Beschwerden:** Rötung, Reizung und schleimiger Ausfluss sind meist nach dem Aufwachen am stärksten.
- **Méténier-Zeichen:** Das Oberlid lässt sich bereits bei leichtem Zug mühelos nach oben oder zur Seite umschlagen.
- **Fremdkörpergefühl:** Ein ständiges Kratzen oder Brennen, als befände sich Sand im Auge.
- **Asymmetrie:** Die Symptome treten oft stärker an dem Auge auf, auf dessen Seite der Patient bevorzugt schläft.

Ursachen und Risikofaktoren

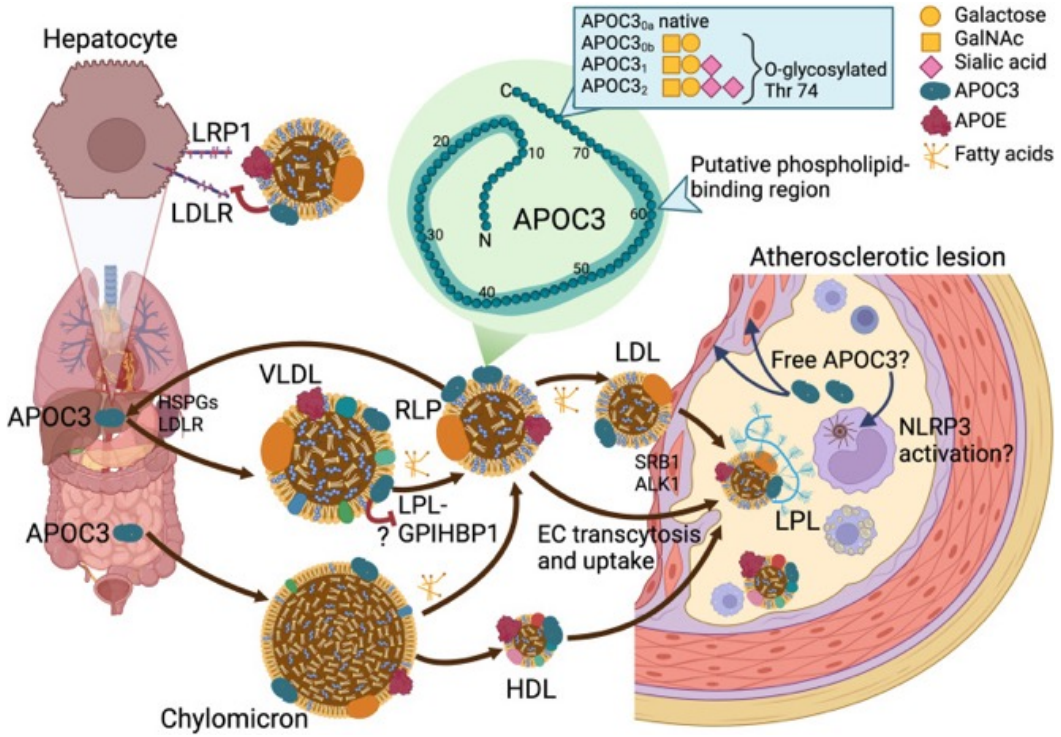
Die genaue Ursache ist unklar, jedoch spielen mechanischer Stress (z. B. Augenreiben) und Veränderungen der Bindegewebsfasern eine Rolle. Betroffen sind überproportional häufig:

- **Männer mittleren Alters** mit Übergewicht.
- Personen mit **Obstruktiver Schlafapnoe (OSA):** Nahezu 100 % der FES-Patienten leiden auch an Schlafapnoe.
- Patienten mit **Keratokonus** (einer kegelförmigen Verformung der Hornhaut).

Das Gen **APOC3** (Apolipoprotein C-III) ist ein entscheidender Regulator des Fettstoffwechsels im menschlichen Körper. Es befindet sich auf Chromosom 11 und kodiert für ein kleines Protein (ApoC-III), das vor allem in der **Leber** und im **Darm** hergestellt wird.

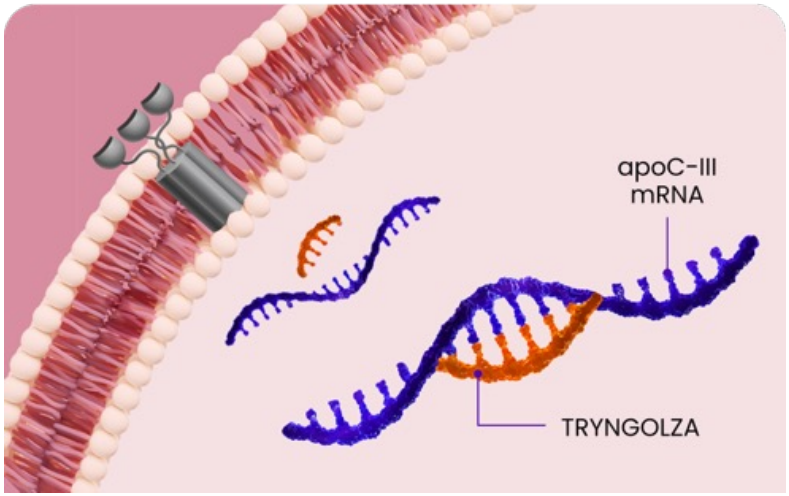
Funktion und gesundheitliche Bedeutung
ApoC-III zirkuliert im Blut auf Fettpartikeln wie VLDL und Chylomikronen. Seine Hauptaufgaben sind:

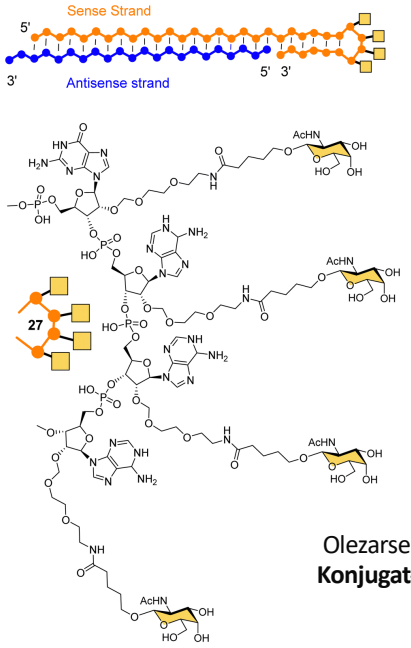
- **Hemmung des Fettabbaus:** Es blockiert das Enzym Lipoproteinlipase (LPL), welches Triglyceride (Blutfette) abbaut und vielleicht GPIHBP1.
- **Verzögerung der Ausscheidung:** Es verhindert, dass die Leber verbleibende Fettpartikel (Remnants) effizient aus dem Blut aufnimmt.
- **Förderung von Entzündungen:** Hohe Werte können Entzündungsprozesse in den Gefäßwänden fördern, was die Entstehung von **Arteriosklerose** (Gefäßverkalkung) begünstigt



GPIHBP1 (Glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1) ist ein wichtiges Protein in Kapillarendothelzellen, das die Lipoproteinlipase (LPL) aus dem Subendothelraum in das Kapillarlumen transportiert und dort stabilisiert. Es fungiert als essenzielle Plattform für den Abbau triglyceridreicher Lipoproteine. Defekte in diesem Protein führen zu schwerer Hypertriglyzeridämie.

Olezarsen ist ein Antisense-Oligonukleotid, das gegen Apolipoprotein C-3 gerichtet ist. Es bindet an die mRNA, die für dieses Protein kodiert und verursacht so deren Abbau. Dadurch sinken die Proteinlevel, was wiederum den Abbau von Triglyceriden erhöht.



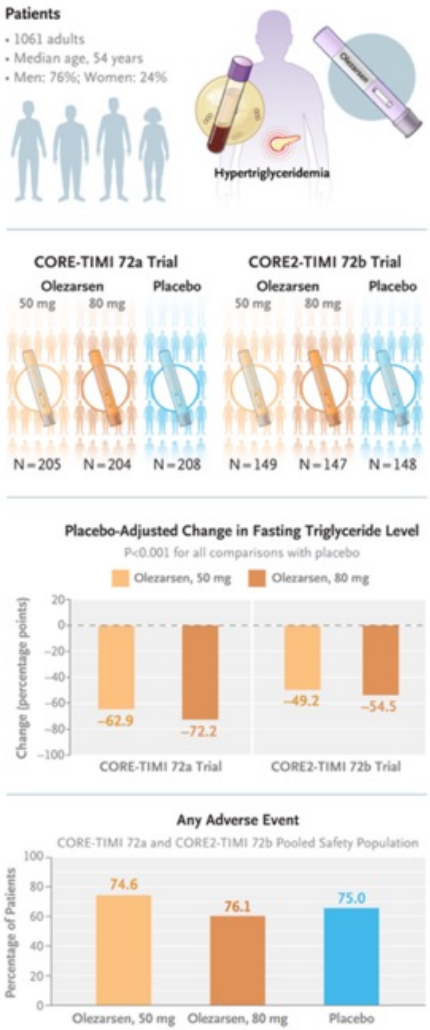


Olezarsen nutzt ein **Liganden-Konjugat-System**.

Olezarsen enters liver cells (hepatocytes) through a targeted, receptor-mediated process. After subcutaneous injection, the drug's **GalNAc3 (triantennary N-acetylgalactosamine) ligand** binds with high affinity to **asialoglycoprotein receptors (ASGPR)** on the surface of hepatocytes. This binding triggers receptor-mediated endocytosis, allowing the drug to enter the cell.

Olezarsen for Managing Severe Hypertriglyceridemia and Pancreatitis Risk

Patients with severe hypertriglyceridemia have an increased risk of acute pancreatitis. The efficacy and safety of olezarsen, an antisense oligonucleotide targeting apolipoprotein C-III messenger RNA, have not been established in this population. We conducted two double-blind, randomized, placebo-controlled trials (CORE-TIMI 72a and CORE2-TIMI 72b). Patients with severe hypertriglyceridemia were assigned in a 1:1:1 ratio to receive olezarsen at a dose of 50 mg, olezarsen at a dose of 80 mg, or placebo monthly for 12 months. The primary outcome was the percent change in the triglyceride level at 6 months, reported as the difference between each olezarsen dose group and the placebo group (placebo-adjusted change). Secondary lipid outcomes included the percent change in the triglyceride level at 12 months and in apolipoprotein C-III, remnant cholesterol, and non–high-density lipoprotein (non-HDL) cholesterol at 6 months and 12 months. Acute pancreatitis events were assessed across both trials.



Severe hypertriglyceridemia, defined as a serum triglyceride level of 500 mg per deciliter or higher (≥5.65 mmol per liter), affects approximately 1 in 100 persons and can have clinical consequences, including an increased risk of life-threatening acute pancreatitis. Conventional triglyceride-lowering therapies, such as fibrates and n–3 fatty acids, often have modest effects on the triglyceride level and have not been shown to reduce the risk of acute pancreatitis.

Olezarsen targets apolipoprotein C-III messenger RNA, leading to a reduction in the plasma apolipoprotein C-III level and thereby facilitating triglyceride clearance through derepression of lipoprotein lipase and increased hepatic uptake of triglyceride-rich lipoprotein remnants. The CORE-TIMI 72a and CORE2-TIMI 72b trials were designed to evaluate the efficacy and safety of olezarsen in patients with severe hypertriglyceridemia.

The first and subsequent drafts of the manuscript were written by the first author, and all the authors agreed with the decision to submit the manuscript for publication. The authors vouch for the completeness and accuracy of the data and for the fidelity of each trial to the protocol.

Trial Population

Patients were eligible for the trials if they were at least 18 years of age and had severe hypertriglyceridemia, defined as a fasting triglyceride level of at least 500 mg per deciliter obtained on two occasions while they were receiving stable lipid-lowering therapy according to the local standard of care. Patients were excluded if they had genetically confirmed familial chylomicronemia syndrome, acute pancreatitis at the time of screening or in the 4 weeks before screening, poorly controlled diabetes mellitus (glycated hemoglobin level, ≥9.5%), or an estimated glomerular filtration rate of less than 30 ml per minute per 1.73 m^2.

Outcomes

The primary outcome was the percent change from baseline in the fasting triglyceride level at 6 months, reported for each trial individually as the difference between each olezarsen dose group and the placebo group (placebo-adjusted change).

Characteristics

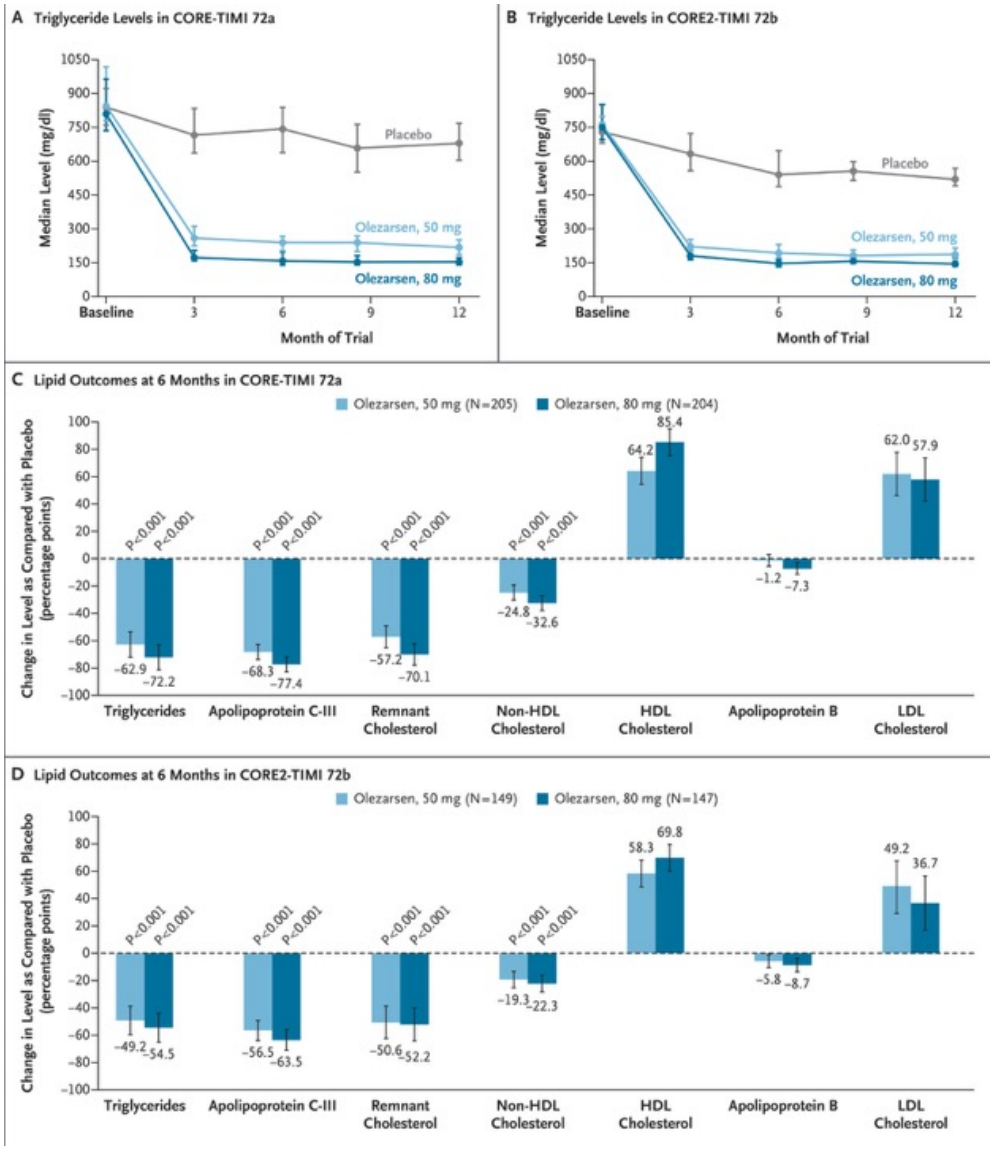
Characteristic	CORE-TIMI 72a			CORE2-TIMI 72b		
	Placebo (N=208)	Olezarsen, 50 mg (N=205)	Olezarsen, 80 mg (N=204)	Placebo (N=148)	Olezarsen, 50 mg (N=149)	Olezarsen, 80 mg (N=147)
Median age (IQR) — yr	54 (45–62)	54 (45–61)	54 (45–61)	54 (44–62)	55 (48–62)	55 (48–62)
Female sex — no. (%)	42 (20.2)	52 (25.4)	53 (26.0)	27 (18.2)	39 (26.2)	37 (25.2)
Race — no. (%)†						
White	195 (93.8)	191 (93.2)	189 (92.6)	124 (83.8)	125 (83.9)	114 (77.6)
Black	7 (3.4)	2 (1.0)	4 (2.0)	1 (0.7)	3 (2.0)	5 (3.4)
Asian	5 (2.4)	3 (1.5)	4 (2.0)	17 (11.5)	15 (10.1)	13 (8.8)
Hispanic or Latino — no./total no. (%)†	10/202 (5.0)	7/195 (3.6)	12/200 (6.0)	31/148 (20.9)	33/149 (22.1)	35/147 (23.8)
Median BMI (IQR)‡	30.9 (28.2–34.6)	31.2 (28.4–35.2)	31.2 (28.1–34.7)	32.2 (28.3–36.1)	30.9 (27.9–34.8)	30.7 (27.7–33.5)
Atherosclerotic cardiovascular disease — no. (%)	54 (26.0)	37 (18.0)	50 (24.5)	45 (30.4)	41 (27.5)	45 (30.6)
Diabetes mellitus — no. (%)	113 (54.3)	128 (62.4)	127 (62.3)	102 (68.9)	102 (68.5)	101 (68.7)
Chronic kidney disease — no. (%)	10 (4.8)	11 (5.4)	18 (8.8)	13 (8.8)	25 (16.8)	12 (8.2)
History of pancreatitis — no. (%)	48 (23.1)	51 (24.9)	43 (21.1)	21 (14.2)	17 (11.4)	20 (13.6)
Median triglyceride level (IQR) — mg/dl	838.2 (606.2–1233.0)	845.5 (630.0–1427.0)	810.0 (579.8–1396.0)	729.8 (577.0–1097.2)	762.0 (600.5–1114.5)	750.5 (572.0–1145.5)
Triglyceride level ≥880 mg/dl — no. (%)	95 (45.7)	101 (49.3)	96 (47.1)	57 (38.5)	49 (32.9)	57 (38.8)
Median apolipoprotein C-III level (IQR) — mg/dl	34.1 (26.1–43.0)	34.6 (28.4–50.9)	33.8 (25.5–45.3)	34.8 (27.1–44.0)	34.9 (28.0–44.1)	34.1 (26.0–43.9)
Median remnant cholesterol level (IQR) — mg/dl§	130.4 (92.7–187.5)	137.6 (97.3–197.3)	130.4 (82.2–180.1)	109.6 (76.8–165.8)	127.9 (87.0–164.0)	125.0 (79.5–199.2)
Median non-HDL cholesterol level (IQR) — mg/dl	199.2 (161.0–242.0)	197.5 (160.5–252.0)	203.2 (160.8–258.4)	181.0 (147.0–217.0)	197.5 (159.0–240.0)	186.0 (149.5–241.0)
Median apolipoprotein B level (IQR) — mg/dl	101.6 (87.1–121.8)	105.0 (88.2–125.0)	101.8 (81.0–122.2)	103.5 (81.7–118.8)	109.2 (93.9–129.5)	101.5 (85.8–120.3)
Median LDL cholesterol level (IQR) — mg/dl	58.5 (41.0–80.5)	59.0 (41.8–83.3)	57.5 (37.2–84.8)	57.8 (39.2–81.5)	66.6 (44.8–90.0)	60.0 (40.5–81.0)
Median glycated hemoglobin level (IQR) — %	6.3 (5.5–7.5)	6.5 (5.6–7.5)	6.1 (5.5–7.6)	6.8 (5.8–7.8)	6.6 (5.8–7.8)	6.6 (5.7–7.9)
Median creatinine level (IQR) — mg/dl	0.9 (0.8–1.1)	0.9 (0.8–1.1)	0.9 (0.8–1.0)	0.9 (0.8–1.1)	0.9 (0.8–1.1)	0.9 (0.7–1.0)
Median platelet count (IQR) — cells/μl	226,167 (191,167–265,833)	233,000 (192,000–282,500)	228,000 (190,125–264,367)	238,500 (201,000–273,292)	236,333 (201,000–279,667)	236,667 (182,667–272,667)
Median INR (IQR)	1.0 (1.0–1.1)	1.0 (1.0–1.1)	1.0 (1.0–1.1)	1.0 (1.0–1.1)	1.0 (1.0–1.1)	1.0 (1.0–1.1)
Lipid-lowering therapy — no. (%)	203 (97.6)	200 (97.6)	203 (99.5)	147 (99.3)	149 (100.0)	146 (99.3)
Statin	147 (70.7)	144 (70.2)	153 (75.0)	114 (77.0)	111 (74.5)	115 (78.2)
Ezetimibe	53 (25.5)	46 (22.4)	43 (21.1)	31 (20.9)	29 (19.5)	37 (25.2)
Fibrate	146 (70.2)	133 (64.9)	130 (63.7)	90 (60.8)	87 (58.4)	88 (59.9)
n–3 Fatty acid	70 (33.7)	68 (33.2)	70 (34.3)	48 (32.4)	46 (30.9)	38 (25.9)
Niacin	1 (0.5)	2 (1.0)	2 (1.0)	4 (2.7)	6 (4.0)	5 (3.4)
PCSK9 inhibitor	3 (1.4)	4 (2.0)	11 (5.4)	3 (2.0)	3 (2.0)	2 (1.4)
Two or more therapies	144 (69.2)	129 (62.9)	138 (67.6)	90 (60.8)	95 (63.8)	96 (65.3)
Median MRI-PDFF — %¶	14.5 (7.6–19.1)	15.0 (10.2–23.9)	13.2 (9.8–19.0)	13.4 (9.0–20.2)	15.6 (9.7–24.8)	13.3 (6.7–18.3)

Lipid Outcomes at 6 Months.

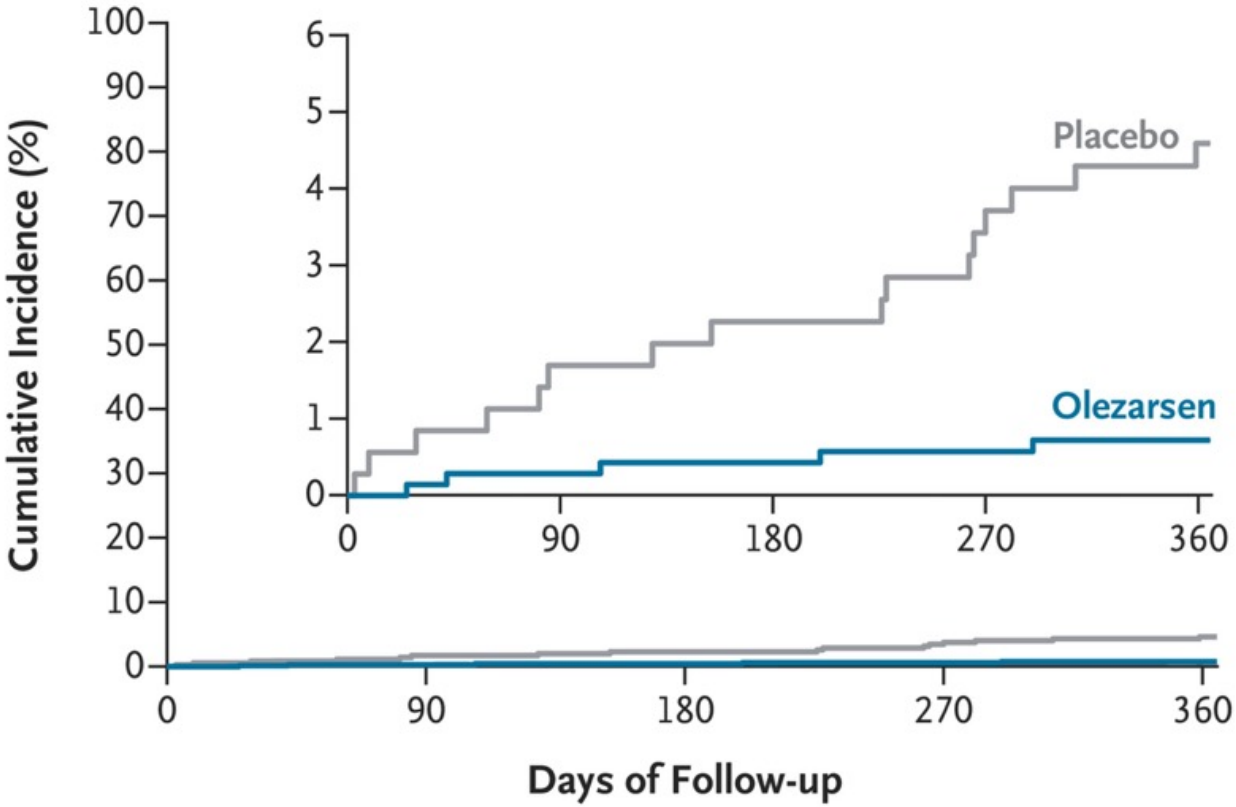
Variable	CORE-TIMI 72a			CORE2-TIMI 72b		
	Placebo (N=208)	Olezarsen, 50 mg (N=205)	Olezarsen, 80 mg (N=204)	Placebo (N=148)	Olezarsen, 50 mg (N=149)	Olezarsen, 80 mg (N=147)
Triglycerides						
Level at baseline — mg/dl	1208.0±1295.4	1168.8±825.8	1168.5±973.7	1018.6±1053.7	967.8±599.9	1088.4±964.5
Level at 6 mo — mg/dl	1083.7±1105.1	389.9±581.6	267.1±300.5	809.6±935.4	315.3±383.8	289.6±349.0
LSM change (95% CI) — %	-0.4 (-7.8 to 6.9)	-63.4 (-70.6 to -56.1)	-72.7 (-80.0 to -65.4)	-13.6 (-22.9 to -4.3)	-62.8 (-72.1 to -53.5)	-68.1 (-77.6 to -58.7)
Placebo-adjusted LSM change (95% CI) — percentage points	—	-62.9 (-72.2 to -53.6)	-72.2 (-81.4 to -63.1)	—	-49.2 (-59.7 to -38.8)	-54.5 (-65.1 to -44.0)
P value vs. placebo	—	<0.001	<0.001	—	<0.001	<0.001
Apolipoprotein C-III						
Level at baseline — mg/dl	37.4±15.9	39.4±16.0	36.9±15.0	36.5±13.6	38.0±15.6	36.9±14.8
Level at 6 mo — mg/dl	35.3±18.1	10.8±10.9	6.9±7.4	31.5±17.0	11.7±13.2	8.3±9.4
LSM change (95% CI) — %	-3.6 (-7.9 to 0.7)	-72.0 (-76.3 to -67.6)	-81.0 (-85.5 to -76.6)	-13.5 (-20.1 to -7.0)	-70.1 (-76.7 to -63.4)	-77.0 (-83.6 to -70.4)
Placebo-adjusted LSM change (95% CI) — percentage points	—	-68.3 (-73.9 to -62.8)	-77.4 (-83.0 to -71.9)	—	-56.5 (-63.9 to -49.2)	-63.5 (-70.9 to -56.0)
P value vs. placebo	—	<0.001	<0.001	—	<0.001	<0.001
Remnant cholesterol						
Level at baseline — mg/dl	150.9±83.1	157.5±85.5	145.4±81.3	127.8±74.3	140.3±83.6	144.2±83.7
Level at 6 mo — mg/dl	148.9±96.6	65.1±57.4	46.3±39.3	118.1±98.2	57.1±54.6	49.0±51.0
LSM change (95% CI) — %	4.7 (-1.7 to 11.0)	-52.6 (-58.8 to -46.3)	-65.4 (-71.4 to -59.3)	0.8 (-9.8 to 11.5)	-49.8 (-60.4 to -39.2)	-51.4 (-62.2 to -40.6)
Placebo-adjusted LSM change (95% CI) — percentage points	—	-57.2 (-65.3 to -49.2)	-70.1 (-77.9 to -62.2)	—	-50.6 (-62.4 to -38.7)	-52.2 (-64.2 to -40.1)
P value vs. placebo	—	<0.001	<0.001	—	<0.001	<0.001
Non-HDL cholesterol						
Level at baseline — mg/dl	221.0±109.8	224.2±94.9	218.7±102.3	191.1±91.0	210.6±73.5	205.2±82.2
Level at 6 mo — mg/dl	208.7±96.2	155.7±76.0	133.1±53.2	171.5±99.2	147.6±63.2	134.4±55.8
LSM change (95% CI) — %	-2.8 (-7.0 to 1.3)	-27.6 (-31.9 to -23.4)	-35.5 (-39.7 to -31.2)	-7.4 (-12.7 to -2.0)	-26.7 (-32.1 to -21.3)	-29.6 (-35.1 to -24.2)
Placebo-adjusted LSM change (95% CI) — percentage points	—	-24.8 (-30.3 to -19.3)	-32.6 (-38.0 to -27.3)	—	-19.3 (-25.3 to -13.3)	-22.3 (-28.4 to -16.1)
P value vs. placebo	—	<0.001	<0.001	—	<0.001	<0.001
HDL cholesterol						
Level at baseline — mg/dl	26.1±12.1	25.6±8.2	25.6±8.1	26.7±9.3	28.7±8.6	27.7±8.9
Level at 6 mo — mg/dl	27.7±13.6	42.4±16.3	48.6±18.7	29.3±12.5	47.0±17.6	48.8±18.4
LSM change (95% CI) — %	9.1 (1.5 to 16.8)	73.4 (65.6 to 81.1)	94.5 (86.7 to 102.3)	13.4 (4.4 to 22.3)	71.6 (62.8 to 80.4)	83.1 (74.4 to 91.9)
Placebo-adjusted LSM change (95% CI) — percentage points	—	64.2 (54.4 to 74.1)	85.4 (75.5 to 95.2)	—	58.3 (48.5 to 68.1)	69.8 (60.0 to 79.6)
Apolipoprotein B						
Level at baseline — mg/dl	104.4±26.8	109.1±34.9	101.2±30.7	101.2±27.4	113.1±26.6	104.8±30.7
Level at 6 mo — mg/dl	102.1±27.6	102.8±34.7	92.2±31.4	97.3±25.0	100.3±30.0	91.6±30.0
LSM change (95% CI) — %	-2.3 (-5.6 to 1.1)	-3.5 (-6.9 to -0.1)	-9.5 (-13.0 to -6.1)	-2.4 (-6.8 to 1.9)	-8.2 (-12.5 to -3.9)	-11.2 (-15.5 to -6.9)
Placebo-adjusted LSM change (95% CI) — percentage points	—	-1.2 (-5.6 to 3.1)	-7.3 (-11.6 to -3.0)	—	-5.8 (-10.6 to -0.9)	-8.7 (-13.6 to -3.9)
LDL cholesterol						
Level at baseline — mg/dl	63.1±33.9	65.6±36.3	64.2±37.0	62.4±33.0	70.8±35.0	64.8±34.3
Level at 6 mo — mg/dl	66.7±37.2	94.9±46.6	88.8±43.1	67.2±34.7	95.4±45.2	88.3±43.8
LSM change (95% CI) — %	7.2 (-5.1 to 19.5)	69.1 (56.8 to 81.5)	65.1 (52.6 to 77.7)	36.0 (17.9 to 54.2)	85.2 (67.3 to 103.0)	72.7 (54.9 to 90.5)
Placebo-adjusted LSM change (95% CI) — percentage points	—	62.0 (46.2 to 77.8)	57.9 (42.2 to 73.7)	—	49.2 (29.1 to 69.3)	36.7 (17.0 to 56.4)

Adverse Events and Laboratory Measures (CORE-TIMI 72a and CORE2-TIMI 72b Pooled Safety Population).

Event or Measure	Placebo (N=356)	Olezarsen, 50 mg (N=354)	P Value vs. Placebo	Olezarsen, 80 mg (N=351)	P Value vs. Placebo
Adverse events — no. (%)					
Any adverse event	267 (75.0)	264 (74.6)	0.86	267 (76.1)	0.64
Adverse event leading to discontinuation of olezarsen or placebo	7 (2.0)	12 (3.4)	0.25	15 (4.3)	0.09
Any serious adverse event	49 (13.8)	31 (8.8)	0.04	38 (10.8)	0.24
Serious adverse event leading to discontinuation of olezarsen or placebo	1 (0.3)	4 (1.1)	0.22	2 (0.6)	0.57
Injection-site reaction					
Any	3 (0.8)	36 (10.2)	<0.001	58 (16.5)	<0.001
Mild	3 (0.8)	34 (9.6)	<0.001	52 (14.8)	<0.001
Moderate†	0	4 (1.1)	0.06	10 (2.8)	<0.001
Severe	0	0	—	0	—
Possible hypersensitivity event‡					
Any	11 (3.1)	25 (7.1)	0.02	24 (6.8)	0.03
Mild	10 (2.8)	21 (5.9)	0.05	17 (4.8)	0.16
Moderate	1 (0.3)	4 (1.1)	0.21	9 (2.6)	0.04
Severe	0	0	—	0	—
Hepatic steatosis adverse event — no. (%)‖	4 (1.1)	9 (2.5)	0.17	8 (2.3)	0.24
Laboratory measures					
Hepatic measures					
ALT or AST ≥3× ULN — no./total no. (%)	7/351 (2.0)	9/347 (2.6)	0.60	24/346 (6.9)	0.003
ALT or AST ≥5× ULN — no./total no. (%)	3/351 (0.9)	3/347 (0.9)	0.99	5/346 (1.4)	0.47
Total bilirubin ≥2× ULN — no./total no. (%)	1/351 (0.3)	1/347 (0.3)	0.99	2/346 (0.6)	0.56
LSM absolute change in INR from baseline to highest value (95% CI)§	0.1 (0.1 to 0.1)	0.1 (0.1 to 0.1)	0.89	0.1 (0.1 to 0.1)	0.13
LSM absolute change in MRI-PDFF from baseline to 12 mo (95% CI)¶	0.14 (-1.50 to 1.79)	2.28 (0.59 to 3.96)	0.05	4.18 (2.52 to 5.85)	<0.001
Renal measures — no./total no. (%)					
eGFR decrease ≥30%	47/351 (13.4)	31/347 (8.9)	0.06	35/346 (10.1)	0.18
eGFR decrease ≥50%	7/351 (2.0)	3/347 (0.9)	0.22	10/346 (2.9)	0.45
UPCR ≥500**	50/352 (14.2)	42/347 (12.1)	0.41	47/346 (13.6)	0.81
UPCR ≥1000**	16/352 (4.5)	18/347 (5.2)	0.70	14/346 (4.0)	0.74
Platelet-count thresholds — no./total no. (%)					
<100,000 cells/μl	12/352 (3.4)	7/347 (2.0)	0.26	25/347 (7.2)	0.03
<75,000 cells/μl	6/352 (1.7)	2/347 (0.6)	0.18	7/347 (2.0)	0.76

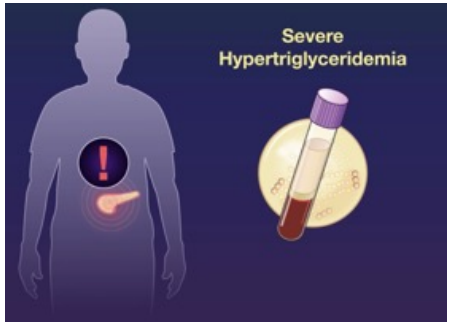


Triglyceride Levels through 12 Months and Lipid Outcomes at 6 Months.
Panels A and B show the median triglyceride levels in the CORE-TIMI 72a trial and the CORE2-TIMI 72b trial, respectively. Panels C and D show the results for the primary outcome (the percent change from baseline in the triglyceride level at 6 months) as well as secondary and exploratory lipid outcomes in the CORE-TIMI 72a trial and the CORE2-TIMI 72b trial, respectively. I bars indicate 95% confidence intervals. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. HDL denotes high-density lipoprotein and LDL low-density lipoprotein.



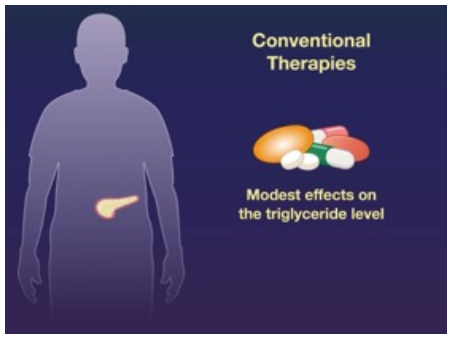
Cumulative Incidence of Acute Pancreatitis Events.

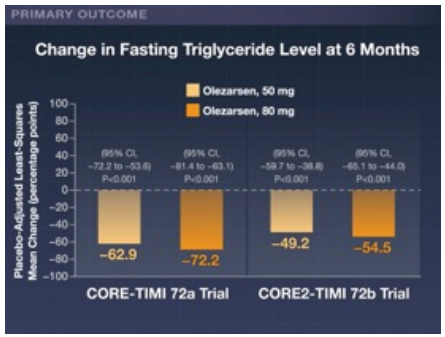
Shown are the results of a time-to-first-event analysis of acute pancreatitis events in the pooled olezarsen group and the pooled placebo group across both the CORE-TIMI 72a trial and the CORE2-TIMI 72b trial. The inset shows the same data on an enlarged y axis.

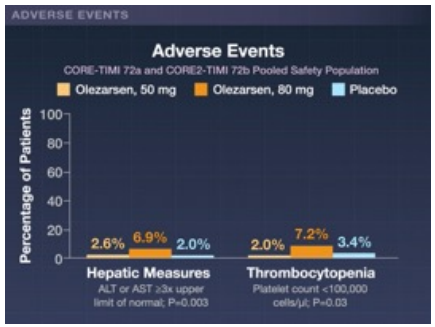

Severe
Hypertriglyceridemia

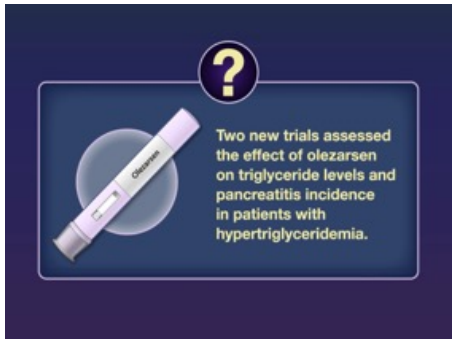

1061 Adults
Fasting triglyceride levels 500 mg/dl or higher on two occasions, despite lipid-lowering therapy
CORE-TIMI 72a Trial
CORE2-TIMI 72b Trial
Olezarsen 50 mg N=205
Olezarsen 80 mg N=204
Placebo N=208
Olezarsen 50 mg N=149
Olezarsen 80 mg N=147
Placebo N=148
Once monthly for 12 months

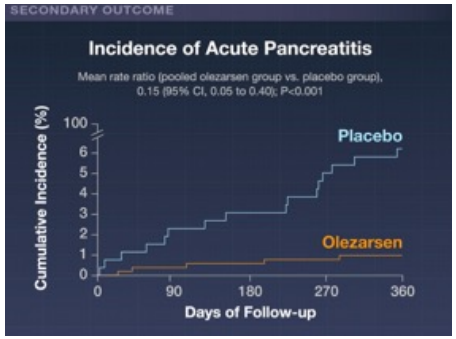

ADVERSE EVENTS
Adverse Events
CORE-TIMI 72a and CORE2-TIMI 72b Pooled Safety Population
Olezarsen, 50 mg
Olezarsen, 80 mg
Placebo
Percentage of Patients
100
80
60
40
20
0
74.6%
76.1%
75.0%
Any Adverse Event

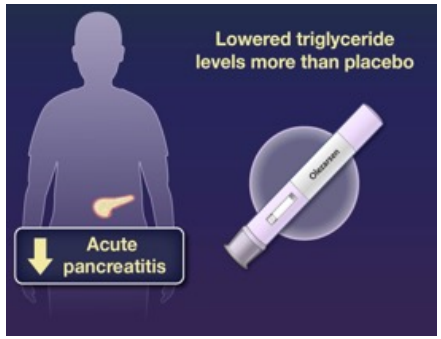

Conventional
Therapies
Modest effects on
the triglyceride level


PRIMARY OUTCOME
Change in Fasting Triglyceride Level at 6 Months
Olezarsen, 50 mg
Olezarsen, 80 mg
Placebo-Adjusted Least-Squares Mean Change (percentage points)
100
80
60
40
20
0
-20
-40
-60
-80
-100
(95% CI, −72.2 to −53.6) P<0.001
(95% CI, −61.4 to −63.1) P<0.001
(95% CI, −59.7 to −38.8) P<0.001
(95% CI, −65.1 to −44.0) P<0.001
−62.9
−72.2
−49.2
−54.5
CORE-TIMI 72a Trial
CORE2-TIMI 72b Trial

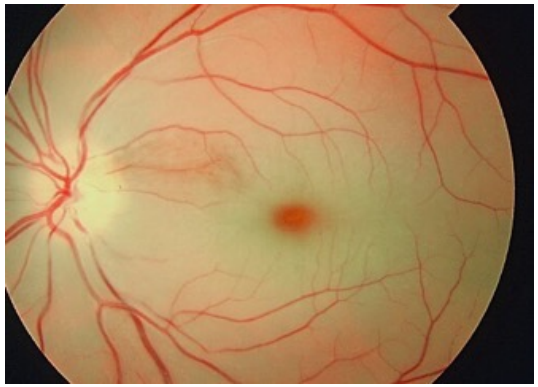

ADVERSE EVENTS
Adverse Events
CORE-TIMI 72a and CORE2-TIMI 72b Pooled Safety Population
Olezarsen, 50 mg
Olezarsen, 80 mg
Placebo
Percentage of Patients
100
80
60
40
20
0
2.6%
6.9%
2.0%
2.0%
7.2%
3.4%
Hepatic Measures
ALT or AST ≥3x upper limit of normal; P=0.003
Thrombocytopenia
Platelet count <100,000 cells/µl; P=0.03

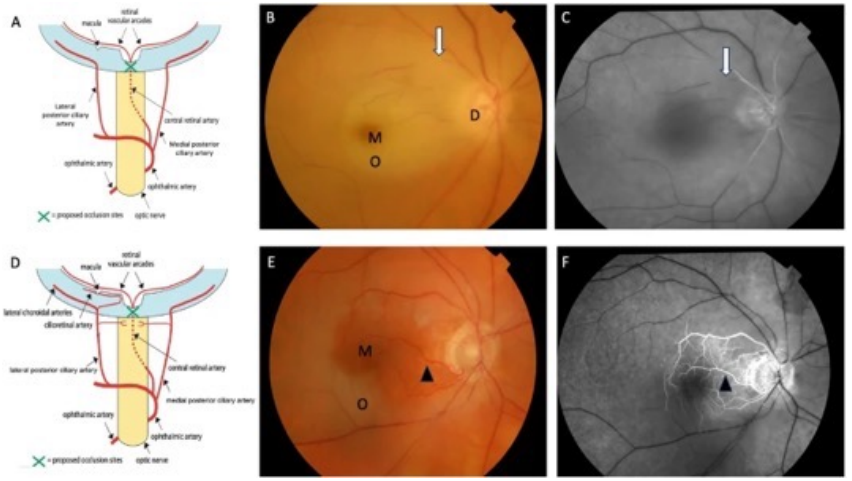

Olezarsen
Two new trials assessed the effect of olezarsen on triglyceride levels and pancreatitis incidence in patients with hypertriglyceridemia.


SECONDARY OUTCOME
Incidence of Acute Pancreatitis
Mean rate ratio (pooled olezarsen group vs. placebo group), 0.15 (95% CI, 0.05 to 0.40); P<0.001
Cumulative Incidence (%)
100
6
5
4
3
2
1
0
Placebo
Olezarsen
0
90
180
270
360
Days of Follow-up


Lowered triglyceride levels more than placebo
Olezarsen
Acute pancreatitis

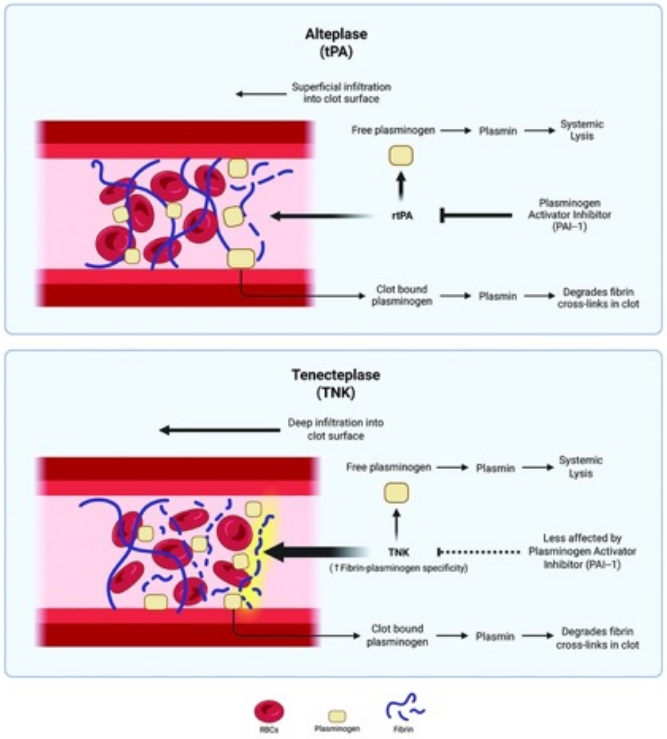
Central retinal artery occlusion (CRAO) is an ocular emergency, often called an "eye stroke," causing sudden, painless, and severe monocular vision loss. It is caused by an artery blockage, usually an embolus from the carotid artery or heart. Treatment is limited and must be immediate to restore blood flow, with poor prognosis for vision recovery if not treated within 105–240 minutes.

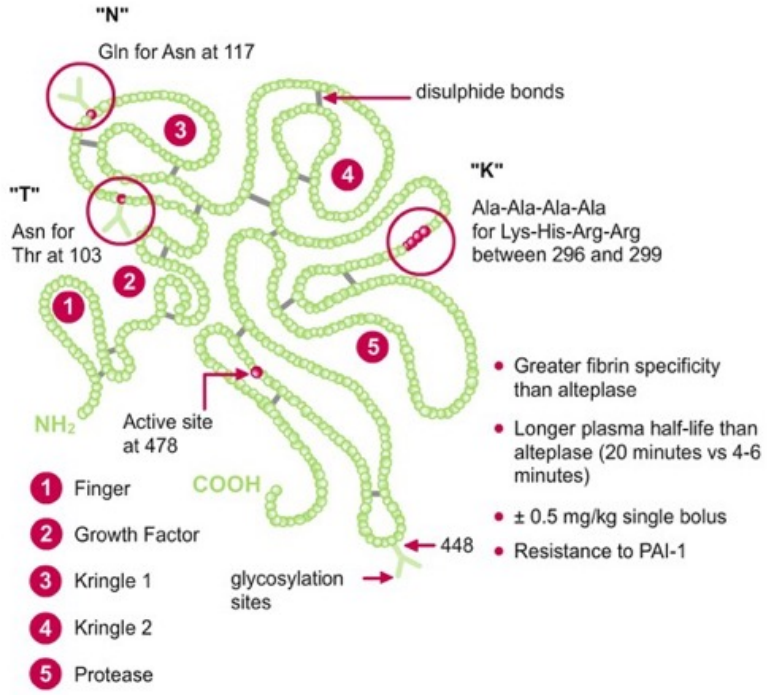




A The central retinal artery is a branch of the ophthalmic artery. In central retinal artery occlusion (green cross marks site of occlusion), the blood supply to the retina is interrupted. **B** Clinical fundus photograph of the right eye in a patient with acute CRAO showing disc oedema (D), retinal oedema (O) around the macula (M) result in a cherry-red appearance of the macula and arterial attenuation (white arrow). **C** FFA at 58 s showing delayed arterial perfusion (white arrow) **D** Patients with a cilioretinal artery have supplied to the macula stemming from the short posterior ciliary artery. Therefore, in CRAO (green cross), the macula is supplied. **E** Coloured fundus photograph, and **F** FFA showing the perfused macula (M) supplied by the cilioretinal artery (arrowhead) but there is oedema around the macula (O). CRAO central retinal artery occlusion. FFA fundus fluorescein angiography.

Tenecteplase ist ein intravenös verabreichtes rekombinantes Protein (rTPA), das Plasminogen aktiviert.

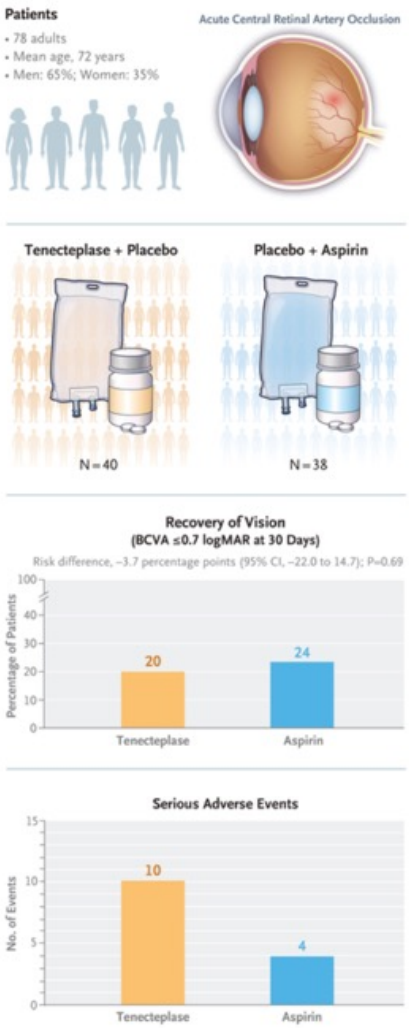




A Randomized Trial of Tenecteplase in Acute Central Retinal Artery Occlusion

Central retinal artery occlusion can result in permanent vision loss. Effective treatment is lacking.

We conducted a phase 3, double-blind, double-dummy, randomized, controlled trial involving adults with acute, nonarteritic central retinal artery occlusion who had symptom onset within 4.5 hours before treatment. Patients were assigned, in a 1:1 ratio, to receive intravenous tenecteplase (at a dose of 0.25 mg per kilogram of body weight) and oral placebo or intravenous placebo and oral aspirin (at a dose of 300 mg). The primary end point was vision recovery, defined as a best corrected visual acuity (BCVA) in the affected eye at 30 days of up to 0.7 logMAR (logarithm of the minimum angle of resolution; equivalent to ≥20/100). Key secondary visual end points were a BCVA of up to 0.5 logMAR (equivalent to ≥20/63), mean improvement in BCVA, and perimetry score at 30 days. Key safety end points included symptomatic intracranial hemorrhage, major bleeding, and death.



Central retinal artery occlusion is an ophthalmologic emergency that carries a high risk of permanent blindness if prompt reperfusion is not achieved. Patients typically present with sudden, painless monocular vision loss and an afferent pupillary defect. Funduscopy usually shows signs of acute retinal ischemia, including retinal pallor, a cherry-red spot, segmented blood flow, and attenuated retinal arteries, although the fundus may appear normal. In the acute phase, optical coherence tomography (OCT) usually shows inner retinal hyperreflectivity and thickening, which can aid in the diagnosis. Central retinal artery occlusion is typically caused by embolism from a carotid plaque or a cardiac thrombus, but it can result from any type of ischemic event.

Although central retinal artery occlusion is considered a cerebrovascular event, key differences between retinal and cerebral vascular anatomy limit the extrapolation of treatment effects from acute ischemic stroke therapies. Despite various attempted interventions, no therapy has been shown to have clear efficacy in the initial treatment of the condition. Although thrombolysis is the cornerstone of treatment in acute ischemic stroke, its role in treating patients with central retinal artery occlusion remains uncertain.

The target population consisted of patients in whom central retinal artery occlusion had been diagnosed and who had a best corrected visual acuity (BCVA) of 1.0 logMAR or greater in the affected eye, corresponding to a decimal BCVA of 0.1 or lower or a fraction BCVA of 20/200 or less.
Adults who were at least 18 years of age and who had central retinal artery occlusion and could receive trial treatment within 4.5 hours after symptom onset were eligible. All eligible patients were first assessed by an ophthalmologist. The diagnosis was based on a typical history and findings from the acute ophthalmologic examination. Given the 4.5-hour treatment window, arteritic central retinal artery occlusion could not be ruled out by laboratory or imaging studies and was assessed clinically. Patients were then assessed by an acute-stroke team. A neurologic examination (which included assigning a score on the National Institutes of Health Stroke Scale) and neuroimaging (in accordance with the standard stroke protocol at each participating hospital) were performed to rule out a concomitant intracranial vascular event. Written informed consent was obtained from all the patients before administration of the investigational medicinal product; proxy consent was not permitted.

End Points

The primary end point was a BCVA of 0.7 logMAR or lower in the affected eye at 30 days after treatment, equivalent to a decimal BCVA of at least 0.2 or a fraction BCVA of at least 20/100. Because a BCVA of at least 1.0 logMAR was an inclusion criterion, the primary end point reflected an improvement in on-chart BCVA of at least 0.3 logMAR, equivalent to at least 15 letters on the Early Treatment Diabetic Retinopathy Study chart, a change that is widely regarded as a clinically meaningful improvement in visual acuity.

Characteristic	Tenecteplase (N=40)	Aspirin (N=38)
Age — yr	71±10	72±9
Female sex — no. (%)	15 (38)	12 (32)
Weight — kg	82±19	84±19
Mean NIHSS score†	0	0
Modified Rankin scale score — no. (%)‡		
0	32 (80)	32 (84)
1	5 (12)	4 (11)
2	3 (8)	2 (5)
Current smoker or history of smoking — no. (%)	9 (22)	5 (13)
Hypertension — no. (%)	31 (78)	25 (66)
Cardiac valvular disease — no. (%)	3 (8)	1 (3)
Heart failure — no. (%)	3 (8)	1 (3)
Coronary artery disease — no. (%)	10 (25)	6 (16)
Carotid artery disease — no. (%)§	2 (5)	9 (24)
Atrial fibrillation — no. (%)	1 (2)	1 (3)
Diabetes mellitus — no. (%)	6 (15)	0
Dyslipidemia — no. (%)	24 (60)	19 (50)
Previous transient ischemic attack or stroke — no. (%)	4 (10)	4 (11)
Cause — no. (%)		
Carotid-artery atherosclerosis§	16 (40)	17 (45)
Small-vessel disease	6 (15)	5 (13)
Cardioembolism	3 (8)	2 (5)
Other	5 (12)	1 (3)
Unknown	10 (25)	13 (34)

Efficacy End Points at 30 Days.

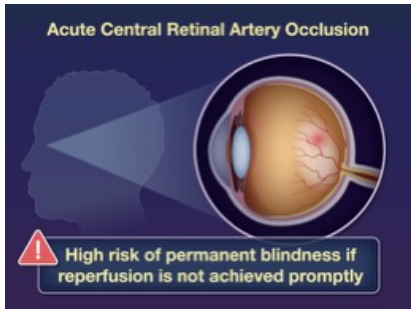
End Point	Tenecteplase (N = 40)	Aspirin (N = 38)	Risk Difference (95% CI)
Primary end point: BCVA of ≤0.7 logMAR — no. of patients/total no. (%)†	8/40 (20)	9/38 (24)	−0.04 (−0.22 to 0.15)
Secondary end points‡			
BCVA of ≤0.5 logMAR — no. of patients/total no. (%)	8/40 (20)	7/38 (18)	0.02 (−0.16 to 0.19)
Mean change in BCVA from baseline — logMAR	−0.73±0.92	−0.60±0.91	−0.12 (−0.53 to 0.28)
Mean number of test points seen on Esterman perimetry — no. out of 100§	35±36	37±38	−1.71 (−13.37 to 9.96)
Mean NIHSS score at discharge	0.1±0.3	0±0.2	
Mean NIHSS score at 30 days	0.2±0.5	0	
Mean mRs score at discharge	1.3±1.1	1.3±0.8	
Mean mRs score at 30 days	1.4±0.3	1.4±1.0	
Mean EQ-5D-5L index value at 30 days¶	0.84±0.25	0.87±0.13	
Mean VFQ-25 score at 30 days‖	74.6±20.3	74.1±18.6	
Neovascularization in the affected eye at 30 days — no. (%)	1 (2)	1 (3)	
Subgroup treated ≤3 hr after onset — no./total no. (%)			
Patients with BCVA of ≤0.7 logMAR	7/31 (23)	5/23 (22)	0.01 (−0.22 to 0.23)
Patients with BCVA of ≤0.5 logMAR	7/31 (23)	4/23 (17)	0.05 (−0.16 to 0.27)

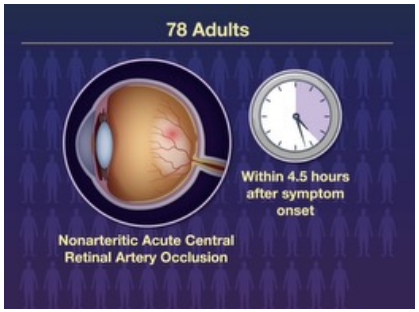
Tenecteplase did not help at all!

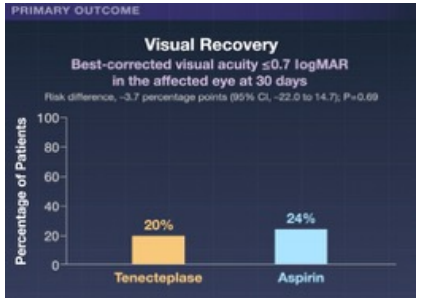
Safety End Points.

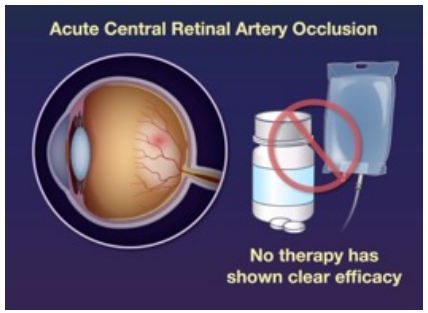
End Point	Tenecteplase (N=40)	Aspirin (N=38)
	no. of patients (%)	
Death at 30 days	1 (2)	0
Symptomatic intracranial hemorrhage*	1 (2)	0
Any intracranial hemorrhage at 24 hr	2 (5)	0
Any systemic bleeding at 30 days†	1 (2)	2 (5)
Ischemic stroke‡	1 (2)	1 (3)
Reocclusion of central retinal artery§	1 (2)	
Giant-cell arteritis¶	1 (2)	0
Carotid endarterectomy or stenting	3 (8)	2 (5)
Hypotension or syncope	1 (2)	1 (3)
Adverse events‖	19 (48)	13 (34)
Mild	12 (30)	11 (29)
Moderate	13 (32)	3 (8)
Severe	3 (8)	5 (13)
Life-threatening	1 (2)	0
Death	1 (2)	0

Tenecteplase led to more adverse events, including 1 death

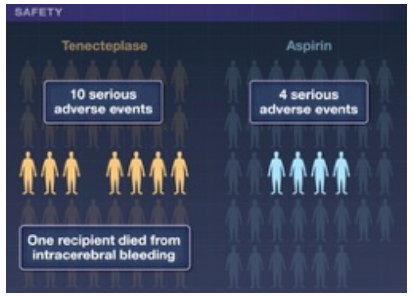

Acute Central Retinal Artery Occlusion
High risk of permanent blindness if reperfusion is not achieved promptly


78 Adults
Within 4.5 hours after symptom onset
Nonarteritic Acute Central Retinal Artery Occlusion


PRIMARY OUTCOME
Visual Recovery
Best-corrected visual acuity ≤0.7 logMAR in the affected eye at 30 days
Risk difference, −3.7 percentage points (95% CI, −22.0 to 14.7); P=0.69
Percentage of Patients
100
80
60
40
20
0
20%
24%
Tenecteplase
Aspirin

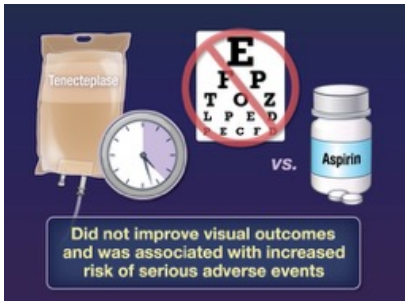

Acute Central Retinal Artery Occlusion
No therapy has shown clear efficacy


78 Adults
Tenecteplase
Placebo
Placebo
Aspirin
N=40
N=38

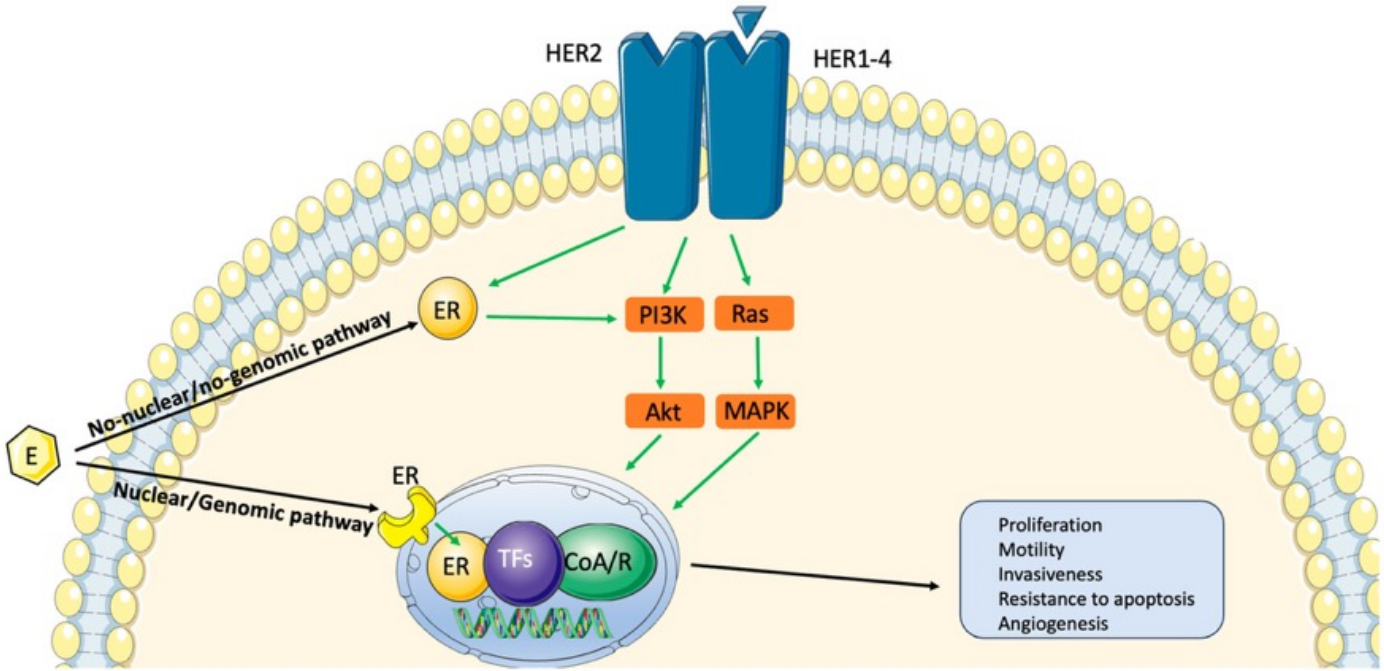

SAFETY
Tenecteplase
Aspirin
10 serious adverse events
4 serious adverse events
One recipient died from intracerebral bleeding


Tenecteplase
Improve outcomes in acute central retinal artery occlusion

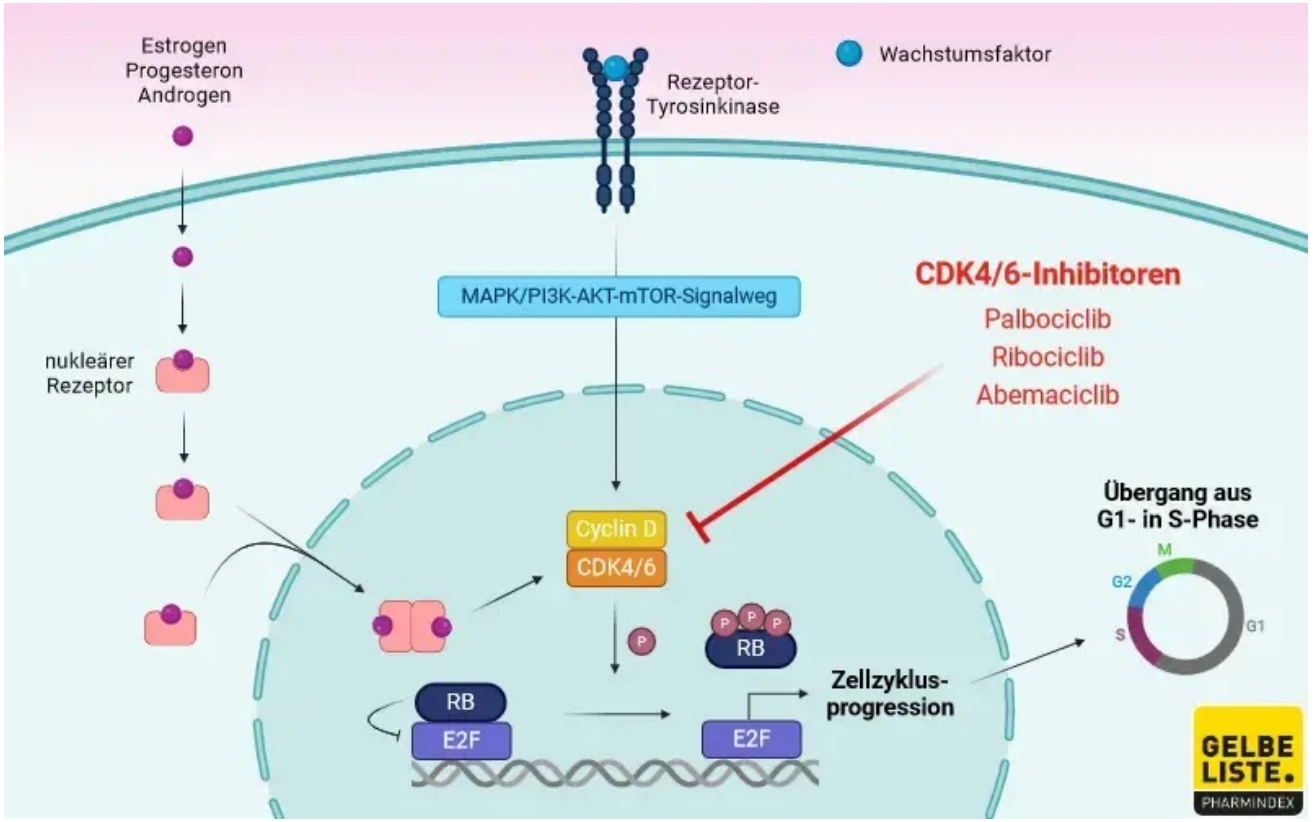

PRIMARY OUTCOME
Visual Recovery
Best-corrected visual acuity ≤0.7 logMAR in the affected eye at 30 days
≥20/100
≤0.7 logMAR


Tenecteplase
VS.
Aspirin
Did not improve visual outcomes and was associated with increased risk of serious adverse events

Hormone receptor-positive (HR+) / HER2-positive (HER2+) breast cancer, sometimes called "triple-positive" (if PR+), is a distinct subtype where cells overexpress HER2 proteins and have estrogen/progesterone receptors. Affecting about 10-14% of cases, this cancer utilizes crosstalk between hormonal and HER2 pathways to grow, requiring combined treatment with targeted therapies (e.g., Trastuzumab), hormone therapy, and chemotherapy.



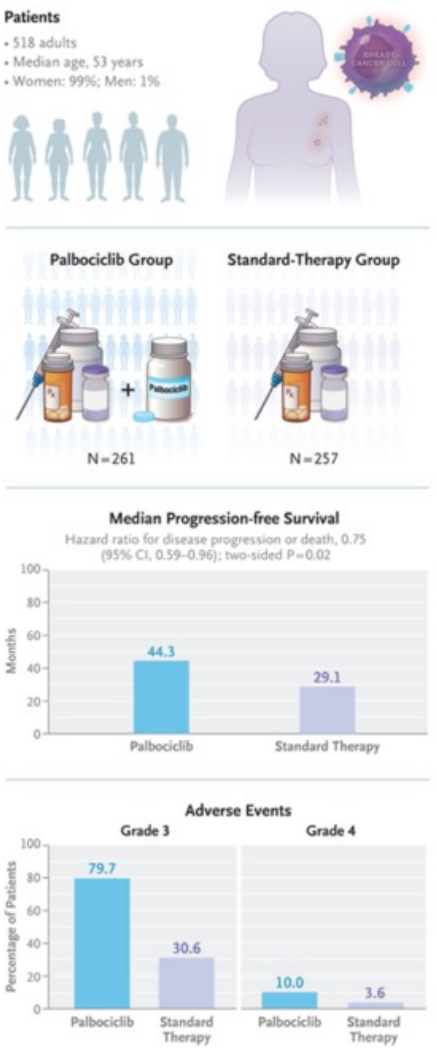
Palbociclib (Handelsname Ibrance) ist ein CDK4/6-Inhibitor, der seit 2016 zur Behandlung von fortgeschrittenem oder metastasiertem, Hormonrezeptor-positivem (HR+), HER2-negativem Brustkrebs zugelassen ist. Es wird in Kombination mit einer Antihormontherapie eingesetzt, um das Tumorwachstum durch Hemmung der Zellteilung zu bremsen.



Palbociclib for Hormone-Receptor–Positive, HER2-Positive Advanced Breast Cancer

Dual anti–human epidermal growth factor receptor 2 (HER2) therapy plus chemotherapy followed by maintenance treatment with HER2-targeted and endocrine therapies is standard first-line treatment for hormone-receptor–positive, HER2-positive metastatic breast cancer. On the basis of preclinical and clinical data, the addition of palbociclib (a selective inhibitor of cyclin-dependent kinases 4 and 6) may overcome resistance to both endocrine and HER2-directed therapies.

In this phase 3, open-label, randomized trial, we enrolled patients with hormone-receptor–positive, HER2-positive metastatic breast cancer who did not have disease progression after four to eight cycles of chemotherapy plus HER2-targeted therapy. Patients were randomly assigned in a 1:1 ratio to receive maintenance HER2-targeted and endocrine therapies with or without palbociclib. The primary end point was investigator-assessed progression-free survival. Secondary end points included the objective response, clinical benefit, safety, and overall survival.



The identification of human epidermal growth factor receptor 2 (HER2)–positive breast cancer as a distinct clinical subtype has driven the development of transformative HER2-targeted therapies. More than 50% of HER2-positive breast cancers coexpress estrogen receptors, progesterone receptors, or both, which forms a biologically distinct subgroup.
The current standard first-line treatment for hormone-receptor–positive, HER2-positive metastatic breast cancer consists of induction chemotherapy, combined with trastuzumab and pertuzumab for several cycles, followed by maintenance therapy with dual HER2 blockade and endocrine therapies. Preclinical studies have shown crosstalk between HER2 and estrogen-receptor signaling pathways, which can promote resistance when only one pathway is targeted. The axis of cyclin D1 and cyclin-dependent kinases 4 and 6 (CDK4/6) has also been implicated as a driver of tumor initiation, proliferation, and survival in HER2-positive breast cancer, as well as of resistance to both endocrine and HER2-directed therapies. These findings provide a compelling rationale for concurrent inhibition of HER2, estrogen receptor, and the cell cycle through CDK4/6 inhibition to improve disease control and potentially survival outcomes in patients with hormone-receptor–positive, HER2-positive advanced breast cancer.

Patients

Eligible patients were women or men who were 18 years of age or older with histologically confirmed hormone-receptor–positive and HER2-positive advanced breast cancer. The hormone receptor with positivity could be either the estrogen or progesterone receptor. Status with respect to hormone receptor and HER2 was assessed locally. Hormone-receptor positivity was defined as at least 1% tumor-cell nuclear staining on immunohistochemical (IHC) analysis. HER2 positivity was defined as an IHC score of 3+ or gene amplification performed by in situ hybridization, according to the guidelines of the American Society of Clinical Oncology and the College of American Pathologists. Eligible patients were required to have a disease-free interval of at least 6 months after any previous neoadjuvant or adjuvant anti-HER2 therapy until metastatic diagnosis and to have received no previous systemic therapy for metastatic disease other than induction therapy. Patients with asymptomatic central nervous system (CNS) metastases at diagnosis were eligible; for those who had received previous CNS radiotherapy, a minimum of 3 weeks was required between completion of CNS radiotherapy and day 1 of cycle 1, with no ongoing requirement for glucocorticoid therapy.

End Points

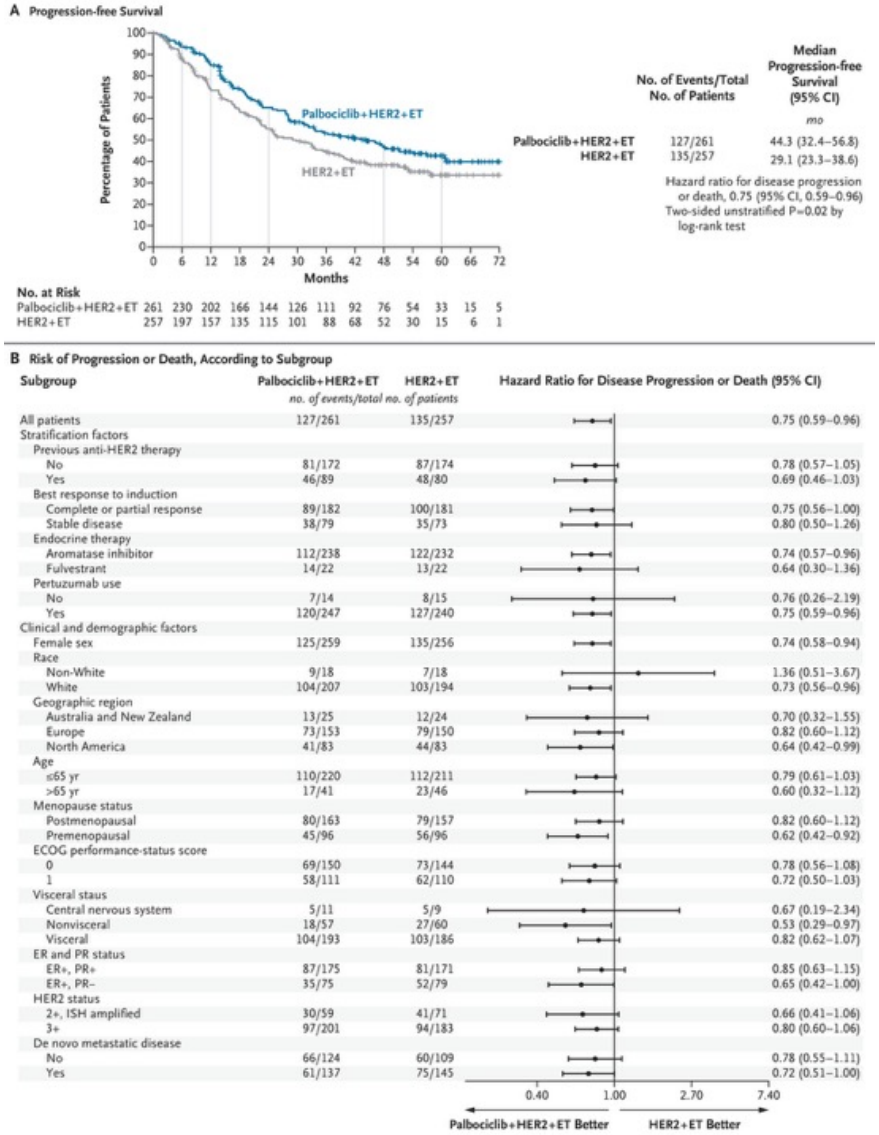
The primary end point was investigator-assessed progression-free survival, which was defined as the time from randomization to documented disease progression or death from any cause, whichever occurred first.

Characteristic	Palbociclib+ HER2+ET (N=261)	HER2+ET (N=257)	Total (N=518)
Age — yr			
Median (IQR)	53.5 (43.6–60.4)	53.0 (45.1–62.8)	53.4 (44.2–61.4)
Range	28.7–81.7	29.9–84.3	28.7–84.3
Race or ethnic group — no. (%)†			
Asian Indian, Chinese, or other Asian	6 (2.3)	4 (1.6)	10 (1.9)
Black	4 (1.5)	11 (4.3)	15 (2.9)
White	207 (79.3)	194 (75.5)	401 (77.4)
Other ethnic group	8 (3.1)	3 (1.2)	11 (2.1)
Missing data	36 (13.8)	45 (17.5)	81 (15.6)
Geographic region — no. (%)			
North America	83 (31.8)	83 (32.3)	166 (32.0)
Western Europe, Australia, or New Zealand	178 (68.2)	174 (67.7)	352 (68.0)
Sex — no. (%)			
Female	259 (99.2)	256 (99.6)	515 (99.4)
Male	2 (0.8)	1 (0.4)	3 (0.6)
ECOG performance-status score — no. (%)‡			
0	150 (57.5)	144 (56.0)	294 (56.8)
1	111 (42.5)	110 (42.8)	221 (42.7)
Missing data	0	3 (1.2)	3 (0.6)
Menopausal status — no. (%)			
NA because of male sex	2 (0.8)	1 (0.4)	3 (0.6)
Postmenopausal	163 (62.5)	157 (61.1)	320 (61.8)
Premenopausal	96 (36.8)	96 (37.4)	192 (37.1)
Missing data	0	3 (1.2)	3 (0.6)
Estrogen-receptor status — no. (%)§			
Negative	10 (3.8)	3 (1.2)	13 (2.5)
Positive	251 (96.2)	251 (97.7)	502 (97.5)
Missing data	0	3 (1.2)	3 (0.6)
Progesterone-receptor status — no. (%)§			
Negative	75 (28.7)	79 (30.7)	154 (29.9)
Positive	185 (70.9)	174 (67.7)	359 (69.3)
Unknown	1 (0.4)	1 (0.4)	2 (0.4)
Missing data	0	3 (1.2)	3 (0.6)
HER2 assessment — no. (%)¶			
2+, ISH amplified	59 (22.6)	71 (27.6)	130 (25.1)
3+	201 (77.0)	183 (71.2)	384 (74.1)
Missing data	1 (0.4)	3 (1.2)	4 (0.8)
Site of metastases — no. (%)‖			
Central nervous system	11 (4.2)	9 (3.5)	20 (3.9)
Nonvisceral	57 (21.8)	60 (23.3)	117 (22.6)
Visceral	193 (73.9)	186 (72.4)	379 (73.6)
Missing data	0	2 (0.8)	2 (0.4)
Number of cycles of induction treatment			
Median (IQR)	6.0 (6.0–7.0)	6.0 (6.0–7.0)	6.0 (6.0–7.0)
Range	4.0–8.0	4.0–8.0	4.0–8.0
Missing data	0	3 (1.2)	3 (0.6)
De novo metastatic disease — no. (%)**			
No	124 (47.5)	109 (42.4)	233 (45.0)
Yes	137 (52.5)	145 (56.4)	282 (54.4)
Missing data	0	3 (1.2)	3 (0.6)
Previous adjuvant or neoadjuvant anti-HER2 therapy — no. (%)††			
No	172 (65.9)	174 (67.7)	346 (66.8)
Yes	89 (34.1)	80 (31.1)	169 (32.6)
Missing data	0	3 (1.2)	3 (0.6)
Best response to induction therapy by investigator assessment — no. (%)††‡‡			
Complete or partial response	182 (69.7)	181 (70.4)	363 (70.1)
Stable disease	79 (30.3)	73 (28.4)	152 (29.3)
Missing data	0	3 (1.2)	3 (0.6)
Receipt of dual anti-HER2 therapy — no. (%)††			
No	14 (5.4)	15 (5.8)	29 (5.6)
Yes	247 (94.6)	240 (93.4)	487 (94.0)
Missing data	0	2 (0.8)	2 (0.4)
Type of endocrine therapy — no. (%)††			
Aromatase inhibitor	238 (91.2)	232 (90.3)	470 (90.7)
Fulvestrant	22 (8.4)	22 (8.6)	44 (8.5)
Missing data	1 (0.4)	3 (1.2)	4 (0.8)

Standard care for ER+ (estrogen receptor-positive) breast cancer centers on endocrine therapy to block hormone-driven growth, often following surgery and radiation. Key treatments include selective estrogen receptor modulators (SERMs) like tamoxifen for pre/postmenopausal women, or aromatase inhibitors (AIs) for postmenopausal women.

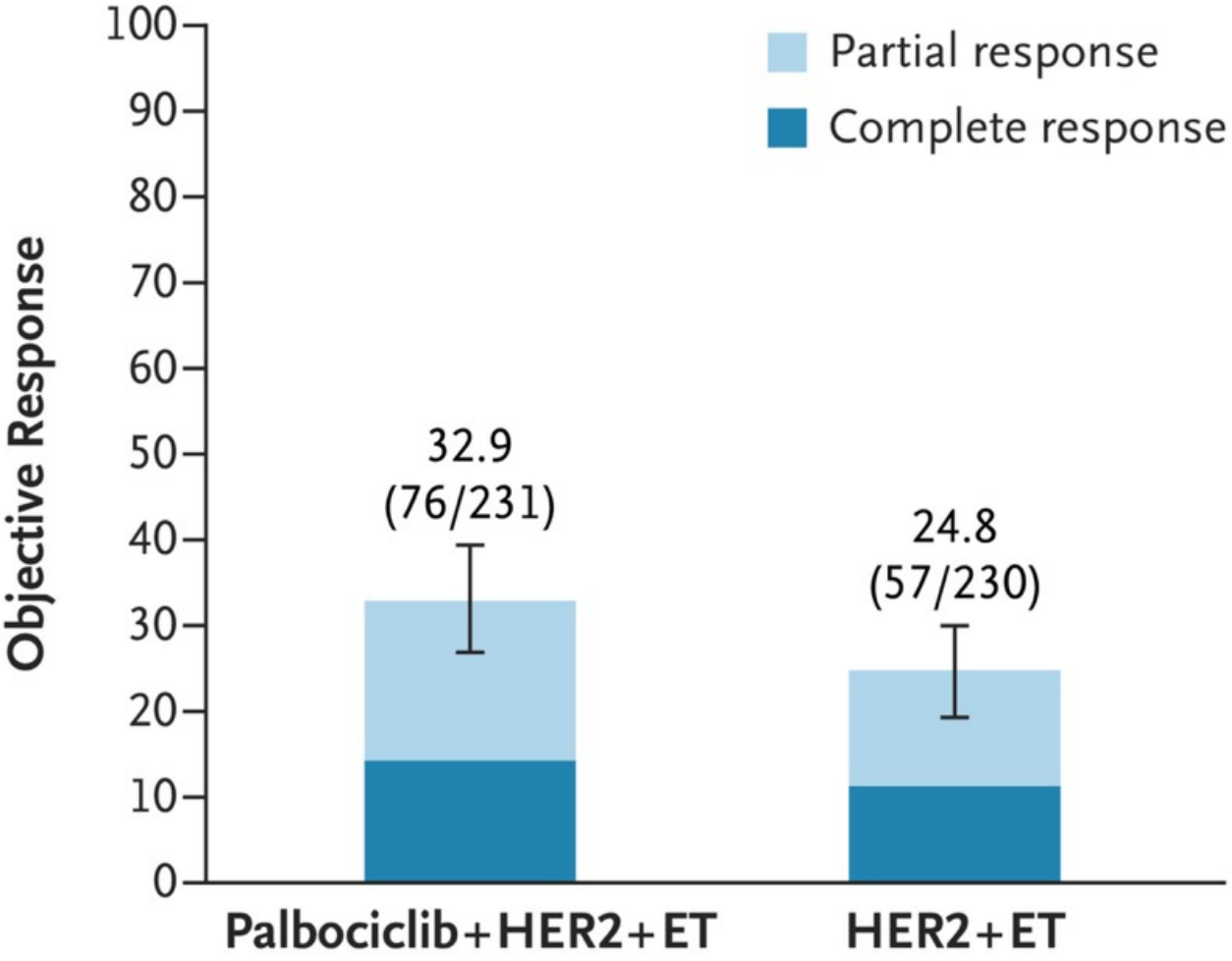
Adverse Events.

Adverse Events	Palbociclib+HER2+ET (N=261)		HER2+ET (N=248)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Neutropenia†	203 (77.8)	158 (60.5)	19 (7.7)	5 (2.0)
Diarrhea	184 (70.5)	25 (9.6)	93 (37.5)	3 (1.2)
Fatigue†	140 (53.6)	13 (5.0)	99 (39.9)	0
Leukopenia†	99 (37.9)	42 (16.1)	12 (4.8)	2 (0.8)
Arthralgia	95 (36.4)	4 (1.5)	119 (48.0)	2 (0.8)
Anemia†	80 (30.7)	8 (3.1)	20 (8.1)	1 (0.4)
Nausea	77 (29.5)	1 (0.4)	38 (15.3)	1 (0.4)
Headache	67 (25.7)	4 (1.5)	45 (18.1)	2 (0.8)
Thrombocytopenia†	65 (24.9)	3 (1.1)	4 (1.6)	0
Abdominal pain†	62 (23.8)	4 (1.5)	19 (7.7)	5 (2.0)
Hot flush†	58 (22.2)	0	70 (28.2)	0
Rash†	58 (22.2)	0	42 (16.9)	0
Covid-19†	57 (21.8)	2 (0.8)	25 (10.1)	0
Pruritus	55 (21.1)	4 (1.5)	41 (16.5)	0
Stomatitis	54 (20.7)	5 (1.9)	11 (4.4)	0
Mucosal inflammation	52 (19.9)	4 (1.5)	10 (4.0)	0
Muscle spasms	51 (19.5)	1 (0.4)	27 (10.9)	0
Epistaxis	49 (18.8)	0	14 (5.6)	0
Pyrexia	43 (16.5)	3 (1.1)	13 (5.2)	1 (0.4)
Cough†	42 (16.1)	0	29 (11.7)	0
Vomiting	41 (15.7)	2 (0.8)	21 (8.5)	3 (1.2)
Dizziness	37 (14.2)	2 (0.8)	23 (9.3)	1 (0.4)
Hypokalemia†	37 (14.2)	3 (1.1)	13 (5.2)	3 (1.2)
Peripheral neuropathy	35 (13.4)	0	21 (8.5)	1 (0.4)
Decreased appetite	34 (13.0)	2 (0.8)	13 (5.2)	0
Aspartate aminotransferase increased	33 (12.6)	3 (1.1)	11 (4.4)	2 (0.8)
Back pain	33 (12.6)	1 (0.4)	33 (13.3)	1 (0.4)
Constipation	33 (12.6)	0	24 (9.7)	0
Upper respiratory tract infection	32 (12.3)	1 (0.4)	18 (7.3)	0
Myalgia	31 (11.9)	0	27 (10.9)	1 (0.4)
Alanine aminotransferase increased	29 (11.1)	7 (2.7)	10 (4.0)	2 (0.8)
Alopecia	28 (10.7)	0	9 (3.6)	0
Insomnia	28 (10.7)	1 (0.4)	30 (12.1)	0
Urinary tract infection	28 (10.7)	2 (0.8)	21 (8.5)	1 (0.4)
Vulvovaginal dryness	28 (10.7)	1 (0.4)	10 (4.0)	0
Ejection fraction decreased	24 (9.2)	1 (0.4)	28 (11.3)	8 (3.2)



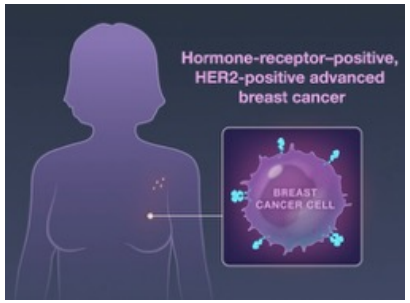
Progression-free Survival in the Intention-to-treat Population and According to Stratified and Clinicopathologic Features.

Panel A shows investigator-assessed progression-free survival in the group that received palbociclib plus anti–human epidermal growth factor receptor 2 therapy and endocrine therapy (palbociclib+HER2+ET) as compared with the group that received anti-HER2 therapy and endocrine therapies (HER2+ET) alone. At a median follow-up of 53.5 months, patients in the palbociclib group had significantly longer progression-free survival than those in the standard-therapy group (median duration, 44.3 months vs. 29.1 months; hazard ratio for death or disease progression, 0.75; 95% confidence interval, 0.59 to 0.96; two-sided P=0.02). Tick marks indicate data censoring. Panel B is a forest plot showing hazard ratios and 95% confidence intervals for disease progression or death in predefined subgroups. The data are divided according to stratified subgroups at the time of randomization and according to clinicopathologic features. In the category of pertuzumab use, "no" indicates that patients received only trastuzumab monotherapy and "yes" indicates that patients received both trastuzumab and pertuzumab. The Eastern Cooperative Oncology Group (ECOG) performance-status score is a measure of the patient's functional ability on a scale of 0 (fully active) to 5 (death). An immunohistochemical (IHC) score of 2+ indicates equivocal HER2 protein expression and requires reflex in situ hybridization (ISH) testing to determine HER2 gene amplification status; an IHC score of 3+ indicates HER2-positive disease. De novo metastatic disease was defined as metastatic disease in a patient who had received no previous anti-HER2 therapy and who enrolled in the trial within 1 year after the diagnosis of the primary breast cancer. ER denotes estrogen receptor, and PR progesterone receptor.

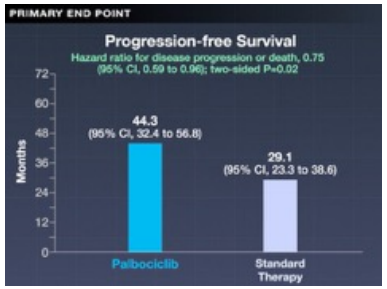


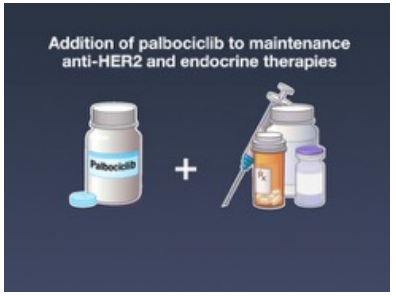
Tumor Response.

Shown is the percentage of patients who had a confirmed objective (partial or complete) response in the group that received palbociclib plus anti-HER2 and endocrine therapies as compared with those who received anti-HER2 and endocrine therapies alone. This analysis does not include patients who had a complete response after they had undergone induction therapy before randomization.


Hormone-receptor–positive, HER2-positive advanced breast cancer
BREAST CANCER CELL

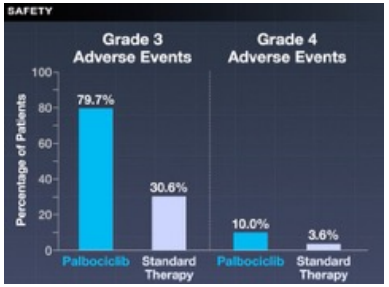

Maintenance HER2-targeted and endocrine therapies
+
Palbociclib
CDK4/6 inhibitor palbociclib
?
Improve outcomes


PRIMARY END POINT
Progression-free Survival
Hazard ratio for disease progression or death, 0.75 (95% CI, 0.59 to 0.96); two-sided P=0.02
Months
72
60
48
36
24
12
0
44.3 (95% CI, 32.4 to 56.8)
29.1 (95% CI, 23.3 to 38.6)
Palbociclib
Standard Therapy

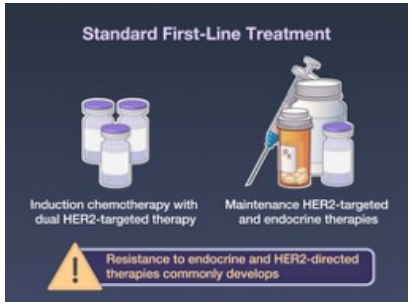

Addition of palbociclib to maintenance anti-HER2 and endocrine therapies
Palbociclib
+


Standard First-Line Treatment
Induction chemotherapy with dual HER2-targeted therapy
Maintenance HER2-targeted and endocrine therapies

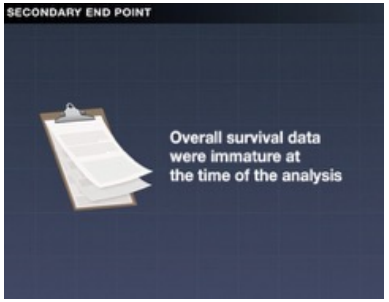

PATINA Trial
• 518 Patients
• Hormone-receptor–positive
• HER2-positive advanced breast cancer
• No disease progression after induction chemotherapy plus dual HER2-targeted therapy
BREAST CANCER CELL


SAFETY
Grade 3 Adverse Events
Grade 4 Adverse Events
Percentage of Patients
100
80
60
40
20
0
79.7%
30.6%
10.0%
3.6%
Palbociclib
Standard Therapy
Palbociclib
Standard Therapy

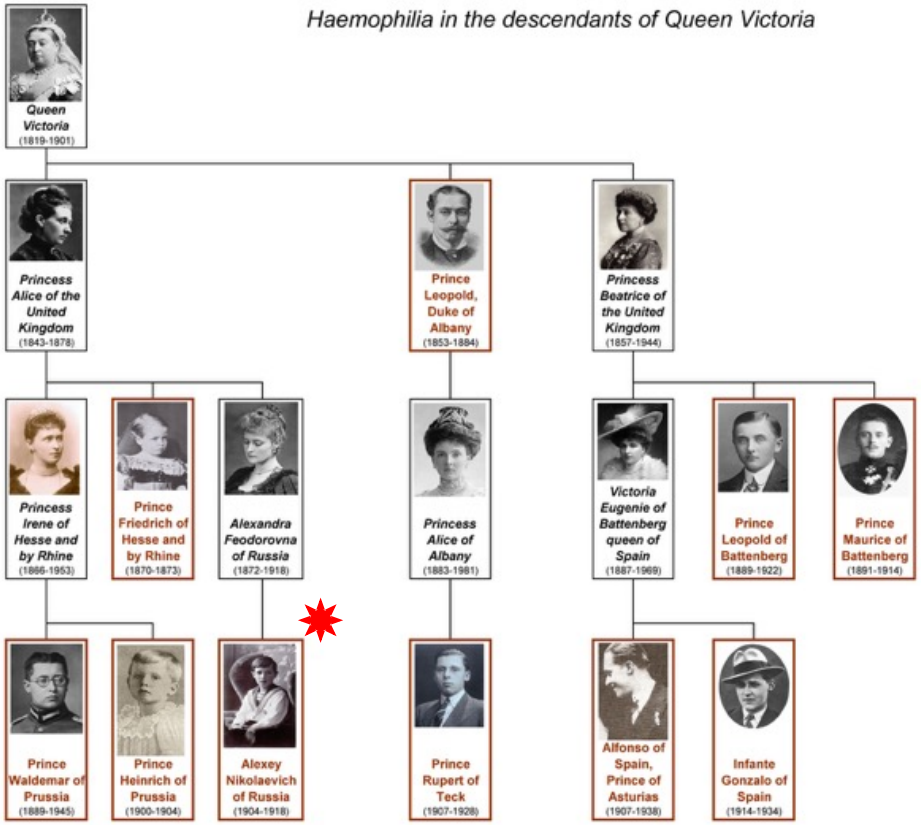

Addition of palbociclib to maintenance anti-HER2 and endocrine therapies
Palbociclib
+
Significantly longer progression-free survival
An increased incidence of neutropenia


Standard First-Line Treatment
Induction chemotherapy with dual HER2-targeted therapy
Maintenance HER2-targeted and endocrine therapies
Resistance to endocrine and HER2-directed therapies commonly develops

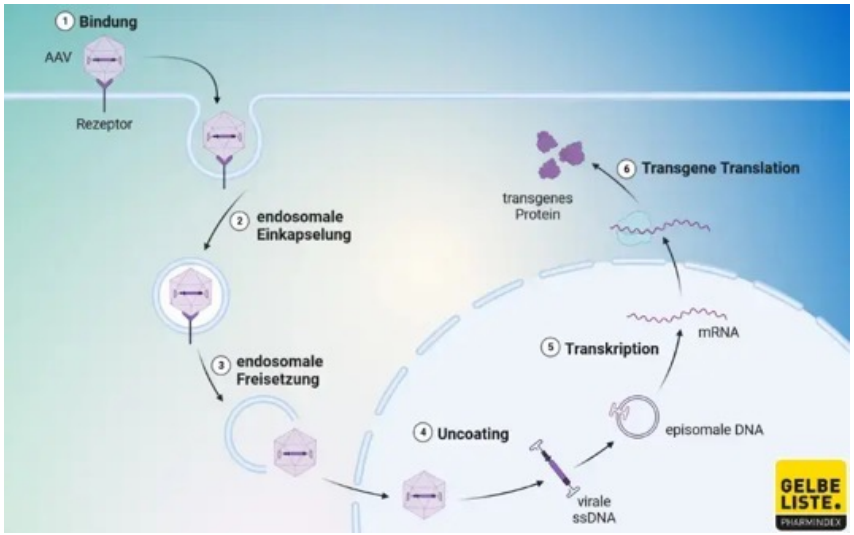

Maintenance Anti-HER2 + Endocrine Therapies + Palbociclib
+
Palbociclib
N=261
Maintenance Anti-HER2 + Endocrine Therapies
N=257


SECONDARY END POINT
Overall survival data were immature at the time of the analysis

Queen Victoria (1819–1901) was a carrier of Hemophilia B (factor IX deficiency), likely due to a spontaneous mutation, introducing it into European royalty. She passed the gene to three of her nine children—Leopold, Alice, and Beatrice—leading to its spread through the German, Russian, and Spanish royal houses.



Etranacogene dezaparvovec (Handelsname: **Hemgenix**) ist die weltweit erste zugelassene **Gentherapie** zur Behandlung von Erwachsenen mit **Hämophilie B** (Bluterkrankheit Typ B)



•**Wirkweise:** Ein modifiziertes Virus (AAV5-Vektor) schleust eine funktionelle Kopie des **Faktor-IX-Gens** direkt in die Leberzellen ein. Dort produziert der Körper den fehlenden Gerinnungsfaktor eigenständig.

•**Anwendung:** Es handelt sich um eine **einmalige intravenöse Infusion**.

•**Besonderheit:** Es nutzt die sogenannte "Padua-Variante" des Gens, die eine besonders hohe Gerinnungsaktivität (bis zu 8-mal höher als normal) erzeugt.

Wirkmechanismus

Etranacogen dezaparvovec ist ein Gentherapeutikum, das den menschlichen Gerinnungsfaktor IX exprimiert. Das Therapeutikum basiert auf einem nicht-replizierenden, rekombinanten Vektor, der vom Adeno-assoziierten Virus Serotyp 5 (AAV5) abgeleitet ist. Dieser Vektor trägt eine kodon-optimierte cDNA der menschlichen Gerinnungsfaktor IX-Variante R338L, auch bekannt als FIX-Padua.

Um sicherzustellen, dass die Expression des Faktors hauptsächlich in der Leber stattfindet, wird die cDNA von einem leberspezifischen Promotor, dem LP1, gesteuert. Durch diese spezifische Konstruktion ermöglicht Etranacogen dezaparvovec eine zielgerichtete und effiziente Produktion von Gerinnungsfaktor IX in den Leberzellen des Patienten, was zur Behandlung von Hämophilie B beiträgt.

Final Analysis of a Study of Etranacogene Dezaparvovec for Hemophilia B

Prophylactic treatment for hemophilia B necessitates lifelong, regular intravenous factor IX infusions. Gene therapy offers the possibility of a single-dose treatment that produces durable endogenous factor IX expression and disease control. Etranacogene dezaparvovec comprises an adeno-associated virus serotype 5 (AAV5) vector and the highly active Padua factor IX variant. The primary analysis of this study showed that etranacogene dezaparvovec reduced annualized bleeding rates and adverse events were mainly of low-grade severity. Final data from 5 years of follow-up are now available.

In this open-label, phase 3 study, after a lead-in period (≥6 months) of factor IX prophylaxis, we administered a single infusion of etranacogene dezaparvovec in men with hemophilia B (factor IX activity level, ≤2 IU per deciliter), regardless of preexisting AAV5 neutralizing antibodies. The prespecified 5-year analyses included adjusted annualized bleeding rates (difference between the post-treatment period of months 7 through 60 after gene therapy and the lead-in period), factor IX expression, and safety outcomes.

Conclusions

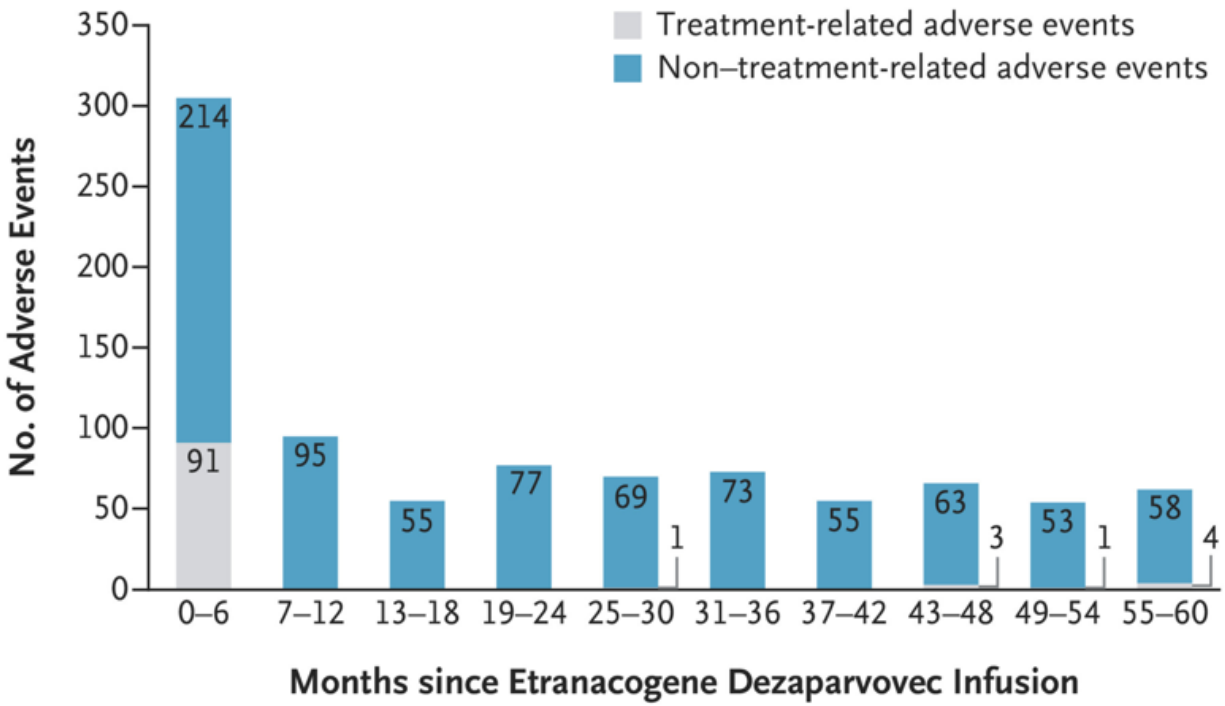
Sustained endogenous factor IX expression and low annualized bleeding rates over a 5-year period were observed after an infusion of etranacogene dezaparvovec.

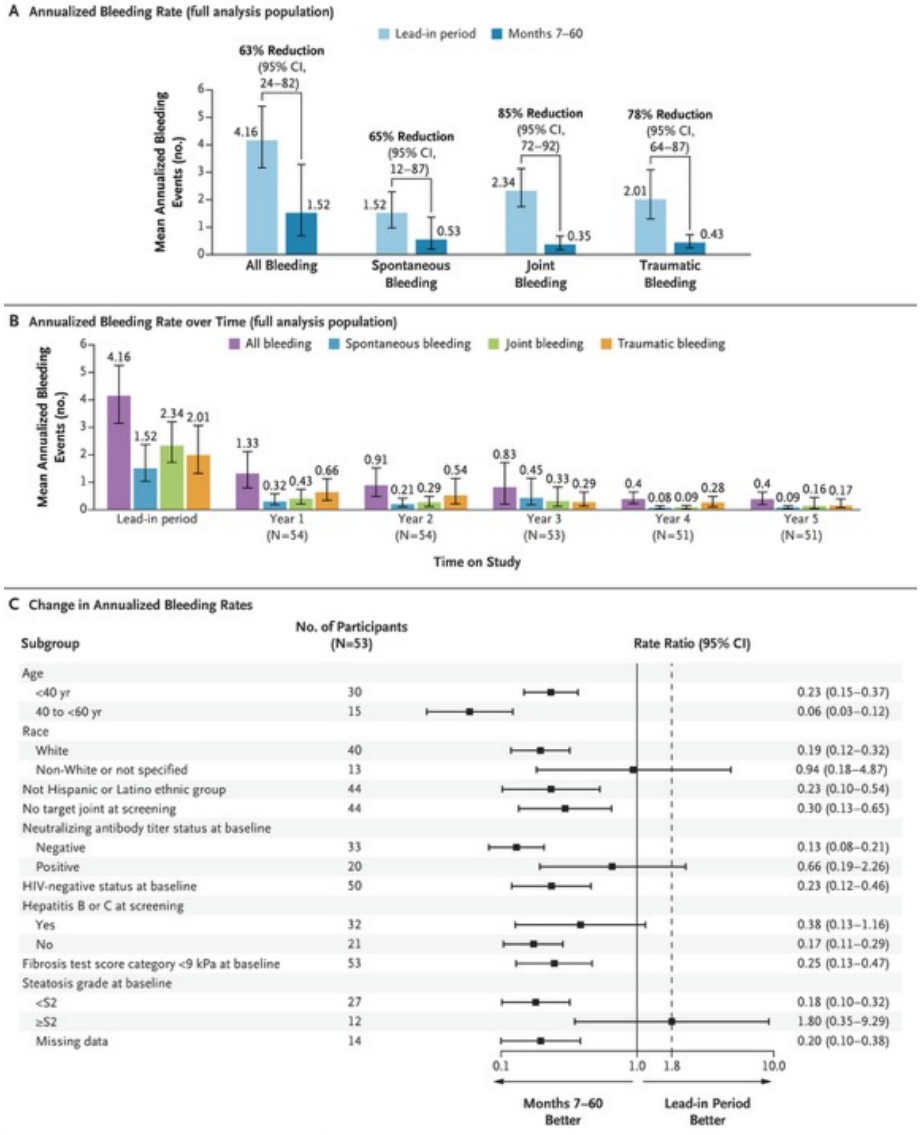
A phase 2b study of etranacogene dezaparvovec in 3 participants with severe or moderately severe hemophilia B (factor IX activity level, ≤2 IU per deciliter) showed that substituting wild-type factor IX with the factor IX Padua variant generated endogenous factor IX activity levels of at least 5 IU per deciliter at 6 weeks postinfusion (the primary efficacy end point). The mean factor IX activity level was 40.8 IU per deciliter at 1 year after gene therapy and was sustained at 45.7 IU per deciliter at 5 years.

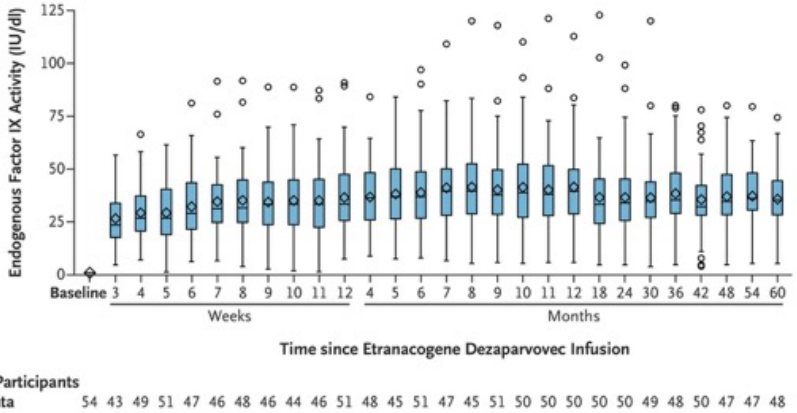
On the basis of the initial phase 2b data, a pivotal phase 3 study, Health Outcomes with Padua Gene; Evaluation in Hemophilia B (HOPE-B), of etranacogene dezaparvovec was conducted in 54 participants with severe or moderately severe hemophilia B. Earlier data from preclinical and clinical studies suggested that preexisting neutralizing antibodies to the AAV5 vector capsid of etranacogene dezaparvovec did not preclude hepatocyte transduction. Consequently, and in contrast to the majority of other hemophilia gene therapy trials, the HOPE-B study did not exclude persons with preexisting AAV5 neutralizing antibodies.

The primary analysis of the HOPE-B study showed that treatment with etranacogene dezaparvovec, assessed during months 7 through 18, was noninferior to standard care (factor IX prophylaxis for ≥6 months) with regard to the prespecified primary efficacy end point (the annualized bleeding rate), which supported the approval of etranacogene dezaparvovec for the treatment of hemophilia B. Further observation showed stability of endogenous factor IX activity levels. Here, we report the results of the final analysis of the HOPE-B study after 5 years of follow-up.

Event	Months 0 through 6 after Gene Therapy (N=54)		Months 7 through 60 after Gene Therapy (N=54)	
	no. of participants (%)	*no. of events*	*no. of participants (%)*	*no. of events*
Any adverse event	53 (98)	307†	53 (98)	605
Adverse events occurring in ≥5% of participants				
Covid-19	NA	NA	18 (33)	20
Fatigue	13 (24)	14	5 (9)	6
Arthralgia	13 (24)	18	19 (35)	36
Headache	13 (24)	23	11 (20)	12
Nasopharyngitis	13 (24)	16	8 (15)	10
Hepatic steatosis	NA	NA	13 (24)‡	13
Alanine aminotransferase increased	11 (20)	12	NA	NA
Pain in extremity	NA	NA	8 (15)	9
Influenza-like illness	7 (13)	11	3 (6)	4
Blood creatine kinase increased	7 (13)	9	5 (9)	5
Aspartate aminotransferase increased	6 (11)	7	5 (9)	5
Cough	6 (11)	6	4 (7)	4
Oropharyngeal pain	6 (11)	6	NA	NA
Joint swelling	NA	NA	6 (11)	6
Arthritis	NA	NA	5 (9)	5
Ligament sprain	NA	NA	5 (9)	5
Malaise	5 (9)	7	NA	NA
Urinary tract infection	NA	NA	4 (7)	6
Influenza	3 (6)	3	4 (7)	7
Bursitis	NA	NA	4 (7)	4
Back pain	4 (7)	4	14 (26)	16
Pain	4 (7)	4	NA	NA
Diarrhea	4 (7)	4	3 (6)	3
Nausea	4 (7)	4	4 (7)	4
Dizziness	4 (7)	4	4 (7)	4
Parasthesia	NA	NA	4 (7)	4
Osteoarthritis	NA	NA	4 (7)	4
Chest pain	NA	NA	4 (7)	4
Skin abrasion	NA	NA	4 (7)	4
Vitamin D deficiency	NA	NA	4 (7)	4
Anemia	NA	NA	4 (7)	4
Depression	NA	NA	4 (7)	4
Insomnia	NA	NA	3 (6)	3
Dyspnea	NA	NA	3 (6)	8
Rash	NA	NA	3 (6)	6
Upper respiratory tract infection	NA	NA	3 (6)	4
Coronavirus infection	NA	NA	3 (6)	3
Sinusitis	NA	NA	3 (6)	3
Muscle spasms	NA	NA	3 (6)	4
Musculoskeletal chest pain	NA	NA	3 (6)	4
Atrial fibrillation	NA	NA	3 (6)	3
Myalgia	3 (6)	3	NA	NA
Chills	3 (6)	3	NA	NA
Infusion-related reaction	3 (6)	3	NA	NA
C-reactive protein increased	3 (6)	3	3 (6)	3
Blood glucose increased	NA	NA	3 (6)	3
Blood creatinine increased	NA	NA	3 (6)	3
Toothache	3 (6)	3	6 (11)	10
Hemorrhoids	3 (6)	3	3 (6)	4
Hypertension	3 (6)	3	5 (9)	5
Iron-deficiency anemia	3 (6)	3	NA	NA
Fall	NA	NA	3 (6)	3
Limb injury	NA	NA	3 (6)	3







Etranacogene dezaparvovec (Hemgenix) is an adeno-associated virus vector serotype 5 (AAV5) based gene therapy that does not bind to a traditional "receptor" but rather utilizes AAV5 capsid-mediated tropism to target liver cells (hepatocytes). It binds to specific receptor molecules on hepatocytes to deliver the Padua factor IX gene.

Discussion

The end-of-study data from the HOPE-B study showed that a single dose of etranacogene dezaparvovec led to durable and effective endogenous factor IX Padua expression that was sustained over a 5-year period in participants with severe or moderately severe hemophilia B. Annualized bleeding rates remained low, and a marked decrease in exogenous factor IX consumption was observed. Furthermore, most gene therapy–related adverse events occurred in the first 6 months after the infusion, and no AAV-related oncogenicity had been reported at 5 years after infusion. To inform clinical practice, data for individual participants regarding factor IX expression and bleeding events over the 5-year follow-up were provided. Of the 52 participants with a response who stopped factor IX prophylaxis after the etranacogene dezaparvovec infusion, only 1 resumed factor IX prophylaxis during the 5-year follow-up period.

Possible complications, including factor IX inhibitors and thrombotic events, were not observed. Specifically, thrombotic microangiopathy, which has complicated some studies that used high doses of systemically administered non-AAV5 serotype vectors, was not observed in this study. This favorable safety profile is notable considering the presence of AAV5 total binding IgG (which is potentially capable of activating complement) in 24% of the treated participants and AAV5 neutralizing antibodies in 39%.

showcase

Die **Schaufensterkrankheit**, medizinisch als **periphere arterielle Verschlusskrankheit (pAVK)** bezeichnet, ist eine Durchblutungsstörung der Beine, bei der verengte oder verschlossene Arterien die Sauerstoffzufuhr zur Muskulatur einschränken.

Das Wichtigste auf einen Blick:

- **Symptome:** Typisch sind krampfartige Schmerzen in der Wade, im Oberschenkel oder Gesäß, die beim Gehen auftreten und nach einer kurzen Pause (beim „Schaufensterbummel“) wieder verschwinden. In fortgeschrittenen Stadien treten Ruheschmerzen oder schlecht heilende Wunden auf.
- **Ursache:** Meist liegt eine Arteriosklerose (Gefäßverkalkung) zugrunde. Hauptrisikofaktoren sind **Rauchen**, Diabetes, Bluthochdruck und erhöhte Blutfettwerte.
- **Diagnose:** Erfolgt durch Spezialisten (Angiologen) mittels Pulsprüfung, Messung des Knöchel-Arm-Index (ABI) und Ultraschall.
- **Behandlung:**
  - **Lebensstil:** Absoluter Rauchstopp und eine Ernährungsumstellung.
  - **Training:** Gezieltes Gefäßtraining zur Förderung der Kollateralbildung (Umgehungskreisläufe).
  - **Eingriffe:** Bei starken Einschränkungen kommen Katheterbehandlungen (Ballon oder Stent) oder Bypass-Operationen zum Einsatz.

Peripheral Artery Disease in the Legs

Summary

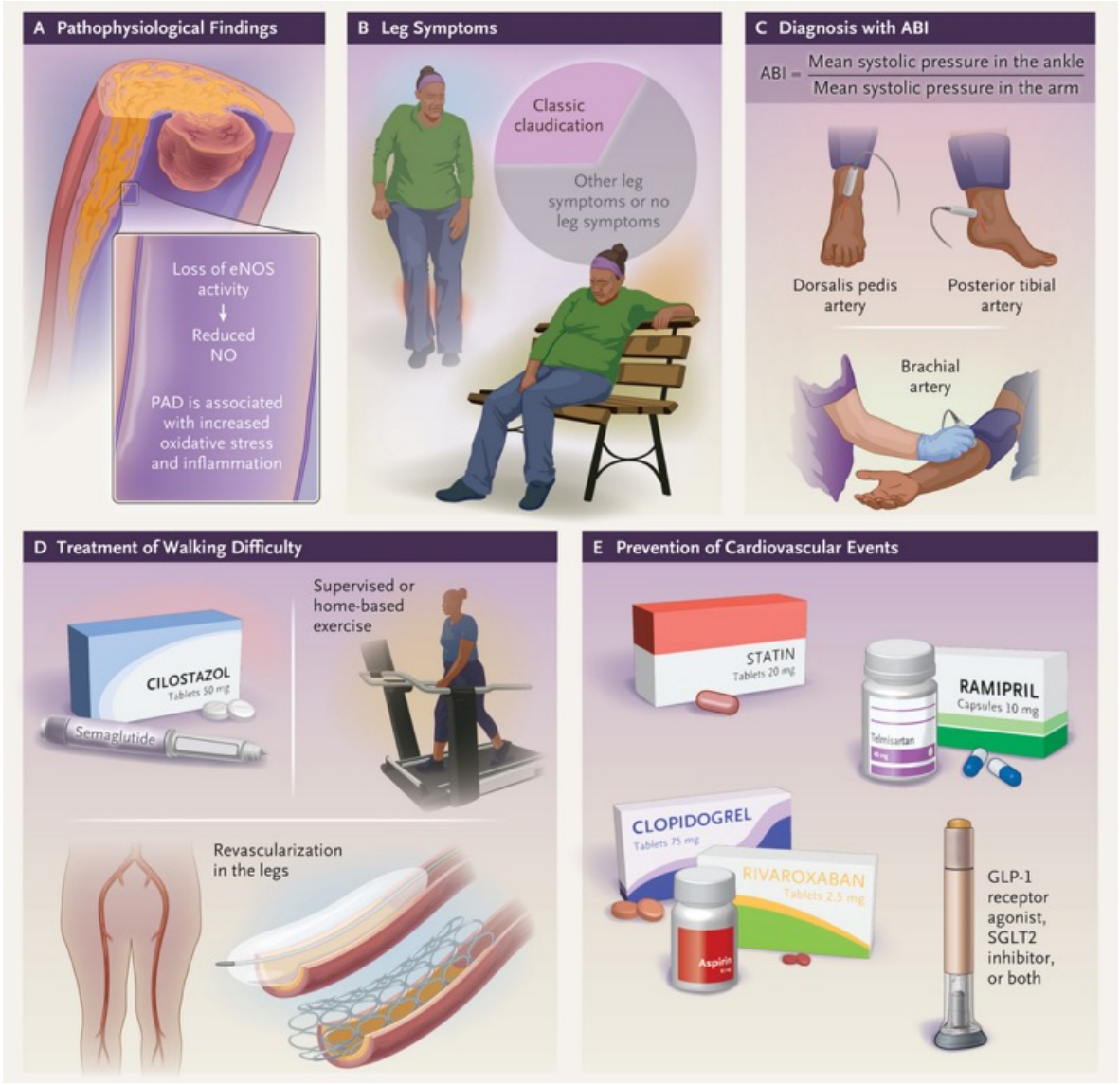
Peripheral artery disease affects approximately 236 million persons worldwide and is diagnosed with an ankle–brachial index of less than 0.90. Among older persons, 3.3% of those without peripheral artery disease, 18.1% with mild disease, and 52.0% with severe disease could not complete a 6-minute walk test without resting. To prevent cardiovascular events in persons with peripheral artery disease, intensive cholesterol-lowering medications (statins), antiplatelet medications or low-dose aspirin with rivaroxaban, blood-pressure lowering to less than 130/80 mm Hg, and semaglutide are recommended, along with sodium–glucose cotransporter 2 inhibitors in patients with diabetes. Supervised walking exercise and structured home-based walking exercise each improve walking ability in persons with peripheral artery disease. Revascularization in the legs should be reserved for those with persistent disease symptoms that do not respond to exercise.

A 62-year-old woman with type 2 diabetes, hypertension, and a history of cigarette smoking presents with exertional leg symptoms consistent with peripheral artery disease. She reports pain in the buttocks and lower legs with walking that resolves within 10 minutes after rest. Walking more than one or two blocks is difficult because of these symptoms. Her blood pressure is 150/70 and pulse is 82 beats per minute. No femoral bruits are audible, the calf muscles are atrophic, and the dorsalis pedis and posterior tibial pulses are grade 1+ bilaterally (range, grade 0 to 3+, with grade 3+ indicating a normal pulse). The ankle–brachial index (ABI; the ratio of the posterior tibial or dorsalis pedis systolic pressure to the brachial systolic pressure) is 0.56 on the right side and 0.64 on the left side. She has no symptoms or history of heart failure. Because of difficulty walking, she no longer engages in activities she enjoys. How would you treat this patient?

Peripheral Artery Disease in the Legs

- Up to 90% of persons with peripheral artery disease do not have classic claudication symptoms, and approximately 60% are asymptomatic.
- An ankle–brachial index (the ratio of the systolic blood pressure in the ankle to the systolic blood pressure in the arm) of less than 0.90 is 72 to 89% accurate for diagnosing the disease.
- In population studies, 10-year cardiovascular mortality was greater among persons with peripheral artery disease than among those without the condition for both men (18.7% vs. 4.4%) and women (12.6% vs. 4.1%).
- In a study involving older participants, 3.3% of those without peripheral artery disease, 18.1% of those with mild disease, and 52.0% of those with severe disease could not complete a 6-minute walk test without resting.

- Interventions for preventing cardiovascular events in persons with peripheral artery disease include intensive cholesterol-lowering medications (such as statins), antiplatelet medications or low-dose aspirin with rivaroxaban, blood-pressure lowering to less than 130/80 mm Hg, semaglutide, and sodium–glucose cotransporter 2 inhibitors for persons with diabetes.
- Supervised walking exercise and structured home-based walking exercise can each improve walking ability in persons with peripheral artery disease, cilostazol and semaglutide provide modest benefits, and revascularization in the legs should be reserved for persons with persistent disease symptoms that do not respond to exercise.



Diagnosis and Treatment of Peripheral Artery Disease.

Pathophysiological findings include endothelial damage with reduced activity of endothelial nitric oxide synthase (eNOS) and lower abundance of nitric oxide (NO) (Panel A). This damage results in early atherosclerosis, which progresses and includes a thrombotic component. Inflammation also contributes to the atherosclerosis. Classic symptoms include calf pain during walking activity that increases with greater walking distance and resolves within 10 minutes after rest (Panel B). However, approximately two thirds of patients have exertional leg symptoms other than classic claudication or report no exertional leg symptoms (i.e., are asymptomatic). The ankle–brachial index (ABI) is the ratio of the posterior tibial or dorsalis pedis systolic pressure (or their mean) to the mean of the brachial artery systolic pressures (Panel C). The systolic pressures are measured with Doppler ultrasonography. An ABI of less than 0.90 is consistent with peripheral artery disease (PAD). Treatment of leg symptoms and walking difficulty in peripheral artery disease includes walking exercise (supervised or structured home-based walking exercise), cilostazol, semaglutide, or leg revascularization (or a combination of these therapies) (Panel D). Prevention of cardiovascular events may include a potent statin, blood-pressure treatment (ramipril or telmisartan) to maintain a blood pressure less than 130/80, antiplatelet therapy (aspirin or clopidogrel) or rivaroxaban plus aspirin, and a glucagon-like peptide-1 (GLP-1) receptor agonist, a sodium–glucose cotransporter 2 (SGLT2) inhibitor (for patients with peripheral artery disease and diabetes), or both (Panel E).

Overview of PAD in the Legs.

Characteristic	Evidence
No. of persons affected	PAD affects approximately 12.5 million persons in the United States[1] and approximately 236 million persons worldwide.[2]
Prevalence	PAD occurs in approximately 10 to 12% of persons 65 years of age or older[4] and in approximately 15 to 20% of those older than 80 years.[4]
Risk factors	Older age, cigarette smoking, diabetes mellitus, high cholesterol, hypertension, sedentary lifestyle, and elevated lipoprotein(a) levels are risk factors for PAD.[3]
Symptoms	Most persons with PAD have difficulty walking long distances,[5] most do not have classic symptoms of intermittent claudication, many report no exertional leg symptoms, and others have atypical symptoms such as hip pain or low back pain when walking that resolves with rest.[5,6]
Diagnosis	An ABI of less than 0.90 is 69 to 79% sensitive, 83 to 99% specific, and 72 to 89% accurate for diagnosing PAD.[7] In a population study, an absent dorsalis pedis pulse was 50% sensitive and 73% specific for diagnosing PAD and an absent posterior tibial pulse was 71% sensitive and 91% specific.[8]
Adverse outcomes	
Cardiovascular events	The rate of cardiovascular events and death from cardiovascular causes among persons with PAD is 2 to 3 times as high as that among persons without PAD, even after adjustment for potential confounders.[3,9,10] Among 48,294 participants in epidemiologic studies, death from cardiovascular causes had occurred in 18.7% of men with PAD and 4.4% of men without PAD[9] and in 12.6% of women with PAD and 4.1% of women without PAD at 10-year follow-up.[9] Among 13,885 patients with symptomatic PAD and either an ABI of less than 0.80 or previous lower-extremity revascularization, 10.7% had a myocardial infarction, ischemic stroke, or death from cardiovascular causes at a median follow-up of 30 months.[10]
Major adverse limb events	The incidence of major adverse limb events (severe leg ischemia resulting in revascularization or amputation) ranges from 12.9 to 15.2% over 1.8 to 2.7 years of follow-up.[11-13] Major adverse limb events are more common after leg revascularization.[11-13]
Walking impairment	Persons with PAD have difficulty walking longer distances. For example, among 740 persons 55 years of age or older (460 persons with PAD) who underwent a 6-minute walk test, 29.5% of those with an ABI of less than 0.90 stopped to rest during the test as compared with 3.3% of those with a normal ABI of 1.10 to 1.40, with adjustment for confounders.[5] In addition, the distance walked in 6 minutes decreases at a significantly faster rate among persons with PAD than those without PAD.[14,15]

First-Line Therapies for Walking Disability in Patients with PAD.

Variable	Cilostazol[19,21]	Leg Revascularization[27-29]	Supervised Walking Exercise[22,30-32]	Home-Based Walking Exercise[22,32-34]
Description	Phosphodiesterase 3 inhibitor	Surgical removal of plaque or bypass of occluded artery Nonsurgical catheter-based (endovascular) balloon angioplasty, stent placement, lithotripsy, or atherectomy	Typically performed on a treadmill in the presence of an exercise physiologist, nurse, or coach	Performed in or around the home not in the presence of an exercise physiologist or a nurse but with regular contact with a coach
Indications	Patients with PAD and leg symptoms limiting walking ability; contraindicated in patients with any heart failure	Patients with disabling PAD symptoms that have not responded adequately to exercise therapy	Recommended for all persons with PAD	Recommended for all persons with PAD
Dose or prescription	Begin with 50 mg twice daily and adjust up to 100 mg twice daily	NA	Three times weekly, with a goal of working up to 50 minutes per session if possible	Three to five times weekly for 30 to 50 minutes per session
Efficacy	Resulted in a maximal treadmill walking distance that was approximately 40 m longer than that with placebo	Increase in maximal treadmill walking distance by 110 to 202 m (within-group comparison) with femoropopliteal endovascular angioplasty and by 316 to 685 m (within-group comparison) with aortoiliac endovascular angioplasty	Resulted in a 6-minute walking distance that was 31.8 m longer and a maximal treadmill walking distance that was 180 m longer than that with control	Resulted in a 6-minute walking distance that was 55.6 m longer and a maximal treadmill walking distance that was 50 to 55 m longer than that with control
Adverse effects	Headache, palpitations, or diarrhea	Repeat revascularization, restenosis, or acute limb ischemia	Generally safe, with possibility of a cardiovascular event, fall, or worsening of foot ulcer	Generally safe, with possibility of a cardiovascular event, fall, or worsening of foot ulcer
Other considerations	If a patient does not have improved walking ability after 12 weeks, cilostazol should be discontinued.	Shorter length of stenosis and the absence of diabetes, current smoking, and chronic kidney disease are associated with better outcomes of endovascular procedures.	Supervised walking exercise is covered by CMS for up to 24 weeks in a lifetime. Many patients with PAD do not have access to supervised exercise or find it burdensome to travel for exercise.	Home-based walking exercise is not covered by CMS or insurance. Structured programs with behavioral change interventions are most effective.

Walking Exercise Therapies for PAD.

	Supervised Walking Exercise	Structured Home-Based Walking Exercise
Definition	Walking for exercise at a health care facility in the presence of a coach (typically an exercise physiologist or nurse)	Walking for exercise in or around the home, without direct supervision but with regular contact with a coach (by telephone or occasional in-person sessions)
Frequency of exercise	Three times weekly[22]	Three to five times weekly[32-34]
Characteristics	Repeated bouts of walking exercise to attain maximal ischemic leg pain within 10 minutes after the start of each bout[22]	Walking at a pace that induces ischemic leg symptoms within 10 minutes after the start of exercise[33,34]
Coach's role	Provides direct supervision and feedback during exercise	Helps patient adhere to walking exercise using behavioral methods such as setting walking exercise goals, managing ischemic leg symptoms during exercise, monitoring exercise activity relative to goals, and building self-efficacy
Effects as compared with control		
6-Minute walk distance	Increases by 31.8 m[22]	Increases by 55.6 m[22]
Maximal treadmill walking distance	Increases by approximately 180 m[22,32]	Increases by approximately 50 to 55 m[32-34]
Durability	Benefits are gone by 6 months after exercise ends, and possibly earlier.[31]	Although benefit wanes when the intervention ends, persistent benefit has been observed at 6 months after completion of the home-based exercise program.[35]
Advantages	Presence of a coach during exercise can be motivating and provides immediate assistance with management of ischemic leg symptoms.	Walking in or around the home is convenient and accessible for many patients with PAD.
Disadvantages	Traveling three times weekly for exercise is burdensome. Centers for supervised exercise are not widely available.	Absence of an in-person coach requires more initiative from patients with PAD.
Insurance coverage	Covered by Medicare	Not covered by Medicare
Other	Medicare also covers supervised nonwalking exercise, such as cycling or resistance training.	Structured home-based exercise programs with varying intervention characteristics, such as coach contact by telephone or weekly in-person visits, have been shown to be effective.

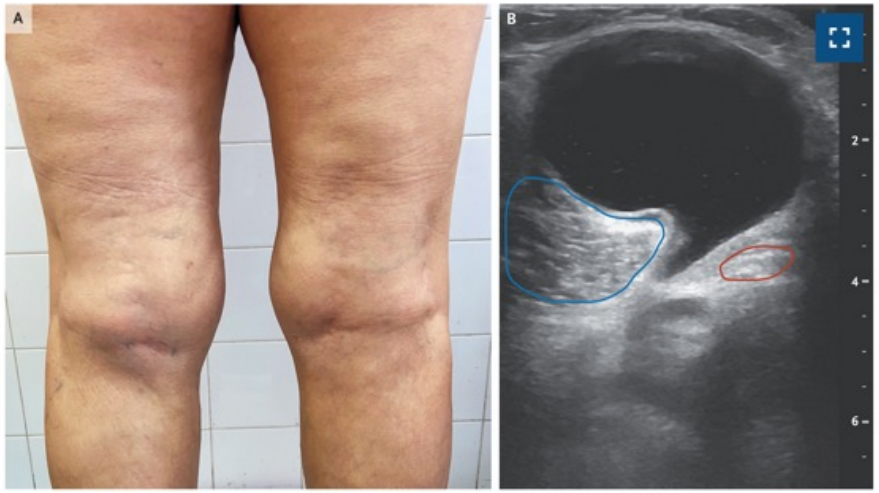
Areas of Uncertainty

First, the most effective combinations and the best timing of therapies (i.e., home-based or supervised exercise, cilostazol, GLP-1 receptor agonists, and leg revascularization) to improve walking performance need to be defined. Currently, no single therapy eliminates walking disability in persons with peripheral artery disease. Second, the effects of medications that reduce inflammation, such as canakinumab, and of those that stimulate skeletal muscle growth, such as bimagrumab, on walking in persons with the disease should be studied. Third, the ability of antiinflammatory medications, such as colchicine, to prevent cardiovascular events is unclear.

Conclusions and Recommendations

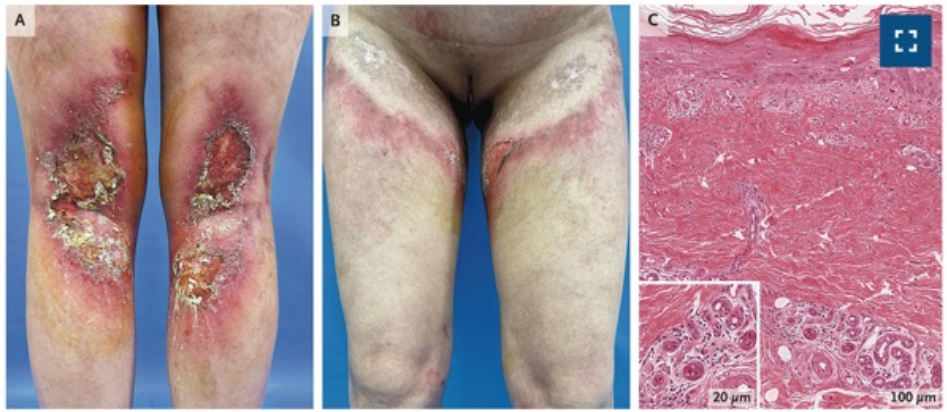
For the patient in the vignette, I would recommend 12 weeks of supervised exercise if the patient can travel for exercise three times weekly and has insurance coverage for supervised exercise. If the patient is not interested in or able to adhere to supervised exercise, or if payment for supervised exercise is difficult, I would recommend structured home-based walking exercise. Cilostazol and semaglutide are reasonable supplemental therapies that can be prescribed for walking impairment. If these treatments do not adequately improve peripheral artery disease symptoms, revascularization can be considered. To prevent cardiovascular events, I would prescribe atorvastatin or rosuvastatin at the highest dose that does not cause unacceptable adverse events, prescribe treatment for lowering blood pressure to less than 130/80 mm Hg, and prescribe either rivaroxaban at a dose of 2.5 mg twice daily with low-dose aspirin or clopidogrel alone. I would consider an SGLT2 inhibitor and semaglutide to reduce cardiovascular events in this patient.

Baker's Cyst



A 63-year-old woman with psoriatic arthritis involving her knees presented to the rheumatology clinic with a 9-month history of pain in the left knee. The patient's psoriatic arthritis had recently been well controlled with leflunomide and monthly golimumab injections. The physical examination was notable for a nontender, palpable mass in the left popliteal fossa that was more prominent when the patient was standing with the knee in full extension (Panel A). Point-of-care musculoskeletal ultrasonography (Panel B) showed a well-defined, anechoic, fluid-filled structure resembling a "speech bubble," with a neck extending into the joint space between the medial head of the gastrocnemius muscle (blue outline) and the semimembranosus tendon (red outline). A diagnosis of a Baker's cyst was made. A Baker's cyst — also known as a popliteal synovial cyst — results when synovial fluid from the knee joint flows into and accumulates in the gastrocnemius–semimembranosus bursa. Baker's cysts are associated with underlying joint disorders, including osteoarthritis, traumatic injury, or inflammatory arthritis (as in this case). Imaging is not always required to make the diagnosis but may help rule out other conditions. Ultrasound-guided aspiration of the cyst was performed, and an intracystic glucocorticoid injection was given. The patient's knee pain abated shortly after treatment, and she had remained pain-free as of the 2-month follow-up.

Toxic Erythema of Chemotherapy



A 55-year-old woman with invasive ductal carcinoma presented to the dermatology clinic with a painful rash in her body folds. Three months earlier, treatment with albumin-bound paclitaxel, liposomal doxorubicin, and cyclophosphamide had been started. One week after the third cycle of chemotherapy, a rash had developed in the patient's armpits that had abated 1 week later. After the fourth and fifth cycles, the rash had recurred and spread to other areas. On physical examination, confluent erythematous plaques with overlying crusting and erosions were noted in the popliteal fossae (Panel A), groin (Panel B), antecubital fossae, axillae, and buttocks. Histopathological analysis of a biopsy sample obtained from the left thigh showed vacuolar changes in basal cells, necrotic keratinocytes, and squamous syringometaplasia of eccrine ducts (Panel C, inset shown at higher resolution). A diagnosis of toxic erythema of chemotherapy was made. Toxic erythema of chemotherapy refers to a spectrum of chemotherapy-induced, nonallergic skin reactions. It may occur in an intertriginous distribution or on the hands and feet, manifesting as hand–foot syndrome. In this case, all three chemotherapeutic agents were thought to be possibly responsible. Treatment with a brief tapering course of oral glucocorticoids, emollients, and wound care was given. The rash did not flare after doses in the sixth cycle of chemotherapy were modified. Three months after presentation, the rash had resolved.

Case 4-2026: An 80-Year-Old Woman with Cough and Hypoxemia

An 80-year-old woman was admitted to this hospital because of cough and hypoxemia.
The patient had been in her usual state of health — active in her community and biking to appointments and social engagements — until 8 weeks before the current presentation, when a productive cough developed. She also had rhinorrhea and headache, as well as fatigue and poor appetite. The patient thought that she might have influenza but did not seek medical care. During the next 3 weeks, rhinorrhea and headache resolved, but cough, fatigue, and poor appetite persisted.
Five weeks before the current presentation, the patient presented to her primary care physician with a pruritic, vesicular rash in a dermatomal distribution on the left flank. She also noted subjective chills. She received a diagnosis of herpes zoster, and treatment with valacyclovir was started, along with acetaminophen as needed for pain. One day later, nausea developed and one episode of vomiting occurred; these symptoms were attributed to the use of valacyclovir. The patient completed a 14-day course of valacyclovir, after which nausea resolved, but cough, fatigue, poor appetite, and chills persisted during the next 3 weeks.

Six days before the current presentation, subjective fever developed, and the patient was evaluated in the urgent care clinic affiliated with her primary care physician's office. She reported that she had lost weight during the previous 8 weeks. The temporal temperature was 37.2°C, the blood pressure 122/86 mm Hg, the heart rate 78 beats per minute, the respiratory rate 18 breaths per minute, and the oxygen saturation 94% while she was breathing ambient air. The weight was 57.4 kg and had decreased by 6.1 kg since the last time her weight had been checked in the clinic, 9 months earlier. The lungs were reportedly clear on auscultation. The blood levels of glucose, electrolytes, aspartate aminotransferase, and alanine aminotransferase were normal, as were the results of kidney-function tests; other laboratory test results are shown. Chest radiography reportedly showed normal lungs with possible trace fluid in the fissure. A 5-day course of oral doxycycline was prescribed, along with benzonatate, and an appointment was scheduled with the patient's primary care physician for evaluation of weight loss.

Variable	Reference Range, Adults, Urgent Care Clinic	6 Days before Current Presentation, Urgent Care Clinic	Reference Range, Adults, This Hospital*	On Current Presentation, This Hospital
Hematocrit (%)	34–47	38.5	36–46	35.3
Hemoglobin (g/dl)	12–16	12.9	12–16	12.1
White-cell count (per μl)	4500–11,000	5900	4000–11,000	7810
Differential count (per μl)				
Neutrophils	1800–8000	4190	1920–7600	6230
Lymphocytes	1000–4800	870	720–4100	740
Monocytes	220–1000	640	160–1100	690
Eosinophils	0–600	180	0–500	70
Basophils	0–300	30	0–150	40
Platelet count (per μl)	150,000–400,000	253,000	150,000–450,000	296,000
C-reactive protein (mg/liter)	—	—	<8.0	52.7
Erythrocyte sedimentation rate (mm/hr)	—	—	0–29	58
Procalcitonin (ng/ml)	—	—	<0.25	0.11
Venous blood gas				
pH	—	—	7.30–7.40	7.48
Partial pressure of oxygen (mm Hg)	—	—	35–50	49
Partial pressure of carbon dioxide (mm Hg)	—	—	38–50	32

One year before the current presentation, the patient had received a diagnosis of metastatic squamous-cell carcinoma of unknown primary site after presenting with a palpable left axillary lymph node. At that time, flow cytometry of the biopsy specimen was performed, but there were insufficient cells for analysis. Combined positron-emission tomography and computed tomography (CT) revealed multiple hypermetabolic lymph nodes in the left cervical chain, as well as a region of hypermetabolism in the left lateral portion of the oropharynx that corresponded with the left tonsillar pillar. The left tonsil was resected but showed no evidence of cancer. The patient underwent lymphadenectomy of the left axillary lymph node with known carcinoma, as well as concurrent dissection of seven additional lymph nodes, which also showed no evidence of cancer. The patient's current medications included citalopram, loratadine, and fluticasone propionate nasal spray. She had no known adverse reactions to medications. Her family history included hypertension in her mother and maternal grandmother; her father had died from gastric cancer at 53 years of age. The patient was single and lived in Massachusetts; she had no pets. She had been sexually active until 2 years before the current presentation. She had retired from her job at a nonprofit organization, for which she had traveled extensively. She had taken trips to South America, Central America, and East Africa; her most recent travel outside the United States was a trip to Kenya, Rwanda, and Tanzania 6 years before the current presentation. She was a lifelong nonsmoker and did not use illicit drugs. She drank one glass of wine per week.

On examination, the temporal temperature was 37.3°C, the blood pressure 158/86 mm Hg, the pulse 93 beats per minute, the respiratory rate 16 breaths per minute, and the oxygen saturation 83% while the patient was breathing ambient air. She was coughing but able to speak in complete sentences without respiratory distress. The oxygen saturation increased to 93% while the patient was receiving supplemental oxygen through a nasal cannula at a rate of 4 liters per minute. The oropharynx was clear. On the pulmonary examination, rhonchi were present over all the lung fields but were most prominent over the right lower lobe. On the cardiac examination, the heart rate and rhythm were regular, without murmurs; no jugular venous distention was noted. There was no clubbing or edema. The remainder of the examination was normal.

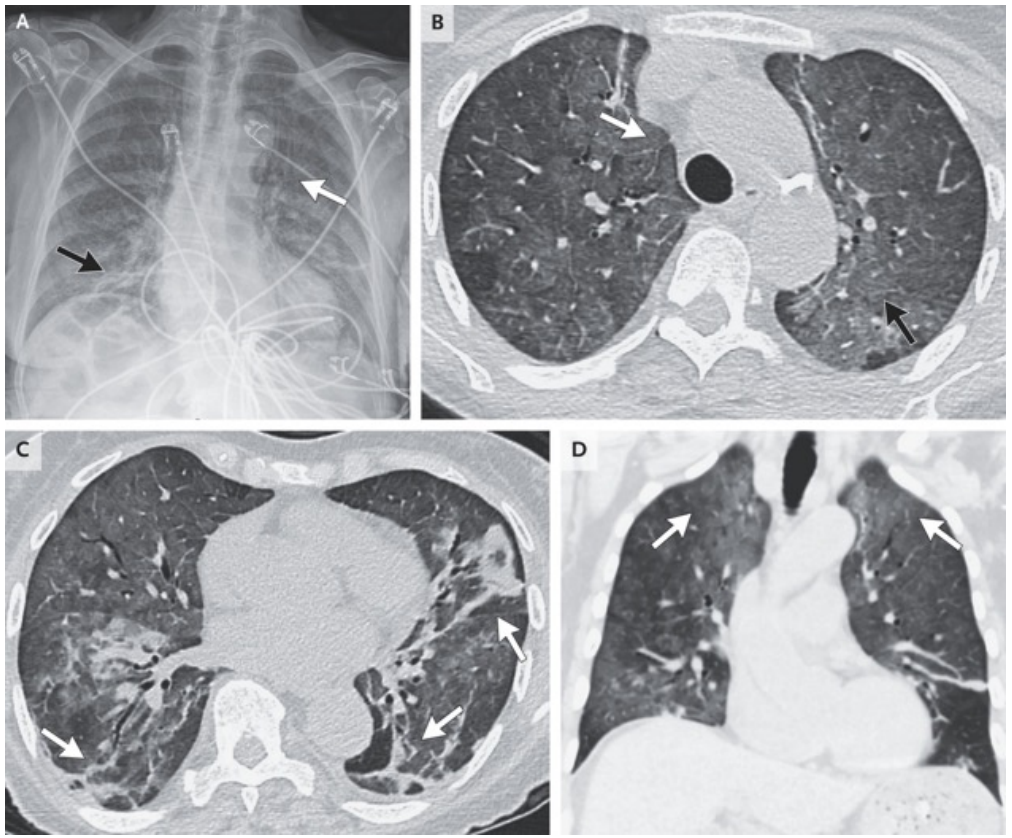
On admission, chest radiography (Figure 1A) revealed hazy perihilar opacities with indistinct pulmonary vasculature, as well as linear opacities at the lung bases that were most likely indicative of subsegmental atelectasis. The cardiac silhouette was normal, and there was no pleural effusion. Subsequent chest CT (Figure 1B, 1C, and 1D) revealed diffuse central (rather than peripheral) ground-glass opacities in both lungs with apical predominance, sparing the lung bases. Trace interlobular septal thickening was present; however, there was no pleural effusion, and the cardiac chambers were normal in size. No evidence of pulmonary nodules, cysts, or bronchiectasis was identified, and no lymphadenopathy was present.

Treatment with intravenous ceftriaxone and oral azithromycin was started. On hospital day 2, the temporal temperature increased to 39.3°C. The blood pressure was 151/79 mm Hg, the heart rate 108 beats per minute, the respiratory rate 16 breaths per minute, and the oxygen saturation 92% while the patient was receiving supplemental oxygen through a nasal cannula at a rate of 4 liters per minute. Blood specimens were obtained for culture.

A diagnostic test was performed.

Differential Diagnosis

This older woman had been in relatively good health until 8 weeks before the current presentation, when cough, fatigue, anorexia, and weight loss developed. She presented with shortness of breath and was found to be febrile and hypoxemic, with diffuse ground-glass opacities seen on chest CT. Given the undifferentiated nature of the patient's subacute respiratory syndrome, I will begin by considering broad categories of disease, including infection, cancer, and autoimmune and connective-tissue disorders.



Der Begriff **ground-glass appearance** (oder *ground-glass opacity*, GGO) wird im Deutschen primär als **Milchglastrübung** oder **Milchglasverdichtung** bezeichnet.

Infection

In this febrile and hypoxemic patient with involvement of the lower respiratory tract, bacterial infection should be considered. However, the progression of symptoms over a period of 8 weeks is uncharacteristic of typical bacterial pneumonia.

Cancer

Approximately 1 year before the current presentation, the patient had received a diagnosis of metastatic squamous-cell carcinoma of unknown primary site with involvement of a left axillary lymph node. This aspect of her medical history suggests the possibility of recurrent or metastatic cancer; however, she had undergone lymphadenectomy of the node with known carcinoma, and there was no evidence of residual disease.

Autoimmune and Connective-Tissue Disorders

Autoimmune disorders merit consideration, given the patient's constitutional symptoms, elevated levels of inflammatory markers, and diffuse ground-glass opacities on chest CT. Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitides, specifically granulomatosis with polyangiitis and microscopic polyangiitis, may result in ground-glass opacities due to pulmonary hemorrhage.

Immunocompromised Host

The patient had a relatively slow progression of symptoms, over a period of 8 weeks, that eventually culminated in a more acute presentation with fever, hypoxemia, and diffuse ground-glass opacities. The clinical course merits consideration of atypical diseases, including those that may be associated with immunocompromise. Although herpes zoster is commonly associated with advanced age, it may also indicate an underlying immunodeficiency syndrome.

Pivoting into this theory requires revisiting this patient's clinical timeline, not just in the past several weeks but in the past decade. The patient had a history of extensive international travel, including trips to East Africa, Central America, and South America. Her last trip had been approximately 6 years earlier, and she had visited Kenya, Rwanda, and Tanzania. She had been sexually active until 2 years before the current presentation, which suggests the possibility that she had acquired human immunodeficiency virus (HIV) infection during her travels to regions of East Africa where the disease is endemic and the prevalence of the virus is higher than the global average.

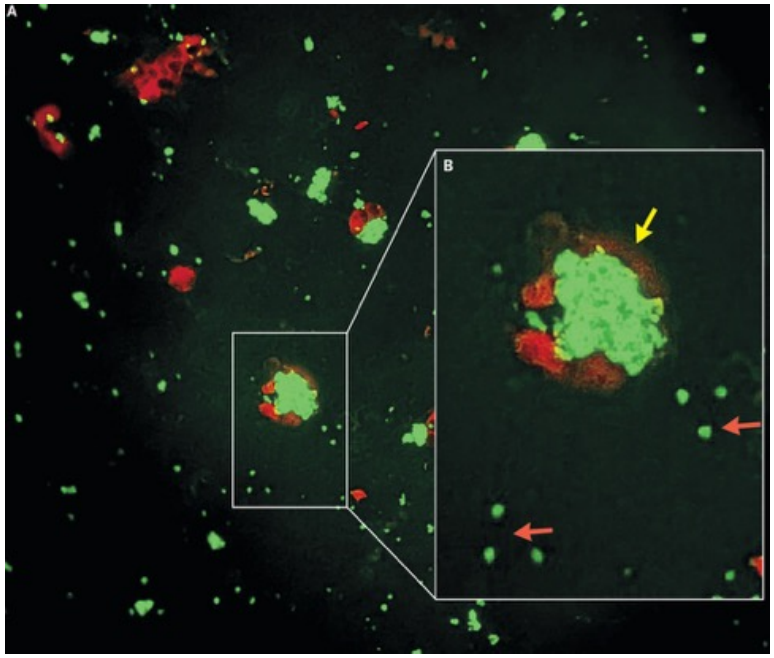
After a relatively quiescent clinical phase in which the CD4 cell count declines, persons with HIV infection are susceptible to an array of opportunistic infections. These include, but are not limited to, tuberculosis and reactivation of VZV infection (at any CD4 cell count), coccidioidomycosis (CD4 cell count, ≤250 per microliter), *Pneumocystis jirovecii* pneumonia (CD4 cell count, ≤200 per microliter), histoplasmosis (CD4 cell count, ≤150 per microliter), cryptococcus and cytomegalovirus infections (CD4 cell count, ≤100 per microliter), and *Mycobacterium avium* complex infection (CD4 cell count, ≤50 per microliter).

To confirm the diagnosis, I would perform serologic testing for HIV-1. Given the possibility of *P. jirovecii* pneumonia, I would perform a direct fluorescent antibody test for *P. jirovecii* on an induced sputum specimen. If the test is negative, I would perform a direct fluorescent antibody test on a bronchoalveolar-lavage (BAL) specimen. The serum level of 1,3-β-d-glucan, which is typically elevated in patients with *P. jirovecii* pneumonia, could also be obtained.

Diagnostic Testing

The first diagnostic test performed in this case was an antigen–antibody combination immunoassay for HIV-1 and HIV-2, which was reactive. Confirmatory and differentiation testing was positive for HIV-1. The plasma HIV-1 viral load was 223,000 copies of RNA per milliliter, and the CD4 cell count was 33 per microliter, findings that established the diagnosis of advanced HIV-1 infection.

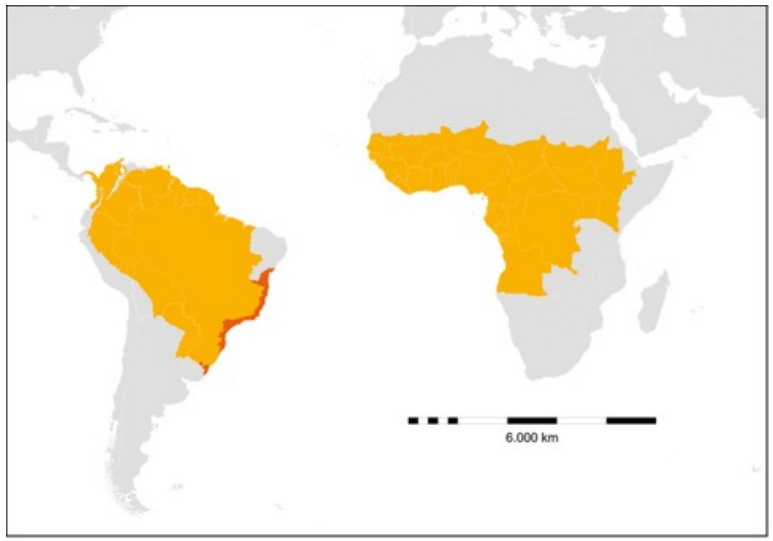
A direct fluorescent antibody test for *P. jirovecii* in the induced sputum was negative. However, a serum test for 1,3-β-d-glucan was strongly positive (>500 pg per milliliter; reference value, <60), a finding that increased suspicion for *P. jirovecii* pneumonia. Because of the high pretest probability of this diagnosis, BAL was performed, and a direct fluorescent antibody test of the fluid for *P. jirovecii* was positive.



Bronchoalveolar-Lavage Specimen.

Panel A shows *Pneumocystis jirovecii* organisms (in green), including trophozoites and cysts, detected by monoclonal antibodies conjugated with fluorescein isothiocyanate, or FITC (MONOFLUO *P. jirovecii* immunofluorescence assay). Cellular material is counterstained with Evans blue (in red). Panel B shows individual cysts (red arrows) and clusters of round cyst forms embedded within the extracellular matrix (yellow arrow) at higher magnification.

Gelbfieber ist eine **schwere, durch Viren verursachte Infektionskrankheit**, die von Stechmücken in tropischen Regionen Afrikas und Südamerikas übertragen wird und **lebensbedrohlich** sein kann. Der wirksamste Schutz ist die **Impfung**, die in vielen Risikogebieten vorgeschrieben ist



Übertragung

Das Gelbfieber-Virus (ein Flavivirus) wird durch Stiche infizierter Stechmücken, hauptsächlich der Gattungen *Aedes* und *Haemagogus*, übertragen. Eine direkte Übertragung von Mensch zu Mensch findet nicht statt.

Impfung: Die Gelbfieberimpfung ist der beste Schutz und bietet nach einer einzigen Dosis lebenslangen Schutz für die meisten Reisenden. Die Impfung muss von einer zugelassenen Impfstelle durchgeführt werden.

Low-dose yellow fever vaccination in infants: a randomised, double-blind, non-inferiority trial

Summary

Background WHO recommends fractional dose vaccination to address yellow fever vaccine shortages during outbreaks. In adults, a 500 IU dose has recently been shown to be non-inferior to the full standard dose, but the minimum effective dose for children is unknown.

Methods We conducted a randomised, double-blind, non-inferiority trial at two centres in Kenya and Uganda, including infants aged 9–12 months with no previous yellow fever vaccination or infection. Participants were randomly assigned 1:1 in blocks of variable sizes of four, six, or eight to receive either the standard dose (>13 000 IU) or 500 IU of the Institut Pasteur de Dakar (Dakar, Senegal) 17D-204 yellow fever vaccine, co-administered with the measles–rubella vaccine. The primary outcome was seroconversion 28 days post-vaccination, defined as a four-fold or greater increase in antibody titre at day 28 from baseline (day 0), as measured by the 50% plaque reduction neutralisation test. Non-inferiority was shown if the lower bound of the 95% CI for the difference in seroconversion rates between doses exceeded –10 percentage points. Safety was assessed in the safety population, which included all participants who received a study vaccine dose. This study is registered with ClinicalTrials.gov (NCT04059471) and is complete.

Findings Between Oct 7, 2021, and June 14, 2023, 420 infants were enrolled and randomly assigned (210 participants in each group). The seroconversion rate at day 28 was 99% (95% CI 96–100; 177 of 179 infants) for the standard dose and 93% (88–96; 166 of 179 infants) for the 500 IU dose in the per-protocol population. The difference in seroconversion rate was –6·15 percentage points (95% CI –10·27 to –2·02); therefore, non-inferiority was not met for the 500 IU dose. 12 serious adverse events were reported in the study (eight in the 500 IU dose group and four in the standard dose group), but all were considered unrelated to vaccination.

Interpretation Compared with the standard yellow fever vaccine dose, a dose of 500 IU did not meet the non-inferiority criterion, suggesting that minimum dose requirements in adults are not generalisable to infants. Therefore, standard yellow fever doses should be used for infants in the routine WHO Expanded Programme on Immunization.

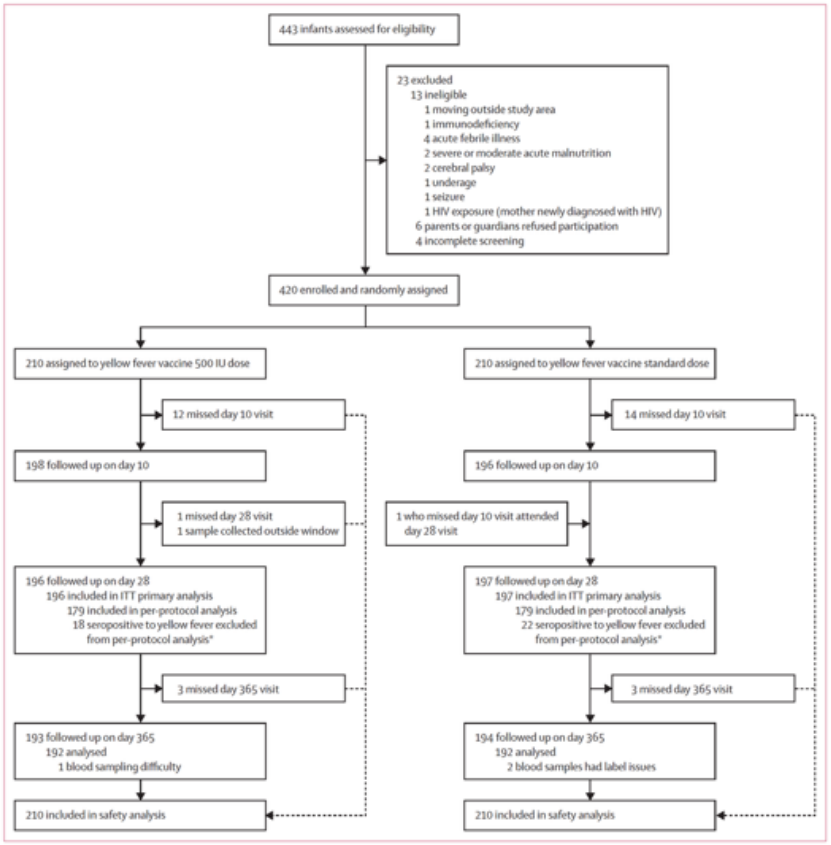


Figure 1: Trial profile
ITT=intention-to-treat. *Reasons are not mutually exclusive.

	500 IU dose group (n=210)	Standard dose group (n=210)
Geographical site		
Kilifi	105 (50%)	105 (50%)
Mbarara	105 (50%)	105 (50%)
Age at enrolment, months	9 (9–9)	9 (9–9)
Sex		
Female	109 (52%)	105 (50%)
Male	101 (48%)	105 (50%)
Body temperature	36·3°C (0·4)	36·4°C (0·4)
Seropositive for yellow fever at baseline*	18 (9%)	22 (10%)
Reported previous flavivirus infection	0	0
Reported previous medical illness	8 (4%)	9 (4%)
HIV exposed at baseline	0	1 (<1%)

Data are n (%) or mean (SD). *Defined as 50% plaque reduction neutralisation test ≥10.

Table 1: **Baseline characteristics of all randomly assigned participants**

	Seroconversion*, n/N (%, 95% CI)	Seroconversion difference†, percentage points (95% CI)	Geometric mean titre (95% CI)	Geometric mean titre ratio‡ (95% CI)	Geometric mean fold increase titre (95% CI)	Geometric mean fold increase ratio‡ (95% CI)
Per-protocol population						
Day 10	..	−32·68 (−41·03 to −24·34)	..	0·11 (0·07–0·17)	..	0·11 (0·07–0·17)
500 IU dose	106/180 (59%, 52–66)	..	43·7 (32·3–59·2)	..	8·7 (6·5–11·8)	..
Standard dose	163/178 (92%, 86–95)	..	388·8 (286·4–527·8)	..	77·8 (57·3–105·6)	..
Day 28	..	−6·15 (−10·27 to −2·02)	..	0·57 (0·41–0·79)	..	0·57 (0·41–0·79)
500 IU dose	166/179 (93%, 88–96)	..	525 (400–689)	..	105 (80–138)	..
Standard dose	177/179 (99%, 96–100)	..	923 (763–1116)	..	185 (153–223)	..
Day 365	..	−8·61 (−13·11 to −4·12)	..	0·31 (0·20–0·47)	..	0·31 (0·20–0·47)
500 IU dose	158/174 (91%, 85–94)	..	596 (425–836)	..	119 (85–167)	..
Standard dose	171/172 (99%, 96–100)	..	1931 (1514–2462)	..	386 (303–492)	..
Intention-to-treat populatin						
Day 10	..	−32·74 (−40·77 to −24·7)	..	0·11 (0·08–0·17)	..	0·11 (0·08–0·17)
500 IU dose	115/198 (58%, 51– 65)	..	46·7 (35·0–62·2)	..	7·8 (5·8–10·5)	..
Standard dose	178/196 (91%, 86–94)	..	414·3 (310·9–551·9)	..	68·2 (50·9–91·4)	..
Day 28	..	−6·64 (−11·07 to −2·22)	..	0·56 (0·41–0·77)	..	0·58 (0·41–0·82)
500 IU dose	179/196 (91%, 86–95)	..	512 (393–667)	..	87 (65–116)	..
Standard dose	193/197 (98%, 95–99)	..	915 (765–1094)	..	151 (122–185)	..
Day 365	..	−9·9 (−14·36 to −5·43)	..	0·31 (0·21–0·46)	..	0·32 (0·21–0·48)
500 IU dose	172/192 (90%, 84–93)	..	615 (446–848)	..	102 (73–143)	..
Standard dose	191/192 (99%, 97–100)	..	1974 (1571–2480)	..	321 (251–411)	..

$PRNT_{50}$=50% plaque reduction neutralisation test. *Seroconversion is defined as a four-fold or greater rise in $PRNT_{50}$ titre at each timepoint from baseline; N is the number of infants in the per-protocol or intention-to-treat population; n is the number seroconverted; seroconversion rate is %=n/N multiplied by 100. †Seroconversion difference=500 IU dose – standard dose. ‡Geometric mean titre ratio and geometric mean fold increase ratio=500 IU/standard; a geometric mean titre ratio or geometric mean fold increase ratio less than 1 favours the standard dose and a ratio greater than 1 favours the 500 IU dose.

Table 2: **Seroconversion and geometric mean titre in the per-protocol and the intention-to-treat populations by $PRNT_{50}$**

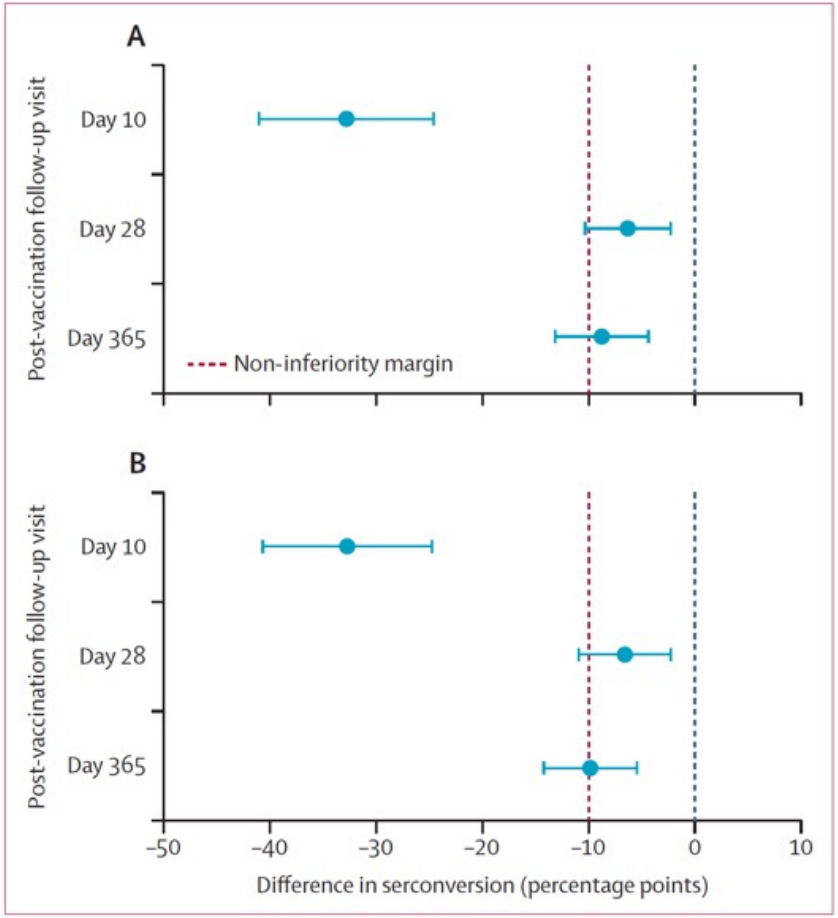


Figure 2: **Seroconversion rate non-inferiority comparison**
Non-inferiority comparison of the seroconversion rate of the 500 IU dose with the full standard yellow fever vaccine dose for the per-protocol (A) and intention-to-treat (B) populations using 50% plaque reduction neutralisation test. Error bars indicate 95% CIs.

	500 IU dose group (n=210)	Standard dose group (n=210)
Number of adverse events reported	175	156
Number of participants with adverse events*	125	109
Number of serious adverse events reported	8	4
Number of participants with serious adverse events*	8	4
Adverse event severity		
Mild	137/175 (78%)	129/156 (82%)
Moderate	37/175 (21%)	27/156 (17%)
Severe	1/175 (1%)	0
Life-threatening	0	0
Participants' adverse event severity†		
Mild	96 (46%)	91 (43%)
Moderate	35 (17%)	26 (12%)
Severe	1 (<1%)	0
Life-threatening	0	0
Adverse event related to vaccination		
Not related	154/175 (88%)	143/156 (91%)
Unlikely	15/175 (9%)	7/156 (4%)
Possibly	4/175 (2%)	5/156 (3%)
Probably related	2/175 (1%)	0
Definitely related	0	1/156 (<1%)

Data are n, n/N (%), or n (%). *Participants who have one or more adverse events or serious adverse events are counted only once. †Participants are counted only once within a particular severity grade or relatedness category.

Table 3: **Summary of all adverse events 28 days after vaccination and serious adverse events throughout follow-up for all consented participants**

Research in context

Evidence before this study

We searched the International Clinical Trials Registry Platform for randomised trials assessing fractional doses of yellow fever vaccine in children using the search term "(yellow fever vaccine) AND (fractional doses) AND (children)" from database inception to April 30, 2025, with no language restrictions. We identified two studies. One study compared a one-fifth dose and a one-half dose to a full dose in children aged 9–23 months in Uganda, reporting similar safety but no published results on vaccine immunogenicity. The other study was a non-inferiority trial in Kenya and Uganda comparing a one-fifth dose to a full dose in children aged 9–59 months, finding that the one-fifth dose was safe and non-inferior to the full dose with respect to immunogenicity. The fractional doses in these studies were well above the WHO recommended minimum potency of 1000 IU. We found no data to inform the minimum yellow fever vaccine dose requirements in children.

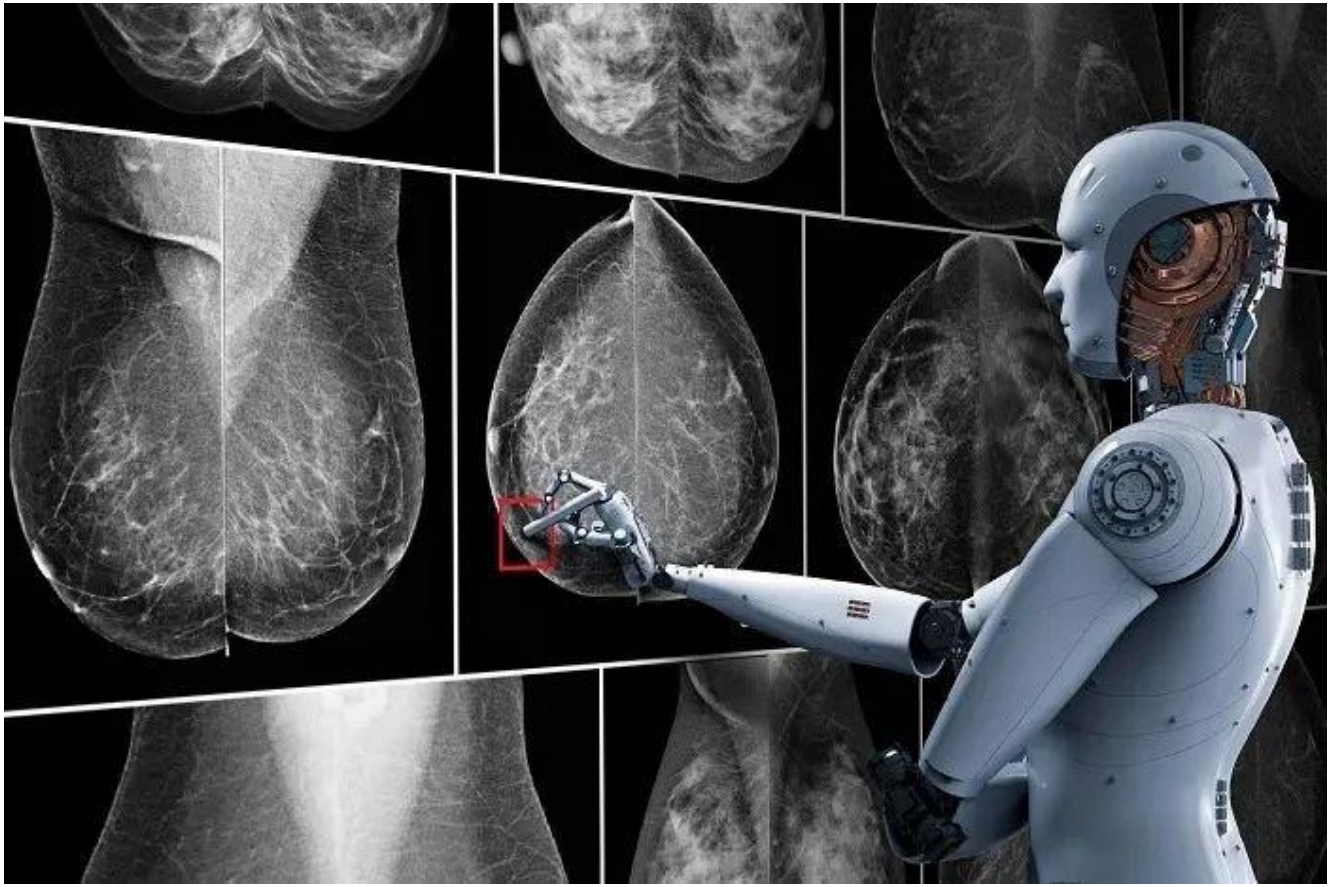
Added value of this study

This study investigated whether the 500 IU dose is non-inferior to full dose in infants receiving yellow fever vaccine concomitantly with the measles–rubella vaccine at age 9–12 months as per the routine WHO Expanded Programme on Immunization in Kenya and Uganda. We showed that the 500 IU dose does not meet the non-inferiority criterion in infants.

Implications of all the available evidence

The minimum dosing evidence from adults does not generalise to children, in whom higher vaccine doses could be required to assure non-inferior seroconversion rates. Lower seroconversion rates with the 500 IU dose might be acceptable in some outbreak scenarios with marked vaccine shortages, but are unlikely to be acceptable in the routine Expanded Programme on Immunization where sufficient vaccine stocks are available.

Künstliche Intelligenz - Mammographie



In Deutschland revolutioniert künstliche Intelligenz (KI) derzeit das **Mammographie-Screening-Programm (MSP)**. Aktuelle Studienergebnisse zeigen, dass KI die Krebserkennung signifikant verbessert und Radiologen massiv entlastet, ohne dass Patientinnen häufiger „falschem Alarm“ ausgesetzt sind.

Aktuelle Studienergebnisse aus Deutschland

Die großangelegte **PRAIM-Studie** (veröffentlicht im Januar 2025) mit über 460.000 Frauen lieferte entscheidende Belege für den Nutzen in der deutschen Praxis:

- **Höhere Erkennungsrate:** Durch KI-Unterstützung stieg die Detektionsrate von Brustkrebs um ca. **17,6 %** (von 5,7 auf 6,7 Fälle pro 1.000 Frauen).
- **Kein Anstieg bei Fehlalarmen:** Die Rückrufrate (Wiedereinbestellung bei Verdacht) blieb stabil oder sank sogar leicht (37,4 vs. 38,3 pro 1.000).
- **Arbeitsentlastung:** Radiologen verbrauchten bis zu **43 % weniger Zeit** für die Befundung von Scans, die von der KI als eindeutig unauffällig markiert wurden.

Interval cancer, sensitivity, and specificity comparing AI-supported mammography screening with standard double reading without AI in the MASAI study: a randomised, controlled, non-inferiority, single-blinded, population-based, screening-accuracy trial

Summary

Background Evidence indicates that artificial intelligence (AI) can improve mammography screening by increasing cancer detection and reducing screen reading workload, but its effect on interval cancers (primary breast cancers diagnosed between two screening rounds or within 2 years after the last scheduled screening that were not detected at screening) is unknown. We aimed to compare the interval cancer rate in AI-supported mammography screening with standard double reading without AI.

Methods In this Swedish randomised, controlled, non-inferiority, single-blinded, population-based screening accuracy trial, participants were allocated in a 1:1 ratio to either AI-supported mammography screening (the intervention group) or standard double reading without AI (the control group). AI was used to triage examinations to single or double reading by radiologists and for detection support. This is a protocol-defined analysis of the primary outcome, interval cancer rate, with a 20% non-inferiority margin. Secondary outcomes reported in this analysis are interval cancer characteristics, sensitivity, specificity, and sensitivity by age, breast density, and cancer type (in-situ and invasive). Other secondary outcomes from the trial that have been previously reported are referenced in the Methods section of this Article. The trial is registered with ClinicalTrials.gov (NCT04838756) and is complete.

Findings Between April 12, 2021, and Dec 7, 2022, 105 934 women were randomly assigned to the intervention or control group, of whom 19 were excluded from the analysis. Median age was 53·8 years (IQR 46·5–63·3) in the intervention group and 53·7 years (46·5–63·2) in the control group. Interval cancer rates were 1·55 (95% CI 1·23–1·92) and 1·76 (1·42–2·15) per 1000 participants in the intervention and control group respectively, a non-inferior proportion ratio of 0·88 (95% CI 0·65–1·18; p=0·41). Descriptively, the intervention group had fewer interval cancers that were invasive (75 *vs* 89), T2+ (38 *vs* 48), or non-luminal A (43 *vs* 59) than the control group. Sensitivity was higher in the intervention group (80·5% [95% CI 76·4–84·2]) than the control group (73·8% [68·9–78·3]; p=0·031), an effect consistent across age and breast density, and for invasive cancer but not for in-situ cancer. Specificity was 98·5% (95% CI 98·4–98·6) for both groups (p=0·88).

Interpretation AI-supported mammography screening showed consistently favourable outcomes compared with standard double reading, with a non-inferior interval cancer rate, fewer interval cancers with unfavourable characteristics, higher sensitivity, and the same specificity, while also reducing screen reading workload. These findings imply that AI-supported mammography screening can efficiently improve screening performance compared with standard double reading and may be considered for implementation in clinical practice.

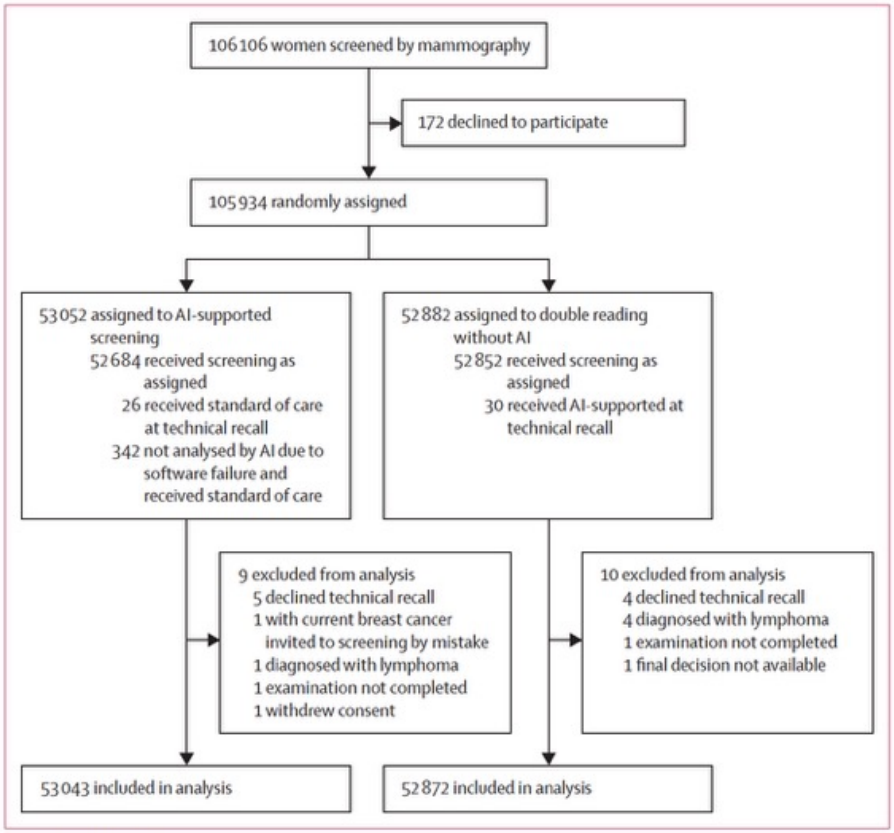


Figure: **Trial profile**
AI=artificial intelligence.

	Intervention group (n=53 043)	Control group (n=52 872)	Standardised differences
Age, years			
Mean (SD)	55·1 (10·2)	55·1 (10·2)	0·00
Median (IQR)	53·8 (46·5–63·3)	53·7 (46·5–63·2)	NA
Range	40–80	40–80	NA
<45	10 316 (19·4%)	10 286 (19·5%)	–0·00
45–49	9689 (18·3%)	9739 (18·4%)	–0·00
50–54	8702 (16·4%)	8710 (16·5%)	–0·00
55–59	6898 (13·0%)	6650 (12·6%)	0·01
60–64	6100 (11·5%)	6281 (11·9%)	–0·01
65–69	5586 (10·5%)	5454 (10·3%)	0·01
≥70	5752 (10·8%)	5752 (10·9%)	–0·00
Screening indication			
General screening	51 921 (97·9%)	51 708 (97·8%)	0·01
History of breast cancer	1071 (2·0%)	1102 (2·1%)	–0·00
Moderate hereditary risk	51 (0·1%)	62 (0·1%)	–0·01
Breast density*			
a	6678/52 910 (12·6%)	6579/52 756 (12·5%)	0·00
b	21 122/52 910 (39·9%)	21 199/52 756 (40·2%)	–0·01
c	19 076/52 910 (36·1%)	19 029/52 756 (36·1%)	–0·01
d	6034/52 910 (11·4%)	5949/52 756 (11·3%)	0·00
Missing	133	116	NA

Data are n (%) or n/N (%) unless otherwise specified. NA=not applicable. *Breast density determined by Transpara software, version 2.1, classified according to the Breast Imaging Reporting and Data System 5th edition, where the classification ranges from a, indicating breasts are almost entirely fatty, to d, where the breasts are extremely dense.

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

	Intervention group (n=53 043)	Control group (n=52 872)	Proportion ratio	p value
Number of recalls*	1110	1027	NA	NA
Number of screen-detected cancers*	338	262	NA	NA
Number of interval cancers	82	93	NA	NA
Number of cancers in total	420	355	NA	NA
Interval cancer rate per 1000	1·55 (1·23–1·92)	1·76 (1·42–2·15)	0·88 (0·65–1·18)	0·41
Sensitivity	80·5% (76·4–84·2)	73·8% (68·9–78·3)	1·09 (1·01–1·18)	0·031
Specificity	98·5% (98·4–98·6)	98·5% (98·4–98·6)	1·00 (0·99–1·01)	0·88

Data are n or point estimate (95% CI). NA=not applicable. *Rates for recall and cancer detection have previously been reported.[8] The numbers are included for contextualisation of sensitivity and specificity.

Table 2: **Interval cancer rate, sensitivity, and specificity**

	Intervention group (n=82)	Control group (n=93)
Age, years		
Mean (SD)	57·2 (9·4)	58·0 (10·3)
Median (IQR)	57·6 (49·0–64·6)	58·1 (48·5–66·3)
Range	40–75	40–74
<50	22 (26·8%)	29 (31·2%)
≥50	60 (73·2%)	64 (68·8%)
Time to diagnosis, months		
Mean (SD)	12·6 (5·5)	13·6 (5·6)
≤12	39 (47·6%)	32 (34·4%)
>12	43 (52·4%)	61 (65·6%)
Breast density*		
a	5 (6·1%)	8 (8·6%)
b	24 (29·3%)	32 (34·4%)
c	42 (51·2%)	35 (37·6%)
d	11 (13·4%)	18 (19·4%)

Data are n (%) unless otherwise specified. *Breast density determined by Transpara software, version 2.1, classified according to the Breast Imaging Reporting and Data System 5th edition, where the classification ranges from a, indicating breasts are almost entirely fatty, to d, where the breasts are extremely dense.

Table 3: **Interval cancer population characteristics**

	Intervention group (n=53 043)	Control group (n=52 872)	Proportion ratio
Number of interval cancers, total	82 (1·55)	93 (1·76)	0·88 (0·65–1·18)
Number of in-situ interval cancers	7 (0·13)	4 (0·08)	NA
Number of invasive interval cancers	75 (1·41)	89 (1·68)	0·84 (0·62–1·14)
Histological type			
Ductal carcinoma in-situ	7 (0·13)	4 (0·08)	NA
No special type	51 (0·96)	66 (1·25)	0·77 (0·53–1·11)
Lobular	18 (0·34)	15 (0·28)	1·20 (0·60–2·37)
Other*	6 (0·11)	8 (0·15)	0·75 (0·26–2·15)
Nuclear grade, in-situ			
I	2 (0·04)	0	NA
II	4 (0·08)	4 (0·08)	NA
III	1 (0·02)	0	NA
Histological grade, invasive			
I	13 (0·25)	14 (0·26)	0·93 (0·44–1·97)
II	36 (0·68)	39 (0·74)	0·92 (0·59–1·45)
III	24 (0·45)	29 (0·55)	0·82 (0·48–1·42)
Missing	2 (0·04)	7 (0·13)	NA
Molecular subtype, invasive			
Luminal A	30 (0·57)	28 (0·53)	1·07 (0·64–1·79)
Non-luminal A	43 (0·81)	59 (1·12)	0·73 (0·49–1·08)
Luminal B	23 (0·43)	30 (0·57)	0·76 (0·44–1·32)
Triple negative	12 (0·23)	16 (0·30)	0·75 (0·35–1·58)
HER2 positive-ER positive	5 (0·09)	7 (0·13)	0·71 (0·23–2·24)
HER2 positive-ER negative	3 (0·06)	6 (0·11)	NA
Missing	2 (0·04)	2 (0·04)	NA
T stage			
Tis	7 (0·13)	4 (0·08)	NA
T1	36 (0·68)	37 (0·70)	0·97 (0·61–1·53)
T2+†	38 (0·72)	48 (0·91)	0·79 (0·52–1·21)
Tx	1 (0·02)	4 (0·08)	NA
N stage			
N0	54 (1·02)	63 (1·19)	0·85 (0·59–1·23)
N1+	28 (0·53)	30 (0·57)	0·93 (0·56–1·56)
M stage			
M0	81 (1·53)	88 (1·66)	0·92 (0·68–1·24)
M1	1 (0·02)	5 (0·09)	NA
TNM stage			
0	7 (0·13)	4 (0·08)	NA
I	27 (0·51)	34 (0·64)	0·79 (0·48–1·31)
II+	48 (0·90)	55 (1·04)	0·87 (0·59–1·28)

Data are n (rate per 1000) and proportion ratio with 95% CIs. The proportion ratio was only calculated for subgroups with at least five cases. NA=not applicable. Tis=tumour in-situ. Tx=primary tumour cannot be assessed. ER=oestrogen receptor. HER2 (also known as ERBB2)=human epidermal growth factor receptor 2. *In the intervention group: three ductal carcinoma in-situ with microinvasion, one mixed invasive (papillary and no special type), one tubular, and one breast adenoid cystic carcinoma. In the control group: one metaplastic, one apocrine, two tubular carcinomas, one breast implant-associated anaplastic large-cell lymphoma, and three women presented with breast cancer metastases without further histological description. †Measuring >20 mm.

Table 4: **Interval cancer characteristics**

	Intervention group (n=53 043)	Control group (n=52 872)	Proportion ratio
Age, years			
<45	27/36 (75·0%)	19/27 (70·4%)	1·07 (0·78–1·44)
45–49	33/46 (71·7%)	31/52 (59·6%)	1·20 (0·90–1·16)
50–54	44/54 (81·5%)	26/34 (76·5%)	1·07 (0·85–1·34)
55–59	42/58 (72·4%)	30/45 (66·7%)	1·09 (0·84–1·41)
60–64	57/71 (80·3%)	44/55 (80·0%)	1·00 (0·84–1·20)
65–69	60/71 (84·5%)	54/70 (77·1%)	1·10 (0·93–1·29)
≥70	75/84 (89·3%)	58/72 (80·6%)	1·11 (0·97–1·27)
Breast density*			
a	33/38 (86·8%)	23/31 (74·2%)	1·17 (0·92–1·49)
b	156/180 (86·7%)	116/148 (78·4%)	1·11 (1·00–1·22)
c	122/164 (74·4%)	96/131 (73·3%)	1·02 (0·89–1·16)
d	27/38 (71·1%)	27/45 (60·0%)	1·18 (0·87–1·62)
Cancer type			
In-situ	68/75 (90·7%)	45/49 (91·8%)	0·99 (0·88–1·10)
Invasive	270/345 (78·3%)	217/306 (70·9%)	1·10 (1·01–1·21)

Data are screen-detected cancers/the total number of cancers (sensitivity %), and the proportion ratio (95% CI). *Breast density determined by Transpara software, version 2.1, classified according to the Breast Imaging Reporting and Data System 5th edition, where the classification ranges from a, indicating breasts are almost entirely fatty, to d, where the breasts are extremely dense.

Table 5: **Sensitivity stratified by age, breast density, and cancer type**

In conclusion, the MASAI trial showed consistently more favourable outcomes with AI-supported mammography screening compared with standard double reading without AI, including the primary outcome of interval cancer rate, showing non-inferiority, and fewer interval cancers with unfavourable characteristics. Further analyses of subsequent screening rounds and cost-effectiveness will clarify the long-term balance of benefits and harms and could provide a strong rationale for implementing AI in population-based mammography screening programmes, particularly in the context of workforce shortages.

Research in context

Evidence before this study

Mammography screening has been associated with reduced breast cancer mortality, largely attributable to the early detection and treatment of the disease. However, despite the double screen reading procedure recommended by European guidelines, some cancers still go undetected in screening. Some of these are rapidly progressive and can appear as interval cancers between screening rounds. Artificial intelligence (AI) has the potential to support radiologists in screen reading and could potentially improve screening performance and reduce the screen reading workload. Before the trial started, we performed a literature search in MEDLINE for studies published in English between Jan 1, 2015, and Dec 31, 2020, that included "breast cancer screening" or "mammography screening", and "artificial intelligence" or "machine learning" in the title or abstract. No prospective trials were identified. Retrospective studies found that AI's accuracy is comparable to that of radiologists and could be used to distinguish between examinations with a high and low probability of malignancy, showing promise to improve screening performance and reduce the screen reading workload, particularly in double reading programmes.

A first clinical safety report from the Mammography Screening with Artificial Intelligence trial (MASAI) showed that an AI-supported screen reading procedure, involving triage and detection support, was considered safe because the cancer-detection rate did not decline despite a 44% reduction in the screen reading workload. A second report of the MASAI trial, focusing on early screening performance and characteristics of screen-detected cancers, showed a 29% increase in cancer detection with the use of AI, without an increase in false positives. The large increase in detection was predominantly of small, lymph-node negative, invasive cancers, including 27% more cancers of the aggressive non-luminal A subtypes (luminal B, triple negative, and human epidermal growth factor receptor 2 positive), which are most likely to benefit from early detection. Meanwhile, results have emerged from other prospective or observational studies with similar objectives to improve performance and efficiency of standard double reading, with findings supporting higher cancer detection and reduced workload, albeit to various degrees (4–18% and 33–45%, respectively). Other randomised controlled trials have been initiated or are in the pre-launch phase, for example the Norwegian AIMS trial (NCT06032390), the Australian BRAIx trial (ACTRN12624001432505), and the UK EDITH trial, but no results are yet available.

Added value of this study

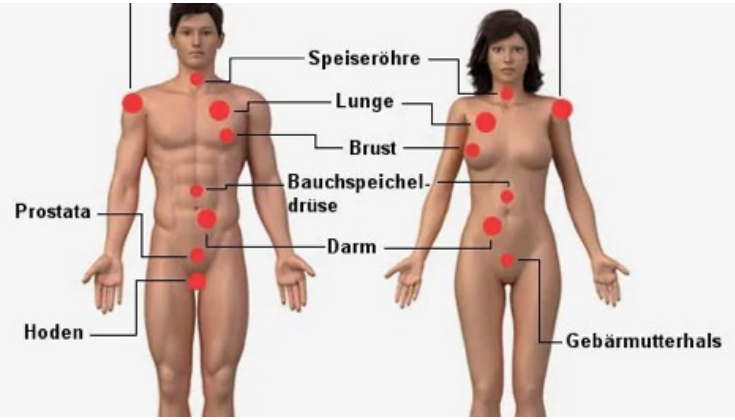
To the best of our knowledge, this is the first randomised controlled trial investigating the use of AI in mammography screening and the first to report on its effect on interval cancer. Interval cancers are associated with less favourable histopathological characteristics and higher breast cancer-specific mortality compared with screen-detected cancers. The interval cancer rate is therefore an important measure of screening efficacy. In this trial, AI-supported screening resulted in a non-inferior interval cancer rate. Although not powered to show superiority, the interval cancers diagnosed in the AI-supported screening group had more favourable characteristics compared with those diagnosed in the standard double reading group without AI. Compared with standard double reading, AI-supported screening resulted in higher sensitivity, an improvement consistent across age and breast density, while the specificity remained the same.

Implications of all the available evidence

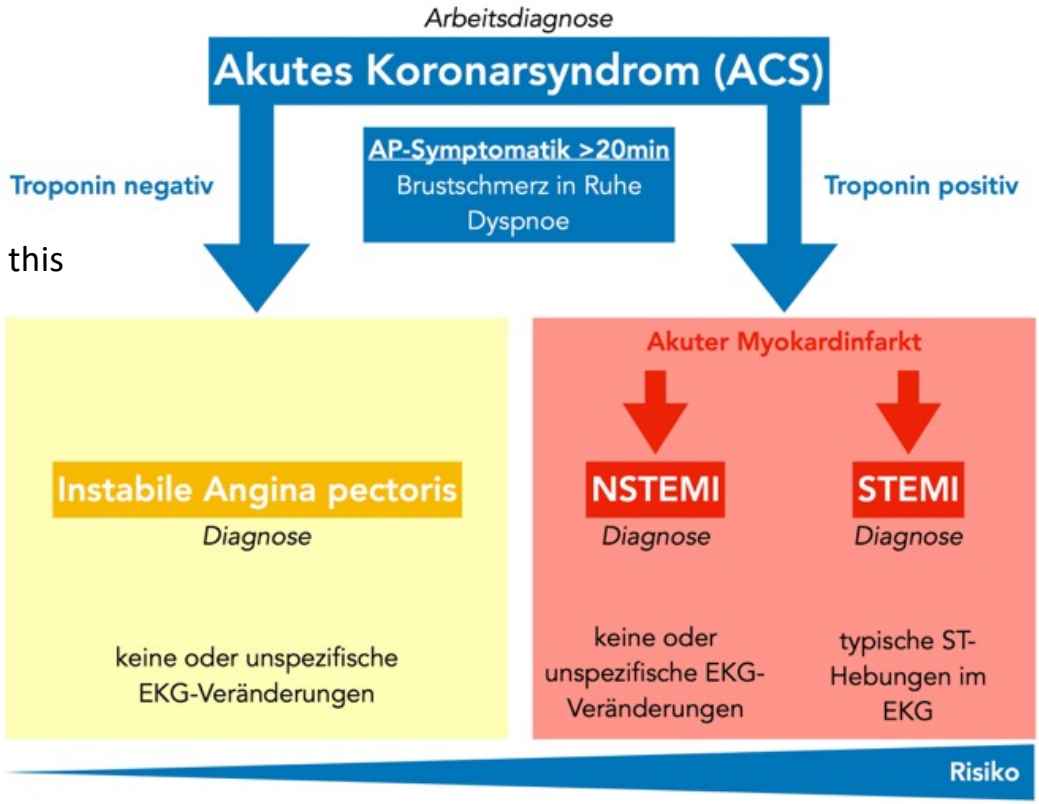
Together with results from the two previous protocol-defined analyses of the MASAI trial, we show that an AI-supported mammography screen reading procedure can be used to improve screening performance, while reducing screen reading workload compared with standard double reading without AI. We observed a large increase in cancer detection and a non-inferior reduction of interval cancer, without an increase in false positives, resulting in higher sensitivity and similar specificity. With AI, the main increase in detection was of small, lymph-node-negative invasive tumours, including non-luminal A subtypes, which was reflected in fewer large, invasive, and non-luminal A interval cancers. These results indicate that AI-supported screening can efficiently contribute to the early detection of clinically relevant breast cancers. Assessment of outcomes in subsequent screening rounds will provide more insight into the clinical implications of using AI. Although not randomised, other studies support the findings of higher cancer detection and reduced workload. Several initiated or planned randomised controlled trials will add to the growing body of evidence. Considering the favourable outcomes in the MASAI trial, a demonstration of cost-effectiveness could support implementing AI in population-based mammography screening programmes, particularly in the context of workforce shortage.

Krebs: Immer mehr Tumor-Erkrankungen in Deutschland

Cured from this

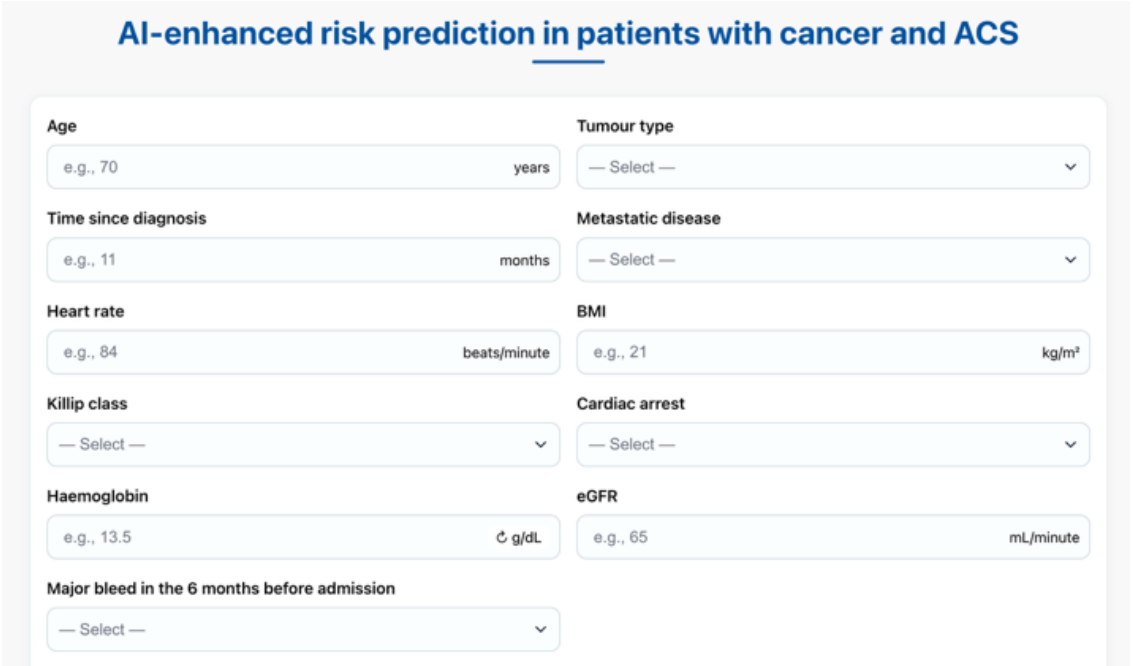


And now this



Das akute Koronarsyndrom (ACS) bei Krebspatienten ist eine hochkomplexe klinische Herausforderung, da Betroffene aufgrund von Tumortherapien (z.B. Anthrazyklinen) und systemischen Effekten ein erhöhtes Thromboserisiko sowie eine gesteigerte Blutungsneigung aufweisen. Da diese Patientengruppe oft aus Studien ausgeschlossen wird, verbessert der neue, auf künstlicher Intelligenz basierende **ONCO-ACS-Score** die Risikobewertung und Behandlung von Herzinfarkten durch die Integration krebsspezifischer Faktoren.

ONCO ACS



Prediction of mortality, bleeding, and ischaemic events in patients with cancer and acute coronary syndrome: a model development and validation study

Summary

Background Accurate assessment of mortality, bleeding, and atherothrombotic risk in patients with cancer and acute coronary syndrome could inform novel personalised treatment strategies, but no standardised tools for this purpose exist. We aimed to develop and validate a clinically applicable risk score for mortality, bleeding, and ischaemic events in patients with cancer and acute coronary syndrome.

Methods In this model development and validation study, we obtained data for 1 017 759 patients who presented with acute coronary syndrome in England, UK (n=815 170; 36 771 with cancer), Sweden (n=194 059; 10 262 with cancer), and Switzerland (n=8530; 203 with cancer) between Jan 1, 2004, and Aug 8, 2023. Machine learning models were developed to predict all-cause mortality, major bleeding events, and ischaemic events, defined as a composite of cardiovascular death, myocardial infarction, and ischaemic stroke, in patients with cancer and acute coronary syndrome from England in a competing risks framework with a prediction horizon of 6 months. Final models (the ONCO-ACS score) were externally validated in geographically distinct held out datasets from the English Midlands, Sweden, and Switzerland.

Findings Patients with cancer and with acute coronary syndrome were characterised by high rates of mortality (cumulative incidence 27·8% [95% CI 27·3–28·3]), major bleeding (7·3% [7·0–7·5]), and ischaemic events (16·1% [15·7–16·4]) and had a distinct risk profile. The ONCO-ACS score was informed by a single set of variables: tumour type, time since cancer diagnosis, metastatic disease, age, haemoglobin, heart rate, estimated glomerular filtration rate, BMI, Killip class, cardiac arrest, and major bleed within 6 months. Accounting for traditional and cancer-related risk factors, ONCO-ACS showed a time-dependent area under the receiver operating characteristic curve (tAUC) at 6 months of 0·84 (0·83–0·85) for all-cause mortality, 0·70 (0·68–0·73) for major bleeding, and 0·79 (0·78–0·81) for ischaemic events on internal validation. On external validation, ONCO-ACS achieved similar performance for all-cause mortality (tAUC at 6 months 0·84 [0·82–0·85] for the English Midlands, 0·80 [0·79–0·82] for Sweden, and 0·83 [0·76–0·91] for Switzerland), major bleeding events (0·70 [0·67–0·74] for the English Midlands, 0·67 [0·65–0·70] for Sweden, and 0·74 [0·57–0·91] for Switzerland), and ischaemic events (0·76 [0·74–0·78] for the English Midlands, 0·70 [0·69–0·72] for Sweden, and 0·73 [0·61–0·86] for Switzerland). ONCO-ACS was well calibrated and decision curve analyses suggested favourable clinical utility. Applying ONCO-ACS to current guidelines suggests that most patients with cancer and acute coronary syndrome qualify for invasive management and long dual antiplatelet therapy using clopidogrel.

Interpretation The ONCO-ACS score provides a validated practical tool for predicting mortality, bleeding, and ischaemic risk in patients with cancer and acute coronary syndrome. Combined assessment of competing outcome risks could facilitate balancing treatment benefits and harms.

Funding British Heart Foundation, Cancer Research UK, Swiss Heart Foundation, University of Zurich Foundation, Kurt-Senta-Herrmann Foundation, Theodor-Ida-Herzog-Egli Foundation, Foundation for Cardiovascular Research–Zurich Heart House, Swedish ALF Research Funds.

	Development cohort (England, excluding Midlands; n=31 193)	Validation cohort 1 (English Midlands; n=5578)	Validation cohort 2 (Sweden; n=10 262)	Validation cohort 3 (Switzerland; n=203)
Age, years	76 (68–82)	75 (68–81)	75 (68–82)	70 (63–77)
Sex				
Female	9769/31 121 (31·4%)	1653/5547 (29·8%)	2958/10 262 (28·8%)	39/203 (19·2%)
Male	21 352/31 121 (68·6%)	3894/5547 (70·2%)	7304/10 262 (71·2%)	164/203 (80·8%)
Ethnicity				
Asian	268/30 834 (0·9%)	42/5542 (0·8%)	98/10 261 (1·0%)	..
Black	732/30 834 (2·4%)	149/5542 (2·7%)	16/10 261 (0·2%)	..
Mixed	59/30 834 (0·2%)	12/5542 (0·2%)	15/10 261 (0·1%)	..
White	29 469/30 834 (95·6%)	5327/5542 (96·1%)	10 113/10 261 (98·6%)	..
Other	306/30 834 (1·0%)	12/5542 (0·2%)	19/10 261 (0·2%)	..
Haemodynamics				
Heart rate, beats per minute	80 (68–96)	79 (66–95)	78 (66–94)	78 (68–89)
Systolic blood pressure, mm Hg	136 (29)	136 (28)	145 (29)	127 (28)
Cardiac arrest	1690/31 193 (5·4%)	272/5578 (4·9%)	122/9295 (1·3%)	16/203 (7·9%)
Killip class				
I	10 064/13 582 (74·1%)	1609/2115 (76·1%)	8273/9725 (85·1%)	153/199 (76·9%)
II	2328/13 582 (17·1%)	336/2115 (15·9%)	1135/9725 (11·7%)	19/199 (9·5%)
III	944/13 582 (7·0%)	119/2115 (5·6%)	178/9725 (1·8%)	9/199 (4·5%)
IV	246/13 582 (1·8%)	51/2115 (2·4%)	139/9725 (1·4%)	18/199 (9·0%)
ST-segment deviation	14 622/29 913 (48·9%)	2937/5373 (54·7%)	5225/7501 (69·7%)	114/192 (59·4%)
Onset-to-door time, min*	190 (103–508)	180 (99–464)	208 (100–570)	215 (112–540)
Cardiometabolic risk factors				
BMI, kg/m²	26 (23–29)	26 (24–30)	26 (24–29)	27 (25–30)
Body surface area, m²†	1·9 (0·2)	1·9 (0·2)	1·9 (0·2)	1·9 (0·2)
Diabetes	6654/30 010 (22·2%)	1215/5384 (22·6%)	2478/10 262 (24·1%)	48/200 (24·0%)
Dyslipidaemia‡	8182/28 456 (28·8%)	1307/4650 (28·1%)	2718/10 176 (26·7%)	106/197 (53·8%)
Smoking status				
Never	11 099/28 162 (39·4%)	2058/5119 (40·2%)	4147/9221 (45·0%)	57/191 (29·8%)
Former	12 345/28 162 (43·8%)	2176/5119 (42·5%)	3713/9221 (40·3%)	88/191 (46·1%)
Current	4718/28 162 (16·8%)	885/5119 (17·3%)	1361/9221 (14·8%)	46/191 (24·1%)
Tumour type				
Anus	131/31 193 (0·4%)	15/5578 (0·3%)	27/10 262 (0·3%)	2/203 (1·0%)
Bladder	1768/31 193 (5·7%)	308/5578 (5·5%)	767/10 262 (7·5%)	18/203 (8·9%)
Brain	92/31 193 (0·3%)	9/5578 (0·2%)	21/10 262 (0·2%)	3/203 (1·5%)
Breast	2995/31 193 (9·6%)	567/5578 (10·2%)	923/10 262 (9·0%)	9/203 (4·4%)
Cervix	110/31 193 (0·4%)	7/5578 (0·1%)	36/10 262 (0·4%)	0/203
Colorectal	4386/31 193 (14·1%)	754/5578 (13·5%)	1341/10 262 (13·1%)	21/203 (10·3%)
Hodgkin lymphoma	147/31 193 (0·5%)	27/5578 (0·5%)	26/10 262 (0·3%)	4/203 (2·0%)
Kidney	1064/31 193 (3·4%)	186/5578 (3·3%)	239/10 262 (2·3%)	6/203 (3·0%)
Larynx	332/31 193 (1·1%)	63/5578 (1·1%)	59/10 262 (0·6%)	2/203 (1·0%)
Leukaemia	1033/31 193 (3·3%)	162/5578 (2·9%)	251/10 262 (2·4%)	10/203 (4·9%)
Liver	235/31 193 (0·8%)	30/5578 (0·5%)	46/10 262 (0·4%)	0/203
Lung	2956/31 193 (9·5%)	469/5578 (8·4%)	417/10 262 (4·1%)	23/203 (11·3%)
Melanoma	1155/31 193 (3·7%)	201/5578 (3·6%)	488/10 262 (4·8%)	13/203 (6·4%)
Mesothelioma	152/31 193 (0·5%)	19/5578 (0·3%)	0/10 262	0/203
Myeloma	716/31 193 (2·3%)	127/5578 (2·3%)	141/10 262 (1·4%)	5/203 (2·5%)
Non-Hodgkin lymphoma	1310/31 193 (4·2%)	249/5578 (4·5%)	345/10 262 (3·4%)	11/203 (5·4%)
Oesophagus	582/31 193 (1·9%)	99/5578 (1·8%)	43/10 262 (0·4%)	6/203 (3·0%)
Ovary	355/31 193 (1·1%)	56/5578 (1·0%)	76/10 262 (0·7%)	2/203 (1·0%)

(Table 1 continues on next page)

	Development cohort (England, excluding Midlands; n=31 193)	Validation cohort 1 (English Midlands; n=5578)	Validation cohort 2 (Sweden; n=10 262)	Validation cohort 3 (Switzerland; n=203)
(Continued from previous page)				
Pancreas	321/31 193 (1·0%)	42/5578 (0·8%)	59/10 262 (0·6%)	3/203 (1·5%)
Prostate	8024/31 193 (25·7%)	1554/5578 (27·9%)	3702/10 262 (36·1%)	46/203 (22·7%)
Small intestine	92/31 193 (0·3%)	18/5578 (0·3%)	34/10 262 (0·3%)	0/203
Stomach	544/31 193 (1·7%)	92/5578 (1·6%)	87/10 262 (0·8%)	2/203 (1·0%)
Testis	83/31 193 (0·3%)	29/5578 (0·5%)	22/10 262 (0·2%)	3/203 (1·5%)
Thyroid	117/31 193 (0·4%)	19/5578 (0·3%)	47/10 262 (0·5%)	0/203
Uterus	550/31 193 (1·8%)	126/5578 (2·3%)	240/10 262 (2·3%)	1/203 (0·5%)
Vulva	126/31 193 (0·4%)	28/5578 (0·5%)	34/10 262 (0·3%)	0/203
Other	1817/31 193 (5·8%)	322/5578 (5·8%)	791/10 262 (7·7%)	13/203 (6·4%)
Time since tumour diagnosis, months	19 (6–38)	20 (7–39)	24 (10–41)	20 (5–37)
Metastatic disease	2747/14 302 (19·2%)	471/2424 (19·4%)	1256/7262 (17·3%)	31/203 (15·3%)
Clinical chemistry and haematology				
Haemoglobin, g/dL	12·3 (2·2)	12·5 (2·2)	13·1 (1·9)	12·6 (2·4)
Troponin elevation§	28 133/29 489 (95·4%)	5119/5355 (95·6%)	9188/10 261 (89·5%)	163/165 (98·8%)
Estimated glomerular filtration rate, mL/min¶	66 (25)	69 (24)	60 (22)	76 (24)
Glucose, mmol/L	7·1 (6·0–9·3)	7·1 (6·0–9·4)	7·0 (5·9–9·0)	7·0 (5·9–9·2)
Total cholesterol, mmol/L	4·4 (3·6–5·4)	4·5 (3·7–5·4)	4·7 (4·0–5·6)	4·4 (3·6–5·4)
Medical history				
Heart failure	1903/28 798 (6·6%)	261/4642 (5·6%)	1575/10 262 (15·3%)	2/203 (1·0%)
Atrial fibrillation	7472/31 193 (24·0%)	1217/5578 (21·8%)	1444/10 262 (14·1%)	5/102 (4·9%)
Hypertension	15 154/29 287 (51·7%)	2483/4745 (52·3%)	6061/10 262 (59·1%)	137/200 (68·5%)
Peripheral vascular disease	1538/28 503 (5·4%)	189/4636 (4·1%)	920/10 262 (9·0%)	11/203 (5·4%)
Chronic kidney disease	2454/28 751 (8·5%)	364/4638 (7·8%)	523/10 262 (5·1%)	33/102 (32·4%)
Obstructive lung disease	5235/28 605 (18·3%)	719/4649 (15·5%)	899/10 262 (8·8%)	31/203 (15·3%)
Peptic ulcer disease	2381/31 193 (7·6%)	351/5578 (6·3%)	734/10 262 (7·2%)	1/102 (1·0%)
Previous ischaemic events				
Myocardial infarction	6086/29 340 (20·7%)	902/4725 (19·1%)	2222/10 262 (21·7%)	34/203 (16·7%)
Cerebrovascular ischaemia	2820/28 796 (9·8%)	364/4640 (7·8%)	1219/10 262 (11·9%)	9/203 (4·4%)
Previous coronary revascularisation				
Percutaneous coronary intervention	2104/28 851 (7·3%)	348/4650 (7·5%)	818/10 262 (8·0%)	40/200 (20·0%)
Coronary artery bypass grafting	2069/28 964 (7·1%)	279/4666 (6·0%)	825/10 262 (8·0%)	12/200 (6·0%)
Previous bleeding events				
Major bleed within 6 months	3372/31 193 (10·8%)	505/5578 (9·1%)	235/10 262 (2·3%)	1/102 (1·0%)
Intracranial haemorrhage	274/31 193 (0·9%)	39/5578 (0·7%)	99/10 262 (1·0%)	..

Data are median (IQR), mean (SD) or n/N (%). *Onset-to-door time refers to the delay from symptom onset to hospital admission. †Estimated according to Du Bois and Du Bois. ‡Defined as elevation in total cholesterol requiring dietary or drug treatment. §Refers to values exceeding the 99th percentile. ¶Estimated according to Chronic Kidney Disease Epidemiology Collaboration 2021 creatinine-based equation.

Table 1: Baseline characteristics of patients in the ONCO-ACS development and validation cohorts

	Development cohort (England excluding Midlands; n=31 193)	Validation cohort 1 (English Midlands; n=5578)	Validation cohort 2 (Sweden; n=10 262)	Validation cohort 3 (Switzerland; n=203)
Type of intervention				
Percutaneous coronary intervention	5161/8049 (64·1%)	1074/1489 (72·1%)	4765/10 262 (46·4%)	177/199 (88·9%)
Angiography only	1181/8049 (14·7%)	183/1489 (12·3%)	2000/10 262 (19·5%)	1/199 (0·5%)
Access site				
Radial	5255/8169 (64·3%)	1375/1940 (70·9%)	3281/10 262 (32·0%)	17/56 (30·4%)
Femoral	2905/8169 (35·6%)	561/1940 (28·9%)	3283/10 262 (32·0%)	39/56 (69·6%)
Brachial	9/8169 (0·1%)	4/1940 (0·2%)	9/10 262 (0·1%)	0/56
Procedural characteristics				
Multivessel disease*	5346/8167 (65·5%)	1139/1895 (60·1%)	3329/6071 (54·8%)	87/199 (43·7%)
Vein graft recanalisation	68/8167 (0·8%)	14/1895 (0·7%)	128/4764 (2·7%)	5/78 (6·4%)
Drug-eluting stent	5211/7810 (66·7%)	1176/1822 (64·5%)	1915/4764 (40·2%)	150/152 (98·7%)
Stent diameter ≤3 mm	2924/7026 (41·6%)	799/1713 (46·6%)	3255/4764 (68·3%)	67/93 (72·0%)
Left ventricular ejection fraction (%)				
<30	1743/13 211 (13·2%)	259/1999 (13·0%)	502/6705 (7·5%)	17/147 (11·6%)
30–49	4607/13 211 (34·9%)	699/1999 (35·0%)	2613/6705 (39·0%)	49/147 (33·3%)
≥50	6861/13 211 (51·9%)	1041/1999 (52·1%)	3590/6705 (53·5%)	81/147 (55·1%)
Periprocedural medication				
$P2Y_{12}$ receptor inhibitor	22 888/28 891 (79·2%)	4172/5131 (81·3%)	4489/4680 (95·9%)	162/167 (97·0%)
Unfractionated heparin	5115/26 371 (19·4%)	944/3854 (24·5%)	415/10 222 (4·1%)	184/203 (90·6%)
Low-molecular-weight heparin	14 924/26 837 (55·6%)	2459/3867 (63·6%)	3682/10 222 (36·0%)	7/203 (3·4%)
Fondaparinux	7396/22 675 (32·6%)	453/3153 (14·4%)	2931/10 222 (28·7%)	3/199 (1·5%)
Bivalirudin	290/9983 (2·9%)	61/1383 (4·4%)	1405/4243 (33·1%)	4/198 (2·0%)
β-blocker	14 266/19 174 (74·4%)	1914/2540 (75·4%)	4402/10 222 (43·1%)	30/102 (29·4%)
Diuretics	9445/26 571 (35·5%)	1332/3861 (34·5%)	2464/10 221 (24·1%)	22/101 (21·8%)
In-hospital complications				
Cardiac arrest	1812/29 947 (6·1%)	321/5549 (5·8%)	236/10 119 (2·3%)	16/102 (15·7%)
Death	3614/31 193 (11·6%)	528/5578 (9·5%)	620/10 262 (6·0%)	16/203 (7·9%)
Discharge medication				
Acetylsalicylic acid	21 198/29 311 (72·3%)	4001/5249 (76·2%)	8813/10 217 (86·3%)	181/187 (96·8%)
$P2Y_{12}$ receptor inhibitor	14 252/22 003 (64·8%)	2785/3900 (71·4%)	6582/10 233 (64·3%)	177/197 (89·8%)
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker	17 584/28 967 (60·7%)	3326/5230 (63·6%)	6494/10 212 (63·6%)	150/187 (80·2%)
Oral anticoagulant	1663/26 384 (6·3%)	269/3857 (7·0%)	780/10 215 (7·6%)	9/152 (5·9%)
β-blocker	18 506/29 087 (63·6%)	3484/5239 (66·5%)	8534/10 213 (83·6%)	145/187 (77·5%)
Statin	20 946/29 108 (72·0%)	3962/5245 (75·5%)	7555/10 213 (74·0%)	176/186 (94·6%)
Aldosterone antagonist	1396/20 942 (6·7%)	218/3799 (5·7%)	177/2797 (6·3%)	1/57 (1·8%)
Oral glucose-lowering medication	2594/28 960 (9·0%)	435/5136 (8·5%)	1094/10 216 (10·7%)	20/201 (10·0%)
Insulin	1447/28 960 (5·0%)	304/5136 (5·9%)	1014/10 219 (9·9%)	15/186 (8·1%)

Data are n/N (%). *Defined as stenosis in any two of the following: left main coronary artery, left anterior descending coronary artery, left circumflex coronary artery, and right coronary artery.

Table 2: **Treatment characteristics of patients in the ONCO-ACS development and validation cohorts**

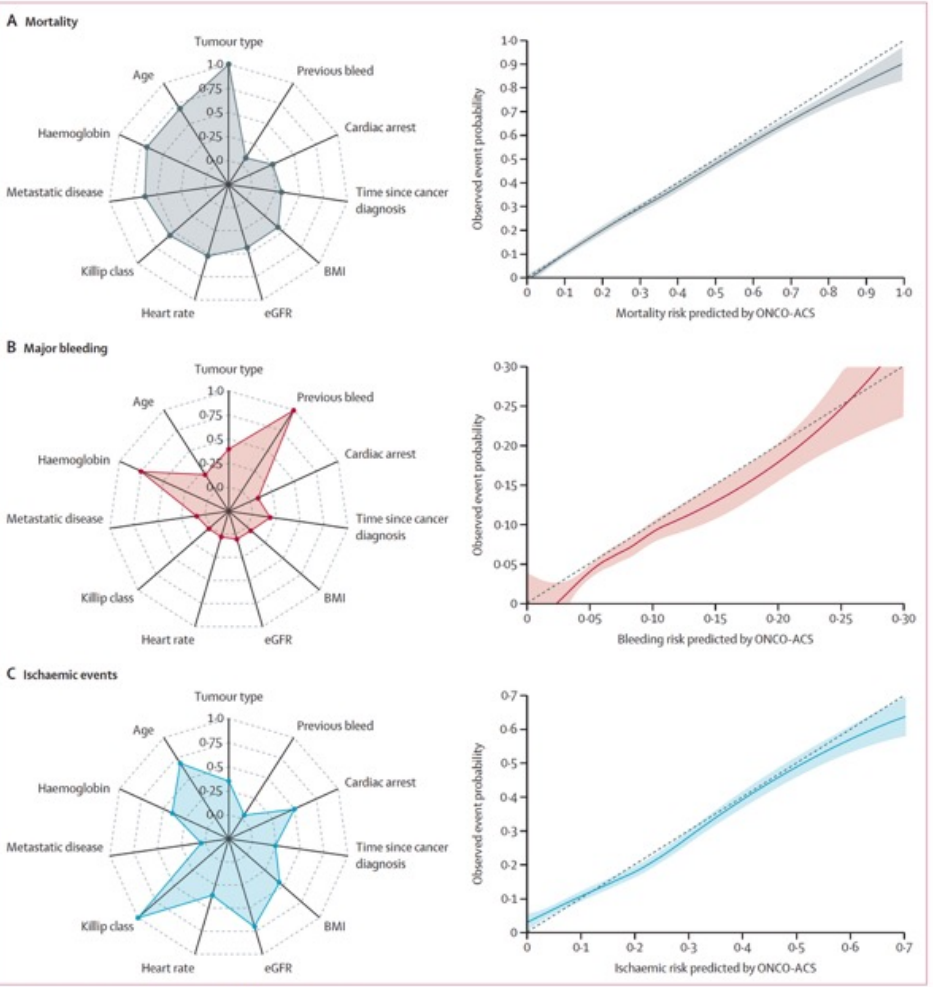


Figure 1: **Outcome-specific risk prediction by ONCO-ACS score**

Variable importance according to mean (ie, aggregated across all patients) absolute SHAP value scaled to the variable with the highest value in the final prediction models, shown as radar plots (left panels) and predicted versus observed event probability for each score outcome (right panels) for all-cause mortality (A), major bleeding (B), and ischaemic events (C) at 6 months. Dashed diagonal lines indicate ideal calibration. Solid lines show smoothed calibration curves with colour bands signifying 95% CIs. Radar plots were based on patients in the training dataset in the development cohort and calibration plots were based on data from external validation cohort 1. Untransformed mean absolute SHAP values are provided in the appendix (p 50). eGFR=estimated glomerular filtration rate. SHAP=Shapley additive explanations.

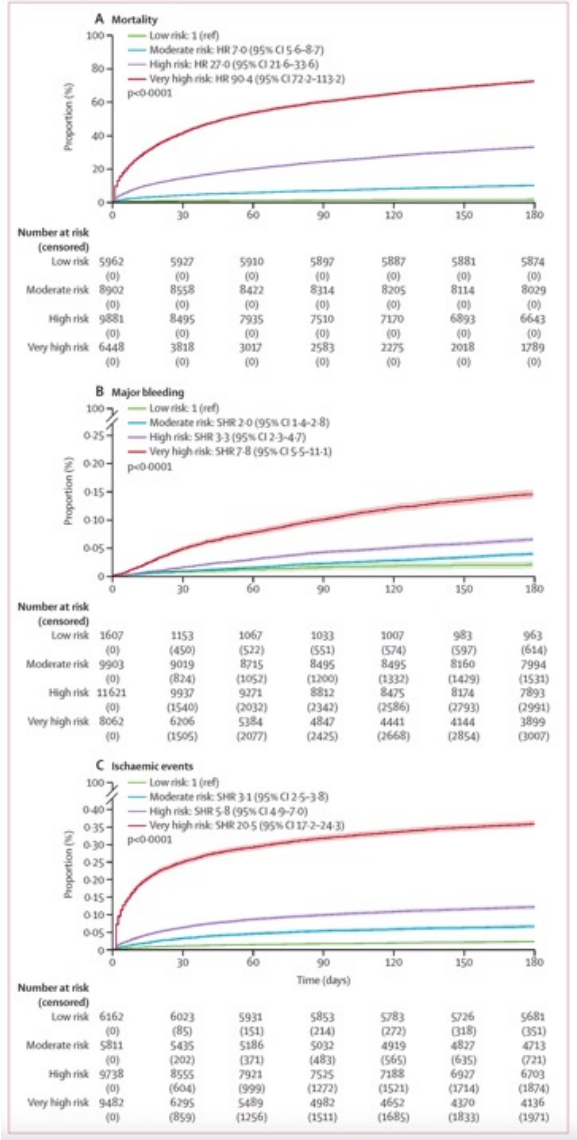


***Figure 2*: Classification of mortality, bleeding, and ischaemic risk in cancer patients with ACS**

Cumulative incidence for all-cause mortality (A), major bleeding (B), and ischaemic events (C) at 6 months in the low risk, moderate risk, high risk, and very high risk groups. The number at risk is indicated. Complete follow-up was available in all participants. For major bleeding and ischaemic events, the numbers in parentheses indicate competing events. Results were based on patients in the development cohort. HR=hazard ratio. SHR=subdistribution hazard ratio.

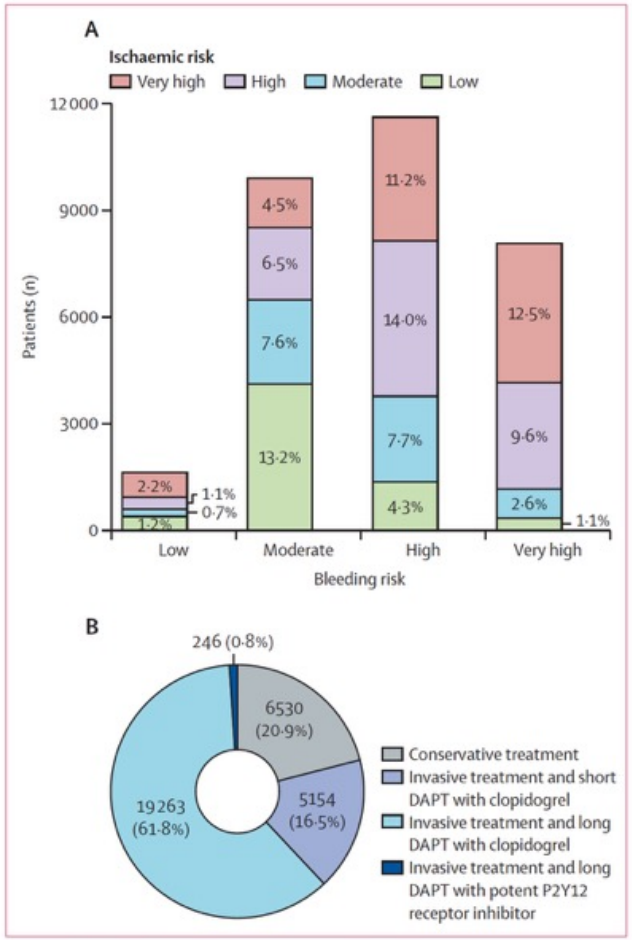


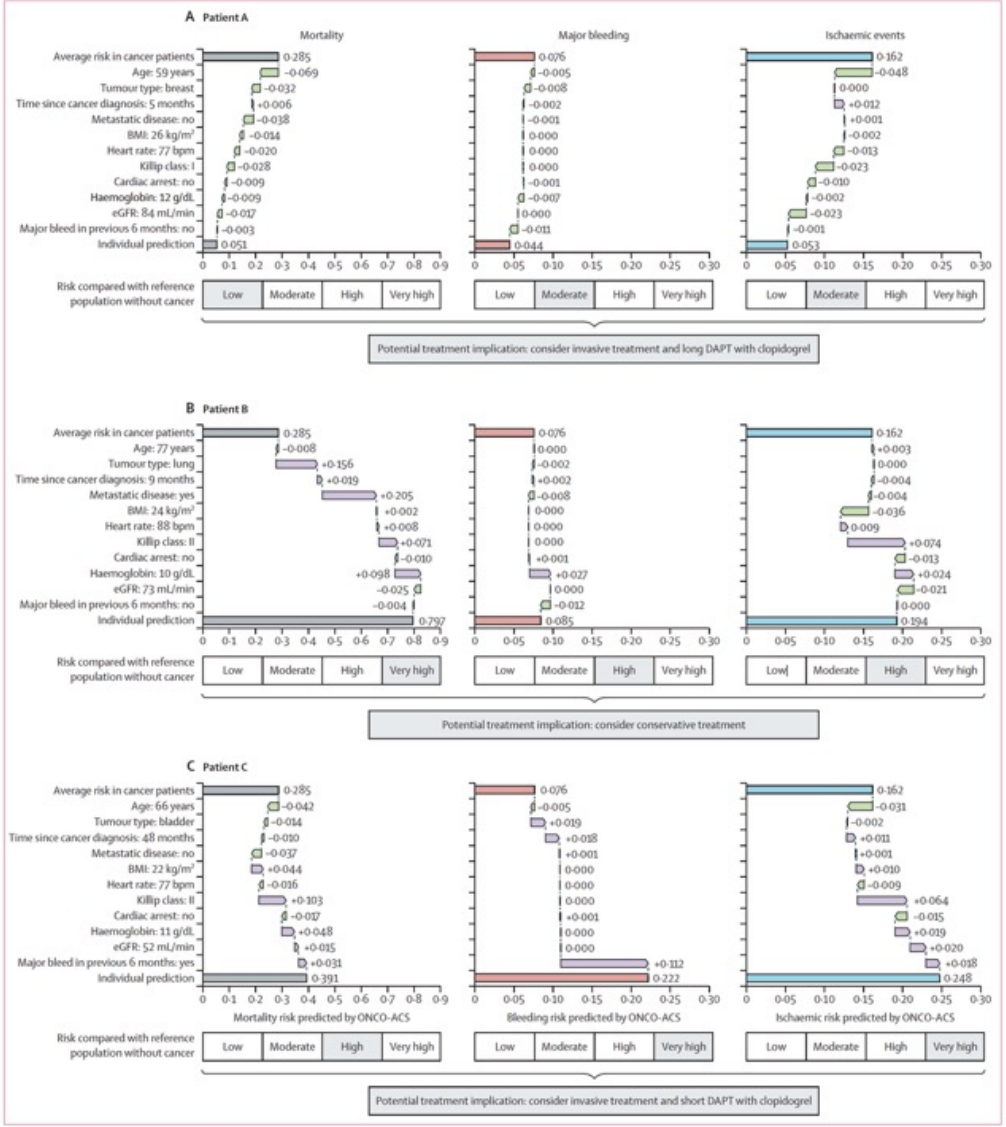
***Figure 3*: Combined assessment of competing outcome risks**

(A) Risk classification according to combined assessment of bleeding and ischaemic risk. (B) Potential treatment stratification in patients with cancer and acute coronary syndrome when applying ONCO-ACS-based risk assessment to current guideline recommendations.[1,2] Results are based on patients in the development cohort (N=31 193), presented as n (%). Absolute patient counts per category are provided in the appendix (pp 31–32). DAPT=dual antiplatelet therapy.

Figure 4: **Illustrative patient examples**

(A) Example of a hypothetical 59-year-old patient with breast cancer, diagnosed 5 months previously. ONCO-ACS predicted low mortality risk, moderate bleeding risk, and moderate ischaemic risk compared with a reference population without cancer. (B) Example of a hypothetical 77-year-old patient diagnosed with metastatic lung cancer 9 months previously. (C) Example of a hypothetical 66-year-old patient diagnosed with bladder cancer 48 months previously. ONCO-ACS classified this patient as having very high bleeding risk, very high ischaemic risk, and high mortality risk. Data are depicted as waterfall plots to explain the contribution of each feature value in a specific patient to the model prediction. Bars represent absolute increase (purple) or decrease (green) in predicted risk. bpm=beats per minute. DAPT=dual antiplatelet therapy. eGFR=estimated glomerular filtration rate.

Based on data regarding acute coronary syndrome (ACS) in cancer patients, cancers with the highest risk of mortality and adverse cardiovascular events include **lung, gastric, and pancreatic cancers**. These malignancies, along with prostate and breast cancer, are the most frequent types associated with ACS, with lung cancer specifically showing the highest rates of in-hospital mortality.



Research in context

Evidence before this study

The management of patients with cancer and acute coronary syndrome is challenging due to a complex interplay of overall mortality, bleeding risk, and ischaemic risk. We systematically searched PubMed from database inception to Jan 15, 2025, for any published studies using the search terms: "acute coronary syndrome", "myocardial infarction", "cancer", "malignancy", "neoplasm", and "malignant", with no language restrictions. No articles were excluded. Patients with cancer were systematically excluded from clinical trials and established risk stratification tools in acute coronary syndrome. Available risk scores do not account for cancer characteristics or for competing risks, which are particularly relevant due to high event rates in patients with cancer and acute coronary syndrome. No risk classification system for cancer patients with acute coronary syndrome is currently available.

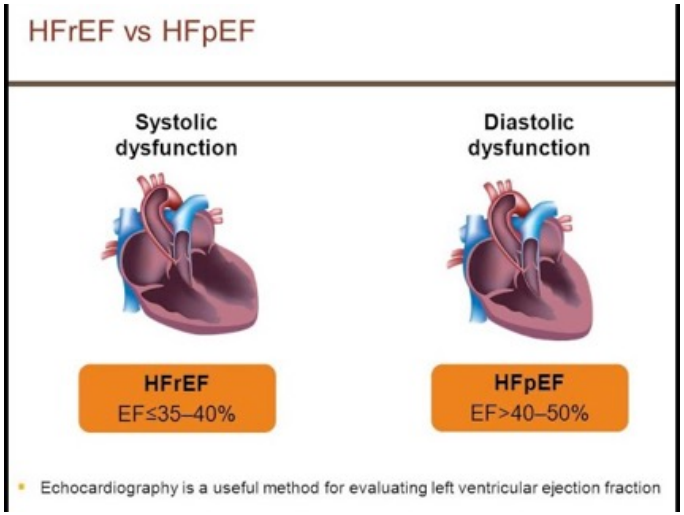
Added value of this study

We used nationwide cohorts of individuals with acute coronary syndrome from England, Sweden, and Switzerland, including 1 017 759 patients, of whom 47 236 had cancer. Patients with cancer and acute coronary syndrome were characterised by different clinical characteristics and a distinct risk profile. Leveraging a machine learning-based approach, we developed and externally validated, for the first time, a novel cancer-specific risk tool for mortality, bleeding, and ischaemic events after the acute coronary syndrome (the ONCO-ACS score). Based on 11 clinically available variables, the ONCO-ACS score simultaneously predicts the risk of multiple clinically relevant outcomes to support decision making. ONCO-ACS considers competing event risks and enables risk stratification of patients with cancer and acute coronary syndrome. Risk groups were based on a cancer-free reference population to facilitate the contextualisation of existing clinical evidence and the design of future clinical trials in cancer patients with acute coronary syndrome.

Implications of all the available evidence

The ONCO-ACS score provides a validated, practical tool for predicting mortality, major bleeding, and ischaemic events in patients with cancer and acute coronary syndrome. In the context of a comprehensive clinical evaluation, this standardised tool can support personalised treatment decisions. Early risk stratification based on multiple competing risks can inform tailored strategies for interventional procedures and antithrombotic therapy in patients with cancer and acute coronary syndrome. The ONCO-ACS score might further guide the design of dedicated randomised controlled trials in patients with cancer and acute coronary syndrome.

HFrEF steht für "**Heart Failure with reduced Ejection Fraction**" (Herzinsuffizienz mit reduzierter Ejektionsfraktion) und beschreibt eine Form der Herzschwäche, bei der der Herzmuskel das Blut nicht mehr stark genug auswirft, was zu einer **Auswurffraktion (EF) von 40 % oder weniger** führt. Die Ejektionsfraktion misst, wie viel Prozent des Blutes pro Herzschlag aus der linken Herzkammer gepumpt wird, und eine reduzierte EF (< 40 %) deutet auf eine systolische Dysfunktion hin, oft verursacht durch Schäden wie nach einem Herzinfarkt.



Heart failure with reduced ejection fraction

Heart failure is a complex clinical syndrome affecting around 70 million individuals globally. It has a prevalence of 2% in Europe and North America and approximately 1% in Asia and South America. Accurate diagnosis relies on the presence of typical signs and symptoms, elevated natriuretic peptide concentrations, and evidence of cardiac structural or functional abnormalities using cardiac imaging techniques. Approximately half of all heart failure cases are attributed to reduced left ventricular systolic function—classified as heart failure with reduced ejection fraction (HFrEF). Current guideline-directed medical therapy has markedly improved survival and quality of life for patients with HFrEF. Contemporary management emphasises early initiation and rapid uptitration of four foundational drug classes—renin-angiotensin system inhibitors or angiotensin receptor-neprilysin inhibitors, β blockers, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter 2 inhibitors—alongside diuretics for the symptom relief of volume overload. Despite advances in management, heart failure remains a leading cause of cardiovascular morbidity and mortality, partly due to absence of implementation of, and poor adherence to, medications. Future directions to improve outcomes include the integration of personalised medicine approaches, multiomic profiling, and innovative clinical trial designs to address residual risk and identify novel therapeutic targets. This Seminar provides an overview of the current diagnostic and pharmacological management of patients with HFrEF, highlighting the progress and outlining the challenges that remain.

RAS Blockade, Beta Blockade, MR Blockade, and SGLT2 Inhibition. Diuretics as needed for congestion

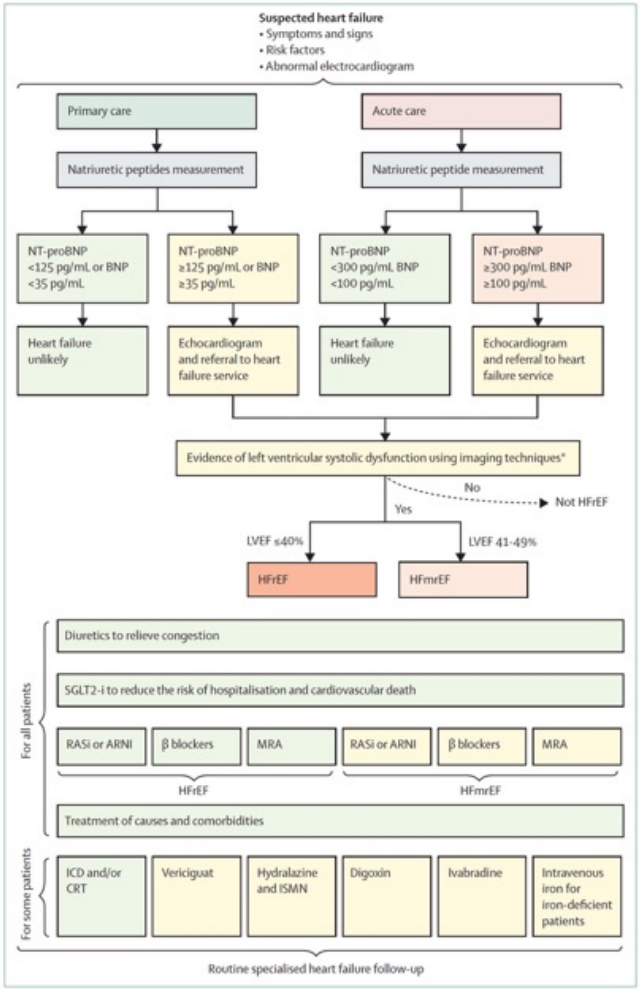


Figure 1: **Pragmatic approach to the diagnosis and treatment of HFrEF and HFmrEF**
Green=Class I recommendations. Orange=Class II recommendations. ARNI=angiotensin receptor-neprilysin inhibitors. BNP=brain natriuretic peptide. HFrEF=heart failure with reduced ejection fraction. HFmrEF=heart failure with mildly reduced ejection fraction. ICD=implantable cardioverter defibrillator. ISMN=isosorbide mononitrate. LVEF=left ventricular ejection fraction. MRA=mineralocorticoid receptor antagonists. NT-proBNP=N-terminal pro-brain natriuretic peptide. RASi=renin-angiotensin system inhibitors. SGLT2-i=sodium-glucose cotransporter 2 inhibitors. *Echocardiography or cardiac magnetic resonance imaging.

	Initial dose	Target dose	Main side effects or contraindications
Sodium-glucose cotransporter 2 inhibitors			
Empagliflozin	10 mg once a day	10 mg once a day	Diabetes ketoacidosis; urinary tract infections; type I diabetes
Dapagliflozin	10 mg once a day	10 mg once a day	Diabetes ketoacidosis; urinary tract infections; type I diabetes
Mineralocorticoid receptor antagonists			
Spironolactone	12·5–25 mg once a day	50 mg once a day	Hyperkalaemia; worsening renal function; gynecomastia
Eplerenone	25 mg once a day	50 mg once a day	Hyperkalaemia; worsening renal function; constipation; rash
Finerenone	10 mg once a day	40 mg once a day	Hyperkalaemia; worsening renal function; pruritus
Renin angiotensis system inhibitors and angiotensin receptor blockers, +/- neprilysin inhibitor			
Captopril	6·25 mg three times a day	50 mg three times a day	Hyperkalaemia; worsening renal function; hypotension; renal artery stenosis; angiooedema; cough; metallic taste; neutropenia/agranulocytosis; rash
Enalapril	2·5 mg twice a day	10–20 mg twice a day	Hyperkalaemia; worsening renal function; hypotension; renal artery stenosis angiooedema; cough
Lisinopril	2·5–5 mg once a day	20–35 mg once a day	Hyperkalaemia; worsening renal function; hypotension; renal artery stenosis; angiooedema; cough
Ramipril	2·5 mg twice a day	5 mg twice a day	Hyperkalaemia; worsening renal function; hypotension; renal artery stenosis; angiooedema; cough; gastrointestinal upset; dry mouth (rare)
Trandolapril	0·5 mg once a day	4 mg once a day	Hyperkalaemia; worsening renal function; hypotension; renal artery stenosis; angiooedema; cough; gastrointestinal discomfort; diarrohoea; dry skin
Candesatan	4 mg once a day	32 mg once a day	Hyperkalaemia; worsening renal function; hypotension; renal artery stenosis; angiooedema; dizziness
Losartan	25 mg once a day	150 mg once a day	Hyperkalaemia; worsening renal function; hypotension; renal artery stenosis; angiooedema; rash; dyspepsia; hypouricemia
Valsartan	20 mg twice a day	160 mg twice a day	Hyperkalaemia; worsening renal function; hypotension; renal artery stenosis; angiooedema; insomnia; arthralgia
Sacubitril–valsartan	Sacubitril 24 mg twice a day; valsartan 26 mg twice a day	Sacubitril 97 mg twice a day; valsartan 103 mg twice a day	Hyperkalaemia; worsening renal function; hypotension; renal artery stenosis; angiooedema
β blockers			
Bisoprolol	1·25 mg once a day	10 mg once a day	Severe asthma; bradycardia; hypotension; dry eyes; nausea; Raynaud's phenomenon; low mood; erectile dysfunction
Carvedilol	3·125 mg twice a day	25 mg twice a day	Severe asthma; bradycardia; hypotension; dry eyes; low mood; erectile dysfunction; rash; insomnia
Metoprolol succinate (CR/XL)	12·5–25 mg once a day	200 mg once a day	Severe asthma; bradycardia; hypotension; low mood; dry eyes; erectile dysfunction; Raynaud's phenomenon; sleep disorders; visual impairment
Nebivolol	1·25 mg once a day	10 mg once a day	Severe asthma; bradycardia; hypotension; low mood; dry eyes; erectile dysfunction; Raynaud's phenomenon; sleep disorders; visual impairment
Other agents			
Ivabradine	5 mg twice a day	7·5 mg twice a day	Acute MI; congenital QT syndrome; bradycardia; atrioventricular block; dizziness; headache; hypertension; blurred vision
Vericiguat	2·5 mg once a day	10 mg once a day	Hypotension; anaemia; dizziness; gastrointestinal symptoms; headache
Digoxin	62·5 mcg once a day	250 mcg once a day	Risk of digitalis toxicity in hypercalcaemia; hypokalaemia; hypomagnesaemia; hypoxia; CKD
Hydralazine–isosorbide dinitrate	Hydralazine 37·5 mg three times a day; isosorbide dinitrate 20 mg three times a day	Hydralazine 75 mg three times a day; isosorbide dinitrate 40 mg three times a day	Worsening angina pectoris; dizziness; flushing; gastrointestinal disorders; headache; hypotension; joint disorders; lupus-like syndrome myalgia; palpitations

CKD=chronic kidney disease. HFrEF=heart failure with reduced ejection fraction. MI=myocardial infarction.

Table 1: **Recommended pharmacological treatment for HFrEF**

	Initial dose	Maximum dose	Half-life	Main side effects or contraindications
Loop diuretics				
Furosemide	20–40 mg	400–600 mg	1–3 h	Hypokalaemia; hyponatremia; hypovolemia; worsening renal function
Bumetanide	0·5–1 mg	10–15 mg	1–1·5 h	Hypokalaemia; hyponatremia; hypovolemia; worsening renal function
Torsemide	10 mg	200–300 mg	3–6 h	Hypokalaemia; hyponatremia; hypovolemia; worsening renal function
Thiazides				
Hydrochlorothiazide	12·5–25 mg	200 mg	6–15 h	Hypokalaemia; hypochloraemia; hyperglycaemia; hyperuricaemia; nausea; postural hypotension; systemic lupus erythematosus; worsening renal function
Bendroflumethiazide	2·5 mg	10 mg	3–4 h	Hypokalaemia; hypochloraemia; hyperglycaemia; hyperuricaemia; nausea; postural hypotension; systemic lupus erythematosus; worsening renal function
Indapamide	2·5 mg	5 mg	14–24 h	Hypokalaemia; hypochloraemia; hyperglycaemia; hyperuricaemia; nausea; postural hypotension; acute porphyrias; worsening renal function
Metolazone	2·5 mg	20 mg	6–20 h	Hypokalaemia; hypochloraemia; hyperglycaemia; hyperuricaemia; nausea; postural hypotension; cute porphyrias; worsening renal function
Chlorthalidone	25 mg	100 mg	45–60 h	Hypokalaemia; hypochloraemia; hyperglycaemia; hyperuricaemia; nausea; postural hypotension; worsening renal function
Mineralocorticoid receptor antagonists and K+ sparing agents				
Spironolactone	25 mg	100 mg	Approximately 90 min	Hyperkalaemia; worsening renal function; gynecomastia
Eplerenone	25 mg	50 mg	3–6 h	Hyperkalaemia; worsening renal function; constipation; rash
Amiloride	5 mg	20 mg	6–9 h	Hyperkalaemia; worsening renal function; Addison's disease; alopecia; anaemia; gastrointestinal disorders; arthralgia; asthenia; gout; insomnia; jaundice; sexual dysfunction; skin reactions; tinnitus
Triamterene	150 mg	250 mg	2 h	Diarrhoea; hyperkalaemia; nausea; vomiting; dry mouth; worsening renal function
Sodium-glucose cotransporter 2 inhibitors				
Dapgliflozin	10 mg	10 mg	13 h	Diabetes ketoacidosis; urinary tract infections; type I diabetes
Empagliflozin	10 mg	10 mg	12 h	Diabetes ketoacidosis; urinary tract infections; type I diabetes
Other agents				
Acetazolamide	250–375 mg	500 mg	2–5 h	Metabolic acidosis; nephrolithiasis; paresthesia; electrolyte imbalances
Tolvaptan	15 mg	120 mg	12 h	Appetite decreased; asthenia; constipation; dehydration; diarrhoea; dizziness; gastrointestinal discomfort; headache; hepatic disorders; hyperglycaemia; hypernatraemia; hyperuricaemia; insomnia; muscle spasms; polydipsia; skin reactions

HFrEF=heart failure with reduced ejection fraction.

Table 2: **Diuretic treatmentfor HFrEF**

	Number of patients	NYHA	Setting	LVEF criterion	Mean LVEF	Intervention	Comparator	Loop diuretics	Primary endpoint	Hazard ratio (95% CI)
Angiotensin converting enzyme inhibitor										
CONSENSUS (1987)	459	IV	Chronic	NA	..	Enalapril	Placebo	98%	All-cause mortality	0·60 (0·39–0·92)
SOLVD-T (1989)	2569	II–IV	Chronic	≤35%	25%	Enalapril	Placebo	85%	All-cause mortality	0·84 (0·74–0·95)
SOLVD-P (1992)	4228	I–II	Chronic	≤35%	28%	Enalapril	Placebo	17%	All-cause mortality	0·92 (0·92–1·21)
SAVE (1993)	2231	..	Post-myocardial infarction	<40%	31%	Captopril	Placebo	35%	All-cause mortality	0·79 (0·65–0·95)
AIRE (1993)	2006	I–III	Post-myocardial infarction	NA	..	Ramipril	Placebo	60%	All-cause mortality	0·73 (0·60–0·89)
ATLAS (1999)	3164	II–IV	Chronic	≤30%	23%	High-dose lisinopril	Low-dose lisinopril	..	All-cause mortality	0·92 (0·82–1·03)
Angiotensin II receptor blockers										
ELITE II (2000)	3152	II–IV	Chronic	≤40%	31%	Losartan	Captopril	78%	All-cause mortality	1·13 (0·95–1·35)
Val-HeFT (2001)	5018	II–IV	Chronic	≤40%	27%	Valsartan	Placebo	86%	All-cause mortality	1·02 (0·88–1·18)
CHARM-added (2003)	2548	II–IV	Chronic	≤40%	28%	Candesartan	Ace-i	90%	Cardiovascular death; heart failure hospitalisation	0·85 (0·75–0·96)
CHARM-alternative (2003)	2028	II–IV	Chronic	≤40%	30%	Candesartan	Placebo	85%	Cardiovascular death; heart failure hospitalisation	0·77 (0·67–0·89)
HEEAL (2009)	3846	II–IV	Chronic	≤40%	33%	High-dose losartan	Low-dose losartan	77%	All-cause mortality; heart failure hospitalisation	0·90 (0·82–0·99)
Angiotensin II receptor blockers and neprilysing Inhibitors										
PARADIGM-HF (2014)	8442	I–IV	Chronic	≤40%	30%	Sacubitril–valsartan	Enalapril	80%	Cardiovascular death; heart failure hospitalisation	0·80 (0·73–0·87)
Beta blockers										
MERIT-HF (1999)	3991	II–IV	Chronic	≤40%	28%	Metoprolol	Placebo	91%	All-cause mortality	0·66 (0·53–0·81)
CAPRICORN (2001)	1959	..	Post-myocardial infarction	≤40%	33%	Carvedilol	Placebo	35% IV	All-cause mortality	0·77 (0·60–0·98)
COPERNICUS (2002)	2289	III–IV	Chronic	≤25%	20%	Carvedilol	Placebo	99%	All-cause mortality	0·65 (0·52–0·81)
COMET (2003)	1511	II–IV	Chronic	≤35%	26%	Carvedilol	Metoprolol	99%	All-cause mortality	0·83 (0·74–0·93)
SENIORS (2005)	2128	II–IV	Elderly (≥70 years)	≤35%	33%	Nebivolol	Placebo	86%	Death; cardiovascular hospitalisation	0·86 (0·74–0·99)
Mineralocorticoid receptor antagonists										
RALES (1999)	1663	III–IV	Chronic	≤35%	25%	Spironolactone	Placebo	100%	All-cause mortality	0·70 (0·60–0·82)
EPHESUS (2003)	6642	NA	Post-myocardial infarction	≤40%	33%	Eplerenone	Placebo	60%	All-cause mortality	0·85 (0·75–0·96)
EMPHASIS (2011)	2737	II	Chronic	≤35%	26%	Eplerenone	Placebo	84%	Cardiovascular death; heart failure hospitalisation	0·63 (0·54–0·74)
Sodium-glucose cotrasporter 2 inhibitors										
DAPA-HF (2019)	4744	II–IV	Chronic	≤40%	31%	Dapagliflozin	Placebo	93%	Cardiovascular death; heart failure hospitalisation	0·74 (0·65–0·85)
EMPEROR-Reduced (2020)	3730	II–IV	Chronic	≤40%	27%	Empagliflozin	Placebo	87%	Cardiovascular death; heart failure hospitalisation	0·75 (0·65–0·86)

(Table 3 continues on next page)

	Number of patients	NYHA	Setting	LVEF criterion	Mean LVEF	Intervention	Comparator	Loop diuretics	Primary endpoint	Hazard ratio (95% CI)
(Continued from previous page)										
Other treatments										
V-HeFT (1986)	642	..	Chronic	≤45%	30%	Hydralazine and ISDN	Placebo	..	All-cause mortality	0·81
V-HeFT II (1991)	804	I–IV	Chronic	≤45%	29%	Enalapril	Hydralazine and ISDN	100%	All-cause mortality	0·89
DIG (1997)	6800	I–IV	Chronic	≤45%	30%	Digoxin	Placebo	81%	All-cause mortality	0·99 (0·91–1·07)
DIGIT-HF (2025)	1240	II–IV	Chronic	≤40%	28%	Digitoxin	Placebo	87%	All-cause mortality; heart failure hospitalisation	0·82 (0·69–0·98)
A-HeFT* (2004)	1050	III–IV	Black patients	≤35%	24%	Hydralazine and ISDN	Placebo	88%	All-cause mortality; heart failure hospitalisation; quality of life	0·57
BEAUTIFUL (2008)	10 917	I–IV	Ischaemic heart failure	≤40%	32%	Ivabradine	Placebo	59%	Cardiovascular death; heart failure hospitalisation; new myocardial infarction	1·00 (0·91–1·10)
SHIFT (2010)	6558	II–IV	Chronic	≤35%	29%	Ivabradine	Placebo	84%	Cardiovascular death; heart failure hospitalisation	0·82 (0·75–0·90)
VICTORIA (2020)	5050	II–IV	Chronic	≤45%	29%	Vericiguat	Placebo	89%	Cardiovascular death; heart failure hospitalisation	0·90 (0·82–0·98)
VICTOR (2025)	6105	II–IV	Chronic	≤40%	30%	Vericiguat	Placebo	69%	Cardiovascular death; heart failure hospitalisation	0·93 (0·83–1·04)
GALACTIC (2021)	8256	II–IV	Chronic	≤35%	27%	Omecamtiv mecarbil	Placebo	90%	Cardiovascular death; heart failure hospitalisation	0·92 (0·86–0·99)

LVEF=left ventricular ejection fraction. NA=not applicable. NYHA=New York Heart Association Functional Classification. *Discontinued due to high mortality in the placebo group.

Table 3: **Most relevant randomised clinical trials in HFrEF**

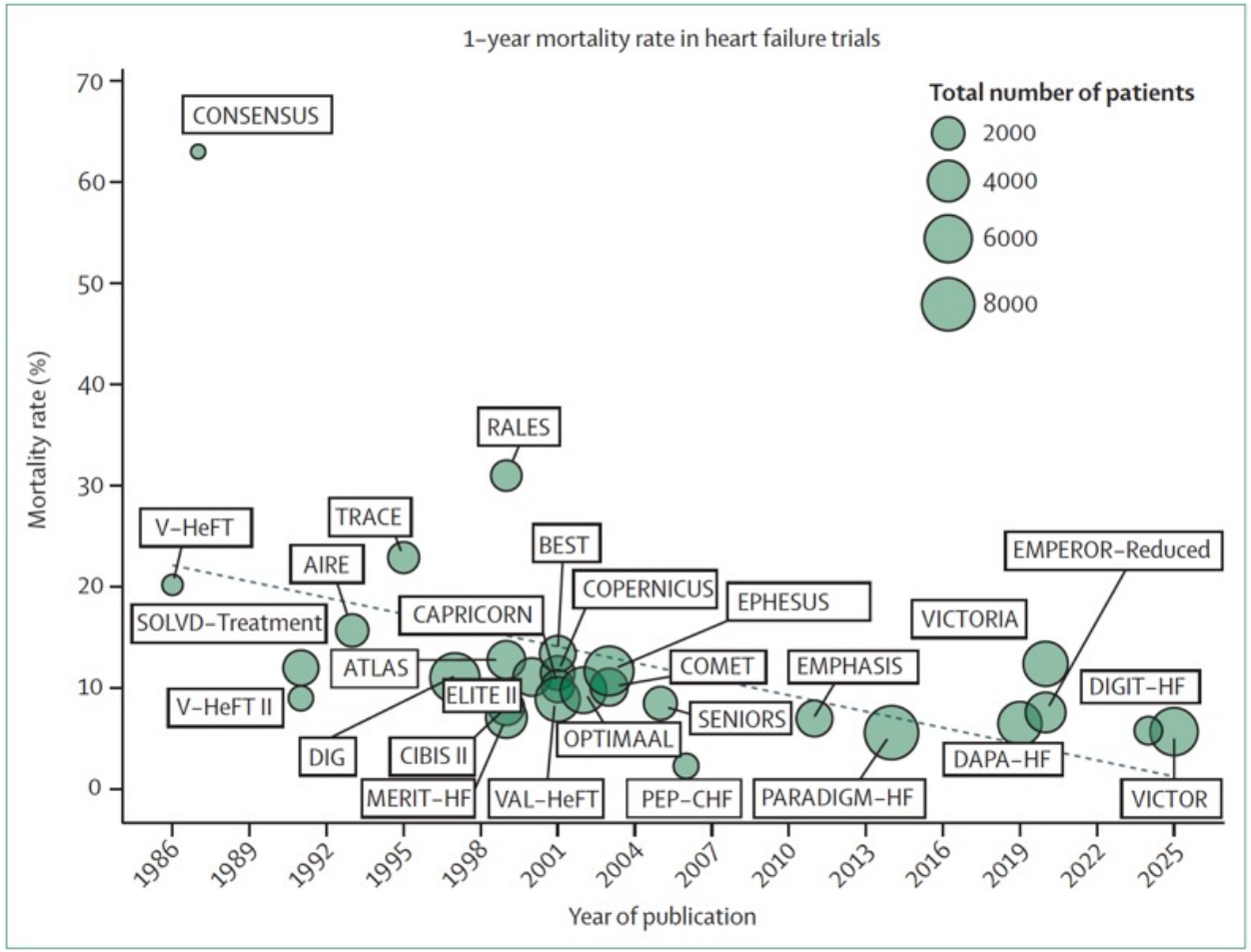


Figure 2: **Reduction of mortality in patients with HFrEF over time**
HFrEF=heart failure with reduced ejection fraction.

Conclusion

Heart failure remains a leading cause of morbidity and mortality worldwide. Current GRMT has improved life expectancy and quality of life. Optimal treatment should involve initiation and rapid up-titration of four cornerstone drug classes (RAS-i or ARNI, β blockers, MRAs, and SGLT2-i) together with diuretics to relieve congestion. In the future, a personalised approach to diagnosis and treatment will continue to drive further advances, improving both the quality and quantity of life for patients with HFrEF globally.

Holding powerful corporations accountable for their health impacts: are corporate rankings effective?

Monitoring the behaviour of transnational corporations is an important public health priority given the many ways corporate actors negatively affect health. Such effects can be mitigated by defining standards of corporate behaviour and implementing regulations to prohibit and sanction harmful behaviour. However, in the past two decades, market signals and corporate scorecards are increasingly being used to incentivise corporate actors to behave in a socially responsible manner. Two examples of relevance to global health are the Access to Medicine Index and the Access to Nutrition Initiative's Global Index. However, this Viewpoint argues that these indices are flawed and could have the perverse effect of reinforcing the power and dominance of the biggest pharmaceutical and food companies, and undermining broader public interest efforts to hold such companies accountable and improve equitable access to healthy foods, medicines, and vaccines.

Powerful corporations significantly impact public health through the production, marketing, and sale of harmful products like tobacco, alcohol, ultra-processed foods, and fossil fuels, which drive chronic diseases like cancer, diabetes, and cardiovascular issues. These "commercial determinants of health" often involve suppressing internal research on risks (e.g., PFAS "forever chemicals" by 3M/DuPont), aggressive marketing, and lobbying against regulations.

Introduction

The harmful effects of transnational corporations on health are now well documented within the growing literature on the commercial determinants of health.[1] Transnational corporations negatively affect health through various direct and indirect pathways.[2,3] Direct pathways include the aggressive supply and marketing of unhealthy commodities, such as ultra-processed foods, tobacco, and alcohol; their over-pricing of life-saving medicines and vaccines through the abuse of intellectual property rights; their exploitation or mistreatment of workers in, for example, the agricultural and manufacturing sectors; and the role of fossil fuel companies in undermining climate science and blocking the transition to clean energy. Indirect pathways include depriving governments of revenue for public health funding through tax abuse[4] and compromising the integrity of science and research.[5]

Panel: A framework for holistic corporate monitoring

Products and services

- Harmful products and services, such as unhealthy foods, unsafe and carcinogenic products, and unmoderated or false information provision
- Harmful practices, such as false and manipulative marketing, overpricing and unaffordability of essential products, abuse of monopoly power, misuse of personal datasets, and environmentally harmful systems of production, supply, and distribution

Internal governance and management

- Financial management, including tax-related conduct
- Labour policies and practices
- Environmental policies and practices
- Investor practices

Outward-facing behaviour

- Actions directed towards politicians and public sector officials
- Actions directed at the academic, scientific, and professional community
- Actions directed at actors within media and civil society

Conclusion

Powerful transnational corporations now have inordinate influence over policies in the domains of food, pharmaceuticals, energy, digital infrastructure, media, and health care, which affects the lives of billions of people. Given what is known about the burden of disease and illness caused by commercial determinants, effective corporate monitoring and accountability is clearly needed. Effective corporate accountability, however, is ultimately about power. We argue that corporate scorecards can either reinforce the current state of excessive corporate power and inadequate regulation or contribute to wider efforts to shift power and establish more effective and accountable systems of governance.

Crucially, notwithstanding their imperfect and incomplete implementation in many countries, the success of the Framework Convention on Tobacco Control[24] and the International Code of Marketing of Breastmilk Substitutes[25] point to the importance of civic, academic, and professional mobilisation under the auspices of WHO to establish standards of corporate behaviour, overcome opposition from powerful actors with vested interests, and ensure that standards are translated into effective and appropriate laws and enforcement mechanisms.

Rethinking the heritability of aging

Life span varies strikingly across the tree of life. Baker's yeast survive for days, fruit flies for weeks to months, bowhead whales for more than two centuries, and bristlecone pines for millennia. Comparative studies have uncovered conserved biological mechanisms that regulate aging, leaving little doubt that genetics places strong constraints on how long organisms live. Nevertheless, classical aging experiments in animals show that there is considerable variability in life span, even among isogenic littermates, indicating that there's more to aging than genetics. Indeed, population-level studies on twins estimate that the heritability of human life span may be as little as 10 to 25%, as do studies on pedigrees. The prevailing view is that individual longevity is influenced largely by environmental factors and lifestyle. Shenhar *et al.* challenge this notion, reporting that human heritability is 55%, considerably higher than previous estimates.

Heritability of intrinsic human life span is about 50% when confounding factors are addressed

How heritable is human life span? If genetic heritability is high, longevity genes can reveal aging mechanisms and inform medicine and public health. However, current estimates of heritability are low—twin studies show heritability of only 20 to 25%, and recent large pedigree studies suggest it is as low as 6%. Here we show that these estimates are confounded by extrinsic mortality—deaths caused by extrinsic factors such as accidents or infections. We use mathematical modeling and analyses of twin cohorts raised together and apart to correct for this factor, revealing that heritability of human life span due to intrinsic mortality is above 50%. Such high heritability is similar to that of most other complex human traits and to life-span heritability in other species.

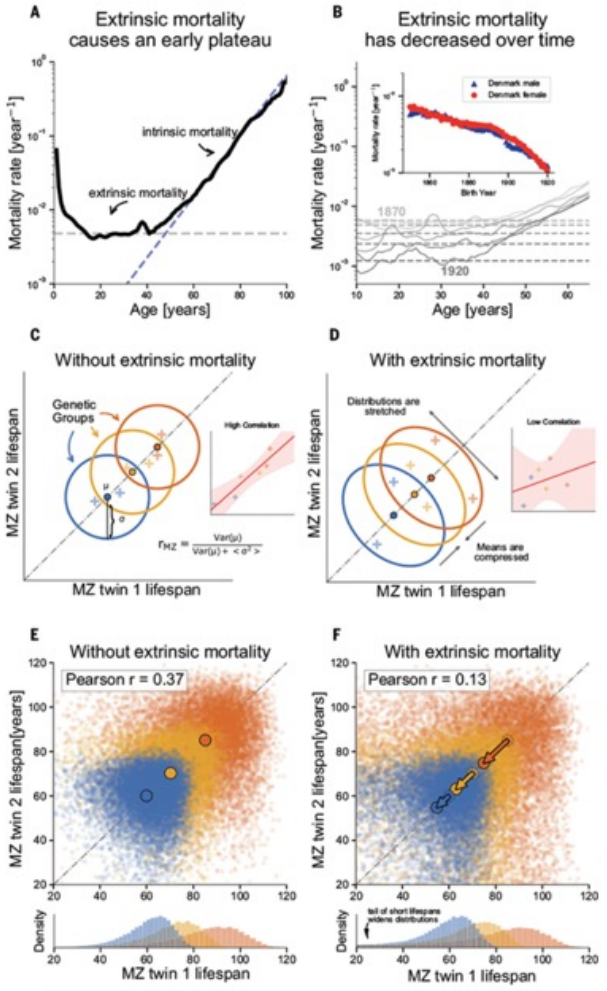


Fig. 1. Extrinsic mortality masks life-span correlations in twin cohorts.

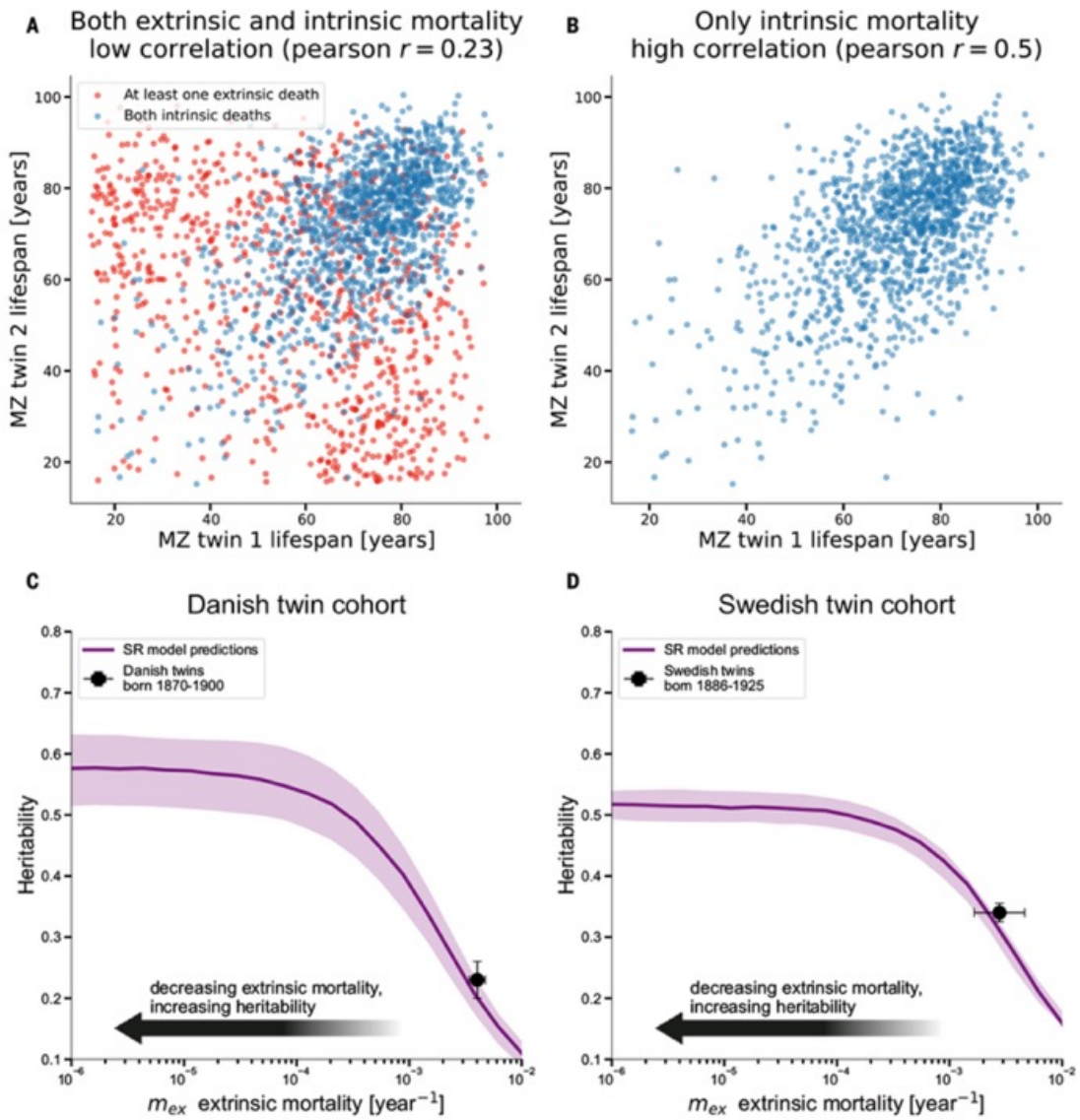


Fig. 2. Life-span heritability increases when accounting for extrinsic mortality. (**A**) Simulation of n = 5000 MZ twin pairs from the Danish twin cohort using the SR model. Twin pairs with at least one extrinsic death are in red. Life-span correlation is about 0.23. (**B**) Same as (A) but without extrinsic deaths. Removing extrinsic deaths increases correlation to 0.5. (**C**) Heritability estimate $2(r_{MZ} - r_{DZ})$ as a function of extrinsic mortality (m_{ex}) for the Danish twin cohort born between 1870 and 1900 ([8]). (**D**) Same as (C) for Swedish twins born between 1886 and 1923.

Home & Design

Ask a Vet: Does my dog need a coat?

A: No, you don't need a jacket for your dog. Waterproof jackets that keep your dog dry can also provide warmth in foggy or rainy conditions. Otherwise, protecting your dog's belly and paws should be the priority when it's cold outside.

When do dogs need help to stay warm?

Active, medium-to-large, healthy and resilient dogs with thick hair coats typically don't require additional warmth unless they are in freezing conditions for more than 30 minutes or so. My dog Bodhi, for example, could romp for hours in the cold rain.

What's the best way to keep my dog warm?

Dogs lose heat through their paw pads and the hairless part of their belly. So covering your dog's back and chest with a wool sweater or a fleece is not the most effective way of keeping them warm, even if it does make them look cute and cozy. In fact, in wet weather, wearing a coat may actually do more harm than good. The garment itself absorbs water, and it also prevents a dog from shaking to get rid of excess water trapped in its coat. That can leave your pooch more vulnerable to hypothermia.