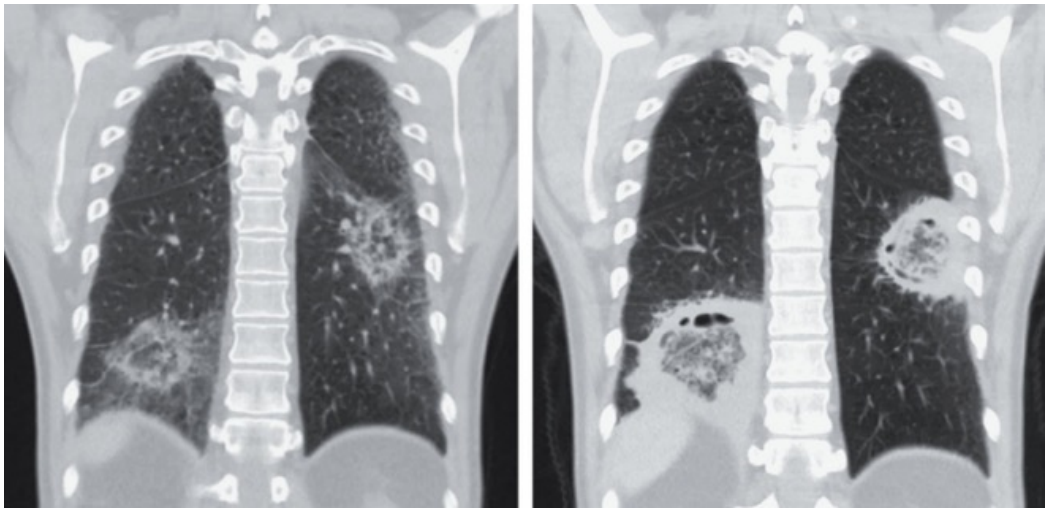
https://www.mdc-berlin.de/de/veroeffentlichungstypen/clinical-journal-club

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



A 49-year-old man with acute myeloid leukemia who had been admitted to the hospital for induction chemotherapy was evaluated for prolonged neutropenic fever. On physical examination, crackles were identified at the lung bases. Computed tomography of the chest is shown. Empiric treatment with amphotericin B was started. After 2 weeks of treatment, repeat CT of the chest is shown. What is the most likely diagnosis?

Cytomegalovirus pneumonia

Leukemic pulmonary infiltrates

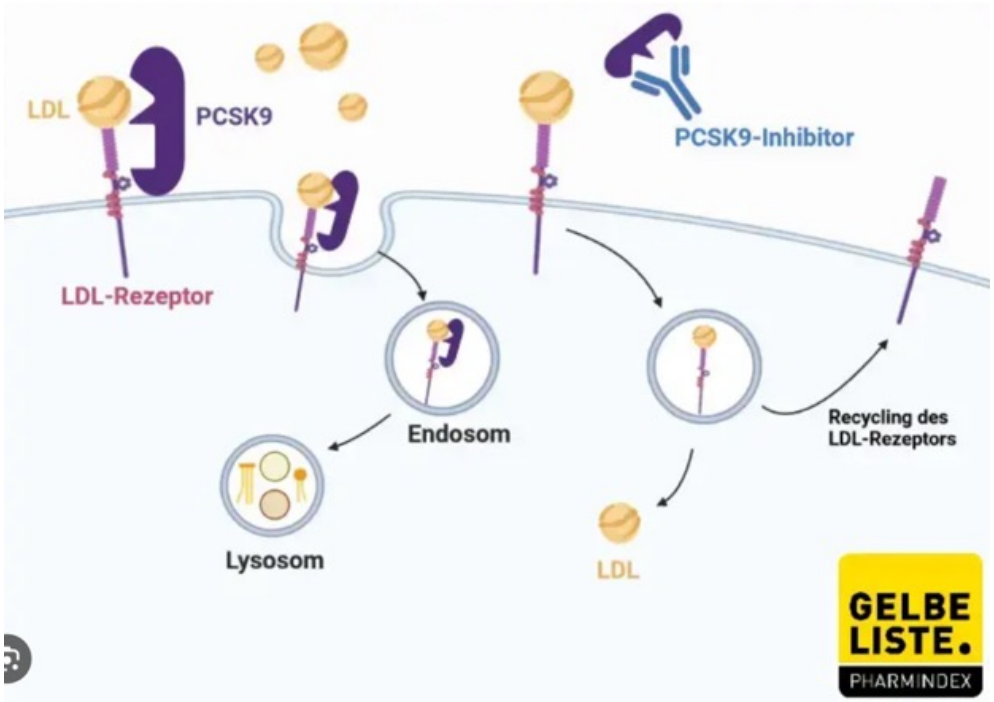
Pulmonary bacterial abscesses

Pulmonary mucormycosis

Pulmonary tuberculosis

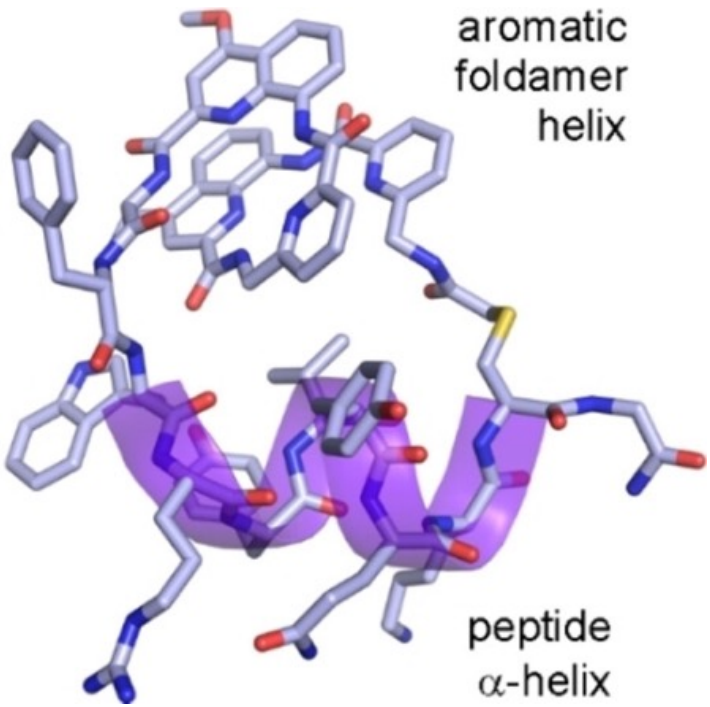
CT of the chest showed rounded opacities with central ground-glass attenuation and ringlike peripheral consolidations, a finding known as the reversed halo sign that can occur with invasive fungal infections. Appropriate treatment with amphotericin B was started, and the findings worsened on the repeat CT owing to neutrophil recovery. The diagnosis was confirmed by findings on histopathology of resected lung tissue and PCR analysis of lung tissue identifying Rhizomucor pusillus.

PCSK9 (Proprotein Convertase Subtilisin/Kexin type 9) ist ein Enzym, das den Abbau von LDL-Rezeptoren in der Leber fördert, wodurch weniger Cholesterin aus dem Blut entfernt wird und der LDL-Wert steigt. PCSK9-Hemmer (z.B. Alirocumab, Evolocumab) sind hochwirksame Antikörper, die dieses Enzym blockieren, die Rezeptoranzahl erhöhen und den LDL-Cholesterinspiegel um bis zu 60 % senken.



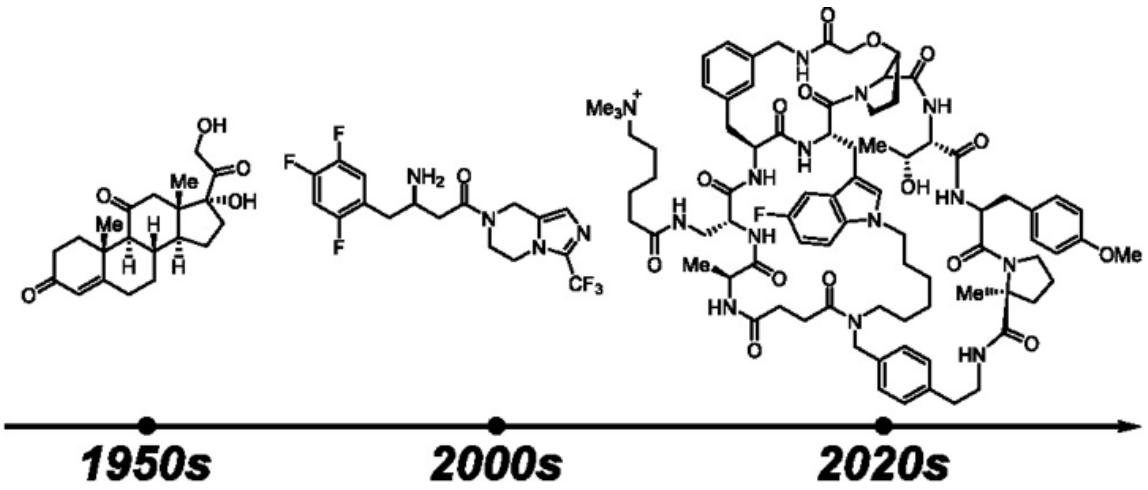
Ein **makrozyklisches Peptid** ist ein Molekül aus Aminosäuren, das mindestens eine **ringförmige Struktur** (Makrozyklus) aufweist. Diese Form entsteht meist durch Verknüpfungen zwischen den Kettenenden oder Seitenketten der Aminosäuren.
In der Medizin gelten sie als Hoffnungsträger ("Golden Middle Ground"), da sie die Vorteile von zwei Welten vereinen:

- **Wie kleine Moleküle:** Sie können oft (je nach Design) in Zellen eindringen und sind chemisch herstellbar.
- **Wie Biologika (Antikörper):** Sie binden hochspezifisch an große, flache Proteinoberflächen und können so **Protein-Protein-Interaktionen** hemmen, die für normale Medikamente "untherapierbar" (*undruggable*) sind.



Enlicitide-Decanoat (zuvor bekannt als **MK-0616**) ist ein in der Entwicklung befindlicher, **oraler PCSK9-Inhibitor** zur Senkung von LDL-Cholesterin. Als makrozyklisches Peptid ist es darauf ausgelegt, die gleiche Wirksamkeit wie bisherige injizierbare PCSK9-Hemmer zu bieten, jedoch in Form einer täglichen Tablette.

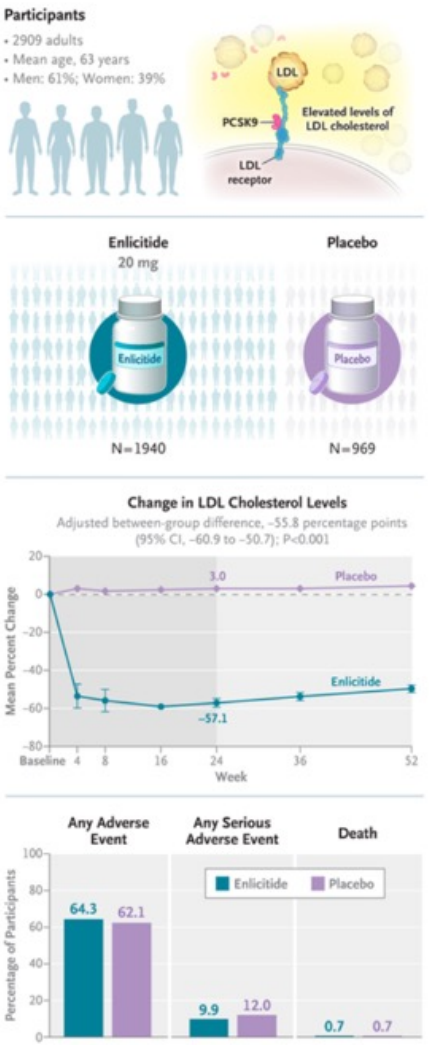
Enlicitide decanoate, an
oral macrocyclic peptide



A Placebo-Controlled Trial of the Oral PCSK9 Inhibitor Enlicitide

Enlicitide decanoate, an oral proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitor, was shown to reduce low-density lipoprotein (LDL) cholesterol levels in a phase 2 trial; longer-term data are needed.

In this multinational, double-blind, randomized, placebo-controlled trial, we enrolled adults with a history of a major atherosclerotic cardiovascular disease event with an LDL cholesterol level of 55 mg per deciliter or higher and those who were at risk for a first atherosclerotic cardiovascular disease event with an LDL cholesterol level of 70 mg per deciliter or higher. Participants were assigned in a 2:1 ratio to receive enlicitide at a dose of 20 mg or placebo daily for 52 weeks. The primary end point was the mean percent change in LDL cholesterol level from baseline to week 24. Key secondary end points were the mean percent change in LDL cholesterol level at week 52 and the mean percent change in levels of non–high-density lipoprotein (non-HDL) cholesterol and apolipoprotein B and the percent change in lipoprotein(a) level at week 24.



Decades of clinical trials have shown the efficacy of lowering low-density lipoprotein (LDL) cholesterol levels for prevention of cardiovascular events, with consistent benefit even in patients with pretreatment LDL cholesterol levels well below 70 mg per deciliter (1.8 mmol per liter). Accordingly, recent guidelines have emphasized targeting LDL cholesterol levels of 55 mg per deciliter (1.4 mmol per liter) or below in persons at highest risk for atherosclerotic cardiovascular disease. Despite this recommendation, more than half of patients do not have levels within this target range.

The most effective nonstatin therapies for lowering LDL cholesterol levels do so through inhibition of proprotein convertase subtilisin–kexin type 9 (PCSK9) and include anti-PCSK9 monoclonal antibodies and small interfering RNA therapies. In randomized trials, anti-PCSK9 monoclonal antibodies reduced atherosclerotic cardiovascular disease events in patients who had had previous cardiovascular events and LDL cholesterol levels of 70 mg per deciliter or higher. PCSK9 inhibitors are infrequently used in clinical practice relative to the number of persons with LDL cholesterol levels that are higher than the target range. One potential barrier to their use is that they are available only in an injectable form. Enlicitide decanoate, an oral macrocyclic peptide that inhibits PCSK9 binding to LDL receptors, reduced LDL cholesterol levels in short-term phase 1 and 2 studies, but longer-term data are lacking. This trial sought to evaluate the efficacy of enlicitide over a 52-week period in participants who had a history of or were at risk for a first atherosclerotic cardiovascular

Trial Population

Eligible participants were adults 18 years of age or older who had a history of a major atherosclerotic cardiovascular disease event and an LDL cholesterol level of 55 mg per deciliter or higher or who were at intermediate-to-high risk for a first atherosclerotic cardiovascular disease event and had an LDL cholesterol level of 70 mg per deciliter or higher. Levels of LDL cholesterol that were used to determine eligibility were based on a fasting lipid panel obtained at the screening visit. Major atherosclerotic cardiovascular disease events included acute coronary syndrome, coronary revascularization, myocardial infarction, ischemic stroke, cerebrovascular arterial revascularization, and peripheral arterial disease with a history of acute limb ischemia, revascularization, or major amputation (i.e., amputation of all or part of an arm or leg, excluding that of only fingers or toes).

Trial Procedures

Participants were randomly assigned in a 2:1 ratio to receive enlicitide at a dose of 20 mg or matching placebo daily for 52 weeks. The enlicitide formulation contained the excipient sodium caprate, a permeation enhancer; the matching placebo formulation did not contain sodium caprate.

End Points

The primary efficacy end point was the mean percent change in LDL cholesterol level from baseline to week 24.

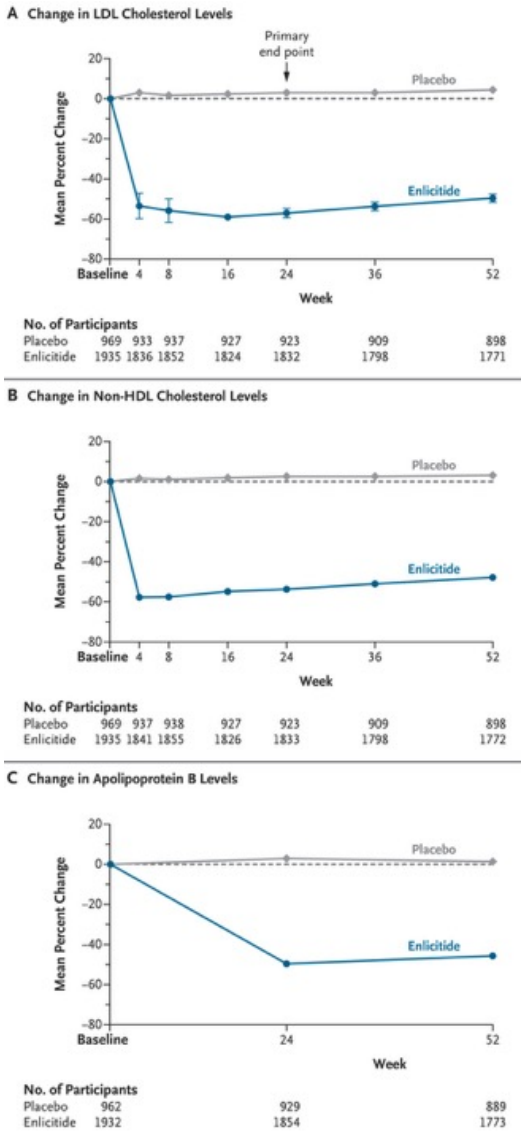
Summary of Primary and Key Secondary Efficacy End Points.

Characteristic	Enlicitide (N = 1940)	Placebo (N = 969)	Total (N = 2909)
Sex — no. (%)			
Male	1165 (60.1)	602 (62.1)	1767 (60.7)
Female	775 (39.9)	367 (37.9)	1142 (39.3)
Age — yr	62.8±10.7	62.7±10.7	62.8±10.7
Race or ethnic group — no. (%)†			
American Indian or Alaska Native	4 (0.2)	2 (0.2)	6 (0.2)
Asian	512 (26.4)	253 (26.1)	765 (26.3)
Black or African American	173 (8.9)	79 (8.2)	252 (8.7)
White	1030 (53.1)	538 (55.5)	1568 (53.9)
Multiple races	221 (11.4)	97 (10.0)	318 (10.9)
Hispanic or Latino ethnic group†‡			
Yes	545 (28.1)	258 (26.6)	803 (27.6)
No	1385 (71.4)	706 (72.9)	2091 (71.9)
History of major ASCVD event — no. (%)§	1125 (58.0)	572 (59.0)	1697 (58.3)
Statin use — no. (%)			
No statin use	65 (3.4)	35 (3.6)	100 (3.4)
Low-intensity statin	24 (1.2)	11 (1.1)	35 (1.2)
Moderate-intensity statin	812 (41.9)	384 (39.6)	1196 (41.1)
High-intensity statin	1039 (53.6)	539 (55.6)	1578 (54.2)
ATP citrate lyase inhibitor use — no. (%)	15 (0.8)	7 (0.7)	22 (0.8)
Cholesterol-absorption inhibitor use — no. (%)	497 (25.6)	254 (26.2)	751 (25.8)
Lipid levels¶			
LDL cholesterol for week 24 analysis — mg/dl	95.0±38.8	98.3±39.2	96.1±38.9
Non-HDL cholesterol — mg/dl	122.5±42.5	123.4±43.5	122.8±42.8
Apolipoprotein B — mg/dl	91.0±26.8	91.5±27.3	91.2±26.9
Median lipoprotein(a) (IQR) — nmol/liter	39.6 (13.7–144.5)	37.2 (12.8–152.3)	38.9 (13.5–147.9)
LDL cholesterol for week 24 post hoc reanalysis — mg/dl	95.2±38.6	98.3±39.2	96.2±38.8

End Point	Enlicitide (N = 1935)			Placebo (N = 969)			Estimated Difference in % Change	P Value
	no. of participants	*value*	*% change from baseline (95% CI)*	*no. of participants*	*value*	*% change from baseline (95% CI)*	*percentage points (95% CI)*	
Primary end point								
LDL cholesterol at week 24 — mg/dl†	1832	38.7±35.6	−57.1 (−61.8 to −52.5)	923	98.6±42.5	3.0 (0.9 to 5.1)	−55.8 (−60.9 to −50.7)	<0.001
Secondary end points								
LDL cholesterol at week 52 — mg/dl	1771	45.7±42.2	−50.4 (−54.2 to −46.6)	898	99.4±42.5	4.0 (1.7 to 6.3)	−47.6 (−52.7 to −42.5)	<0.001
Non-HDL cholesterol at week 24 — mg/dl	1833	56.9±40.4	−53.7 (−55.0 to −52.5)	923	123.5±47.3	2.6 (0.8 to 4.5)	−53.4 (−55.5 to −51.2)	<0.001
Apolipoprotein B at week 24 — mg/dl	1854	45.8±27.4	−49.6 (−50.8 to −48.5)	929	92.6±30.4	2.9 (1.3 to 4.4)	−50.3 (−52.1 to −48.5)	<0.001
Median lipoprotein(a) at week 24 (IQR) — nmol/liter	1849	20.8 (6.6 to 95.9)	−29.0 (−50.4 to −7.0)	926	33.8 (11.8 to 151.0)	0.0 (−14.9 to 13.3)	−28.2 (−30.3 to −26.0)	<0.001
Exploratory end points‡								
Non-HDL cholesterol at week 52 — mg/dl	1772	64.3±47.8	−47.8 (−49.4 to −46.3)	898	124.0±48.0	3.1 (1.1 to 5.1)	−50.9 (−53.5 to −48.4)	—
Apolipoprotein B at week 52 — mg/dl	1773	49.4±31.2	−45.7 (−47.1 to −44.3)	889	91.3±30.1	1.4 (−0.2 to 3.1)	−47.2 (−49.4 to −45.0)	—
Median lipoprotein(a) at week 52 (IQR) — nmol/liter	1769	22.5 (6.9 to 106.7)	−25.8 (−46.8 to −3.6)	887	36.3 (12.0 to 151.2)	0.0 (−13.3 to 16.7)	−28.5 (−30.7 to −26.2)	—
Post hoc reanalysis‡								
LDL cholesterol at week 24§	1832	38.8±35.5	−59.6 (−61.1 to −58.1)	923	98.6±42.5	3.0 (0.9 to 5.1)	−59.7 (−62.3 to −57.1)	—
LDL cholesterol at week 52§	1771	45.7±42.2	−52.7 (−54.4 to −50.9)	898	99.4±42.5	4.0 (1.7 to 6.3)	−52.4 (−55.1 to −49.7)	—

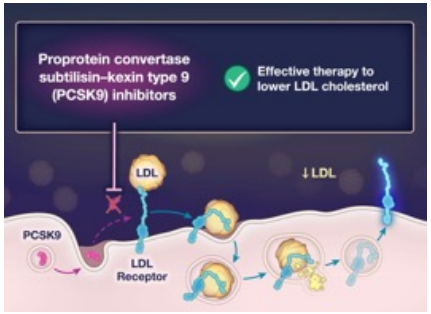
Summary of Adverse Events during the 52-Week Treatment and 8-Week Follow-up Period.

Event	Enlicitide (N=1935)	Placebo (N=969)	Estimated Difference†
	number (percent)		*percentage points (95% CI)*
Any adverse event	1244 (64.3)	602 (62.1)	2.2 (−1.5 to 5.9)
Any serious adverse event	191 (9.9)	116 (12.0)	−2.1 (−4.6 to 0.3)
Any moderate or severe adverse event	649 (33.5)	314 (32.4)	1.1 (−2.5 to 4.7)
Discontinuation of trial regimen due to adverse event	60 (3.1)	40 (4.1)	—
Death	13 (0.7)	7 (0.7)	—
New-onset or worsening diabetes mellitus	119 (6.1)	56 (5.8)	0.4 (−1.5 to 2.1)
Drug-induced liver injury‡	0	0	—
Most common adverse events (≥2.5% in either group)			
Diabetes mellitus	79 (4.1)	42 (4.3)	—
Exceeded the prescribed daily dose	80 (4.1)	30 (3.1)	—
Nasopharyngitis	74 (3.8)	40 (4.1)	—
Upper respiratory tract infection	69 (3.6)	45 (4.6)	—
Coronavirus disease 2019	66 (3.4)	22 (2.3)	—
Headache	50 (2.6)	25 (2.6)	—
Hypertension	50 (2.6)	22 (2.3)	—
Diarrhea	48 (2.5)	27 (2.8)	—
Back pain	48 (2.5)	21 (2.2)	—
Urinary tract infection	49 (2.5)	17 (1.8)	—
Bronchitis	30 (1.6)	24 (2.5)	—

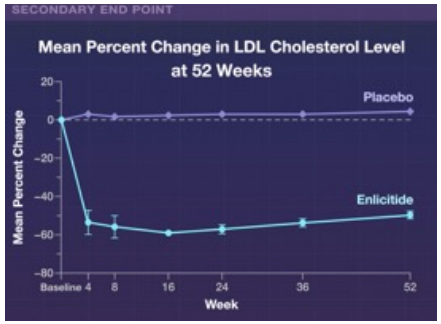


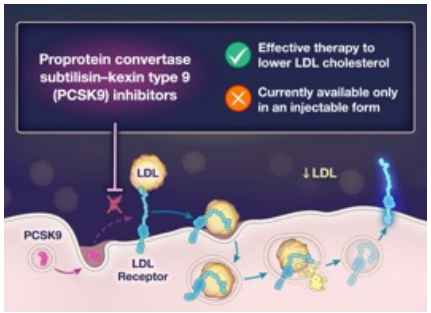
Primary and Key Secondary End Points.

Panel A shows the mean percent change in low-density lipoprotein (LDL) cholesterol levels from baseline through the end of the 52-week treatment period, including the value at week 24 (the primary end point). I bars indicate standard errors. In this analysis, LDL cholesterol beta-quantification–derived values of 0 or less were set to 1 mg per deciliter, in accordance with the statistical analysis plan. Panel B shows the mean percent change in non–high-density lipoprotein (non-HDL) cholesterol levels, and Panel C shows the mean percent change in apolipoprotein B levels.


Proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitors
Effective therapy to lower LDL cholesterol
LDL
↓LDL
PCSK9
LDL Receptor

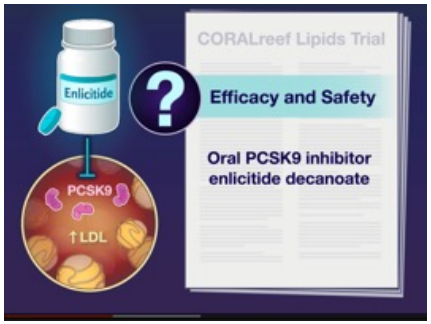

2909 Adults
• History of an atherosclerotic cardiovascular disease event
• LDL ≥55 mg/dl
• At risk for a first atherosclerotic cardiovascular disease event

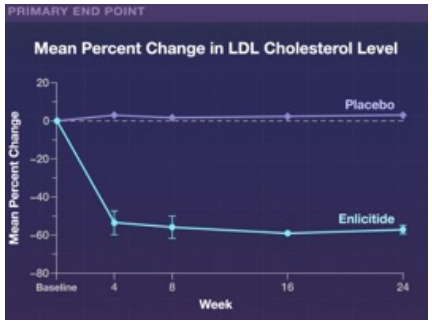

SECONDARY END POINT
Mean Percent Change in LDL Cholesterol Level at 52 Weeks
Placebo
Enlicitide
Mean Percent Change
20
0
-20
-40
-60
-80
Baseline 4 8 16 24 36 52
Week

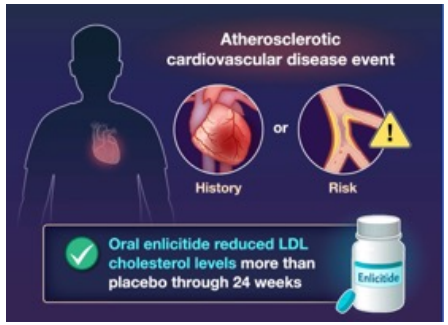

Proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitors
Effective therapy to lower LDL cholesterol
Currently available only in an injectable form
LDL
↓LDL
PCSK9
LDL Receptor


Enlicitide
20 mg
Placebo
Enlicitide
Placebo
N=1940
N=969
Once daily for 52 weeks

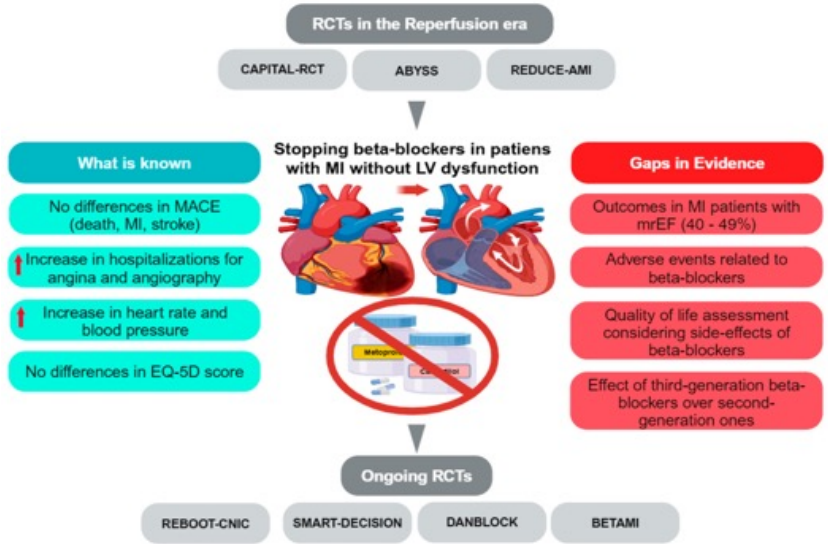

SAFETY
Any Adverse Events
Any Serious Adverse Events
Death
Percentage of Patients
100
80
60
40
20
0
64.3%
62.1%
9.9%
12.0%
0.7%
0.7%
Enlicitide
Placebo


Enlicitide
CORALreef Lipids Trial
Efficacy and Safety
Oral PCSK9 inhibitor enlicitide decanoate
PCSK9
↑LDL


PRIMARY END POINT
Mean Percent Change in LDL Cholesterol Level
Placebo
Enlicitide
Mean Percent Change
20
0
-20
-40
-60
-80
Baseline 4 8 16 24
Week

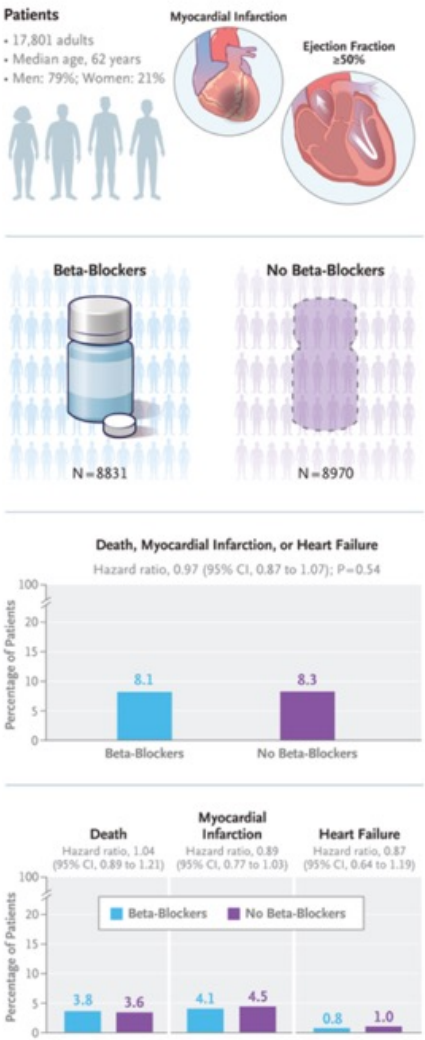

Atherosclerotic cardiovascular disease event
or
History
Risk
Oral enlicitide reduced LDL cholesterol levels more than placebo through 24 weeks
Enlicitide

Beta-Blocker sind ein Eckpfeiler nach einem Herzinfarkt (MI), insbesondere bei Patienten mit reduzierter Pumpfunktion (LVEF ≤ is less than or equal to ≤ 40%) oder Herzinsuffizienz, da sie das Herz entlasten, den Sauerstoffbedarf senken und das Risiko für Herzrhythmusstörungen reduzieren. Bei Patienten mit erhaltener Pumpfunktion (LVEF > 50%) ist der Nutzen einer Langzeittherapie nach modernen Standards (Stents, Statine) umstritten, wobei aktuelle Studien teilweise keinen oder nur geringen Zusatznutzen zeigten, während die Leitlinien weiterhin zu einer individuellen Bewertung raten.



Beta-Blockers after Myocardial Infarction with Normal Ejection Fraction

The benefit of beta-blockers after myocardial infarction in patients with a preserved left ventricular ejection fraction (LVEF) is unclear. We conducted a meta-analysis at the individual-patient level using data from five open-label trials that randomly assigned patients with recent myocardial infarction, no other indications for beta-blocker therapy, and an LVEF of at least 50% to receive beta-blocker therapy or no beta-blocker therapy. The primary end point was a composite of death from any cause, myocardial infarction, or heart failure. Event rates were analyzed with a one-stage fixed-effects Cox proportional-hazards model.



Beta-blocker therapy has been considered the standard of care after myocardial infarction on the basis of evidence from seminal trials performed in the early 1980s. Since then, advances in diagnostics, coronary-artery reperfusion, revascularization techniques, and pharmacologic treatments have markedly improved outcomes. These advances have led to uncertainty about the continued need for beta-blockers after myocardial infarction in patients without heart failure or a reduced left ventricular ejection fraction (LVEF <40%).
Current guidelines provide divergent recommendations on the usefulness of beta-blockers in patients after myocardial infarction: the European Society of Cardiology designates a class IIA recommendation for patients without a reduced LVEF, whereas the American Heart Association and American College of Cardiology guidelines designate a class I recommendation for all patients with myocardial infarction regardless of LVEF.
Five open-label, randomized trials that assessed the effects of beta-blockers in patients with recent myocardial infarction and a mildly reduced or preserved LVEF have yielded apparently conflicting results.

Methods

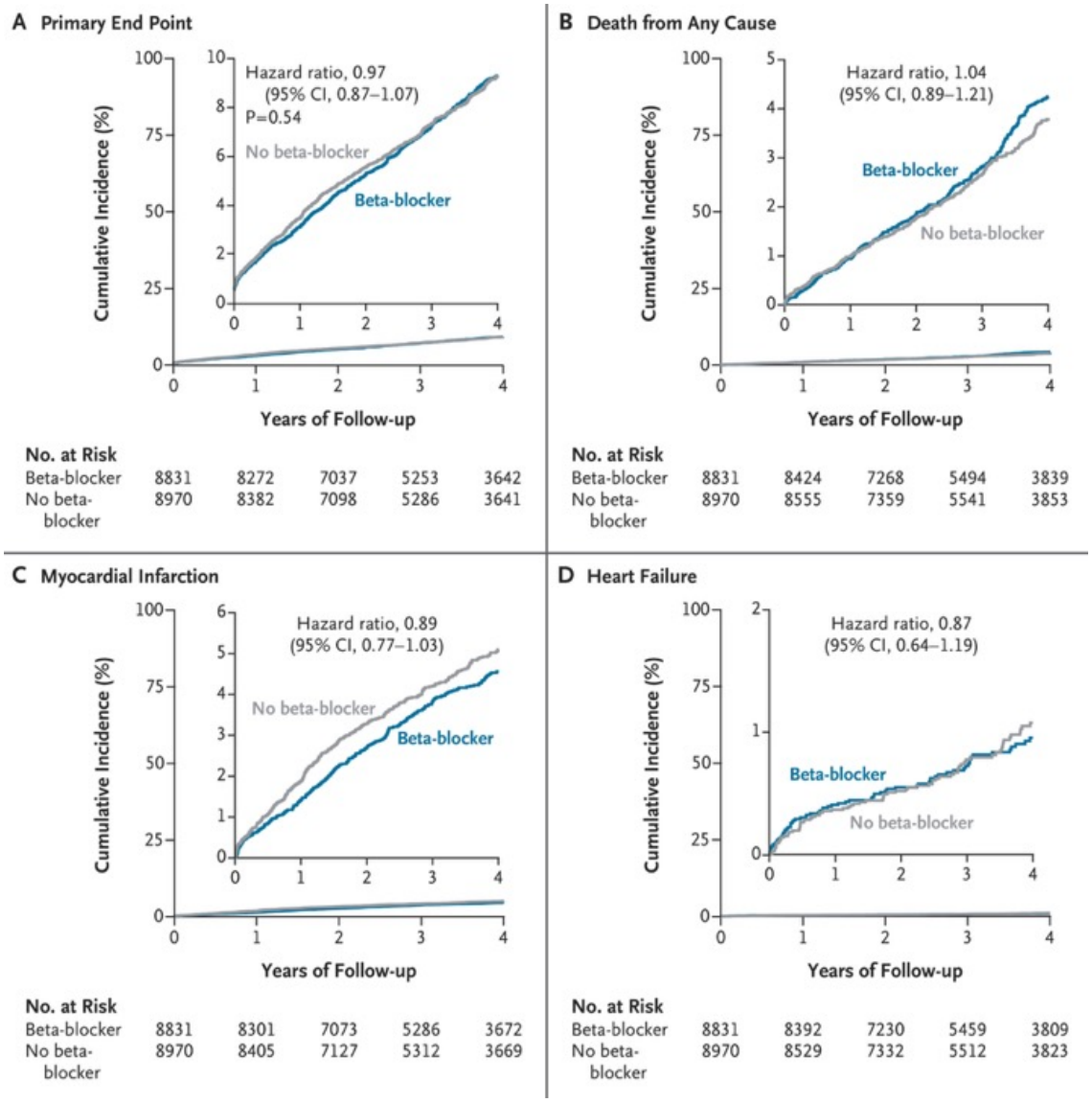
Individual Trials, Search Strategy, and Selection Criteria

This preplanned meta-analysis pooled individual-level data of patients with a preserved LVEF (≥50%) from the REBOOT (Treatment with Beta-Blockers after Myocardial Infarction without Reduced Ejection Fraction), REDUCE-AMI (Randomized Evaluation of Decreased Usage of Beta-Blockers after Acute Myocardial Infarction), BETAMI (Norwegian Beta-Blocker Treatment after Acute Myocardial Infarction in Revascularized Patients without Reduced Left Ventricular Ejection Fraction), DANBLOCK (Danish Trial of Beta-Blocker Therapy after Myocardial Infarction without Heart Failure), and CAPITAL-RCT (Carvedilol Post-Intervention Long-Term Administration in Large-Scale Randomized Controlled Trial) trials. All these trials were investigator-initiated, open-label, randomized, superiority trials designed to evaluate the effect of beta-blockers after myocardial infarction. Patients with myocardial infarction within 14 days before randomization with a preserved or mildly reduced LVEF (≥40%) who met the eligibility criteria.

Characteristic	Beta-Blockers (N=8831)	No Beta-Blockers (N=8970)
Median age (IQR) — yr†	62 (55–71)	62 (55–71)
Female sex — no. (%)	1837 (20.8)	1856 (20.7)
Country — no. (%)		
Spain	2933 (33.2)	2998 (33.4)
Sweden, Estonia, or New Zealand‡	2485 (28.1)	2482 (27.7)
Norway	1207 (13.7)	1234 (13.8)
Denmark	1126 (12.8)	1151 (12.8)
Italy	759 (8.6)	769 (8.6)
Japan	321 (3.6)	336 (3.7)
Medical history — no./total no. (%)		
Current smoker	2762/8279 (33.4)	2794/8375 (33.4)
Hypertension	4194/8822 (47.5)	4261/8951 (47.6)
Diabetes mellitus	1483/8813 (16.8)	1523/8938 (17.0)
Dyslipidemia	2650/6334 (41.8)	2726/6471 (42.1)
Previous myocardial infarction§¶	583/7292 (8.0)	603/7384 (8.2)
Stroke‖¶	188/8504 (2.2)	179/8615 (2.1)
STEMI as index myocardial infarction — no./total no. (%)	4022/8830 (45.5)	4108/8970 (45.8)
In-hospital treatment — no./total no. (%)		
Percutaneous coronary intervention	8306/8784 (94.6)	8399/8909 (94.3)
Coronary-artery bypass grafting	169/8283 (2.0)	199/8399 (2.4)
No revascularization	350/8481 (4.1)	366/8954 (4.1)
Beta-blocker therapy — no./total no. (%)		
Beta-blocker therapy before randomization¶	923/8551 (10.8)	931/8572 (10.9)
Type of beta-blocker therapy after randomization		
Bisoprolol	4136/8746 (47.3)	
Metoprolol	4000/8746 (45.7)	
Carvedilol	446/8746 (5.1)	
Other	164/8746 (1.9)	

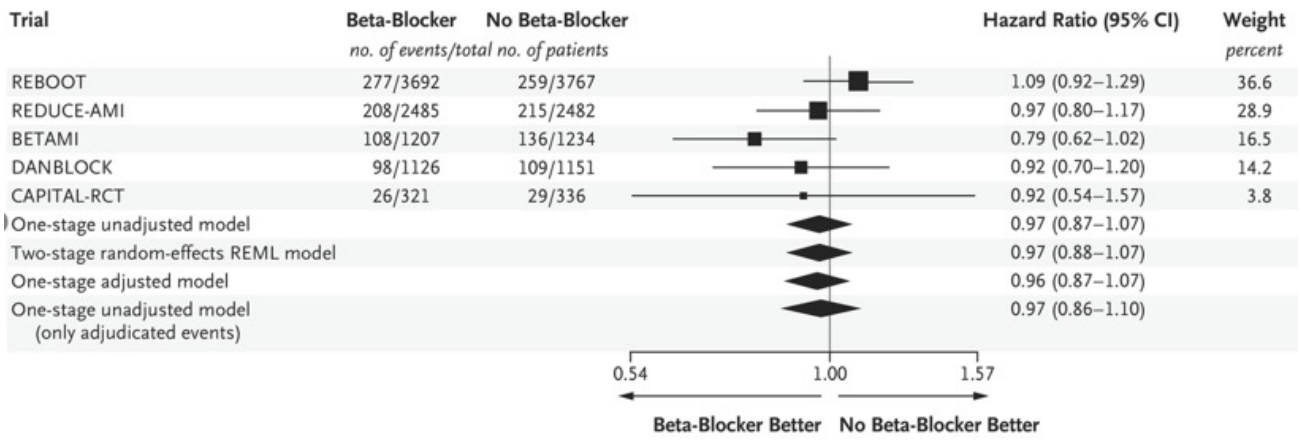
Treatment Estimates for the Primary, Secondary, and Safety End Points.

End Point	Beta-Blockers (N=8831)	No Beta-Blockers (N=8970)	Hazard Ratio† (95% CI)
	number/total number (percent)		
Primary end point			
Composite of death from any cause, myocardial infarction, or heart failure	717/8831 (8.1)	748/8970 (8.3)	0.97 (0.87 to 1.07)‡
Key secondary end points			
Death from any cause	335/8831 (3.8)	326/8970 (3.6)	1.04 (0.89 to 1.21)
Myocardial infarction	360/8831 (4.1)	407/8970 (4.5)	0.89 (0.77 to 1.03)
Heart failure	75/8831 (0.8)	87/8970 (1.0)	0.87 (0.64 to 1.19)
Other secondary end points			
Cardiac death§	97/7624 (1.3)	78/7736 (1.0)	1.26 (0.94 to 1.70)
Unplanned coronary revascularization¶	315/6346 (5.0)	315/6488 (4.9)	1.03 (0.88 to 1.20)
Malignant ventricular arrhythmias¶‖	16/6025 (0.3)	23/6152 (0.4)	0.71 (0.37 to 1.34)
Safety end points			
Ischemic stroke	115/8831 (1.3)	94/8970 (1.0)	2.6 (−0.73 to 4.4)
Advanced atrioventricular block‖	69/8510 (0.8)	68/8634 (0.8)	1.03 (0.73 to 1.44)



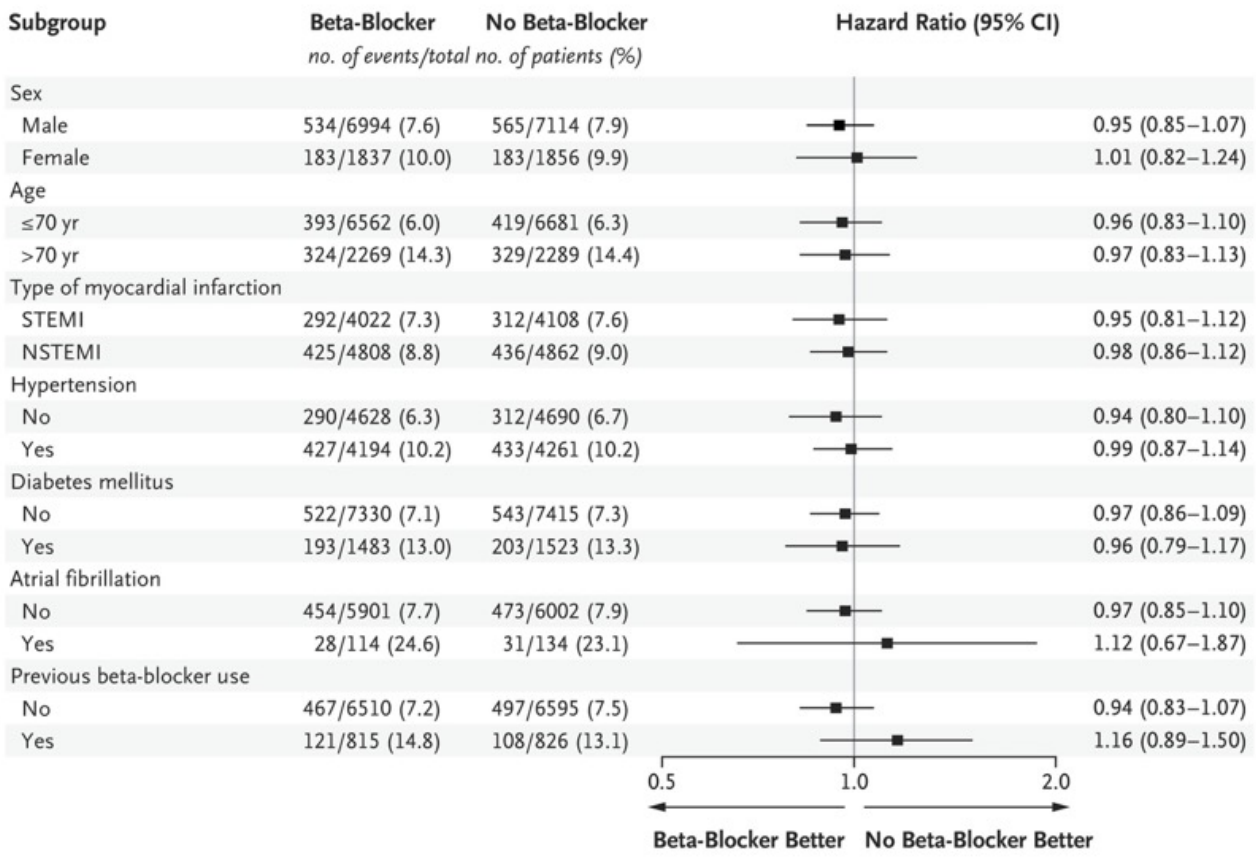
Kaplan–Meier Curves for the Primary End Point and Its Components.

Shown are the Kaplan–Meier curves of the cumulative incidence of death from any cause, myocardial infarction, or heart failure (the composite primary end point) (Panel A) and of the individual components of the primary end point (the secondary end points) (Panels B, C, and D). The widths of the confidence intervals for the secondary end points have not been adjusted for multiplicity and should not be used in place of hypothesis testing. The insets show the same data on an expanded y axis.



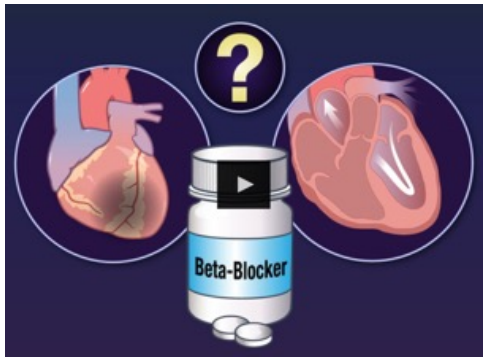
Treatment Estimates and Sensitivity Analyses.

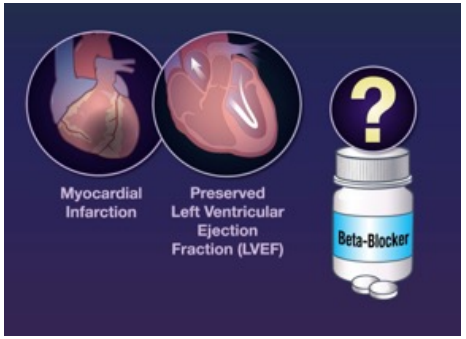
Shown are the treatment estimates for each trial included in the meta-analysis of individual-patient data and the sensitivity analyses of the study. The between-trial variance was estimated to be 0.005 (95% CI, 0.000 to 0.104), and the amount of variance due to heterogeneity was estimated as 20.0%. The widths of the confidence intervals for the secondary end points have not been adjusted for multiplicity and should not be used in place of hypothesis testing. Squares indicate hazard ratios, horizontal lines indicate 95% confidence intervals, and diamonds indicate the overall pooled effect size and its 95% confidence interval. In the two-stage fixed-effects model, trials were weighted as the inverse of the variance.

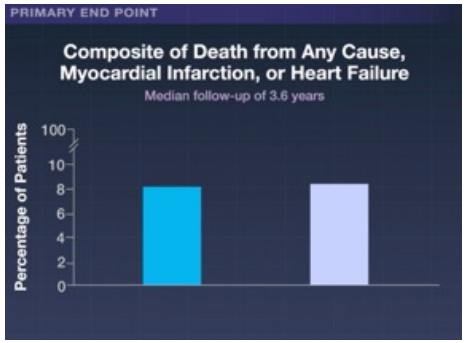


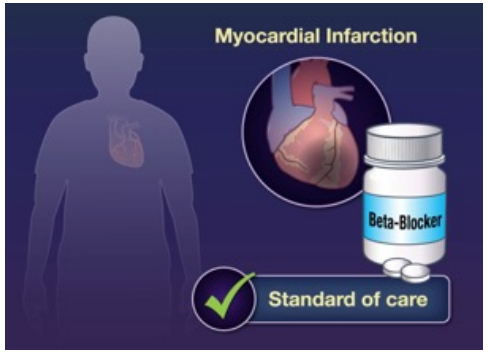
Prespecified Subgroup Analyses of the Primary End Point.

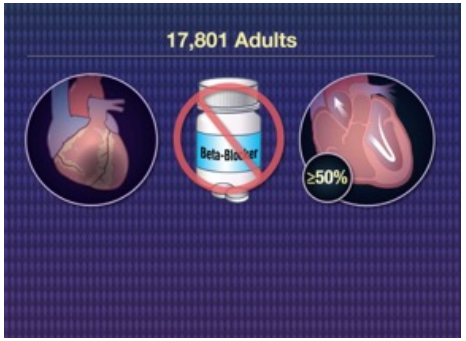
Shown are the analyses of the primary end point with stratification according to prespecified subgroups. Data on atrial fibrillation were not available in the REDUCE-AMI trial, and data on previous beta-blocker therapy were not available in the DANBLOCK trial. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing. NSTEMI denotes non–ST-segment elevation myocardial infarction, and STEMI ST-segment elevation myocardial infarction.

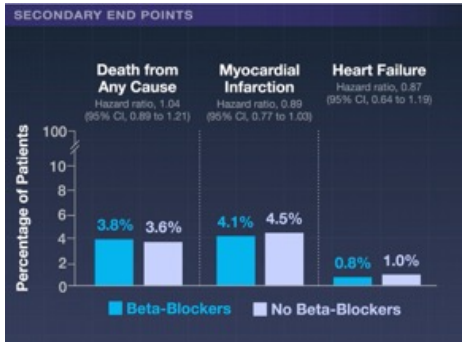

?
Beta-Blocker


Myocardial Infarction
Preserved Left Ventricular Ejection Fraction (LVEF)
?
Beta-Blocker

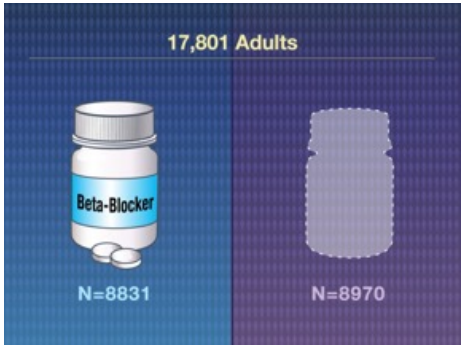

PRIMARY END POINT
Composite of Death from Any Cause, Myocardial Infarction, or Heart Failure
Median follow-up of 3.6 years
Percentage of Patients
100
10
8
6
4
2
0

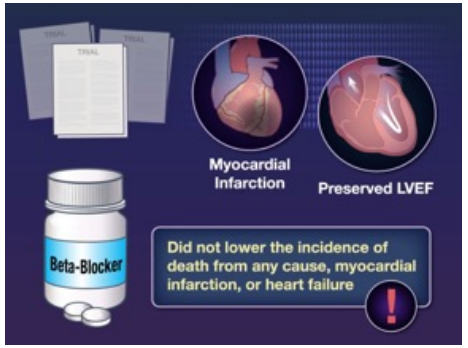

Myocardial Infarction
Beta-Blocker
Standard of care


17,801 Adults
Beta-Blocker
≥50%


SECONDARY END POINTS
Death from Any Cause
Hazard ratio, 1.04
(95% CI, 0.89 to 1.21)
Myocardial Infarction
Hazard ratio, 0.89
(95% CI, 0.77 to 1.03)
Heart Failure
Hazard ratio, 0.87
(95% CI, 0.64 to 1.19)
Percentage of Patients
100
10
8
6
4
2
0
3.8%
3.6%
4.1%
4.5%
0.8%
1.0%
Beta-Blockers
No Beta-Blockers


Advances in:
Diagnostics
Reperfusion
Revascularization
Pharmacologic Treatments
?
Beta-Blocker

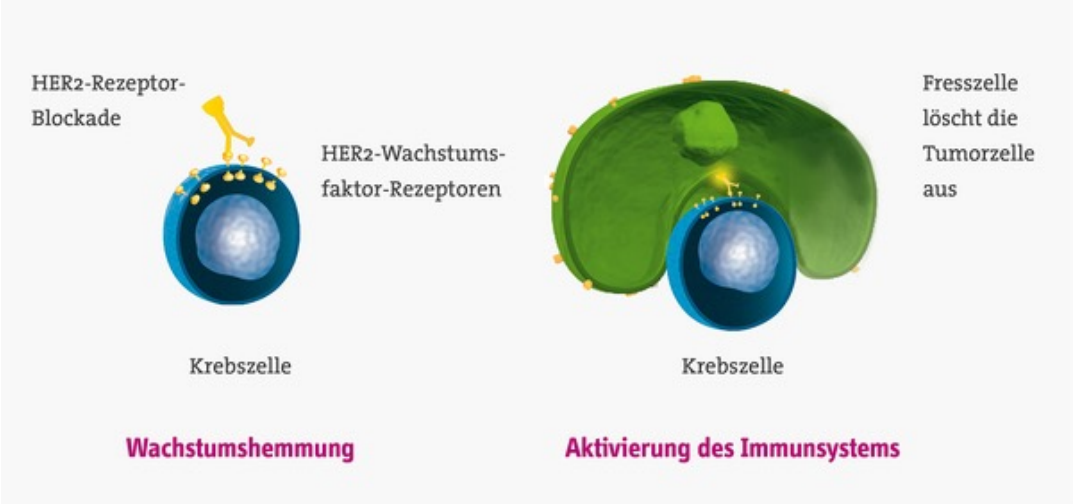

17,801 Adults
Beta-Blocker
N=8831
N=8970


Myocardial Infarction
Preserved LVEF
Beta-Blocker
Did not lower the incidence of death from any cause, myocardial infarction, or heart failure
!

HER2-positiver Brustkrebs ist eine Form des Mammakarzinoms, bei der die Tumorzellen eine Überexpression des **Human Epidermal Growth Factor Receptor 2 (HER2)** aufweisen. Dieses Protein fördert das Wachstum und die Teilung der Krebszellen, weshalb diese Tumoren ohne Behandlung oft aggressiver wachsen.

Bedeutung des HER2-Status

- **Diagnose:** Der Status wird mittels Gewebeuntersuchung (Immunhistochemie - IHC oder In-situ-Hybridisierung - ISH) bestimmt.
- **Häufigkeit:** Etwa jede fünfte Brustkrebspatientin ist betroffen.
- **HER2-low:** Neuere Einstufungen erkennen auch Tumoren mit geringer HER2-Expression ("HER2-low"), was zusätzliche Therapieoptionen wie **Trastuzumab-Deruxtecan** eröffnet.



Pertuzumab ist ein humanisierter monoklonaler Antikörper, der zur gezielten Behandlung von **HER2-positivem Brustkrebs** eingesetzt wird.

Wichtige Fakten:

- **Wirkungsweise:** Es ist ein „Dimerisierungs-Inhibitor“. Er bindet an eine spezifische Stelle (Subdomäne II) des HER2-Rezeptors und verhindert, dass dieser sich mit anderen HER-Rezeptoren (wie HER3) verbindet. Dadurch werden Signale blockiert, die das Krebswachstum fördern.
- **Therapieform:** Es wird meist in Kombination mit **Trastuzumab** und einer Chemotherapie (wie Docetaxel) verabreicht. Diese „duale Blockade“ ist effektiver als eine Einzeltherapie.

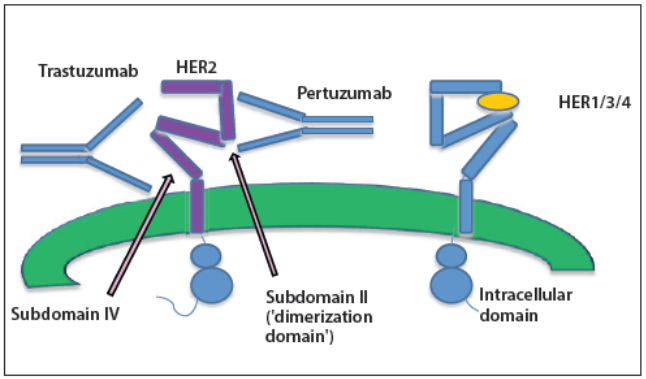
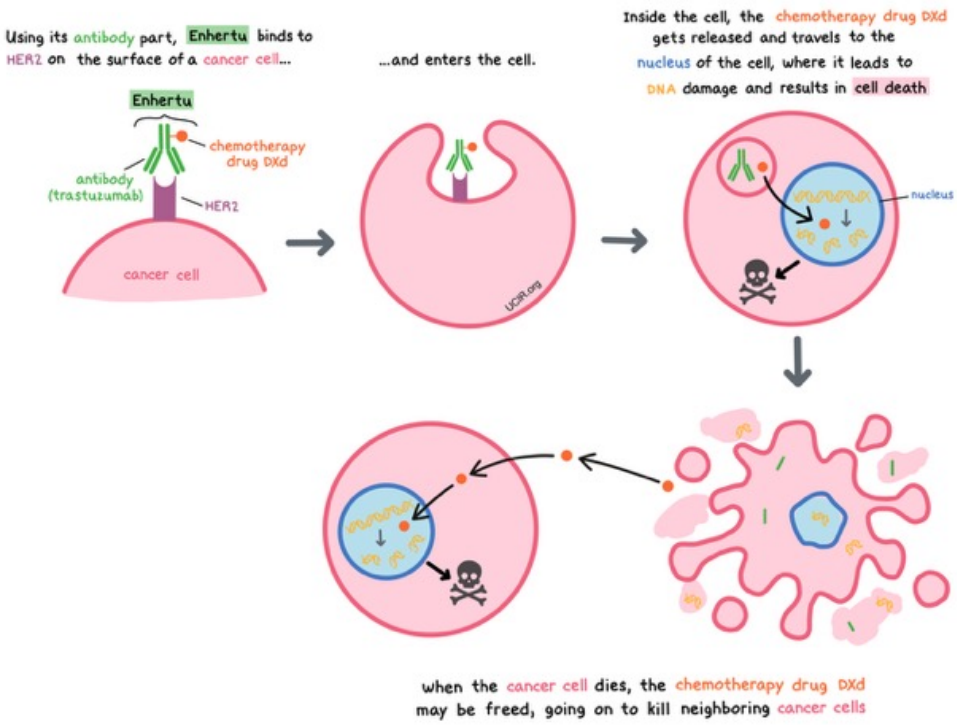


Figure 1: Mechanisms of Action of Trastuzumab and Pertuzumab—Trastuzumab and pertuzumab are similar in that they are both IgG 1 monoclonal antibodies that activate ADCC. Their mechanisms of action differ. Trastuzumab binds HER2 subdomain IV and inhibits activation of HER2. Pertuzumab binds HER2 subdomain II and inhibits activation of HER2 by interaction with HER1/3/4 molecules. HER = human epidermal growth factor receptor; IgG = immunoglobulin G; ADCC = antibody-dependent cell-mediated cytotoxicity.

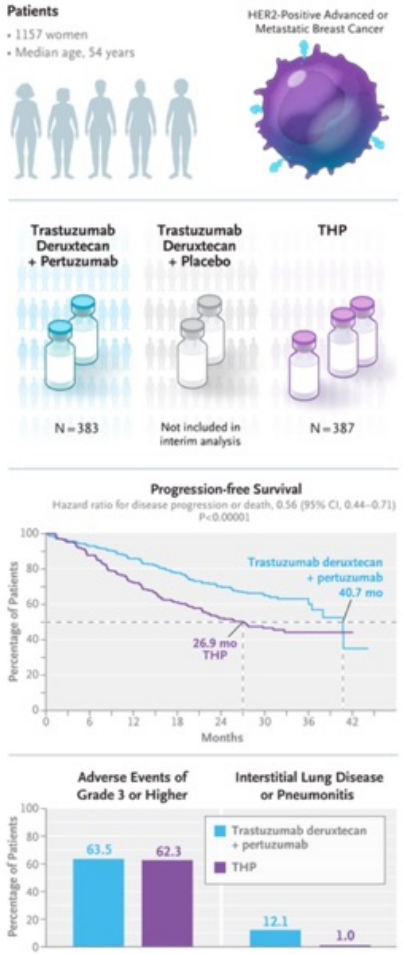
Trastuzumab-Deruxtecan ist ein hochwirksames Antikörper-Wirkstoff-Konjugat (ADC) der dritten Generation zur Behandlung von HER2-positiven und HER2-low Tumoren. Es verbindet den HER2-Antikörper Trastuzumab mit dem Zytostatikum Exatecan. Die Zulassung umfasst den inoperablen oder metastasierten, HER2-positiven/low Brustkrebs sowie den HER2-positiven Lungenkrebs (NSCLC).

Exatecan (auch bekannt als DX-8951f) ist ein potenter, wasserlöslicher Hemmstoff der DNA-Topoisomerase I. Es handelt sich um ein vollsynthetisches Derivat von **Camptothecin**, das speziell entwickelt wurde, um die Wirksamkeit zu erhöhen und Resistenzen zu überwinden.



Trastuzumab Deruxtecan plus Pertuzumab for HER2-Positive Metastatic Breast Cancer

Trastuzumab deruxtecan has shown efficacy in patients with previously treated human epidermal growth factor receptor 2 (HER2)–positive advanced or metastatic breast cancer. The efficacy and safety of trastuzumab deruxtecan in patients with no previous therapy for HER2-positive advanced or metastatic breast cancer are unclear. We conducted a phase 3 trial involving patients with HER2-positive advanced or metastatic breast cancer and no previous chemotherapy or HER2-directed therapy for metastatic disease. Patients were randomly assigned in a 1:1:1 ratio to receive trastuzumab deruxtecan plus pertuzumab; trastuzumab deruxtecan plus placebo; or a taxane, trastuzumab, and pertuzumab (THP). The primary end point was progression-free survival as assessed by blinded independent central review. Secondary end points included objective response, duration of response, and safety.



Human epidermal growth factor receptor (HER) 2–positive breast cancer (immunohistochemistry 3+ or in situ hybridization–positive) accounts for approximately 20% of breast cancers. HER2-targeted therapies have improved outcomes that had previously been poor, but many patients do not receive a diagnosis until their disease has advanced or metastasized, while others go on to have metastases despite initial treatment. Standard first-line therapy for HER2-positive advanced or metastatic breast cancer is a taxane plus the HER2-directed monoclonal antibodies trastuzumab and pertuzumab (the three-drug regimen is known as THP). The use of THP is based on the primary analysis of the 2012 phase 3 Clinical Evaluation of Pertuzumab and Trastuzumab (CLEOPATRA) trial, which established that, added to chemotherapy, dual HER2 blockade resulted in significantly longer progression-free survival than trastuzumab alone (median, 18.5 vs. 12.4 months; $P<0.001$).

Patients were randomly assigned in a 1:1:1 ratio to receive trastuzumab deruxtecan plus pertuzumab; trastuzumab deruxtecan plus placebo; or THP (paclitaxel or docetaxel [per physician choice] plus trastuzumab and pertuzumab). If trastuzumab deruxtecan was discontinued owing to adverse events (except grade ≥2 interstitial lung disease, after which no treatment with trastuzumab deruxtecan or trastuzumab was permitted), patients could remain in the trial and receive trastuzumab plus pertuzumab or trastuzumab plus placebo (according to randomized group). THP was administered according to local institutional standards; patients received a taxane for a minimum of six cycles or until the occurrence of unacceptable toxic effects, then continued with trastuzumab plus pertuzumab. Patients with hormone receptor–positive disease could receive concurrent endocrine therapy (aromatase inhibitor or tamoxifen) after taxane discontinuation or six cycles of trastuzumab deruxtecan.

End Points

The primary end point was progression-free survival as assessed by blinded independent central review, with disease progression.

Characteristic	Trastuzumab Deruxtecan plus Pertuzumab (N=383)	THP (N=387)
Median age (range) — yr	54 (27–85)	54 (20–81)
Female sex — no. (%)	383 (100)	387 (100)
Race — no. (%)†		
Asian	190 (49.6)	196 (50.6)
White	138 (36.0)	146 (37.7)
Black	12 (3.1)	5 (1.3)
Other	19 (5.0)	21 (5.4)
Not reported	24 (6.3)	19 (4.9)
Geographic region — no. (%)		
Asia	188 (49.1)	191 (49.4)
Western Europe and North America	87 (22.7)	78 (20.2)
Rest of the world	108 (28.2)	118 (30.5)
ECOG performance-status score — no. (%)‡		
0	256 (66.8)	246 (63.6)
1	127 (33.2)	141 (36.4)
Hormone-receptor status — no. (%)		
Positive	207 (54.0)	209 (54.0)
Negative	176 (46.0)	178 (46.0)
HER2 status on IHC analysis — no. (%)		
2+	56 (14.6)	69 (17.8)
3+	318 (83.0)	315 (81.4)
HER2-low status: IHC 2+ and ISH-negative	0	0
HER2 status on ISH — no. (%)		
Positive	364 (95.0)	373 (96.4)
Negative	1 (0.3)	0
Data not available	18 (4.7)	14 (3.6)
Newly diagnosed disease — no. (%)	200 (52.2)	200 (51.7)
CNS metastasis — no. (%)§	25 (6.5)	22 (5.7)
Visceral metastasis — no. (%)	281 (73.4)	268 (69.3)
PIK3CA mutation — no. (%)	116 (30.3)	121 (31.3)
Any metastatic site — no. (%)	379 (99.0)	383 (99.0)
Previous adjuvant or neoadjuvant therapy — no. (%)¶	166 (43.3)	169 (43.7)
Chemotherapy	159 (41.5)	152 (39.3)
Taxane	134 (35.0)	136 (35.1)
Anthracycline	108 (28.2)	111 (28.7)
Cyclophosphamide	111 (29.0)	108 (27.9)
Carboplatin	25 (6.5)	22 (5.7)
Other	36 (9.4)	29 (7.5)
Endocrine therapy	74 (19.3)	85 (22.0)
Tamoxifen	48 (12.5)	52 (13.4)
Fulvestrant	0	2 (0.5)
Anastrozole or letrozole	31 (8.1)	39 (10.1)
Exemestane	8 (2.1)	4 (1.0)
Gonadotropin-releasing hormone analogues	8 (2.1)	10 (2.6)
Other	1 (0.3)	5 (1.3)
Targeted therapy	112 (29.2)	108 (27.9)
CDK4/6 inhibitor	0	1 (0.3)
Trastuzumab	110 (28.7)	108 (27.9)
Pertuzumab	31 (8.1)	24 (6.2)
Pyrotinib	1 (0.3)	1 (0.3)
Trastuzumab emtansine	3 (0.8)	4 (1.0)
Hormonal therapy in first-line advanced or metastatic context — no. (%)	5 (1.3)	5 (1.3)

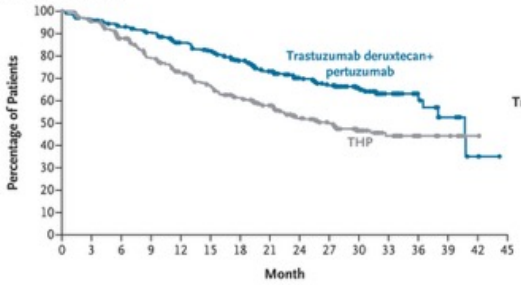
Antitumor Activity as Assessed by Blinded Independent Central Review (Full Analysis Population).

Variable	Trastuzumab Deruxtecan plus Pertuzumab (N=383)	THP (N=387)
Confirmed objective response (95% CI) — %	85.1 (81.2–88.5)	78.6 (74.1–82.5)
Best confirmed response — no. (%)		
Complete response	58 (15.1)	33 (8.5)
Partial response	268 (70.0)	271 (70.0)
Stable disease	38 (9.9)	56 (14.5)
Progressive disease	13 (3.4)	12 (3.1)
Not evaluable	5 (1.3)	12 (3.1)
Median duration of response (95% CI) — mo	39.2 (35.1–NC)	26.4 (22.3–NC)

Drug-Related Adverse Events (Safety Analysis Population).

Event	Trastuzumab Deruxtecan plus Pertuzumab (N=381)		THP (N=382)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	number of patients (percent)			
Any adverse event	373 (97.9)	209 (54.9)	369 (96.6)	200 (52.4)
Nausea	271 (71.1)	19 (5.0)	110 (28.8)	1 (0.3)
Diarrhea	213 (55.9)	26 (6.8)	207 (54.2)	20 (5.2)
Neutropenia†	186 (48.8)	91 (23.9)	170 (44.5)	127 (33.2)
Fatigue‡	184 (48.3)	30 (7.9)	132 (34.6)	8 (2.1)
Alopecia§	176 (46.2)	0	191 (50.0)	2 (0.5)
Vomiting	160 (42.0)	9 (2.4)	51 (13.4)	2 (0.5)
Transaminases increased¶	137 (36.0)	17 (4.5)	72 (18.8)	8 (2.1)
Anemia‖	135 (35.4)	32 (8.4)	149 (39.0)	14 (3.7)
Leukopenia**	112 (29.4)	17 (4.5)	117 (30.6)	67 (17.5)
Decreased appetite	109 (28.6)	9 (2.4)	59 (15.4)	3 (0.8)
Weight decreased	91 (23.9)	10 (2.6)	26 (6.8)	1 (0.3)
Thrombocytopenia††	89 (23.4)	24 (6.3)	17 (4.5)	3 (0.8)
Constipation	85 (22.3)	1 (0.3)	26 (6.8)	0
Hypokalemia	82 (21.5)	39 (10.2)	24 (6.3)	6 (1.6)
Peripheral sensory neuropathy‡‡	43 (11.3)	0	109 (28.5)	4 (1.0)

A Progression-free Survival



	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Trastuzumab Deruxtecan+ Pertuzumab	383	40.7 (36.5–NC)
THP	387	26.9 (21.8–NC)

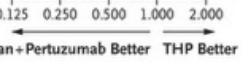
Hazard ratio for disease progression or death, 0.56 (95% CI, 0.44–0.71)
P<0.00001 (prespecified P-value boundary for superiority, 0.00043)

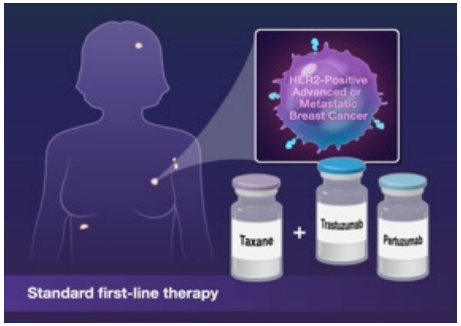
Progression-free Survival as Assessed by Blinded Independent Central Review (Full Analysis Population), Including Subgroup Analysis.

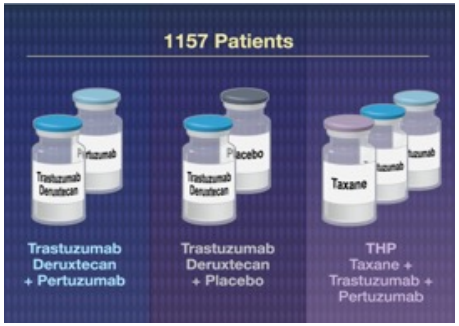
The full analysis population included the patients who underwent randomization. Panel A shows a Kaplan–Meier analysis of progression-free survival among patients assigned to receive trastuzumab deruxtecan plus pertuzumab and those assigned to receive a taxane, trastuzumab, and pertuzumab (a combination known as THP). Panel B shows a forest-plot analysis of progression-free survival according to subgroup. The sizes of the circles are proportional to the number of events. Eastern Cooperative Oncology Group (ECOG) performance-status scores are assessed on a 5-point scale, with higher scores indicating greater disability. HER2 denotes human epidermal growth factor receptor 2, and NC not calculable.

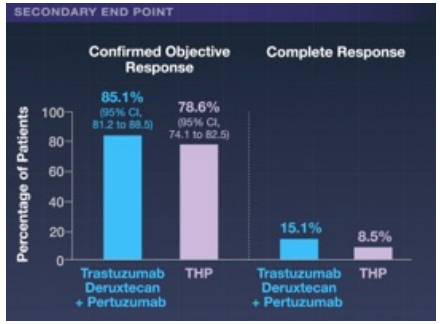
B Subgroup Analysis of Progression-free Survival

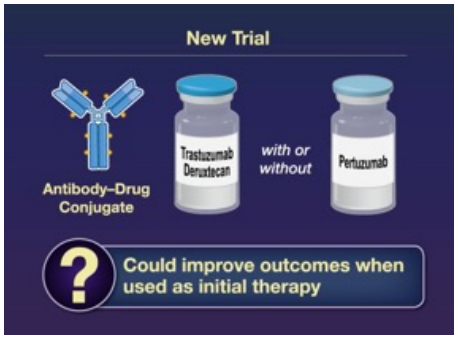
Subgroup	Trastuzumab Deruxtecan+ Pertuzumab	THP	Median Progression-free Survival (95% CI)		Hazard Ratio for Disease Progression or Death (95% CI)
			Trastuzumab deruxtecan+ pertuzumab	THP	
	no. of events/no. of patients		*mo*		
All patients	118/383	172/387	40.7 (36.5–NC)	26.9 (21.8–NC)	0.56 (0.44–0.71)
Disease status					
Newly diagnosed	52/200	85/200	NC (36.5–NC)	31.2 (23.5–NC)	0.49 (0.35–0.70)
Recurrent	66/183	87/187	38.0 (26.9–NC)	22.5 (18.1–NC)	0.63 (0.46–0.87)
Hormone-receptor status					
Positive	65/207	87/209	38.0 (36.0–NC)	27.7 (22.4–NC)	0.61 (0.44–0.84)
Negative	53/176	85/178	40.7 (40.7–NC)	22.6 (17.3–32.7)	0.52 (0.37–0.73)
PIK3CA mutation status					
Detected	41/116	64/121	36.0 (29.7–NC)	18.1 (15.1–25.6)	0.52 (0.35–0.77)
Not detected	76/266	108/266	40.7 (38.0–NC)	32.7 (24.4–NC)	0.57 (0.43–0.77)
Brain metastasis at baseline					
Present	10/25	15/22	31.8 (18.5–NC)	9.5 (5.6–13.3)	0.30 (0.12–0.68)
Not present	108/358	157/365	40.7 (36.5–NC)	27.6 (22.6–NC)	0.58 (0.45–0.74)
Previous exposure to anti-HER2 therapies					
Yes	39/115	51/112	38.0 (26.9–NC)	21.5 (15.3–NC)	0.55 (0.36–0.83)
No	79/268	121/275	40.7 (36.5–NC)	27.6 (22.5–NC)	0.56 (0.42–0.74)
Previous exposure to pertuzumab					
Yes	5/31	12/26	40.8 (25.4–NC)	19.8 (7.5–NC)	NC
No	113/352	160/361	40.7 (36.0–NC)	27.4 (22.4–NC)	0.61 (0.48–0.77)
Previous exposure to endocrine therapy					
Yes	28/80	40/88	38.0 (25.4–NC)	23.7 (19.4–NC)	0.67 (0.41–1.09)
No	90/303	132/299	40.7 (36.5–NC)	27.4 (21.4–NC)	0.54 (0.41–0.70)
Previous exposure to anthracycline					
Yes	40/110	57/111	38.0 (25.7–NC)	19.4 (13.0–27.7)	0.50 (0.33–0.76)
No	78/273	115/276	40.7 (36.5–NC)	31.2 (23.3–NC)	0.58 (0.43–0.77)
Age at randomization					
<65 yr	90/315	139/315	40.7 (36.5–NC)	27.4 (22.4–NC)	0.50 (0.38–0.65)
≥65 yr	28/68	33/72	27.6 (14.9–NC)	21.5 (13.9–NC)	0.92 (0.55–1.51)
Geographic region					
Asia	62/188	87/191	40.7 (36.5–NC)	27.2 (21.5–NC)	0.60 (0.43–0.83)
Western Europe and North America	27/87	31/78	36.0 (30.6–NC)	31.2 (15.8–NC)	0.60 (0.35–1.01)
Rest of the world	29/108	54/118	NC (38.0–NC)	24.4 (14.8–NC)	0.48 (0.30–0.76)
Baseline ECOG performance-status score					
0	71/256	94/246	40.7 (36.5–NC)	NC (27.2–NC)	0.60 (0.44–0.81)
1	47/127	78/141	NC (26.3–NC)	19.2 (13.2–23.5)	0.54 (0.37–0.77)

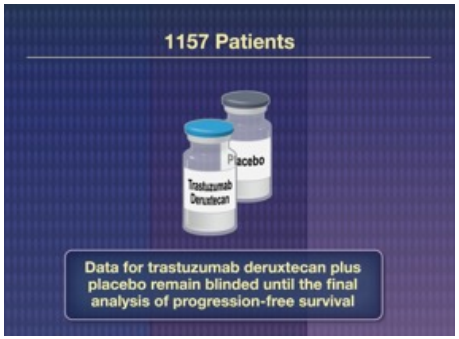


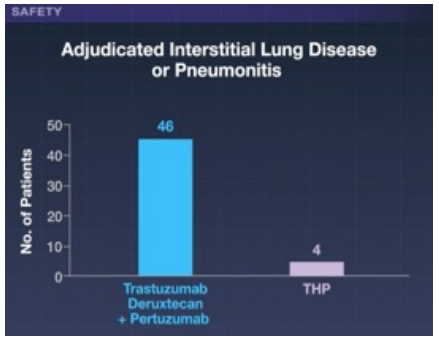

HER2-Positive Advanced or Metastatic Breast Cancer
Taxane
+
Trastuzumab
Pertuzumab
Standard first-line therapy

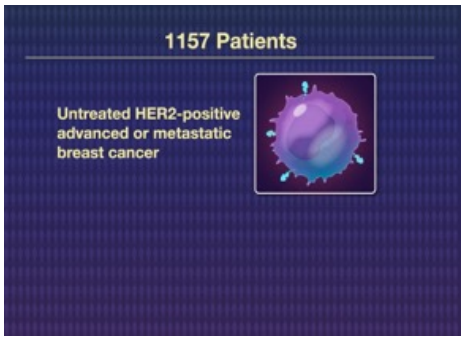

1157 Patients
Trastuzumab Deruxtecan
Pertuzumab
Trastuzumab Deruxtecan + Pertuzumab
Placebo
Trastuzumab Deruxtecan + Placebo
Taxane
Trastuzumab
Pertuzumab
THP Taxane + Trastuzumab + Pertuzumab

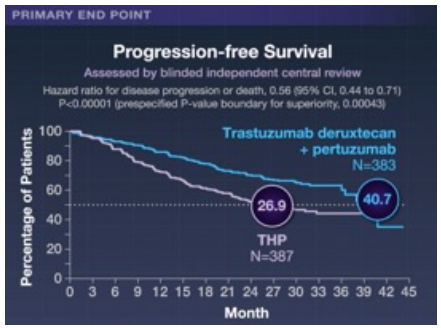

SECONDARY END POINT
Confirmed Objective Response
Complete Response
85.1%
(95% CI, 81.2 to 88.5)
78.6%
(95% CI, 74.1 to 82.5)
15.1%
8.5%
Percentage of Patients
100
80
60
40
20
0
Trastuzumab Deruxtecan + Pertuzumab
THP
Trastuzumab Deruxtecan + Pertuzumab
THP

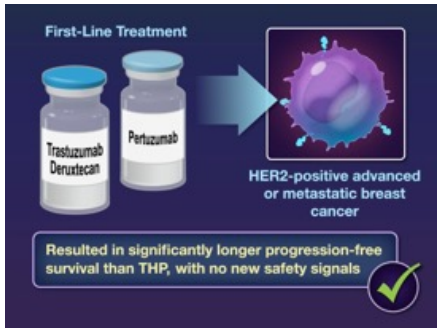

New Trial
Antibody–Drug Conjugate
Trastuzumab Deruxtecan
with or without
Pertuzumab
?
Could improve outcomes when used as initial therapy

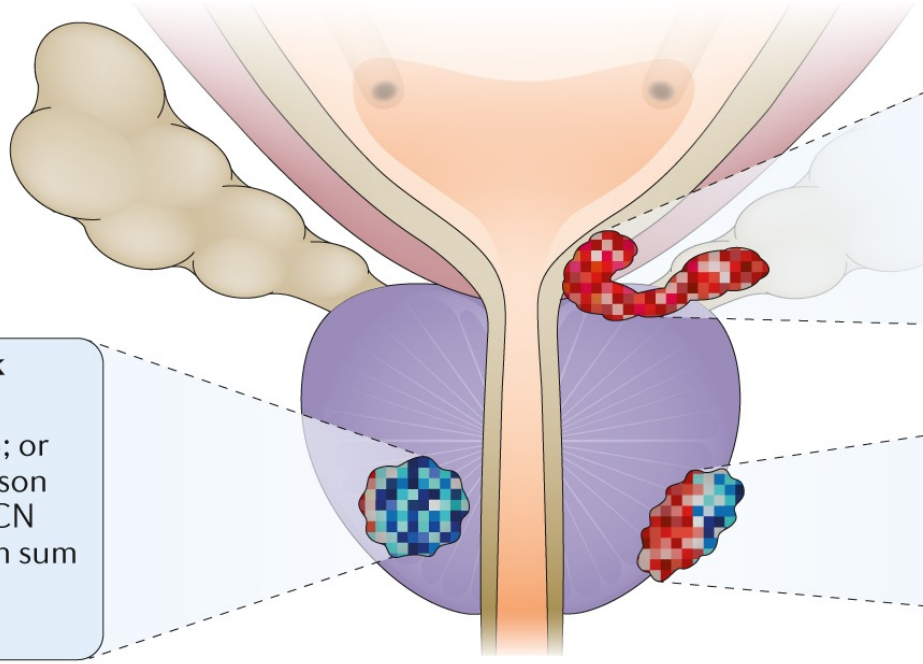

1157 Patients
Trastuzumab Deruxtecan
Placebo
Data for trastuzumab deruxtecan plus placebo remain blinded until the final analysis of progression-free survival


SAFETY
Adjudicated Interstitial Lung Disease or Pneumonitis
No. of Patients
50
40
30
20
10
0
46
4
Trastuzumab Deruxtecan + Pertuzumab
THP


1157 Patients
Untreated HER2-positive advanced or metastatic breast cancer


PRIMARY END POINT
Progression-free Survival
Assessed by blinded independent central review
Hazard ratio for disease progression or death, 0.56 (95% CI, 0.44 to 0.71)
P<0.00001 (prespecified P-value boundary for superiority, 0.00043)
Percentage of Patients
100
80
60
40
20
0
Trastuzumab deruxtecan + pertuzumab
N=383
26.9
40.7
THP
N=387
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45
Month


First-Line Treatment
Trastuzumab Deruxtecan
Pertuzumab
HER2-positive advanced or metastatic breast cancer
Resulted in significantly longer progression-free survival than THP, with no new safety signals



NCCN very-high-risk prostate cancer

Primary Gleason pattern 5; or clinical stage T3b–T4; or >4 biopsy cores with Gleason sum 8–10

Sundi very-high-risk prostate cancer

Primary Gleason pattern 5; or >4 biopsy cores with Gleason sum 8–10; or multiple NCCN high-risk features (Gleason sum 8–10 or PSA >20 ng/ml or clinical stage ≥T3a)

NCCN high-risk prostate cancer

PSA >20 ng/ml; or Gleason sum ≥8; or clinical stage T3a

EAU locally advanced high-risk prostate cancer

Any PSA, any Gleason sum and either clinical stage T3–T4; or clinical positive lymph nodes

EAU localized high-risk prostate cancer

PSA >20 ng/ml; or Gleason sum >7; or clinical stage T2c

D'Amico high-risk prostate cancer

PSA >20 ng/ml; or Gleason sum ≥8; or clinical stage ≥T2c

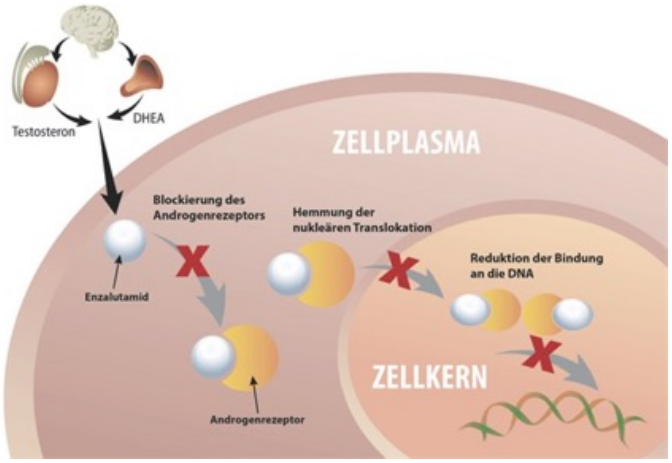
Enzalutamid ist ein hochwirksamer Androgenrezeptor-Inhibitor zur Behandlung von fortgeschrittenem, kastrationsresistentem sowie metastasiertem hormonsensitivem Prostatakrebs. Es hemmt das Tumorwachstum durch eine dreifache Blockade des Androgen-Signalwegs. Die übliche Dosis beträgt 160 mg160 mg täglich.

Wirkung und Anwendung:

•**Wirkmechanismus:** Es bindet an Androgenrezeptoren, verhindert deren Eintritt in den Zellkern und blockiert die Bindung an die DNA, wodurch das Testosteron-Signal unterdrückt wird.

•**Einsatzgebiete:** Zugelassen für metastasierten kastrationsresistenten Prostatakrebs (mCRPC) – sowohl asymptomatisch/leicht symptomatisch nach Versagen der Hormontherapie als auch nach Docetaxel-Chemotherapie . Ebenso für metastasiertes hormonsensitives Prostatakarzinom (mHSPC) in Kombination mit Androgenentzugstherapie .

•**Einnahme:** Die Kapseln werden täglich (einmalig 160 mg) unabhängig von den Mahlzeiten eingenommen.

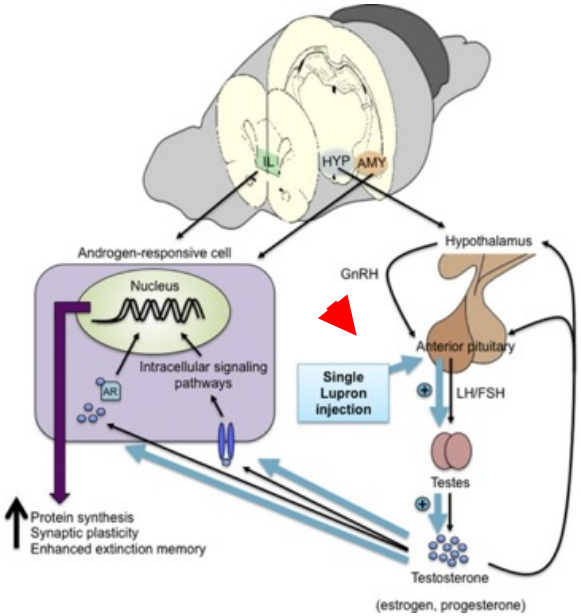


Leuprolid (auch bekannt als **Leuprorelin**) ist ein synthetisch hergestellter Wirkstoff aus der Gruppe der **GnRH-Analoga**. Er wird primär eingesetzt, um die Produktion von Geschlechtshormonen (Testosteron bei Männern, Östrogen bei Frauen) im Körper künstlich zu unterdrücken.

Wichtigste Anwendungsgebiete

Der Wirkstoff findet bei verschiedenen hormonabhängigen Erkrankungen Verwendung:

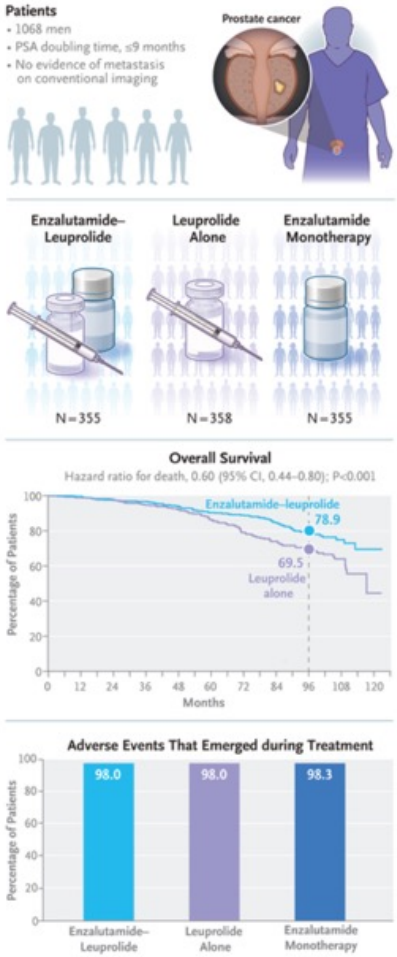
- **Prostatakrebs:** Zur Behandlung von fortgeschrittenem oder metastasiertem Prostatakarzinom, um das Tumorwachstum durch Testosteronentzug zu bremsen.
- **Gynäkologie:** Therapie von **Endometriose**, Myomen der Gebärmutter und fortgeschrittenem **Brustkrebs** bei Frauen vor den Wechseljahren.
- **Kinder:** Behandlung von verfrühter Pubertät (**Pubertas praecox**).
- **Reproduktionsmedizin:** Einsatz im Rahmen der künstlichen Befruchtung (**IVF**) zur Kontrolle des Zyklus.



Improved Survival with Enzalutamide in Biochemically Recurrent Prostate Cancer

In the phase 3 EMBARK trial, enzalutamide plus leuprolide and enzalutamide monotherapy were associated with longer metastasis-free survival than leuprolide alone among patients with biochemically recurrent prostate cancer. The final analysis of overall survival has not been reported.

We randomly assigned patients with prostate cancer who had high-risk biochemical recurrence in a 1:1:1 ratio to receive enzalutamide plus leuprolide (the combination group), leuprolide alone (the leuprolide-alone group), or enzalutamide monotherapy (the monotherapy group). The primary end point was metastasis-free survival, assessed in the combination group as compared with the leuprolide-alone group. Overall survival was an alpha-controlled, key secondary end point. Updated results for prespecified secondary end points, including the time to first use of new antineoplastic therapy and the time to the first symptomatic skeletal event, were summarized descriptively, as was progression-free survival with the first subsequent therapy, an exploratory end point.



Patients who have biochemical recurrence after primary definitive therapy for localized prostate cancer and who have a prostate-specific antigen (PSA) doubling time of 9 months or less are considered to be at high risk for death from prostate cancer. In the phase 3 EMBARK trial, metastasis-free survival was significantly longer with enzalutamide plus leuprolide and with enzalutamide monotherapy than with leuprolide alone among men with prostate cancer with high-risk biochemical recurrence, as was the time to PSA progression, first use of new antineoplastic therapy, distant metastasis, and symptomatic progression. Analyses of patient-reported outcomes in the EMBARK trial further bolstered these findings by showing that enzalutamide plus leuprolide and enzalutamide monotherapy prolonged metastasis-free survival without negatively affecting health-related quality of life as compared with leuprolide alone and that sexual-activity–related quality of life specifically was better with monotherapy than with leuprolide alone.

Patients and Interventions

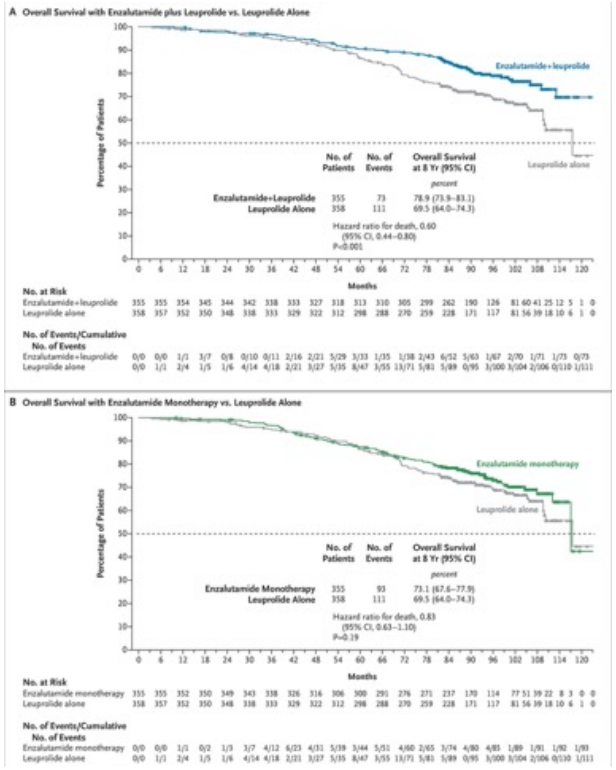
The trial inclusion and exclusion criteria were described previously. Men with prostate cancer and high-risk biochemical recurrence were randomly assigned to receive enzalutamide plus leuprolide (combination group, double-blind), placebo plus leuprolide (leuprolide-alone group, double-blind), or enzalutamide monotherapy (monotherapy group, open-label). High-risk biochemical recurrence was defined as a PSA doubling time of 9 months or less after definitive therapy and a PSA level at screening of at least 1 ng per milliliter for patients who had previously undergone radical prostatectomy (with or without radiotherapy) or at least 2 ng per milliliter above nadir for patients who had received previous primary radiotherapy only.

End Points

The primary end point was metastasis-free survival, as assessed by blinded independent central review in the combination group as compared with the leuprolide-alone group.

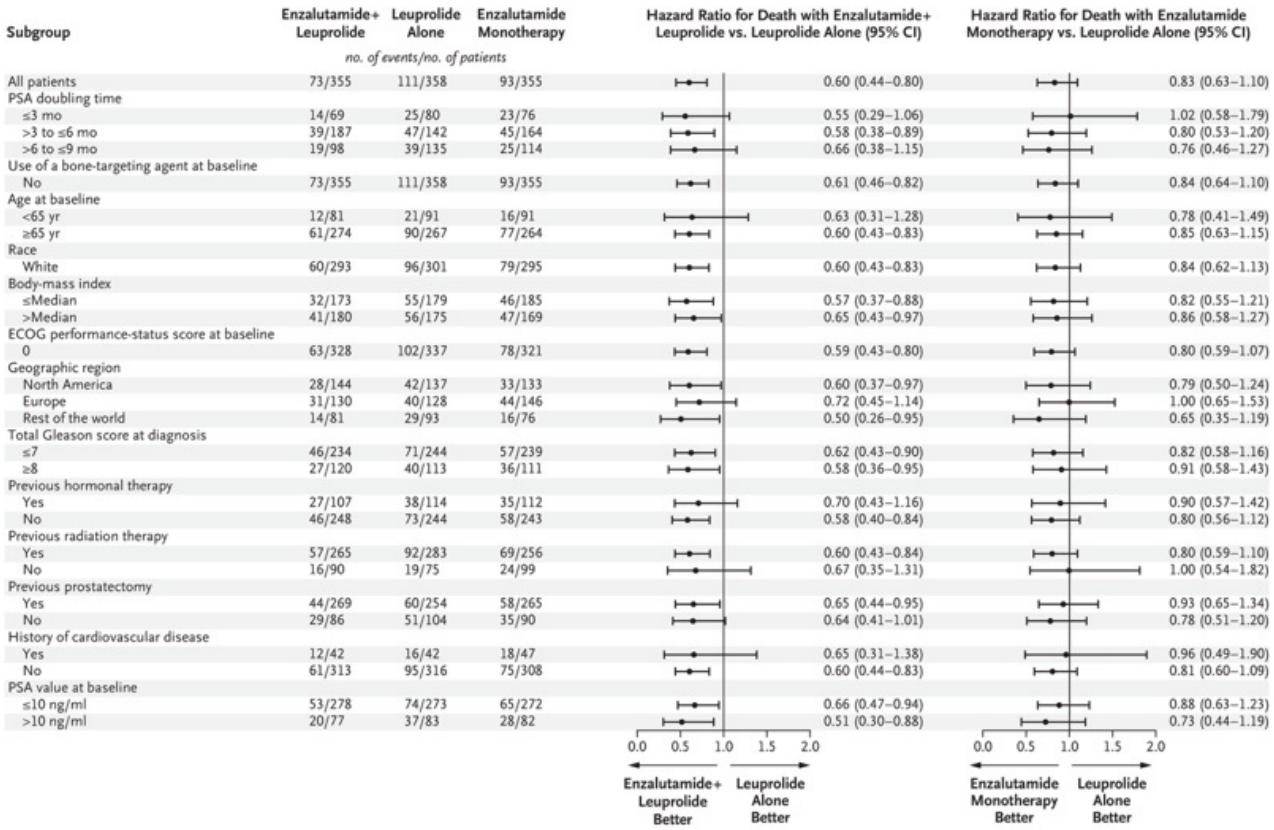
Adverse Events (Safety Population).

Event	Enzalutamide and Leuprolide (N=353)	Leuprolide Alone (N=354)	Enzalutamide Monotherapy (N=354)
	number of patients (percent)		
Adverse event that emerged during treatment	346 (98.0)	347 (98.0)	348 (98.3)
Adverse event that was the primary reason for discontinuation of treatment†	97 (27.5)	45 (12.7)	73 (20.6)
Adverse event that emerged during treatment and led to death‡	10 (2.8)	5 (1.4)	12 (3.4)
Any grade 3 or higher adverse event that emerged during treatment	185 (52.4)	175 (49.4)	203 (57.3)
Adverse event that emerged during treatment and was related to the trial drug§	307 (87.0)	286 (80.8)	316 (89.3)
Any grade 3 or higher adverse event that emerged during treatment and was related to the trial drug§	68 (19.3)	34 (9.6)	72 (20.3)
Serious adverse event that emerged during treatment	143 (40.5)	133 (37.6)	154 (43.5)
Serious adverse event that emerged during treatment and was related to the trial drug§	30 (8.5)	9 (2.5)	27 (7.6)
Adverse events that emerged during treatment and occurred in at least 10% of the patients in any group¶			
Hot flash	246 (69.7)‖	206 (58.2)‖	80 (22.6)
Fatigue	154 (43.6)‖	119 (33.6)‖	170 (48.0)‖
Arthralgia	104 (29.5)	75 (21.2)	89 (25.1)
Fall	104 (29.5)	60 (16.9)	71 (20.1)
Hypertension	92 (26.1)	75 (21.2)	76 (21.5)
Back pain	62 (17.6)	56 (15.8)	67 (18.9)
Diarrhea	55 (15.6)	31 (8.8)	47 (13.3)
Constipation	53 (15.0)	35 (9.9)	38 (10.7)
Hematuria	50 (14.2)	57 (16.1)	53 (15.0)
Dizziness	46 (13.0)	44 (12.4)	47 (13.3)
Headache	46 (13.0)	36 (10.2)	47 (13.3)
Insomnia	45 (12.7)	40 (11.3)	26 (7.3)
Nausea	43 (12.2)	31 (8.8)	57 (16.1)
Asthenia	42 (11.9)	21 (5.9)	41 (11.6)
Pain in arm or leg	42 (11.9)	37 (10.5)	44 (12.4)
Coronavirus disease 2019	38 (10.8)	51 (14.4)	50 (14.1)
Urinary incontinence	38 (10.8)	35 (9.9)	40 (11.3)
Urinary tract infection	33 (9.3)	28 (7.9)	46 (13.0)
Peripheral edema	32 (9.1)	40 (11.3)	37 (10.5)
Gynecomastia	31 (8.8)	32 (9.0)	163 (46.0)‖
Nasopharyngitis	31 (8.8)	26 (7.3)	40 (11.3)
Weight decreased	25 (7.1)	14 (4.0)	42 (11.9)
Nipple pain	13 (3.7)	4 (1.1)	54 (15.3)
Breast tenderness	4 (1.1)	4 (1.1)	51 (14.4)



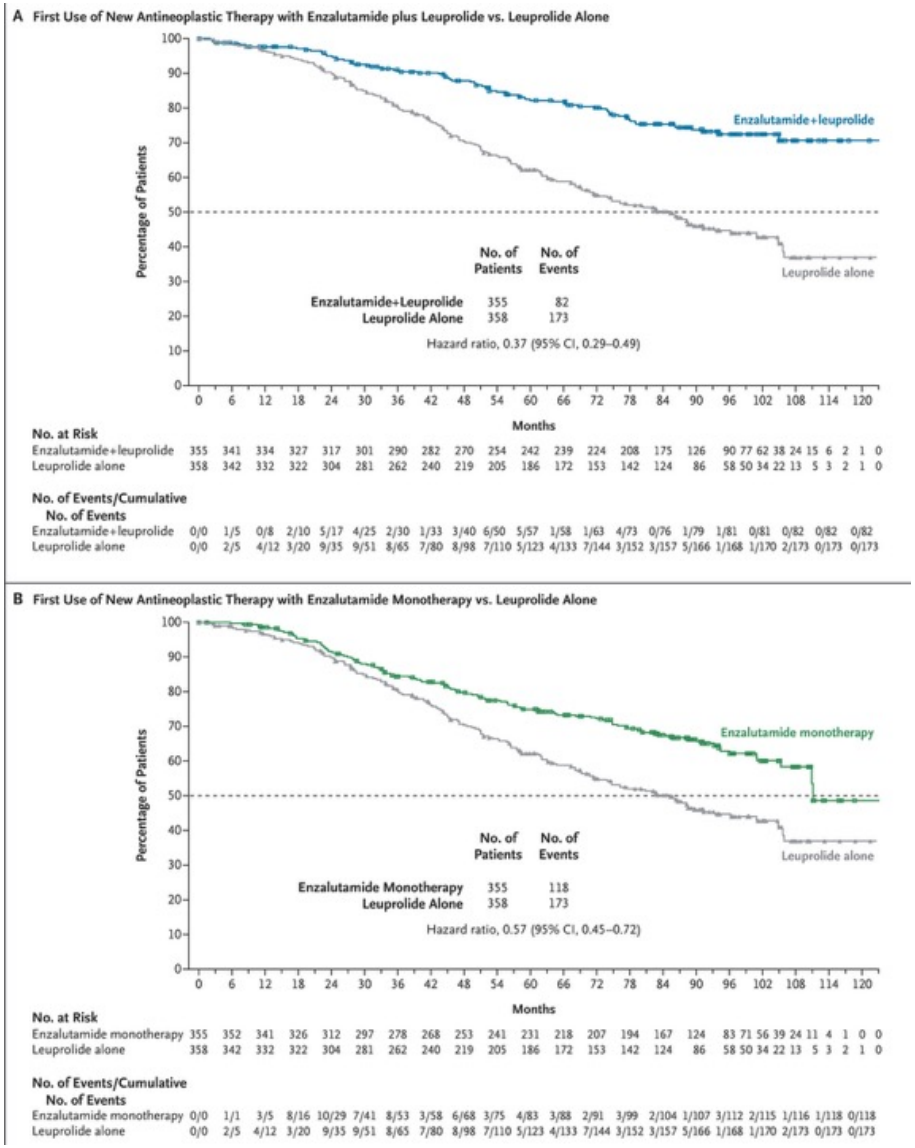
Overall Survival (Intention-to-Treat Population).

Shown are the Kaplan–Meier curves for overall survival, assessed in a time-to-event analysis from randomization to death from any cause, in the combination group as compared with the leuprolide-alone group (Panel A) and in the monotherapy group as compared with the leuprolide-alone group (Panel B). To calculate the hazard ratios, we used a Cox regression model with treatment as the only covariate and stratification according to the prostate-specific antigen (PSA) level at screening, PSA doubling time, and previous hormonal therapy, as reported in the interactive Web-response system. A hazard ratio of less than 1 indicates superiority to leuprolide alone. The two-sided P values were determined on the basis of a log-rank test, stratified according to the PSA level at screening, PSA doubling time, and previous hormonal therapy. The data-cutoff date was May 27, 2025. The squares and triangles in each panel indicate censored data. The dashed horizontal line indicates survival of 50% of the patients.



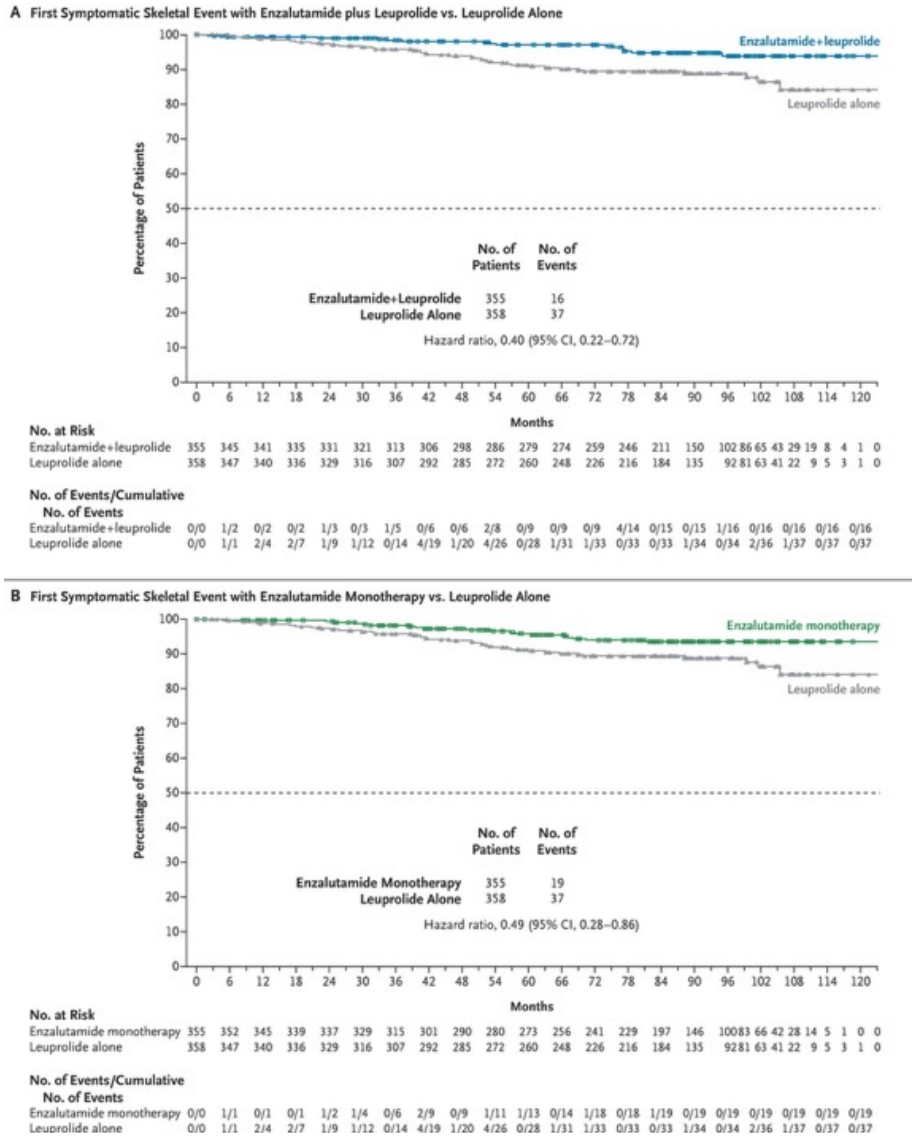
Prespecified Subgroup Analyses of Overall Survival (Intention-to-Treat Population).

The hazard ratios and 95% confidence intervals for the overall trial population are based on a Cox regression model stratified according to the same factors used to stratify randomization (PSA level at screening, PSA doubling time, and previous hormonal therapy). The hazard ratios and 95% confidence intervals for each subgroup are based on an unstratified Cox regression model. A hazard ratio of less than 1 indicates superiority to leuprolide alone. The widths of the confidence intervals have not been adjusted for multiplicity and cannot be used to infer treatment effects. The data-cutoff date was May 27, 2025. Analyses are provided for subgroups that had 10 or more events. The body-mass index is the weight in kilograms divided by the square of the height in meters. Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 4, with higher numbers indicating worse functioning. Gleason scores range from 6 to 10, with higher numbers indicating more aggressive cancer.



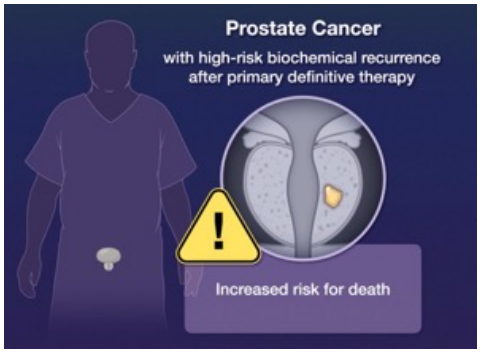
First Use of New Antineoplastic Therapy (Intention-to-Treat Population).

Shown are the Kaplan–Meier curves for the first use of new antineoplastic therapy, assessed in a time-to-event analysis, in the combination group as compared with the leuprolide-alone group (Panel A) and in the monotherapy group as compared with the leuprolide-alone group (Panel B). To calculate the hazard ratios, we used a Cox regression model with treatment as the only covariate and stratification according to the PSA level at screening, PSA doubling time, and previous hormonal therapy, as reported in the interactive Web-response system. The widths of the confidence intervals have not been adjusted for multiplicity and cannot be used to infer treatment effects. The data-cutoff date was May 27, 2025. The squares and triangles in each panel indicate censored data. The dashed horizontal line indicates first use of new antineoplastic therapy in 50% of the patients.

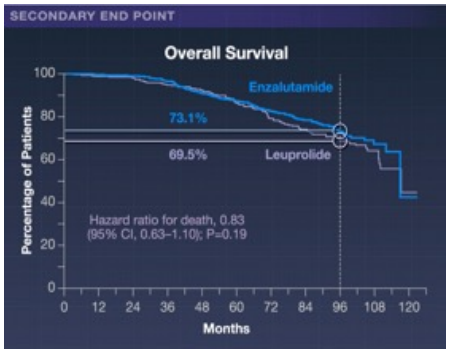


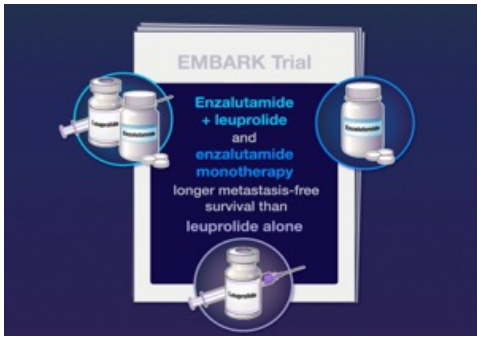
First Symptomatic Skeletal Event (Intention-to-Treat Population).

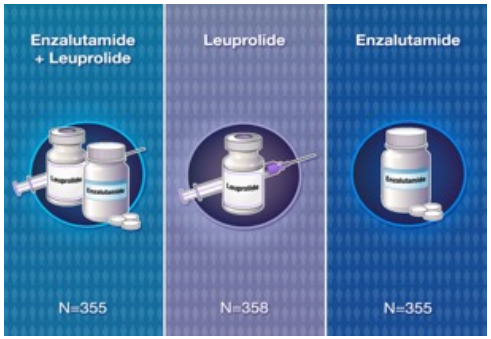
Shown are the Kaplan–Meier curves for the first symptomatic skeletal event, assessed in a time-to-event analysis, in the combination group as compared with the leuprolide-alone group (Panel A) and in the monotherapy group as compared with the leuprolide-alone group (Panel B). The time to the first symptomatic skeletal event was defined as the time from randomization to the use of radiation therapy (external beam radiation therapy or radionuclides) or surgery to bone for prostate cancer, findings of clinically apparent pathologic bone fracture or of spinal-cord compression, or new use of opiate therapy, systemic antineoplastic therapy, or both for bone pain, whichever occurred first. To calculate the hazard ratios, we used a Cox regression model with treatment as the only covariate and stratification according to the PSA level at screening, PSA doubling time, and previous hormonal therapy, as reported in the interactive Web-response system. The widths of the confidence intervals have not been adjusted for multiplicity and cannot be used to infer treatment effects. The data-cutoff date was May 27, 2025. The squares and triangles in each panel indicate censored data. The dashed horizontal line indicates the occurrence of a first symptomatic skeletal event in 50% of the patients.


Prostate Cancer
with high-risk biochemical recurrence after primary definitive therapy
Increased risk for death

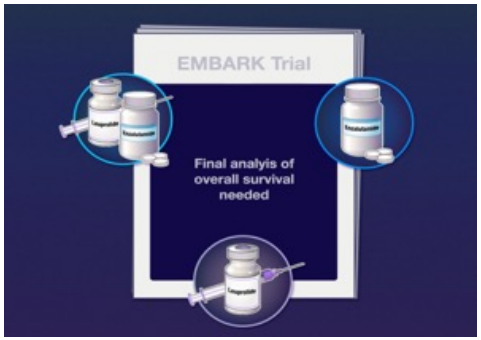

EMBARK Trial
• International
• Phase 3
• Randomized
1068 Patients
• Castration-sensitive prostate cancer
• High-risk biochemical recurrence

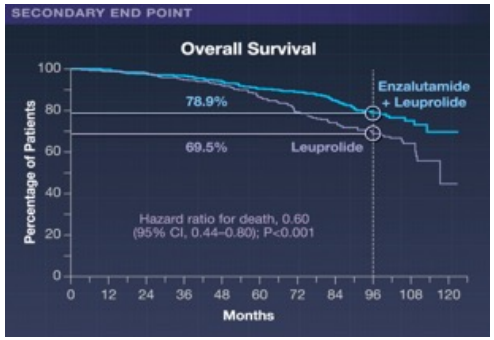

SECONDARY END POINT
Overall Survival
Enzalutamide
73.1%
69.5%
Leuprolide
Hazard ratio for death, 0.83
(95% CI, 0.63–1.10); P=0.19
Percentage of Patients
Months

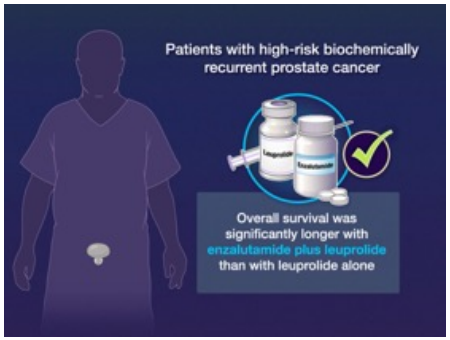

EMBARK Trial
Enzalutamide + leuprolide and enzalutamide monotherapy longer metastasis-free survival than leuprolide alone


Enzalutamide + Leuprolide
Leuprolide
Enzalutamide
N=355
N=358
N=355


SECONDARY END POINT
Overall Survival
Enzalutamide
73.1%
No new safety signals were identified. Adverse events were consistent with those in previous analyses.
Percentage of Patients
Months


EMBARK Trial
Final analyis of overall survival needed

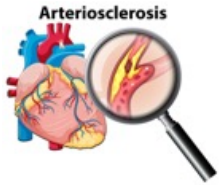

SECONDARY END POINT
Overall Survival
Enzalutamide + Leuprolide
78.9%
69.5%
Leuprolide
Hazard ratio for death, 0.60
(95% CI, 0.44–0.80); P<0.001
Percentage of Patients
Months


Patients with high-risk biochemically recurrent prostate cancer
Overall survival was significantly longer with enzalutamide plus leuprolide than with leuprolide alone

Arteriosclerosis (specifically atherosclerosis) has a strong hereditary component, often clustering in families due to inherited risk factors like high cholesterol, hypertension, and genetic variants affecting plaque formation (e.g., *APOE* gene, *SVEP1*). While genetics increase susceptibility, a family history does not guarantee disease, as lifestyle factors (diet, smoking) play a major role.

Key Aspects of Inheritance and Atherosclerosis:

- **Genetic Risk Factors:** Inherited factors often involve genes controlling lipid metabolism, inflammation, and vascular structure. For instance, a variant in the *SVEP1* gene is linked to increased plaque development.
- **Familial Hypercholesterolemia (FH):** A specific, highly heritable condition causing extremely high cholesterol and premature atherosclerosis, often requiring early, aggressive treatment.
- **Maternal Influence:** Studies indicate that maternal inheritance of certain gene mutations (like FH) may carry a higher risk of severe coronary artery disease (CAD) compared to paternal inheritance.
- **Polygenic Nature:** It is a complex, polygenic disease where numerous genetic variants (polymorphisms) contribute to individual susceptibility, rather than a single gene defect.



The Inherited Basis of Coronary Artery Disease

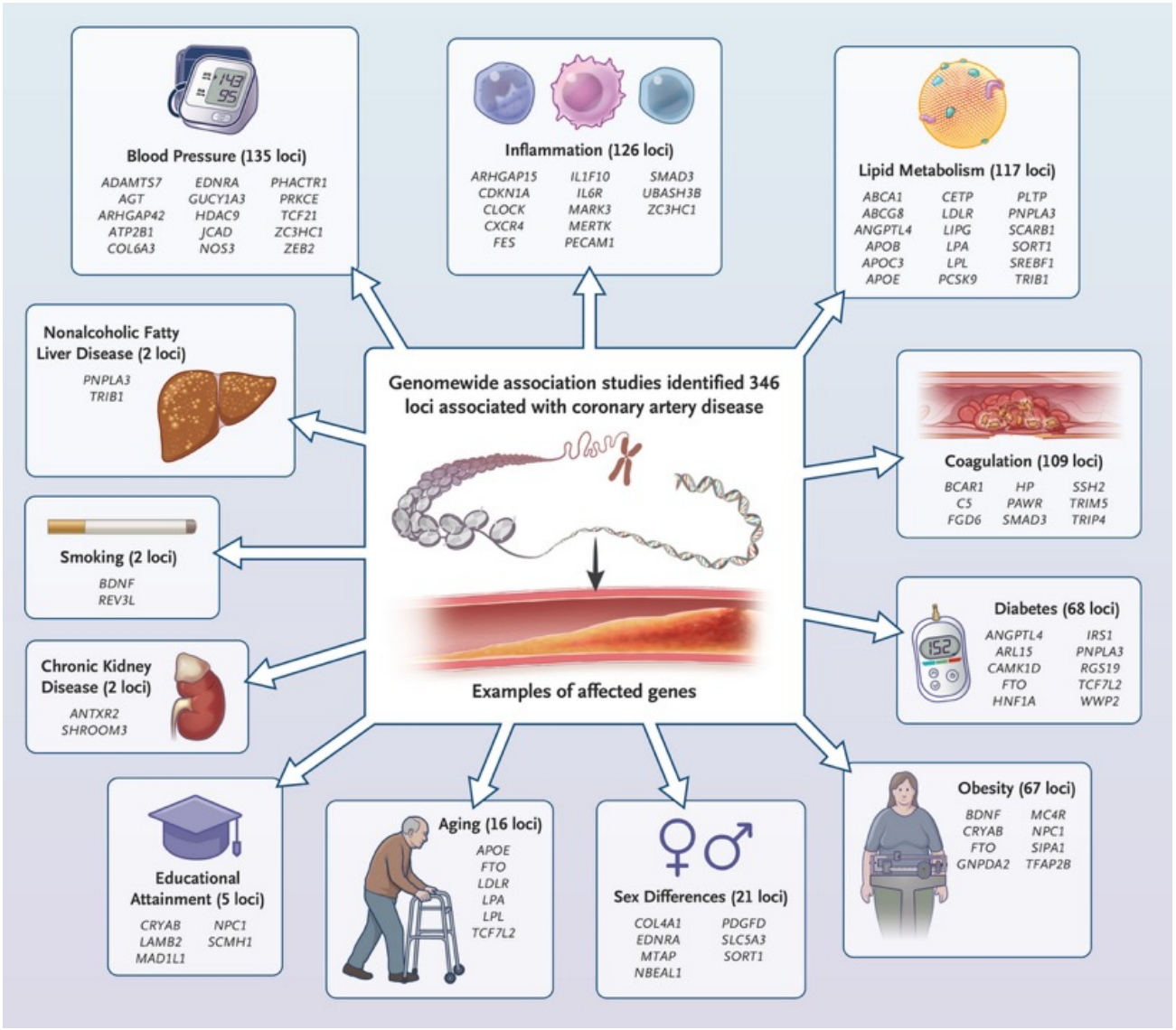
Summary

Investigations of the genetic basis of coronary artery disease have led to advances in mechanistic insights, therapeutics, prevention, and risk prediction. Indeed, most contemporary medicines for coronary artery disease target pathways that promote atherosclerosis due to underpinning genetic mechanisms. Monogenic causes of coronary artery disease occur in approximately 1 out of 250 people and mostly result in massively elevated lipid levels. At the population level, hundreds of common variants with small effect sizes have even greater influence. They can be combined in polygenic risk scores that depict genetic risk in a person relative to the average in the general population. The risk among persons in the highest 5% is 3 to 5 times that among persons with an average score; relative risk derived from the polygenic risk score can be used to multiply the absolute risk derived from a clinical risk score. Key questions remain regarding the clinical value, cost-effectiveness, and implementation strategies required to integrate coronary artery disease polygenic risk scores into clinical practice.

KEY POINTS

The Inherited Basis of Coronary Artery Disease

- Rare loss-of-function variants with large effects have directly implicated specific genes as therapeutic targets, which has provided strong human genetic validation for drug development.
- Genomewide association studies show that common genetic variants account for a substantial proportion of inherited risk for coronary artery disease.
- The variants associated with the risk of coronary artery disease manifest effects across organs and tissues. Many of these variants mediate risk through pathways known to be central to the development of coronary artery disease, but the underlying mechanism for several variants currently remains unknown.
- Genetic association data have enabled causal inference studies through mendelian randomization, which provides a framework for distinguishing causal risk factors from correlated risk markers for coronary artery disease.
- Polygenic risk scores integrate the cumulative effects of common variants into a single measure of inherited coronary artery disease risk, with a continuous population distribution and marked enrichment of events at the upper extremes.
- Polygenic risk scores provide information largely independent of conventional clinical risk factors, including family history, and refine risk stratification for both incident and recurrent coronary artery disease.
- Although genetic risk alleles are fixed at conception, their clinical consequences are modifiable, with evidence that lifestyle interventions and lipid-lowering therapy can attenuate risk among persons with high polygenic risk scores, particularly when applied early.
- There is no consensus about the clinical use of polygenic risk scoring for coronary artery disease, and questions remain regarding robustness across populations, incremental value, cost-effectiveness, and implementation.



Genomic Loci Associated with Coronary Artery Disease.

Genomewide association studies have shown 346 genomic loci with significant associations with coronary artery disease.[4-7] The figure shows, for some of these loci, the causal genes that have also been found to be significantly associated with established risk factors, risk modifiers, and clinical conditions related to the disease. The total numbers of loci with genomewide signals for both coronary artery disease and the respective traits are shown in parentheses (some loci are significantly associated with several traits). A total of 76 risk loci have no association with these traits; the mechanisms underlying the respective associations with coronary artery disease are yet to be discovered. All 346 candidate genes — or, for loci with uncertain candidate genes, the lead single-nucleotide polymorphisms — are shown in the interactive graphic. Additional information can be found in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Monogenic Forms of Coronary Artery Disease

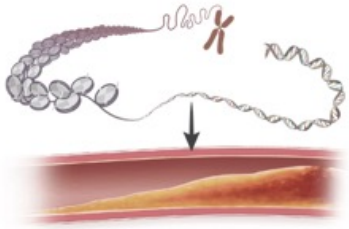
The archetypal molecular genetic cause of coronary artery disease is familial hypercholesterolemia, an incompletely dominant monogenic condition. It was first described by Müller in 1938 and remained the only proven genetic cause of coronary artery disease for approximately 70 years. Familial hypercholesterolemia is found in approximately 4 of every 1000 people who are heterozygous for the disease and in approximately 1 of every 200,000 people who are homozygous for the disease. By their mid-forties, approximately 20% of persons with heterozygous familial hypercholesterolemia have atherosclerotic conditions. Causative genetic variants for familial hypercholesterolemia typically lead to diminished function of low-density lipoprotein (LDL) receptor, altered function of apolipoprotein B, or enhanced function of proprotein convertase subtilisin/kexin type 9 (PCSK9).

Polygenic Contribution to Coronary Artery Disease

Whereas rare damaging variants, such as those in *LDLR*, can profoundly impair health in affected persons, common risk alleles with small effects appear to be more relevant at the population level. In the 1950s, Platt and Pickering argued about whether hypertension is inherited in a monogenic or polygenic fashion. Subsequently, mathematical modeling indicated that multiple common risk alleles with small effects result in more cases of hypertension than do rare variants with strong effects.

Genomewide association studies of coronary artery disease have validated this hypothesis. Genotyping arrays assess alleles of hundreds of thousands of single-nucleotide polymorphisms (SNPs) in parallel and, combined with statistically imputed, nongenotyped SNPs, enable efficient genomewide genotyping of common variants.

Genomewide association studies identified 346 loci associated with coronary artery disease

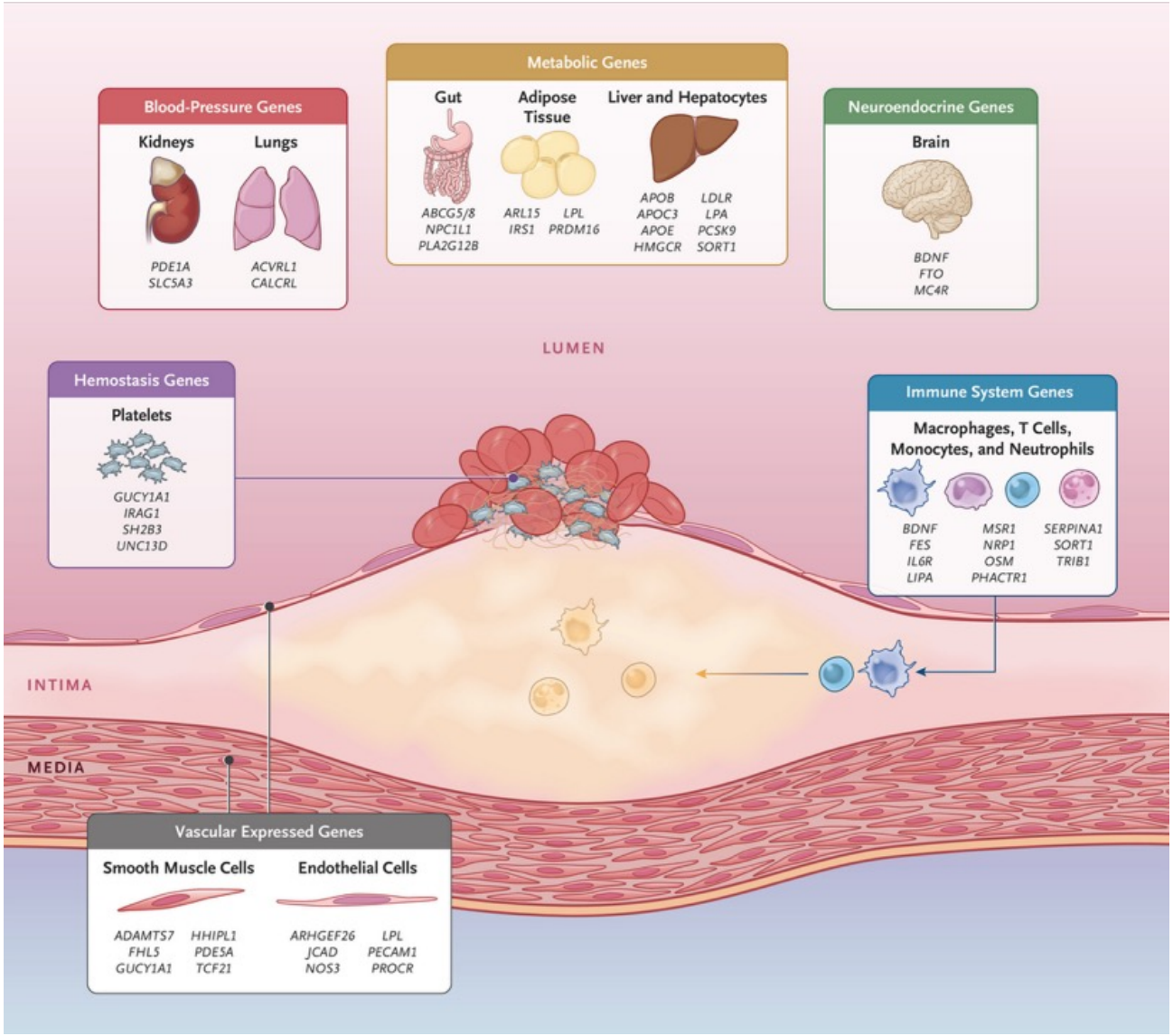


Search for Loci... | Clear search | View Legend

- Blood Pressure (135 loci)
- Immune Response and Inflammation (126 loci)
- Lipid Metabolism (117 loci)
- Coagulation and Thrombosis (109)
- Unknown (76 loci)
- Type 2 Diabetes (68 loci)
- Obesity (67 loci)
- Sex Differences (21 loci)
- Aging (16 loci)
- Educational Attainment (5 loci)
- Smoking (2 loci)
- Chronic Kidney Disease (2 loci)
- Nonalcoholic Fatty Liver Disease (2 loci)

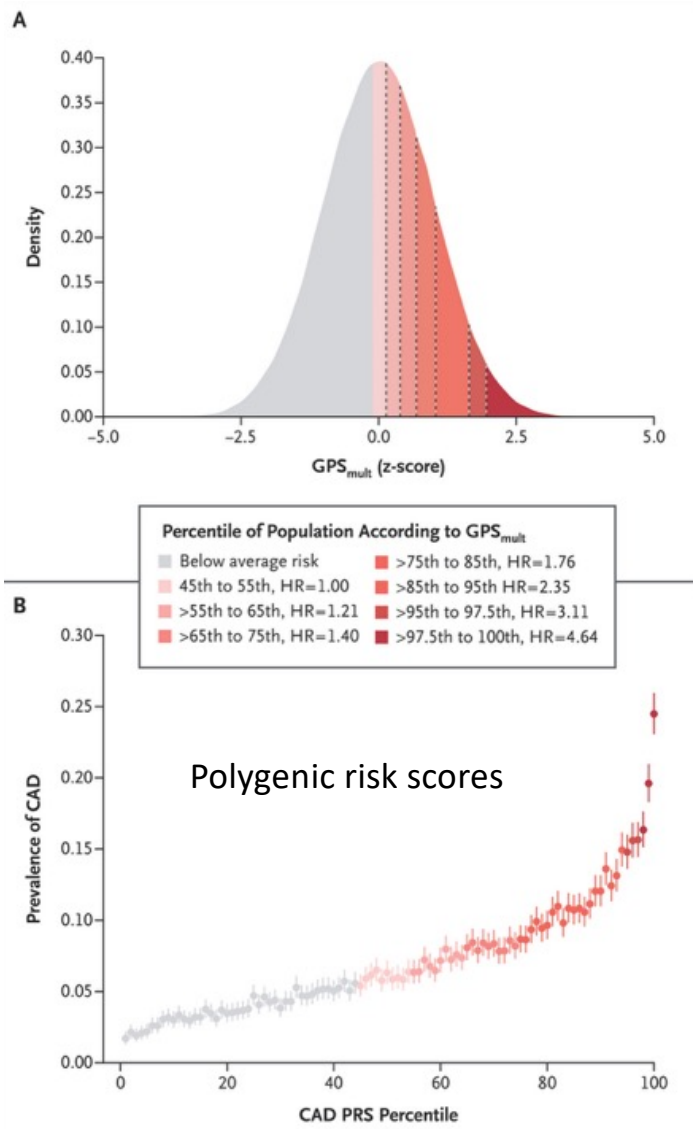
Click/tap a gene to view details.

ABHD2	ABO	ACVRL1	ADAMTS3
ADAMTS7	ADAMTSL4-AS1	AFF4	AGT
ANTXR2	APOB	APOE	APOM
ARHGAP15	ARHGAP42	ARHGEF26	ARID1A
ARNTL	ARVCF	ASS1P13	ATP2B1
ATXN2	BCAR1	BCAS3	BCL11A
BICC1	CAMK1D	CCDC30	CCM2
CDH13	CDKN1A	CENPW	CLOCK
CMIP	CNNM2	CNPY2	COL4A1
COL6A3	COPRS	CRYAB	DOCK8
DOK7	EDNRA	F10	FADS2
FBN2	FER	FES	FGD5
FHL3	FHL5	FIGN	FN1
GEM	GNAS	GUCY1A3	HBS1L
HDAC9	HHIPL1	HMGCR	IRS1
ITGB3	JCAD	JUN	KCNK5
KDM4B	KIAA0040	LAMB2	LDLR
LMOD1	LNPEP	LOX	LOXL1
MAD2L1	MAP1S	MAP3K1	MARK3
MC4R	MECOM	MLH3	MRAS
MTAP	MYH11	NBEAL1	NISCH
NME7	NOS3	NR3C1	OIP5-AS1
PALLD	PAWR	PCDH18	PDE1A
PDE3A	PECAM1	PHACTR1	PLCE1
PLEKHG1	PLEKHJ1	PPAP2B	PPHLN1
PRDM16	PRKCE	RGS19	RRP1B
rs111245230	SBF2	SCD	SGCD
SH3PXD2A	SHROOM3	SIPA1	SLC5A3
SMG6	SWAP70	TBX3	TCF21
TCF7L2	TGFB1	TNS1	TRIB1
UBASH3B	UNC13D	VASP	VEGFA
WT1	WWP2	ZC3HC1	ZEB2
ZKSCAN1	ZNF100	ZNF589	ZNF641



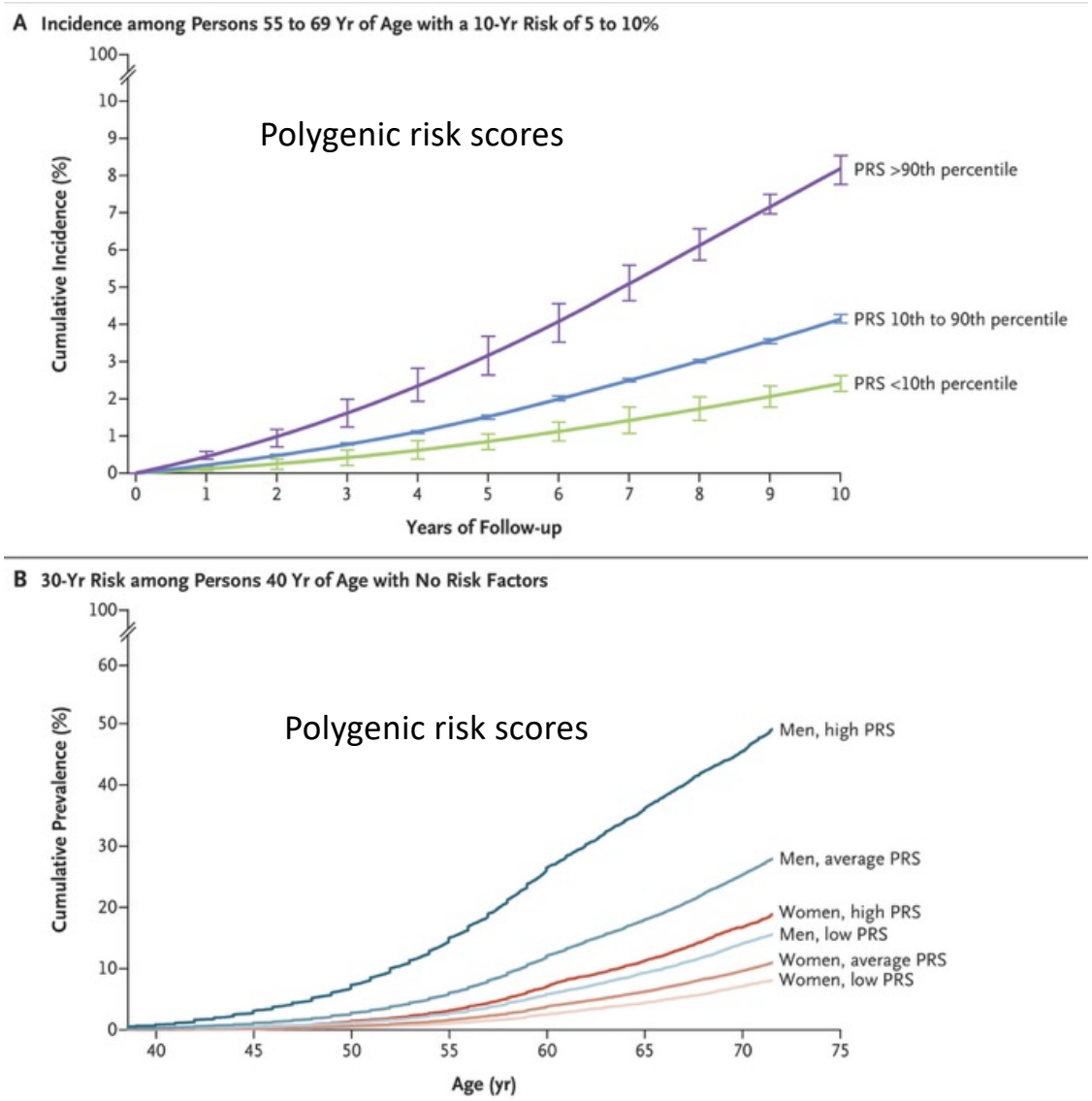
Expression Sites of Genes Affecting Risk of Coronary Artery Disease.

The tissues and organs that most abundantly express genes affecting the risk of coronary artery disease are shown, as are genes at a genomewide level that are significantly associated with coronary artery disease and exemplify those with high tissue-specific expression. The arterial wall is shown at the center, with the key cellular contributors to atherosclerosis highlighted. Additional organs and tissues that are relevant to the pathophysiology of coronary artery disease are shown above the arterial wall. Gene expression was identified with the use of the Human Protein Atlas and was cross-validated with data from the Genotype-Tissue Expression (GTEx) project, STARNET, and the literature.[4,5,7,29–34] Additional information can be found in the Supplementary Appendix.



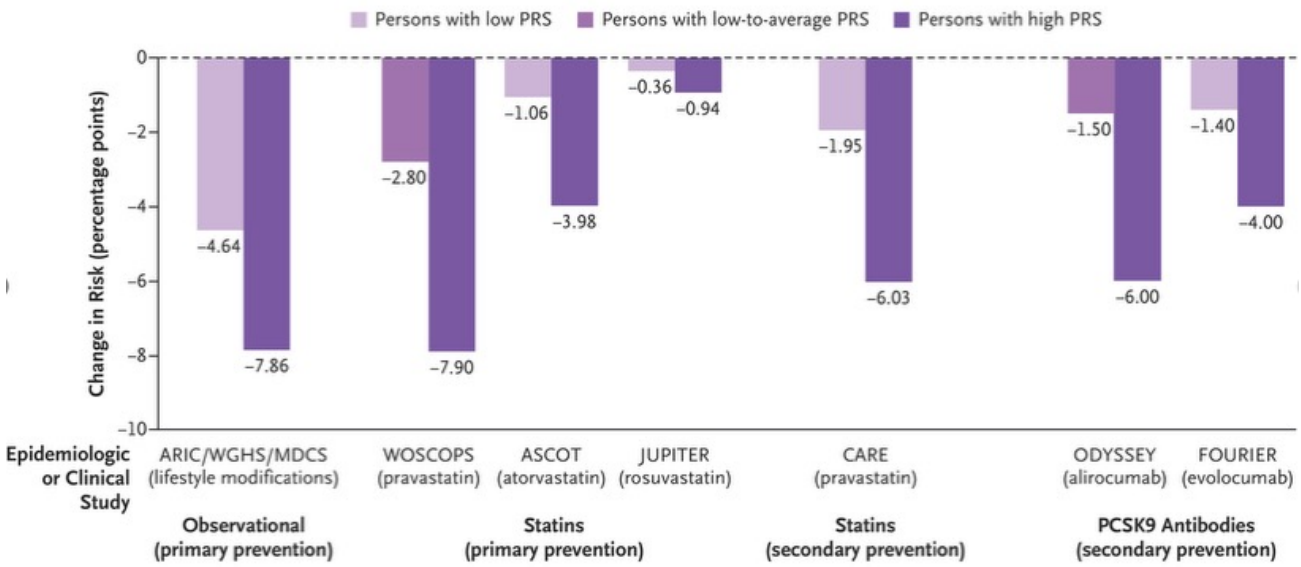
Polygenic Risk Scores (PRSs) for Coronary Artery Disease (CAD).

Each person inherits hundreds of coronary artery disease risk alleles through a play of chance. The numbers of risk alleles carried by persons within a population are distributed under a gaussian curve, as shown in Panel A. Density (y axis) corresponds to the number of observations per GPS_{mult} standard deviation, adjusted for sample size, so that the total area equals one. GPS_{mult} refers to a previously published polygenic risk score for coronary artery disease.[37] Hazard ratios (HR) for coronary artery disease are shown for persons with a PRS above the mean. Panel B shows that although individual risk alleles have small effects, they act multiplicatively, resulting in an exponential increase in risk.[28] Data in both panels are from the U.K. Biobank.



Trajectories for Atherosclerotic Cardiovascular Disease Events According to the Polygenic Risk Category.

Drawing on data from the U.K. Biobank, Panel A shows that among persons 55 to 69 years of age, the risk of an atherosclerotic cardiovascular disease event is 5 to 10%, as calculated with the use of SCORE2. Even though SCORE2 and other risk prediction tools overestimate the incidence among persons included in the U.K. Biobank, the observed incidence largely differs according to the polygenic risk.[43] The samples were randomly split into 10 groups, and the mean cumulative incidence and standard error (I bars) were calculated. Panel B, which also draws on data from the U.K. Biobank, shows that among 40-year-old men and women without clinical risk factors at this age, the long-term risk of coronary artery disease also differs according to the polygenic risk. Currently used clinical risk scores do not adequately predict the long-term risk of coronary artery disease among younger people. In this subgroup of the population, the polygenic risk of coronary artery disease may provide useful information for predicting future risk.



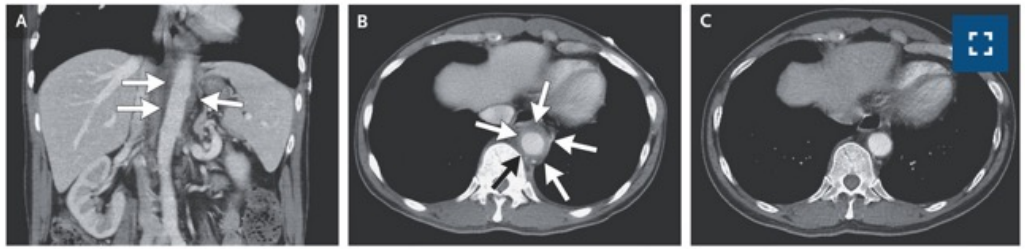
Risk Reduction through Lifestyle Modifications or Lipid-Lowering Treatment, According to the PRS.

Epidemiologic studies and clinical trials have shown that over a span of 20 years, lifestyle modifications are associated with a reduction in incident atherosclerotic cardiovascular disease events, with the greatest risk reduction occurring among persons with a high PRS. Data on lifestyle modifications are from the following epidemiologic studies: Atherosclerosis Risk in Communities (ARIC), the Women's Genome Health Study (WGHS), and the Malmö Diet and Cancer Study (MDCS).[30] Likewise, statin and proprotein convertase subtilisin–kexin type 9 (PCSK9) antibody trials uniformly show a greater absolute risk reduction among persons with a high PRS than among those with a low PRS. Data on lipid-lowering treatment are from the following studies: the West of Scotland Coronary Prevention Study (WOSCOPS),[31] the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER), Cholesterol and Recurrent Events (CARE),[34] Evaluation of Cardiovascular Outcomes after an Acute Coronary Syndrome during Treatment with Alirocumab (ODYSSEY OUTCOMES),[33] and Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER).[32] Additional information can be found in the Supplementary Appendix.

Conclusions

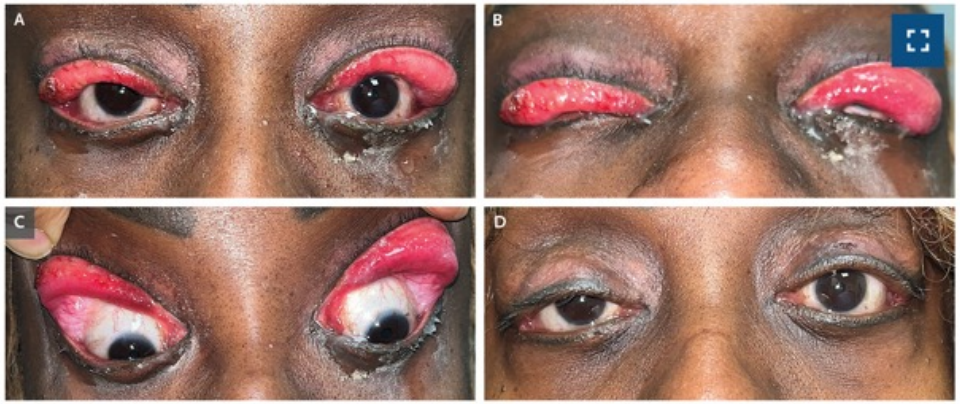
Even larger genomewide association studies and sequencing studies across persons globally will provide more precise information on involved DNA variants, causal genes, and downstream mechanisms. These studies will also help to further refine and standardize polygenic risk scores for coronary artery disease. A plethora of genetic findings from genomewide scans, beginning in 2007, continues to change the perception of how coronary artery disease develops. Hundreds of common genetic variants affecting a wide spectrum of disease mechanisms are found in each person; the more a person carries, the higher the risk of coronary artery disease. Many established treatments have been validated on the basis of these data, and several genetically driven disease pathways are currently being interrogated for their therapeutic potential. The totality of the genetic information about coronary artery disease, captured as familial hypercholesterolemia variants or aggregated as a polygenic risk score, continues to open new opportunities for earlier risk prediction, prevention, and treatment.

Aortitis Due to Large-Vessel Vasculitis



A 63-year-old man with a history of hypertension presented to the emergency department with a 3-month history of chest tightness, palpitations, and abdominal pain. On physical examination, he had tenderness on palpation in the epigastric region. Laboratory studies were notable for an erythrocyte sedimentation rate of 104 mm per hour (reference value, <20) and a C-reactive protein level of 85 mg per liter (reference value, <5); normocytic anemia was also present. Computed tomography of the chest and abdomen (Panel A [coronal view] and Panel B [axial view]), performed after the administration of contrast material, revealed thickening and enhancement of the walls of the descending thoracic and upper abdominal aorta (arrows) and paraaortic fat stranding. Serologic evaluation for autoimmune and infectious conditions was negative. A diagnosis of aortitis due to large-vessel vasculitis was made. Treatment with azathioprine, hydroxychloroquine, and prednisolone was started. After 6 weeks of therapy, the symptoms and elevated levels of inflammatory markers persisted. Treatment with azathioprine was subsequently discontinued, and treatment with subcutaneous tocilizumab every 2 weeks was initiated. Four months later, the symptoms had resolved and the elevated levels of inflammatory markers had normalized. Repeat imaging performed 5 months after initiation of tocilizumab treatment showed resolution of the inflammation of the aortic wall (Panel C [axial view]). Eight months after diagnosis, the patient continued to do well with ongoing treatment with tocilizumab, hydroxychloroquine, and low-dose prednisolone.

Floppy Eyelid Syndrome

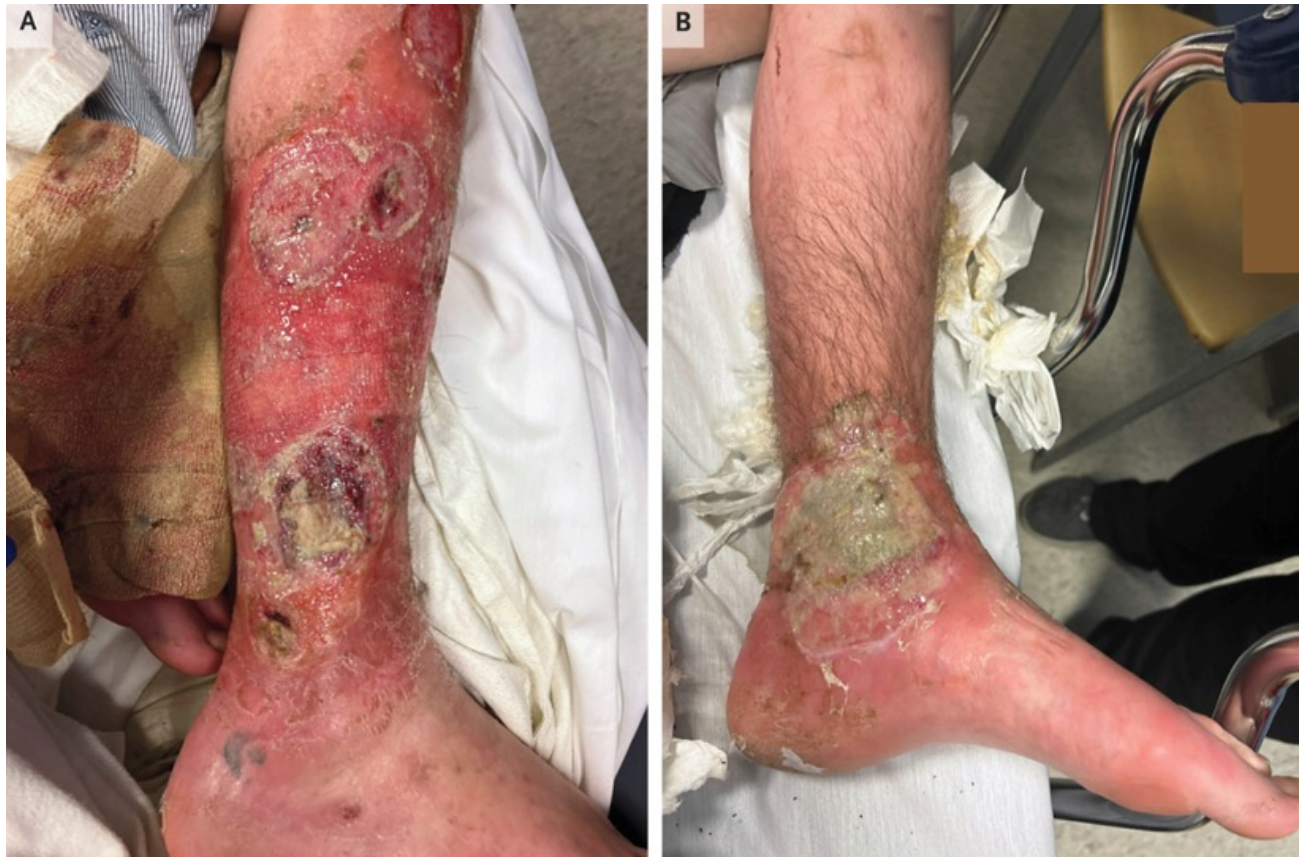


A 39-year-old woman with obesity presented to the ophthalmology clinic with a 6-week history of foreign-body sensation and tearing in both eyes that were worse on awakening. She also reported daytime fatigue, snoring, and difficulty sleeping at night. Ophthalmologic examination showed upper-eyelid eversion with conjunctival hyperemia (Panel A) and incomplete eyelid apposition on attempted closure of both eyes (Panel B). Manual retraction of the upper eyelids while the patient was looking down showed marked laxity with complete eyelid eversion (Panel C). A diagnosis of floppy eyelid syndrome was made. Floppy eyelid syndrome is characterized by excessive laxity of the upper eyelids and results in eyelid malposition and chronic irritation of the ocular surface. The condition is associated with obstructive sleep apnea. The patient was referred for polysomnographic testing, which showed an apnea–hypopnea index of 27 events per hour, a finding consistent with a diagnosis of moderate obstructive sleep apnea. Treatment with nocturnal continuous positive airway pressure and a weight-loss program were initiated. The use of ophthalmic lubricants and eye patches while sleeping was also recommended. Two weeks after the start of treatment, the patient's upper-eyelid eversion resolved (Panel D) and eye closure improved. In addition, her sleep quality improved and daytime drowsiness abated.

A Matter of Time

A 29-year-old woman with active opioid, alcohol, benzodiazepine, tobacco, and cocaine use disorders and recent intravenous drug use presented with acute onset of chills and increased pain and drainage of chronic wounds in both legs. Her wounds first appeared more than a year before presentation and were attributed to xylazine exposure. She had not injected into the wounds or shared needles. She reported that she did not have fever, sweats, rigors, rash, cough, abdominal pain, or dysuria. The wounds in her legs were purulent, erythematous, and painful. She reported no additional medical history and took no medications. Her social history was notable for engaging in occasional unprotected transactional sex. The hemoglobin level was 8.7 g per deciliter with a mean corpuscular volume of 78.5 fl (both unchanged from 1 month earlier), white-cell count 4930 per cubic millimeter with 57% neutrophils and 31% lymphocytes, and platelet count 484,000 per cubic millimeter. The results of a complete metabolic panel were unremarkable. The erythrocyte sedimentation rate was 77 mm per hour, and the C-reactive protein level was 3.1 mg per deciliter. Given concern for SSTI, with possible underlying osteomyelitis, blood cultures were obtained and empirical antimicrobial therapy was initiated with vancomycin.

Xylazine is an α_2-agonist used as a veterinary sedative that is a common contaminant of illicit fentanyl. Its use is associated with severe wounds, sometimes distant from injection sites. The patient's increased wound drainage and chills, especially if accompanied by surrounding cellulitis or other signs of systemic inflammation, suggest the possibility of secondary purulent skin and soft-tissue infection (SSTI).



Purulent Wounds in the Legs.

Panel A shows the right leg, and Panel B shows the left leg.

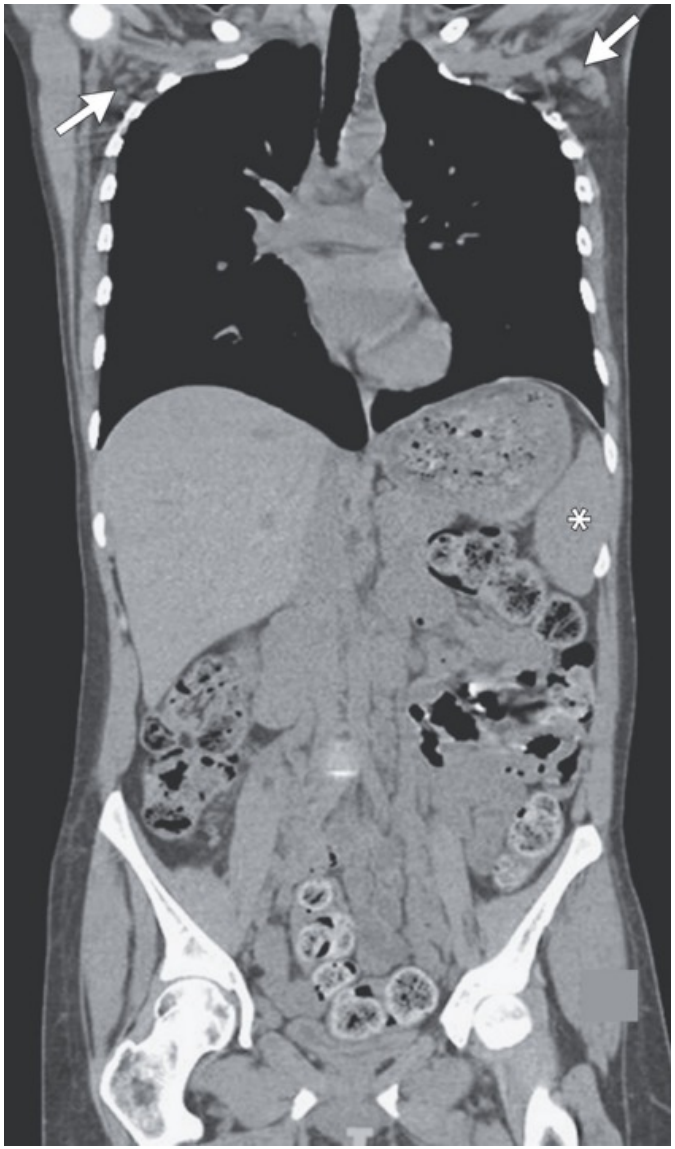
She began to have withdrawal symptoms. These included tremors, anxiety, restlessness, nausea, abdominal pain, and diffuse body aches. Symptom-triggered benzodiazepines and a phenobarbital taper were initiated to treat her sedative hypnotic withdrawal. Methadone, clonidine, and hydromorphone were initiated to treat her opioid withdrawal and opioid use disorder. Fourth-generation HIV testing (which includes testing for the p24 antigen, an early marker of HIV infection, and for antibodies to HIV type 1 [HIV-1] and HIV type 2 [HIV-2]) was negative. Tests for hepatitis B core and surface antibodies were positive; a test for hepatitis B surface antigen was negative. A test for hepatitis C antibodies was positive, and nucleic acid testing for hepatitis C virus was negative. A test for *Treponema pallidum* chemiluminescence antibodies was negative. On further history taking, she disclosed a sexual assault approximately 7 days before presentation and vaginal discharge of recent onset. A sexual assault forensic examination was offered, which the patient declined. Given the recency of the assault, as well as plans to recommend HIV preexposure prophylaxis, nucleic acid testing for HIV was performed and was also negative.

Nucleic acid testing of a urine sample was positive for *Trichomonas vaginalis* and negative for *C. trachomatis* and *N. gonorrhoeae*. Metronidazole was initiated. Blood cultures remained without growth, and the wounds in her legs showed clinical improvement. A CT scan of the legs with intravenous contrast did not identify a soft-tissue abscess but revealed a periosteal reaction of the right distal fibula that was suggestive of chronic osteomyelitis. On hospital day 9, while the patient was awaiting further MRI evaluation for osteomyelitis, drenching night sweats (without fever) developed.

An MRI scan of her legs showed the fibular cortical thickening previously seen on CT, but the T1-weighted bone marrow signal was normal. On review of both CT and MRI findings, the radiologist was not concerned about osteomyelitis. Two additional sets of blood cultures and nucleic acid testing for respiratory pathogens were negative, and levels of thyroid-stimulating hormone and free T4 were in the normal range. Transthoracic echocardiography showed no vegetations or valvular disease. Further history taking confirmed that she had no recent animal exposure or international travel.

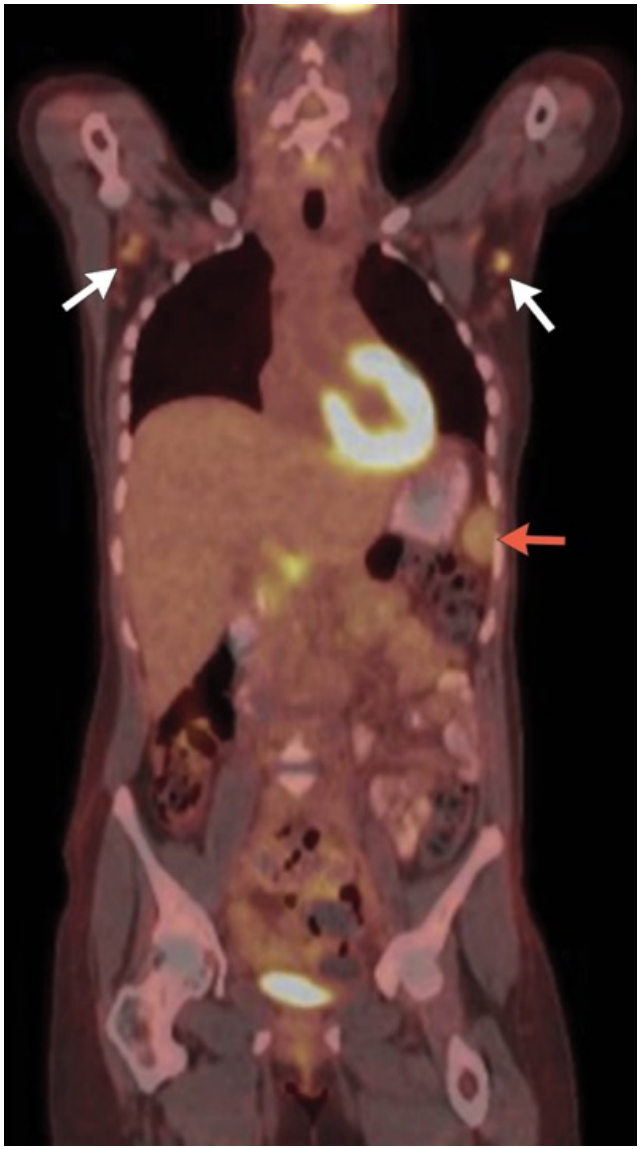
On day 16 of hospitalization, a repeat complete blood count showed a decrease in the white-cell count to 1710 per cubic millimeter with 35% neutrophils, 48% lymphocytes, and 9% atypical lymphocytes. The absolute lymphocyte count was 970 per cubic millimeter (normal range, 1100 to 4800). The hemoglobin and platelet count were stable. CT of the chest, abdomen, and pelvis revealed enlarged bilateral axillary and right retropectoral lymph nodes, measuring up to 1.2 cm, and splenomegaly.

A peripheral-blood smear showed reactive-appearing large, atypical lymphocytes; hypochromic anemia with anisocytosis; and platelets that were normal in number with frequent large forms. Mononucleosis heterophile antibody screening was negative. Antinuclear antibody screening was negative. Given the multifocal lymphadenopathy and persistent and profuse night sweats, there was increasing concern for lymphoma. Consequently, a positron-emission tomography (PET)–CT scan was ordered to further characterize the lymphadenopathy and identify a possible excisional node biopsy site. PET-CT revealed multiple prominent bilateral cervical, axillary, mediastinal, retroperitoneal, pelvic, and inguinal lymph nodes with mild-to-moderate ^{18}F-fluorodeoxyglucose (FDG) avidity, as large as 1.3 cm. The spleen was enlarged and FDG avid. The radiologist's chief concern was for lymphoma.



Coronal View of Computed Tomography (CT) of the Chest, Abdomen, and Pelvis with Intravenous Contrast.

The scan revealed bilateral axillary lymphadenopathy (arrows). Splenomegaly (asterisk) was also noted but is better visualized on other sections.



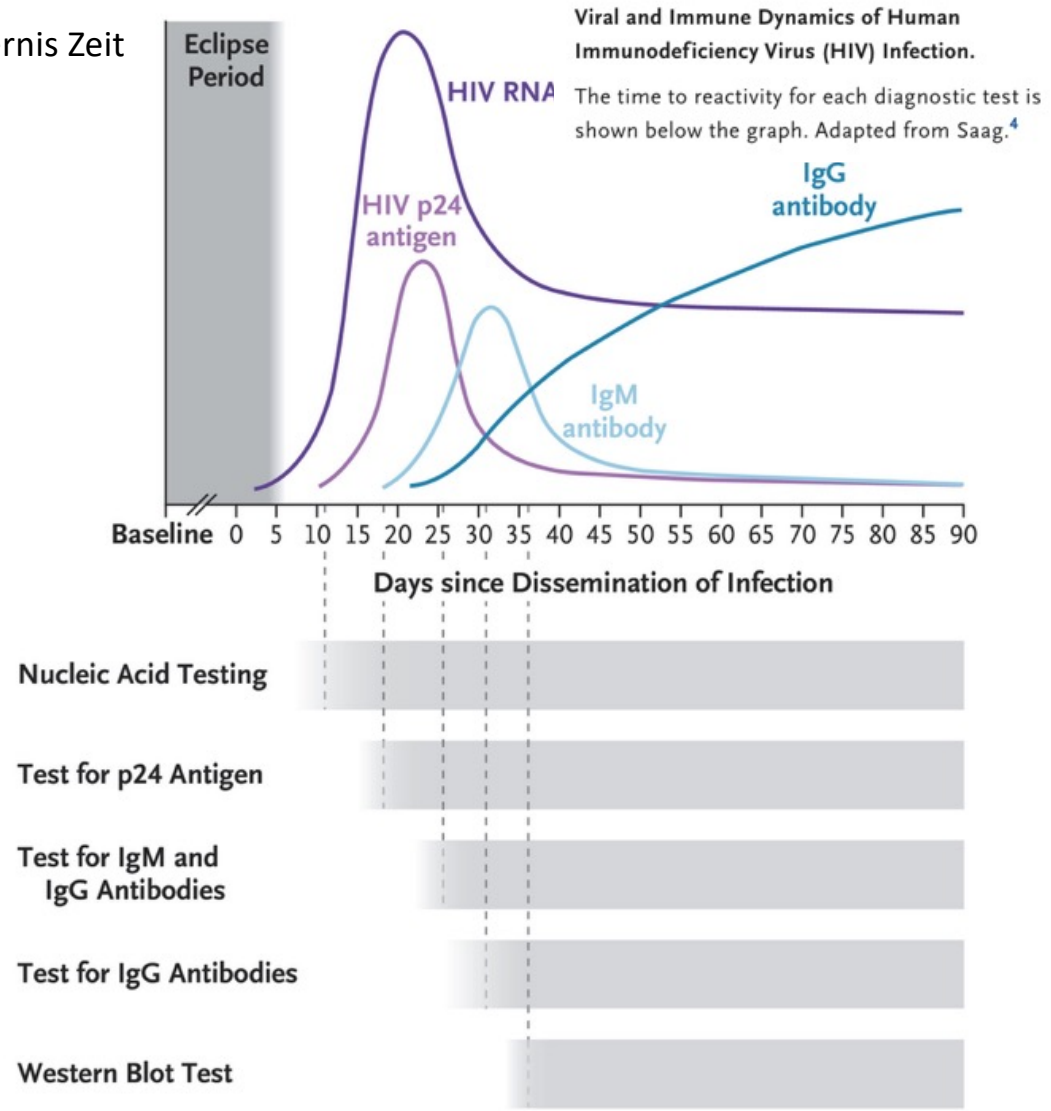
Coronal View of Positron-Emission Tomography–CT.

The scan revealed ^{18}F-fluorodeoxyglucose (FDG)–avid bilateral axillary lymphadenopathy (white arrows). An enlarged spleen with increased FDG intensity was partially visualized (red arrow).

An excisional lymph-node biopsy and bone marrow biopsy were planned. However, before these examinations were undertaken, repeat nucleic acid testing for HIV was positive with a viral load of 4,480,000 copies per milliliter. HIV-1 and HIV-2 antigen–antibody testing was then repeated and was also positive. HIV-1 and HIV-2 differentiation antibody testing was negative. The patient was diagnosed with acute HIV infection. Antiretroviral therapy (ART) with coformulated bictegravir, emtricitabine, and tenofovir alafenamide was initiated, and her night sweats gradually resolved. She was connected with comprehensive care for HIV and substance use disorders and was discharged. She had an undetectable HIV viral load approximately 2 months later and has since maintained an undetectable HIV viral load 20 months after discharge.

At a key juncture in her care, repeat HIV testing returned positive, resulting in a diagnosis of acute HIV infection, despite negative testing for HIV by both fourth-generation antigen–antibody testing and nucleic acid testing during the initial 24 hours of her hospitalization. This narrative highlights the importance of understanding the clinical presentation of acute HIV infection, corresponding viral dynamics, and implications for HIV testing. Acute HIV infection, when symptomatic, most commonly manifests with a mononucleosis-like syndrome. The manifestations most frequently reported in cohort studies include fever (>80 to 90% of patients), fatigue (>70 to 90%), rash (>40 to 80%; typically maculopapular), headache (32 to 70%), and lymphadenopathy (40 to 70%).[1] Approximately 50% of affected persons have night sweats, and leukopenia develops in approximately 40%, as seen in this case. Many persons are asymptomatic.

Finsternis Zeit



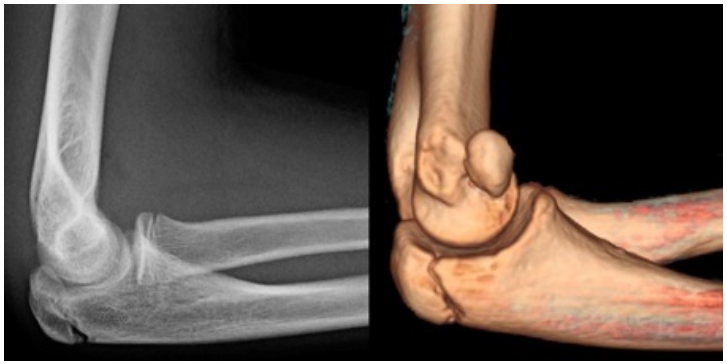
Viral and Immune Dynamics of Human Immunodeficiency Virus (HIV) Infection.

The time to reactivity for each diagnostic test is shown below the graph. Adapted from Saag.[4]

Our patient presented approximately 7 days after a high-risk exposure, and initially, both nucleic acid testing and fourth-generation testing for HIV were negative. When symptoms subsequently developed that were compatible with acute HIV infection (night sweats, lymphadenopathy, and leukopenia), HIV testing with both nucleic acid testing and fourth-generation antigen–antibody testing was repeated and returned positive. Antibody differentiation testing was reflexively performed and was negative, which confirmed the diagnosis of acute HIV infection. The initial negative nucleic acid testing indicates that the patient presented during the eclipse period.

THE LANCET

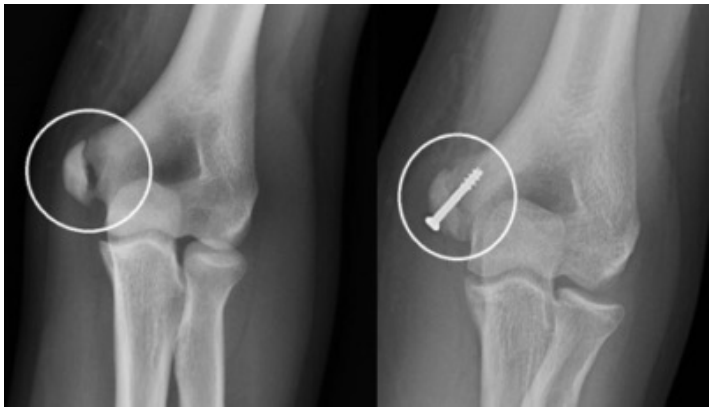
Eine **mediale Epikondylusfraktur** ist eine Fraktur des knöchernen Vorsprungs an der Innenseite des Ellenbogens. Es handelt sich um eine häufige Verletzung bei Kindern und Jugendlichen (Peak: 9–14 Jahre), da dieser Bereich ein Wachstumszentrum (Apophyse) ist.



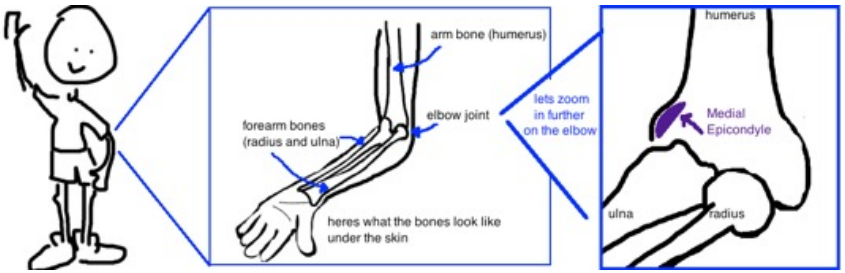
Ursachen & Mechanismen

Die Fraktur entsteht meist durch indirekte Kräfte:

- **Sturz auf den ausgestreckten Arm (FOOSH):** Häufigste Ursache bei Kindern.
- **Ellenbogendislokation:** In etwa **50 % der Fälle** ist die Fraktur mit einer Ausrenkung des Ellenbogens verbunden.
- **Avulsionsverletzung:** Durch plötzliche Kontraktion der Beugemuskulatur, etwa beim **Armdrücken** oder bei Wurfsportarten.



(FOOSH – "Fall On Outstretched Hand")



Die Behandlung einer Fraktur des **Epicondylus medialis** (innerer Ellenbogenknochen) richtet sich primär nach dem Ausmaß der Verschiebung (Dislokation) und Begleitverletzungen.

1. Konservative Behandlung (Nicht-operativ)

Dies ist der Standard für die meisten stabilen oder nur geringfügig verschobenen Frakturen.

- **Indikation:** Verschiebung des Bruchstücks von weniger als 5 mm bis 15 mm (je nach klinischer Richtlinie).
- **Methode:** Ruhigstellung in einer **Oberarm-Gipsschiene** bei einer Ellenbogenbeugung von 90 Grad für etwa **3 bis 4 Wochen**.
- **Nachsorge:** Wöchentliche Röntgenkontrollen sind oft notwendig, um ein weiteres Abdriften des Knochens durch Muskelzug zu überwachen.

2. Operative Behandlung

Eine Operation wird meist dann empfohlen, wenn die Gelenkstabilität gefährdet ist oder das Fragment die Bewegung blockiert.

- **Wichtige Indikationen:**
    - **Eingeklemmtes Fragment:** Das Knochenstück liegt im Gelenkspalt (Inkarzeration).
    - **Offene Frakturen:** Der Knochen hat die Haut durchstoßen.
    - **Starke Verschiebung:** Meist bei mehr als 15 mm Dislokation oder bei Leistungsathleten bereits ab 5 mm.
    - **Nervenverletzungen:** Anzeichen einer Schädigung des **Nervus ulnaris**.

Surgical fixation versus non-surgical care for children with a displaced medial epicondyle fracture of the elbow (the SCIENCE study): a multicentre, randomised controlled, superiority trial and economic evaluation

Summary

Background Displaced medial epicondyle fractures are among the most controversial injuries in children, with increasing trends towards surgical fixation despite little supporting evidence. Approximately half of affected children undergo surgical fixation, while others receive non-surgical care. The SCIENCE trial aimed to determine whether surgical fixation to restore the position of the bone provides superior functional outcomes and is cost-effective compared with non-surgical care.

Methods We conducted a pragmatic multicentre, randomised, superiority trial across 59 hospitals in the UK, Australia, and New Zealand. Recruiting sites were secondary or tertiary care hospitals providing acute paediatric trauma care. Eligible participants were aged 7–15 years with a displaced medial epicondyle fracture and patients were excluded if the injury occurred more than 2 weeks prior, they had a medial epicondyle fragment that was incarcerated (trapped) within the joint, the injury was part of a complex elbow fracture (ie, extending into the joint), or there were additional fractured bones outside of the elbow. Participants were randomly assigned (1:1) to either surgical fixation or non-surgical care using a web-based randomisation software from Oxford Clinical Trials Research Unit, with minimisation (including a random element) stratified by centre and elbow dislocation status at presentation. Participants and their parents and carers could not be masked to treatment. Surgical fixation was performed under general anaesthesia and involved a surgical incision, restoration of the anatomical alignment, and fixing the fragment, typically with a screw or wires. Non-surgical care involved immobilisation of the elbow at approximately 90° of flexion using a cast, splint, or sling. Both groups were allowed mobilisation as pain allowed, although cast immobilisation beyond 4 weeks was discouraged. The primary outcome was upper limb function at 12 months, measured using the Patient Report Outcomes Measurement System (PROMIS) Upper Extremity Score for Children in the intention-to-treat population, which included all participants in the groups to which they were randomly assigned, irrespective of treatment received. Complications and serious adverse events were summarised in a safety (as-treated) population defined by treatment received. A within-trial economic evaluation was undertaken from the perspective of the UK National Health Service and Personal Social Services over a 12-month time period. The trial was registered with ISRCTN, ISRCTN16619778; recruitment is complete and extended follow-up to age 16 years is ongoing.

Findings Between June 10, 2019, and Sept 22, 2023, 647 patients from 59 sites met the inclusion criteria. 146 patients were excluded (64 due to the injury being more than 2 weeks old and 24 because the epicondyle fragment was incarcerated within the joint), 161 families of children meeting the eligibility criteria declined to participate, and for five patients there was no clinician equipoise. 335 participants were randomly assigned to an intervention (166 to the non-surgical care group and 168 to the surgical fixation group) and one was immediately excluded due to a randomisation error. Primary outcome data were collected from 285 (85%) participants. 170 (51%) participants were female and 164 (49%) were male. Mean participant age at baseline was 11·7 years (SD 2·3). At 12 months post-randomisation, the PROMIS Upper Extremity score was 53·1 (SD 7·8) in the non-surgical care group and 54·3 (5·7) in the surgical fixation group (mean treatment difference, 1·57 [95% CI –0·01 to 3·14; p=0·052]). This estimate of treatment effect was below the clinically important difference specified (4 points), supporting the conclusion that a clinically important effect is unlikely. Additional episodes of surgery, either planned or related to complications, occurred in 24 participants in the surgical group and three in the non-surgical group. Among the 150 participants who underwent surgical fixation, there were 14 intraoperative complications from 13 (9%) participants, and seven participants had a postoperative complication (5% participants) each requiring surgery. Routine screw or wire removal was undertaken in a further 17 (11%) participants. From the 184 participants in the non-surgical group, there were five complications among four (2%) participants, three (2%) of which required additional surgery. The mean per patient cost from the NHS and Personal Social Services perspective was £2435 (95% CI 1812 to 3057) more for participants in the surgical fixation group with a mean per patient quality-adjusted life year difference of –0·008 (95% CI –0·039 to 0·024). The probability that surgical fixation is cost-effective at the £20 000 or £30 000 per quality-adjusted life year willingness-to-pay threshold was 0%.

Interpretation The SCIENCE trial demonstrates that surgical fixation offers no clinical benefit and is not cost-effective compared with non-surgical care, while exposing children to avoidable surgical risks. These findings suggest that non-surgical care should be adopted as the default management strategy for these injuries, regardless of initial elbow dislocation status.

Funding National Institute for Health and Care Research (NIHR) Health Technology Assessment programme (17/18/02), with additional support from the NIHR Academy, Oxford NIHR Biomedical Research Centre, and the Starship Foundation (New Zealand).

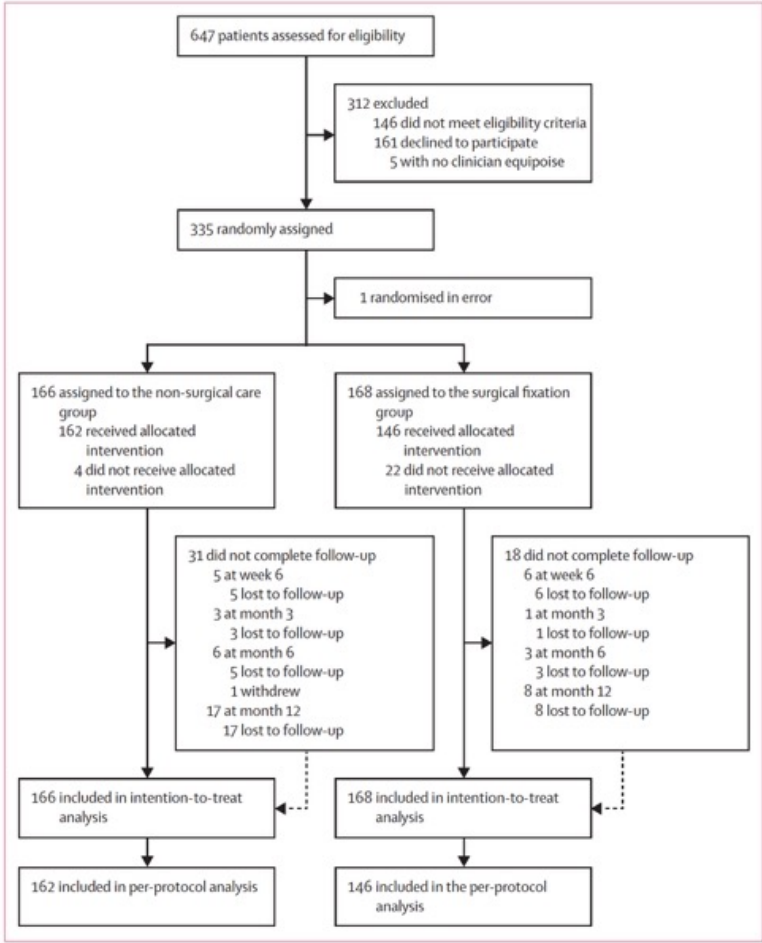


Figure 1: **Trial profile**

	Non-surgical care group (n=166)	Surgical fixation group (n=168)	Total (N=334)
Age, years			
Mean (SD)	11·6 (2·4)	11·8 (2·1)	11·7 (2·3)
Median (IQR)	11·7 (9·6–13·5)	12·3 (10·2–13·4)	11·9 (9·9–13·5)
Range	7·1–15·9	7·0–15·7	7·0–15·9
Sex			
Female	89 (54%)	81 (48%)	170 (51%)
Male	77 (46%)	87 (52%)	164 (49%)
Mechanism of injury			
Gymnastics	28 (17%)	27 (16%)	55 (16%)
Football (soccer)	20 (12%)	17 (10%)	37 (11%)
Rugby	4 (2%)	5 (3%)	9 (3%)
Other sporting injury	39 (23%)	54 (32%)	93 (28%)
Non-sporting injury	75 (45%)	65 (39%)	140 (42%)
Dislocation status			
Dislocated	39 (23%)	41 (24%)	80 (24%)
Not dislocated	127 (77%)	127 (76%)	254 (76%)
Side of injury			
Dominant arm	82 (49%)	89 (53%)	171 (51%)
Not dominant arm	84 (51%)	75 (45%)	159 (48%)
Unsure or ambidextrous	0	4 (2%)	4 (1%)

Table 1: **Baseline characteristics**

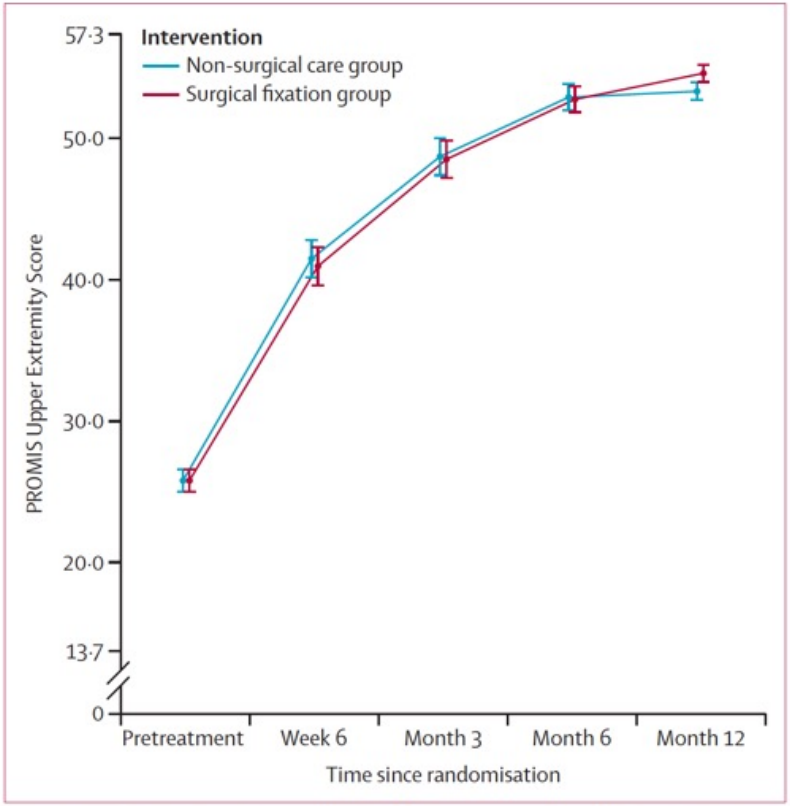


Figure 2: **PROMIS Upper Extremity Scale Scores at each trial timepoint in the non-surgical care and surgical fixation groups**

Data are PROMIS Upper Extremity Scale Scores (95% CI). Higher scores indicate better upper extremity function. PROMIS=Patient Report Outcomes Measurement System.

	Non-surgical care group (n=166)	Surgical fixation group (n=168)	Total (N=334)	Adjusted mean difference (95% CI)	p value
PROMIS*	..	..	..	1·57 (−0·01 to 3·14)	0·052
Mean (SD)	53·1 (7·8)	54·3 (5·7)	53·7 (6·8)	..	..
Median (IQR)	57·3 (50·4 to 57·3)	57·3 (50·9 to 57·3)	57·3 (50·9 to 57·3)	..	..
Range	21·4 to 57·3	35·3 to 57·3	21·4 to 57·3	..	..
Missing	31 (19%)	18 (11%)	49 (15%)	..	..
EQ-5D-3L Utility Score†	..	..	..	0·020 (−0·009 to 0·050)	0·18
Mean (SD)	0·925 (0·152)	0·944 (0·099)	0·935 (0·127)	..	..
Median (IQR)	1·000 (0·848 to 1·000)	1·000 (0·883 to 1·000)	1·000 (0·883 to 1·000)	..	..
Range	0·002 to 1·000	0·585 to 1·000	0·002 to 1·000	..	..
Missing	34 (20%)	21 (13%)	55 (16%)	..	..
EQ-5D VAS‡	..	..	..	1·17 (−1·98 to 4·33)	0·47
Mean (SD)	92·9 (12·7)	93·9 (7·9)	93·5 (10·5)	..	..
Median (IQR)	96·0 (90·8 to 100·0)	96·0 (90·0 to 100·0)	96·0 (90·0 to 100·0)	..	..
Range	4·0 to 100·0	54·0 to 100·0	4·0 to 100·0	..	..
Missing	34 (20%)	21 (13%)	55 (16%)	..	..
Wong-Baker FACES Pain Rating Scale§	..	..	..	−0·11 (−0·41 to 0·19)	0·48
Mean (SD)	0·7 (1·3)	0·7 (1·2)	0·7 (1·2)	..	..
Median (IQR)	0·0 (0·0 to 2·0)	0·0 (0·0 to 2·0)	0·0 (0·0 to 2·0)	..	..
Range	0·0 to 6·0	0·0 to 6·0	0·0 to 6·0	..	..
Missing	32 (19%)	18 (11%)	50 (15%)	..	..
DASH sports and performing arts¶	..	..	..	0·08 (−2·91 to 3·07)	0·96
Mean (SD)	3·3 (11·7)	4·1 (9·4)	3·8 (10·5)	..	..
Median (IQR)	0·0 (0·0 to 0·0)	0·0 (0·0 to 0·0)	0·0 (0·0 to 0·0)	..	..
Range	0·0 to 100·0	0·0 to 56·2	0·0 to 100·0	..	..
Missing	41/137 (30%)	27/137 (20%)	68/274 (25%)	..	..

PROMIS=Patient Report Outcomes Measurement Information System. VAS=Visual Analogue Score. DASH=disabilities of the arm, shoulder, and hand. *PROMIS Bank version 2.0 Upper Extremity Score for Children Computer Adaptive Test has a theoretical T-score range from 13·7 to 57·3, with higher scores indicating better upper-extremity function. †For EQ-5D-3L, higher scores indicate a higher health-related quality of life; UK EQ-5D-3L value sets were used for all participants. ‡VAS ranges from 0 to 100, with higher scores indicating better health. §Wong-Baker FACES Pain Rating Scale ranges from 0 (no pain) to 10 (worst pain). ¶DASH sports and performing arts module ranges from 0 to 100, with lower scores indicating better upper limb function. At baseline, 29 participants in the non-surgical care group and 31 in the surgical fixation group reported that they did not participate in sports or performing arts and were therefore ineligible for this questionnaire; accordingly, DASH analyses throughout the study are based on a slightly reduced number of participants.

Table 2: **Patient-reported outcomes at 12 months by treatment group**

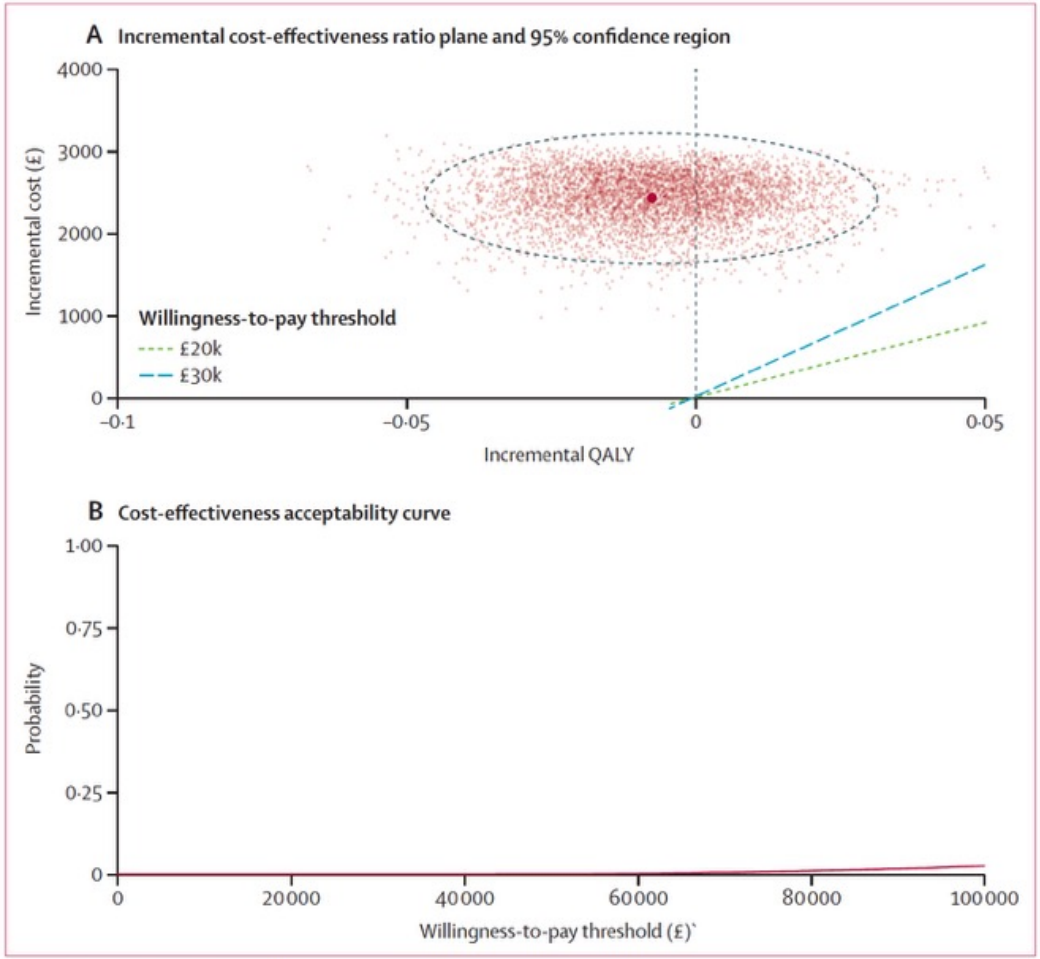


Figure 3: **Cost-effectiveness plane and cost-effectiveness acceptability curve**
The cost-effectiveness plane displays the distribution of incremental cost-effectiveness ratios from bootstrapped simulations comparing surgical fixation with non-surgical care. The cost-effectiveness acceptability curve shows the probability that surgical fixation is cost-effective across a range of willingness-to-pay thresholds, based on the proportion of simulations falling below each threshold.

Research in context

Evidence before this study

We searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) at the time of funding (May, 2017) and repeated the search iteratively during the trial, most recently on Dec 3, 2025, using combinations of the terms "medial epicondyle fracture", "children", "paediatric", "pediatric", "surgery", "operative", "non-operative", and "randomised trial", with Boolean operators and truncation as appropriate. These iterative searches identified only retrospective observational studies that added to the clinical uncertainty until one recent randomised controlled trial from Finland was identified, suggesting that non-surgical care was not inferior to surgical fixation at 12 months; however, uncertainty remained because of its limited sample size of 72 participants.

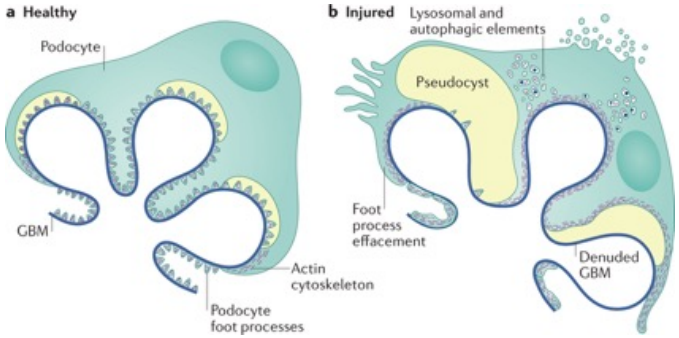
Added value of this study

SCIENCE is the first large, randomised, multicentre trial to address this clinical uncertainty. The trial found no evidence to support the superiority of surgical fixation across a range of outcomes, which included functional recovery, return to activity, and health-related quality of life, while introducing greater cost and more complications.

Implications of all the available evidence

The SCIENCE trial, in combination with the smaller previous trial, now provides clear evidence that routine surgical fixation for displaced medial epicondyle fractures in children offers no meaningful functional advantage over non-surgical care and is not cost-effective. These findings support a shift in routine practice towards non-surgical management as the default approach. The cost-effectiveness results are particularly relevant for health-care commissioners and service planners. This evidence should inform future guideline development and enable more informed conversations between clinicians, children, and their families about treatment choices.

Die Fokal-segmentale Glomerulosklerose (FSGS) ist eine seltene, chronische Nierenerkrankung, bei der es durch Vernarbung (Sklerose) bestimmter Nierenfilter (Glomeruli) zu Eiweißverlust im Urin, Wassereinlagerungen (Ödeme) und Funktionsverlust kommt. Die Therapie umfasst häufig immunsuppressive Medikamente (Kortikosteroide, Ciclosporin), Blutdrucksenker (ACE-Hemmer, AT1-Antagonisten) und Lebensstiländerungen. Sie kann in ein Nierenversagen münden.



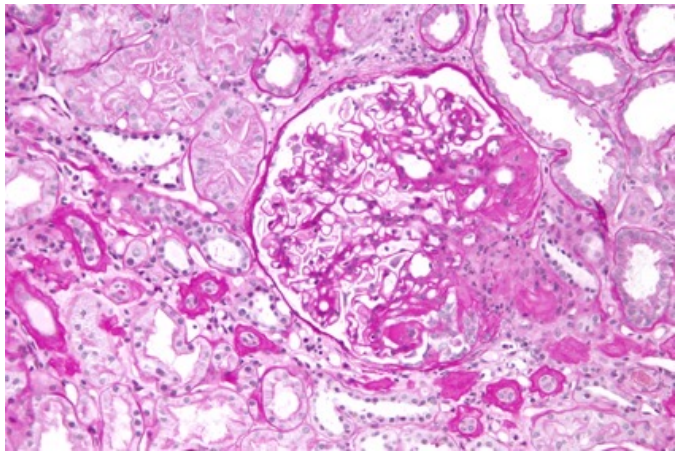
Behandlungen und Management der FSGS

Die Behandlung richtet sich nach der Ursache (primär/genetisch vs. sekundär) und dem Schweregrad.

- **Immunsuppression (insb. bei primärer FSGS):** Kortikosteroide (wie Prednison) sind häufig die erste Wahl. Bei Steroidresistenz können Wirkstoffe wie Ciclosporin oder Mycophenolat-Mofetil eingesetzt werden

.

- **Blutdruck- und Proteinuriekontrolle:** Einsatz von ACE-Hemmern oder AT1-Antagonisten (Sartane) zur Senkung des Blutdrucks und Reduzierung der Eiweißausscheidung.
- **Symptomatische Therapie:** Diuretika gegen Ödeme (Wassereinlagerungen).
- **Allgemeinmaßnahmen:** Eine gesunde Ernährung (mediterrane Diät), Gewichtskontrolle, Rauchstopp und eine salzarme Ernährung sind essenziell.
- **Nierenersatztherapie:** Bei Fortschreiten zum Nierenversagen sind Dialyse oder eine Nierentransplantation notwendig.



TRPC6 (Transient Receptor Potential Cation Channel Subfamily C Member 6) ist ein nicht-selektiver Kationenkanal, der primär Calcium (Ca2+) in Zellen leitet und durch Diacylglycerin (DAG) aktiviert wird. Er spielt eine entscheidende Rolle bei der Regulierung der Nierenfunktion (Schlitzmembran in Podozyten), dem Gefäßtonus und Entzündungsprozessen. Mutationen, die zu einer Überfunktion (Gain-of-function) führen, sind mit familiärer fokal-segmentaler Glomerulosklerose (FSGS) assoziiert.

Wichtige Aspekte von TRPC6 (mechanische Membranspannung):

•**Funktion:** TRPC6 ist an der Kalzium-Homöostase, Zellproliferation und -kontraktion beteiligt. Er wird durch Phospholipase-C-vermittelte Signalwege (DAG) aktiviert.

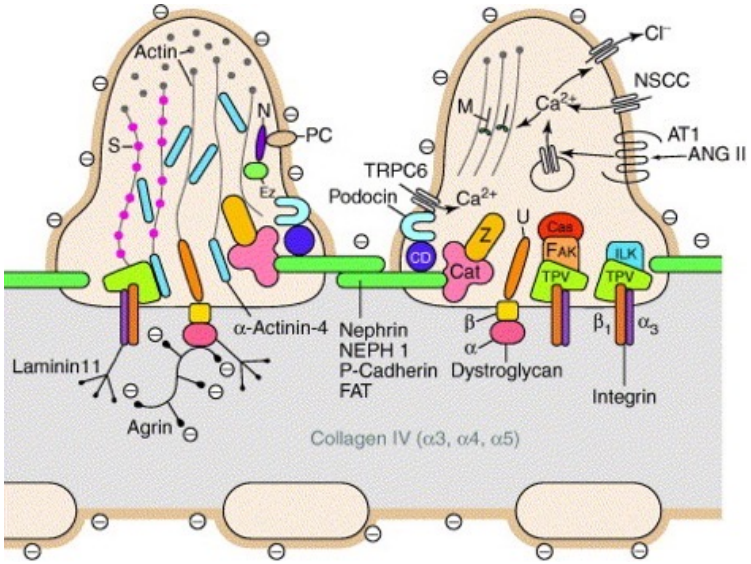
•**Lokalisation:**

Er ist in vielen Geweben, darunter Nierenglomeruli (Podozyten), der glatten Muskulatur und dem ZNS, zu finden

.

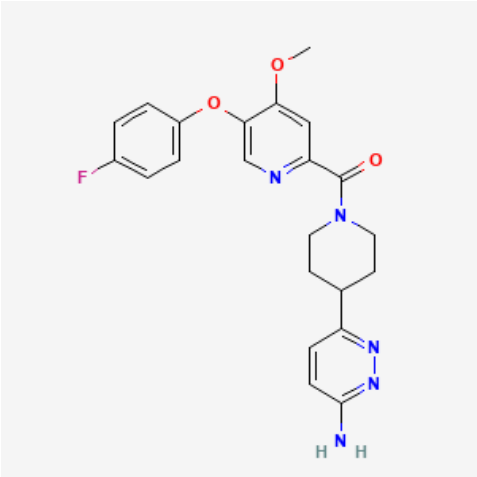
•**Pathophysiologie:** TRPC6-Mutationen oder Überexpression stehen im Zusammenhang mit Nierenerkrankungen (FSGS), pulmonaler Hypertonie und Lungenedemen.

•**Therapeutisches Potenzial:** Da Gain-of-function Mutationen die Nierenfiltrationsbarriere schädigen, sind TRPC6-Blocker Gegenstand der Forschung, um Proteinurie zu behandeln.



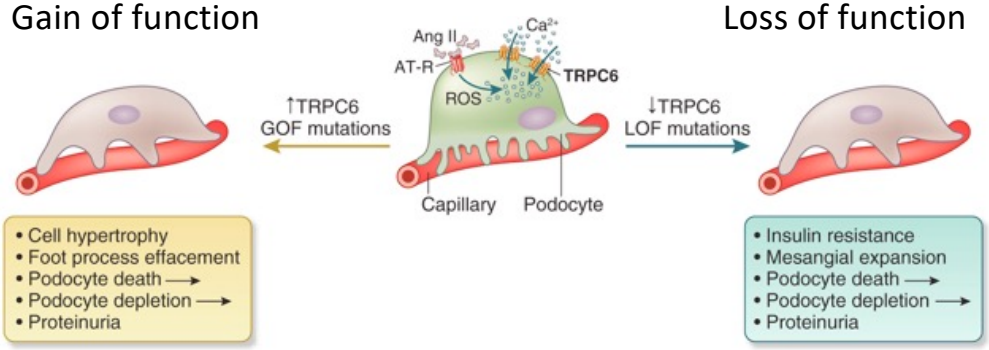
Mechanoreceptor TRPC6

"BI 764198" bezieht sich in erster Linie auf einen experimentellen **TRPC6-Inhibitor** von Boehringer Ingelheim, der als Medikament zur Behandlung bestimmter Nierenerkrankungen und COVID-19-Komplikationen untersucht wurde.



Gain of function

Loss of function



TRPC6 inhibition for the treatment of focal segmental glomerulosclerosis: a randomised, placebo-controlled, phase 2 trial of BI 764198

Summary

Background In focal segmental glomerulosclerosis (FSGS), transient receptor potential cation channel, subfamily C, member 6 (TRPC6) overactivity might cause podocyte loss and progressive kidney function decline. This exploratory study assessed the safety and efficacy of a novel once-daily oral selective TRPC6 inhibitor, BI 764198.

Methods This multicentre phase 2, double-blind, placebo-controlled, randomised controlled trial assessed BI 764198 (20 mg, 40 mg, or 80 mg once daily) versus placebo over 12 weeks in participants aged 18–75 years with biopsy-confirmed primary FSGS (based on the absence of clinical evidence of secondary cause) or with a disease-causing *TRPC6* variant. The study took place in 31 sites in ten countries, and random allocation was performed centrally in blocks in a 1:1:1:1 ratio and was stratified according to use of corticosteroids. Participants were receiving stable conservative and immunosuppressive therapy, with screening urine protein–creatinine ratio (UPCR) at 1·0 g/g or greater and estimated glomerular filtration rate at 30 mL/min per 1·73 m^2 or greater. The primary endpoint was the proportion of participants with proteinuria response (≥25% UPCR reduction from baseline) at week 12. Other key outcomes were safety and tolerability. The study was registered with ClinicalTrials.gov on Jan 27, 2022 (NCT05213624) and is complete as of Jan 3, 2025.

Findings From March 10, 2022, to Sept 3, 2024, 139 participants were screened and 67 were randomly assigned to receive placebo or BI 764198 at doses of 20 mg, 40 mg, or 80 mg (five participants were randomly assigned in error and were not treated). 62 participants received treatment, two of whom had missing baseline or post-baseline UPCR measurements and were not included in the full analysis set. Overall, 37 participants (60%) were male and 25 participants (40%) were female; the mean age was 40·7 years (SD 12·6); and the majority of the trial cohort were White (39 [63%] of 62). Proteinuria responses were observed in eight (44%) of 18, two (14%) of 14, and six (43%) of 14 participants receiving BI 764198 20 mg, 40 mg, and 80 mg, respectively (16 [35%] of 46 for all BI 764198 doses) versus one (7%) of 14 receiving placebo; corresponding odds ratios (ORs) versus placebo were OR 10·0 (95% CI 1·6–118·1), 1·5 (0·2–19·5), and 6·0 (0·9–73·6) for the three doses of BI 764198, and 4·9 (1·0–48·8) for all doses combined. BI 764198 was well tolerated with no meaningful differences in adverse event frequencies across treatment arms; treatment-emergent adverse events were reported by 44 (71%) of 62 participants, with similar frequencies of adverse events observed in the placebo group (ten [71%] of 14) and BI 764198 groups (34 [71%] of 48).

Interpretation BI 764198 lowered proteinuria and was well tolerated by participants in this trial. This is the first evidence of efficacy with a podocyte-targeted therapy in FSGS. Larger randomised controlled trials over longer treatment durations, enabling meaningful subgroup analyses, are planned to evaluate the safety and efficacy of BI 764198 treatment in FSGS and other conditions affected by podocytopathy.

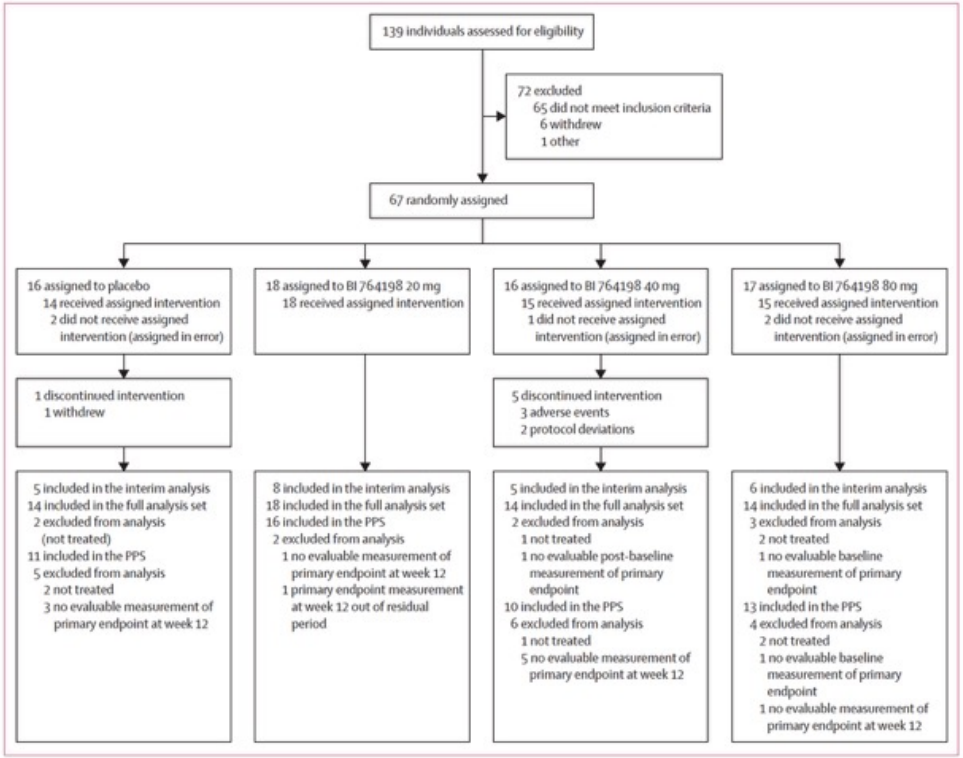


Figure 1: **Trial profile**
PPS=per-protocol analysis set.

Eligible participants were male or female, aged 18–75 years inclusive, with a BMI of 40 kg/m² or below, and urine protein–creatinine ratio (UPCR) of 1·0 g/g or greater. Participants were diagnosed with either primary FSGS via biopsy at any time before screening and without clinical findings indicative of secondary disease or genetic FSGS resulting from a *TRPC6* variant. Participants with monogenic FSGS (except for *TRPC6*), clinical or histological evidence of secondary FSGS, or both were excluded. Full eligibility criteria have been reported previously.[18] The trial enrolled both corticosteroid-naive participants and participants who had ever received, or who had current corticosteroid treatment; further information is included in the appendix (pp 9–10). Sex (male or female) and race and ethnicity data (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Multiple; and Hispanic or Latino or not Hispanic or Latino) were self-reported from a predefined list. Data on gender were not collected. Protocol deviations were reviewed including important deviations (eg, those affecting participant safety and well-being or data integrity), and participants were discontinued from treatment if the protocol deviation was deemed likely to affect their safety.

	Placebo (n=14)	BI 764198 20 mg (n=18)	BI 764198 40 mg (n=15)	BI 764198 80 mg (n=15)	All BI 764198 (n=48)
Age, years	42·2 (11·1)	41·2 (15·0)	39·8 (13·8)	39·8 (10·5)	40·3 (13·1)
Sex					
Male	7 (50%)	9 (50%)	8 (53%)	13 (87%)	30 (63%)
Female	7 (50%)	9 (50%)	7 (47%)	2 (13%)	18 (38%)
Race*					
American Indian or Alaska Native	0	0	0	1 (7%)	1 (2%)
Asian	4 (29%)	3 (17%)	3 (20%)	2 (13%)	8 (17%)
Black or African American	1 (7%)	2 (11%)	0	1 (7%)	3 (6%)
Native Hawaiian or other Pacific Islander	0	1 (6%)	0	1 (7%)	2 (4%)
White	9 (64%)	11 (61%)	10 (67%)	9 (60%)	30 (63%)
Multiple	0	1 (6%)	2 (13%)	1 (7%)	4 (8%)
Bodyweight, kg	76·5 (18·5)	78·6 (20·6)	78·0 (16·5)	83·8 (13·6)	80·0 (17·2)
BMI, kg/m²	26·6 (5·1)	27·0 (6·0)	27·1 (5·1)	27·7 (4·6)	27·3 (5·2)
FSGS disease duration					
Median duration, months (IQR)	24·0 (13·0–97·0)	23·0 (9·0–91·0)	12·0 (3·0–22·0)	27·0 (9·0–166·0)	17·5 (5·0–75·0)
<6 months	2 (14%)	4 (22%)	6 (40%)	2 (13%)	12 (25%)
6 months to <2 years	5 (36%)	6 (33%)	7 (47%)	5 (33%)	18 (38%)
≥2 years	7 (50%)	8 (44%)	2 (13%)	8 (53%)	18 (38%)
Diastolic blood pressure, mm Hg	81·4 (9·9)	75·9 (11·4)	80·1 (8·5)	79·8 (8·8)	78·4 (9·8)
Systolic blood pressure, mm Hg	123·1 (17·0)	121·4 (13·0)	123·2 (16·4)	127·9 (14·4)	124·0 (14·5)
Median eGFR in mL/min per 1·73 m²† (IQR)	45·5 (36·0–70·0)	72·0 (43·0–99·0)	66·0 (44·0–91·0)	46·0 (41·0–72·0)	57·0 (42·5–87·5)
24 h median UPCR, g/g, (IQR)‡	3·7 (2·1–6·0)	4·0 (1·9–6·1)	3·1 (1·3–4·8)	1·9 (1·8–2·8)§	2·8 (1·8–5·4)§
24 h UPCR <3·5 g/g‡	7 (50%)	9 (50%)	8 (53%)	12 (80%)§	29 (60%)§
24 h median (IQR) TPE, g/day‡	5·0 (3·4–7·4)	4· (2·7–6·8)	3·9 (2·0–8·0)	3·2 (2·4–4·2)§	3·9 (2·4–6·4)§
Median (IQR) serum albumin level, g/L	33·5 (30·0–38·0)	35·5 (32·0–39·0)	37·0 (27·0–42·0)	42·0 (38·0–44·0)	38·0 (32·0–4·0)
Immunosuppressive therapy					
Corticosteroid	5 (36%)	4 (22%)	4 (27%)	1 (7%)	9 (19%)
Other	0	3 (17%)¶	3 (20%)‖	0	6 (13%)
Conservative or SoC therapy					
ACE inhibitors or ARB	13 (93%)	11 (61%)	11 (73%)	15 (100%)	37 (77%)
SGLT2 inhibitors	8 (57%)	6 (33%)	6 (40%)	6 (40%)	18 (38%)
MRA	2 (14%)	1 (6%)	3 (20%)	2 (13%)	6 (13%)

Data presented are mean (SD) or n (%) unless otherwise indicated. Percentages might not total 100% owing to rounding. The treated set included all participants who received at least one dose of trial medication. ACE=angiotensin-converting enzyme. ARB=angiotensin receptor blocker. CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration. eGFR=estimated glomerular filtration rate. FSGS=focal segmental glomerulosclerosis. MRA=mineralocorticoid receptor antagonist. SoC=standard of care. TPE=total urinary protein excretion. UPCR=urine protein–creatinine ratio. *Participants who selected multiple race groups on the electronic case report form are summarised in the multiple row. †Screening values, derived from serum creatinine and cystatin C using the CKD-EPI formula. ‡Mean of two 24 h urine samples collected before visit 2. §Data were missing for one participant. ¶Mycophenolate mofetil (n=3). ‖Adalimumab (n=1), mycophenolate sodium (n=1), upadacitinib (n=1).

Table 1: **Participant demographics and disease characteristics at baseline by treatment group in the treated set**

	Placebo (n=14)	BI 764198 20 mg (n=18)	BI 764198 40 mg (n=14)	BI 764198 80 mg (n=14)	All BI 764198 (n=46)
24 h UPCR at baseline in g/g, median (IQR)	3·7 (2·1 to 6·0)	4·0 (1·9 to 6·1)	3·1 (1·3 to 4·8)	1·9 (1·8 to 2·8)	2·8 (1·8 to 5·4)
24 h TPE at baseline in g/day, median (IQR)	5·0 (3·4 to 7·4)	4·2 (2·7 to 6·8)	3·9 (2·0 to 8·0)	3·2 (2·4 to 4·2)	3·9 (2·4 to 6·4)
Primary endpoint					
Participants with ≥25% reduction from baseline 24 h UPCR at week 12, n (%)	1 (7%)	8 (44%)	2 (14%)	6 (43%)	16 (35%)
Predicted probability of ≥25% reduction from baseline in 24 h UPCR at week 12, % (95% CI)*	11% (−2 to 25)	49% (29 to 69)	16% (−2 to 34)	39% (12 to 65)	35% (22 to 49)
UPCR response with BI 764198 versus placebo, odds ratio (95% CI)	Ref	10·0 (1·6 to 118·1)	1·5 (0·2 to 19·5)	6·0 (0·9 to 73·6)	4·9 (1·0 to 48·8)
Placebo-corrected percentage change from baseline at week 12 in 24 h UPCR, % (95% CI)	Ref	−40% (−56 to −17)	−5% (−33 to 36)	−23% (−46 to 9)	−27% (−45 to −1)
Absolute change from baseline at week 12 in 24 h UPCR in g/g, median (IQR) [n]	0·1 (−0·9 to 0·6) [11]	−0·8 (−1·3 to −0·2) [16]	0·3 (−0·3 to 1·0) [10]	−0·4 (−0·7 to 0·1) [13]	−0·4 (−0·9 to 0·2) [39]
Secondary endpoints					
Placebo-corrected percentage change from visit 3 to week 12 in 24 h UPCR, % (95% CI)	Ref	−31% (−51 to −3)	4% (−28 to 51)	−26% (−49 to 7)	−20% (−42 to 9)
Absolute change in 24 h UPCR relative to visit 3 at week 12 in g/g, median (IQR) [n]	0·1 (−0·5 to 0·5) [10]	0·0 (−0·8 to 0·7) [15]	0·7 (−0·2 to 0·9) [10]	−0·4 (−0·8 to 0·2) [12]	−0·1 (−0·7 to 0·7) [35]
Placebo-corrected percentage change from baseline to week 13 in 24 h UPCR, % (95% CI)	Ref	−31% (−50 to −6)	−25% (−46 to 4)	−28% (−50 to 2)	−29% (−45 to −7)
Absolute change in 24 h UPCR relative to baseline at week 13 in g/g, median (IQR) [n]	0·1 (−0·4 to 1·5) [13]	−0·5 (−0·8 to 0·5) [17]	−0·2 (−0·7 to 0·8) [13]	−0·3 (−0·6 to 0·4) [12]	−0·3 (−0·7 to 0·6) [42]
Absolute change in 24 h TPE relative to baseline at week 12 in g/g, median (IQR) [n]	0·1 (−0·8 to 1·8) [11]	−0·5 (−1·6 to −0·1) [16]	−0·4 (−1·1 to 0·6) [10]	−0·9 (−1·0 to 0·1) [13]	−0·6 (−1·3 to 0·2) [39]
Other clinical endpoints					
Absolute change in serum cystatin C relative to baseline at week 12 in mg/L, median (IQR) [n]†	0·00 (−0·04 to 0·08) [12]	−0·02 (−0·04 to 0·03) [18]	0·05 (−0·11 to 0·09) [10]	0·03 (−0·05 to 0·09) [14]	−0·01 (−0·07 to 0·08) [42]
Absolute change in eGFR based on serum cystatin C relative to baseline at week 12 in mL/min per 1·73 m^2, median (IQR) [n]	0·0 (−2·5 to 1·5) [12]	0·0 (−2·0 to 5·0) [18]	−5·0 (−10·0 to 6·0) [10]	−1·5 (−5·0 to 2·0) [14]	0·0 (−5·0 to 5·0) [42]
Absolute change in systolic blood pressure relative to baseline at week 12 in mm Hg, mean (SD) [n]‡	−0·3 (14·6) [13]	2·1 (12·1) [18]	0·6 (7·9) [10]	−4·7 (9·9) [15]	−0·6 (10·7) [43]
Absolute change in diastolic blood pressure relative to baseline at week 12 in mm Hg, mean (SD) [n]‡	1·2 (6·8) [13]	3·2 (10·4) [18]	−2·6 (4·7) [10]	−4·5 (10·9) [15]	−0·8 (10·0) [43]

The full analysis set included all patients who were randomly allocated and treated with trial medication and had evaluable measurements of UPCR at baseline and at least one UPCR measurement after the first dose; patients with missing values at week 12 were counted as non-responders. The treated set included all participants who received at least one dose of trial medication. Placebo-corrected percent change data are based on estimates from ANCOVA with corticosteroid use at random allocation and 24 h UPCR at baseline as covariates. eGFR=estimated glomerular filtration rate. TPE=total urinary protein excretion. UPCR=urinary protein–creatinine ratio. *Logistic regression. Corticosteroid use at random allocation and 24 h UPCR at baseline were used as covariates. †Data are provided to 2 decimal places in accordance with clinical practice. ‡Data are presented for the treated set.

***Table 2*: Primary, secondary, and other clinical endpoints of interest in the full analysis set**

Number of responders

Placebo corrected change from baseline

Number of responders

Change in 24 h UPCr

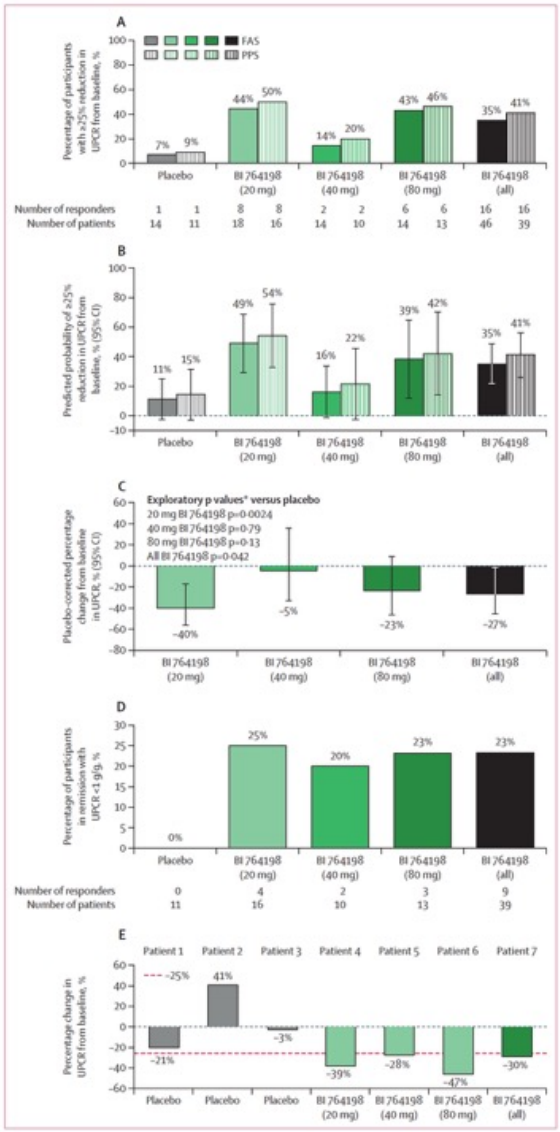


***Figure 2*: 24 h UPCR responses at week 12 relative to baseline by treatment group and in participants with confirmed *TRPC6* variants**

(A) Observed proportion of participants with ≥25% reduction in UPCR from baseline (FAS and PPS). (B) Predicted probability of ≥25% reduction in UPCR from baseline using a logistic regression analysis (FAS and PPS). (C) Placebo-corrected change from baseline in UPCR (FAS)*. (D) Proportion of participants achieving a UPCR of <1 g/g (PPS). (E) Change in 24 h UPCR from baseline at week 12 in participants with confirmed *TRPC6* variants† (PPS). The FAS included all participants who were randomly allocated and treated with evaluable measurements of UPCR at baseline and at least one UPCR measurement after the first dose; participants with missing values at week 12 were counted as non-responders. The PPS included all participants who were randomly allocated and completed treatment with evaluable measurements of the primary endpoint at both baseline and the end-of-treatment visits. FAS=full analysis set. PPS=per-protocol analysis set. *TRPC6*=transient receptor potential cation channel, subfamily C, member 6 . UPCR=urine protein–creatinine ratio. *All exploratory p values are unadjusted and nominal. †One participant with confirmed *TRPC6* variant had no evaluable 24 h UPCR data at baseline and two participants had missing data at week 12 and were omitted from the analysis.

	Placebo (n=14)	BI 764198 20 mg (n=18)	BI 764198 40 mg (n=15)	BI 764198 80 mg (n=15)	All BI 764198 (n=48)
Overall					
Any adverse event	10 (71%)	14 (78%)	10 (67%)	10 (67%)	34 (71%)
Any severe adverse event*	0	2 (11%)	0	0	2 (4%)
Any serious adverse event†	1 (7%)	3 (17%)	0	1 (7%)	4 (8%)
Any treatment-related adverse event‡	3 (21%)	4 (22%)	4 (27%)	2 (13%)	10 (21%)
Leading to study drug discontinuation	0	0	3 (20%)	0	3 (6%)
Deaths	0	0	0	0	0
AESIs (potentially severe DILI)	0	0	0	0	0
Frequently occurring adverse events§ (overall incidence ≥5% of all treated participants)					
Headache	2 (14%)	3 (17%)	2 (13%)	1 (7%)	6 (13%)
Peripheral oedema or oedema	1 (7%)	1 (6%)	1 (7%)	2 (13%)	4 (8%)
Hypertension or increased blood pressure	1 (7%)	1 (6%)	1 (7%)	2 (13%)	4 (8%)
Fatigue	1 (7%)	0	3 (20%)	0	3 (6%)
Nausea	2 (14%)	2 (11%)	0	0	2 (4%)
Arthralgia	2 (14%)	0	2 (13%)	0	2 (4%)
Other relevant adverse events of interest					
Liver enzyme abnormal	1 (7%)	1 (6%)¶	0	0	1 (2%)
ECG QT prolonged	0	0	0	1 (7%)‖	1 (2%)
Lens disorders	0	1 (6%)**	0	0	1 (2%)

The treated set included all participants who received at least one dose of trial medication. AESI=adverse event of special interest. DILI=drug-induced liver injury. ECG=electrocardiogram. MedDRA=Medical Dictionary for Regulatory Activities. QTcF=QT interval corrected by Fridericia formula. *Severe adverse events were defined as incapacitating or causing inability to work or to perform usual activities. †Serious adverse events were defined as life-threatening, requiring hospitalisation or prolongation of hospitalisation, resulting in persistent or significant disability or incapacity, congenital anomalies, resulting in death, or deemed serious for any other reason. ‡As per investigator judgement. §By preferred term according to MedDRA. ¶One event of hepatic enzyme increased that was mild, considered drug-related, and did not result in treatment discontinuation. ‖One participant experienced a 23 ms increase from baseline of QTcF, which was reported as an adverse event of mild intensity, was considered drug-related, and did not result in treatment discontinuation. **One event of lenticular opacities that was non-serious, mild, and not considered related to the study drug.

Table 3: **Summary of adverse events by treatment group in the treated set**

Research in context

Evidence before this study

Focal segmental glomerulosclerosis (FSGS) is a glomerulopathy caused by a wide range of insults that alter the structure and function of podocytes and is classified as a podocytopathy. The prognosis for people with FSGS has improved over time; however, the adverse outcomes of FSGS on kidney survival are severe and there is an urgent need to develop innovative therapies that are safe and effective. Previous clinical trials in FSGS have evaluated non-specific renoprotective agents, including a dual angiotensin II type 1 and endothelin type A receptor antagonist. Altered activity of transient receptor potential cation channel, subfamily C, member 6 (TRPC6) in podocytes has been implicated in the initiation and progression of FSGS. Modulation of TRPC6 might therefore be a novel mechanism to preserve podocyte function and survival in FSGS. To identify existing publications on the topic, we searched PubMed from database inception until July 29, 2025, using the search terms ("glomerulosclerosis" OR "podocytopathies") AND ("podocyte-targeted" OR "podocyte-protective"), with no language restrictions. We identified 19 articles: 12 preclinical studies, five review articles or editorials, and two related to methodology or the pathophysiology of FSGS without testing an intervention. Preliminary data for BI 764198, a novel, potent, oral, selective TRPC6 inhibitor, have been reported. Across five phase 1 studies, BI 764198 was well tolerated in healthy volunteers and in participants with kidney impairment at single and multiple rising doses up to 240 mg. BI 764198 resulted in a reversible increase in serum creatinine, with no increase in cystatin C concentration, indicating no adverse effect on kidney function.

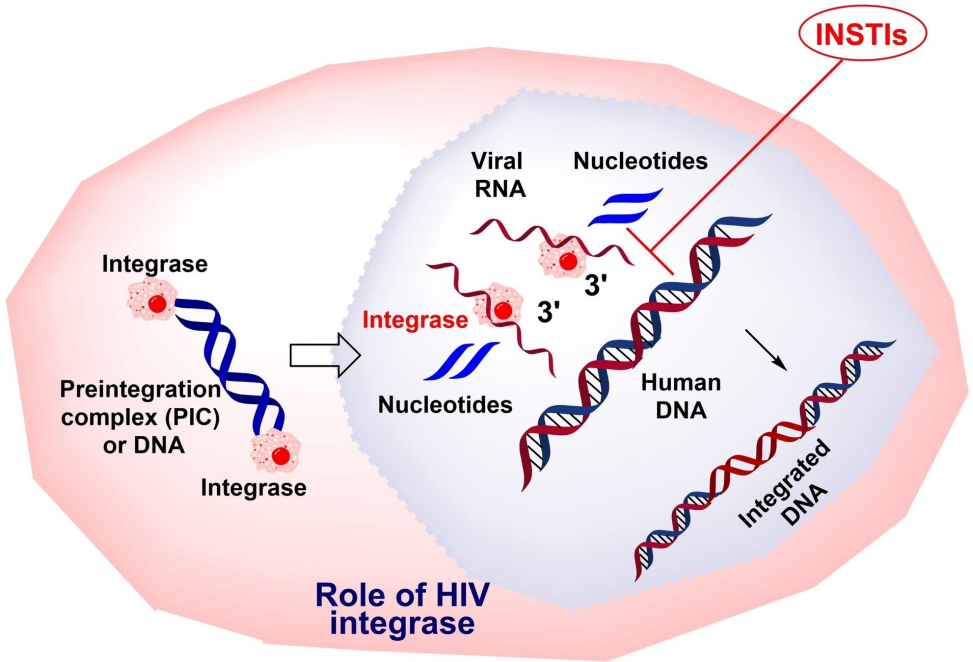
Added value of this study

To our knowledge, this exploratory phase 2 trial represents the first attempt to assess a podocyte-targeted therapeutic agent for the treatment of FSGS. We assessed the efficacy and safety of once-daily BI 764198 in 62 people with primary FSGS (based on absence of clinical evidence of secondary cause) or genetic FSGS resulting from a *TRPC6* variant over a 12-week treatment period. BI 764198 was well tolerated, with a similar incidence of adverse events compared with placebo. Despite a short treatment duration, this trial showed that treatment with BI 764198 resulted in a clinically relevant reduction of proteinuria in FSGS. Notably, 35% of participants receiving BI 764198 (all doses) achieved a proteinuria response (≥25% reduction in 24 h urine protein–creatinine ratio [UPCR] from baseline) compared with 7% of participants receiving placebo. The greatest and clinically important placebo-corrected mean reduction in proteinuria was achieved with the 20 mg dose: −40% (unadjusted nominal p=0·0024). Of note, the efficacy of the drug in terms of proteinuria response was consistent in FSGS resulting from *TRPC6* variants, with responses achieved in four participants receiving BI 764198 treatment versus none receiving placebo. The key value of this study, demonstrating the first evidence of efficacy and safety of a podocyte-targeted therapeutic agent, is to pave the way forward for the continued development of BI 764198 in FSGS and other conditions impacted by podocytopathy.

Implications of all the available evidence

This exploratory trial provides the first evidence to support a treatment benefit in patients with FSGS using a novel targeted therapy to modulate TRPC6 activity in podocytes. BI 764198 reduced proteinuria both in patients with primary FSGS and in patients with genetic *TRPC6*-related FSGS compared with placebo. The findings support the conduct of a phase 3 trial in a comparable FSGS population to evaluate clinical outcomes over a more extended treatment period.

Integrase-Strangtransfer-Inhibitoren (INSTIs) sind hochwirksame antiretrovirale Medikamente der ersten Wahl zur Behandlung von HIV-1, die das Enzym Integrase blockieren und so den Einbau viraler DNA in das Wirtsgenom verhindern. Wichtige Wirkstoffe sind Dolutegravir, Bictegravir, Raltegravir und Cabotegravir, die sich durch hohe Wirksamkeit, gute Verträglichkeit und eine hohe Barriere gegen Resistenzen auszeichnen.



Doravirine und **Islatravir** bilden eine experimentelle, einmal täglich einzunehmende **Zwei-Medikamenten-Kombination** zur Behandlung von HIV-1.

Der aktuelle Stand (Februar 2026)

- **Zulassungsstatus:** Die US-Zulassungsbehörde **FDA** prüft derzeit den Zulassungsantrag (NDA) für dieses Regime. Das Zieldatum für eine Entscheidung (**PDUFA-Datum**) ist der **28.April 2026**.

- **Wirkmechanismus:** Die Kombination nutzt zwei unterschiedliche Wirkstoffklassen:
  - **Doravirine (100 mg):** Ein bereits zugelassener Nicht-nukleosidischer Reverse-Transkriptase-Inhibitor (**NNRTI**).
  - **Islatravir (0,25 mg):** Der erste Wirkstoff einer neuen Klasse, den nukleosidischen Reverse-Transkriptase-Translokations-Inhibitoren (**NRTTIs**).

Switch to fixed-dose doravirine (100 mg) and islatravir (0·25 mg) once daily in virologically suppressed adults with HIV-1 on oral antiretroviral therapy: 48-week results of a phase 3, multicentre, randomised, open-label, non-inferiority trial

Summary

Background Doravirine and islatravir is an investigational, once-daily, single-tablet regimen containing two potent antiretrovirals with complementary mechanisms of action and resistance profiles. We aimed to evaluate the efficacy and safety of switching from stable, oral antiretroviral therapy (ART) to the fixed combination of doravirine (100 mg) and islatravir (0·25 mg) in virologically suppressed adults living with HIV-1.

Methods This phase 3, randomised, active-controlled, open-label, non-inferiority trial was conducted at 53 research, community, and hospital-based clinics in eight countries: Australia, Canada, Colombia, Japan, South Africa, Switzerland, the UK, and the USA. Adults (aged ≥18 years) with a viral load of fewer than 50 copies of HIV-1 RNA per mL on any oral, two-drug or three-drug ART regimen for at least 3 months, with no history of treatment failure, known resistance to doravirine, or active hepatitis B infection, were randomly assigned (2:1) according to a computer-generated randomisation schedule (block size three) to receive oral doravirine (100 mg) and islatravir (0·25 mg) once daily or to continue baseline ART for 48 weeks. Randomisation was stratified by the anchor antiretroviral drug class (integrase strand-transfer inhibitor [INSTI], non-nucleoside reverse transcriptase inhibitor, or protease inhibitor) in the baseline regimen. The primary endpoint (assessed in all treated participants) was the percentage of participants with a viral load of 50 copies per mL or higher at week 48 (analysed according to the US Food and Drug Administration snapshot approach); non-inferiority would be concluded if the upper bound of the multiplicity-adjusted 95% CI for the treatment difference was less than 4%. The safety analysis population included all randomly assigned participants who received at least one dose of study treatment. The trial is registered at ClinicalTrials.gov, NCT05631093, and is ongoing but closed to enrolment.

Der Begriff „INSTI“ bezieht sich im medizinischen Kontext auf Integrase-Strangtransfer-Inhibitoren, eine Klasse von antiretroviralen Medikamenten zur Behandlung von HIV. INSTI-Medikamente blockieren das Enzym, das HIV benötigt, um seine virale DNA in die Wirtszelle zu integrieren.

Findings Between Feb 20 and Oct 24, 2023, 614 individuals were screened for eligibility, of whom 553 were randomly assigned to receive doravirine and islatravir (n=368) or baseline ART (n=185). 551 participants received at least one dose of allocated medication: 366 in the doravirine and islatravir group and 185 in the baseline ART group. Of these 551 participants, 332 (60%) were assigned male and 219 (40%) were assigned female at birth, and the median age was 51 years (IQR 41–59); 250 (45%) identified as Black or African American and 80 (15%) identified as Hispanic, Latino, or Latina. Doravirine and islatravir showed non-inferiority at week 48, with viral loads of 50 copies per mL or higher in five (1·4%) of 366 participants versus nine (4·9%) of 185 participants on baseline ART (difference –3·6% [multiplicity-adjusted 95% CI –7·8 to –0·8]). Treatment-related adverse events were more common with doravirine and islatravir (44 [12·0%] of 366 participants) than with baseline ART (nine [4·9%] of 185 participants; difference 7·2 [95% CI 2·2 to 11·6]). Rates were similar in the doravirine and islatravir group and the baseline ART group for any adverse event (79·5% [291 of 366 participants] *vs* 83·8% [155 of 185 participants]; difference –4·3 [–10·7 to 2·8]), serious adverse events (6·3% [23] *vs* 4·9% [nine]; 1·4 [–3·2 to 5·2]), and discontinuation due to adverse events (0·5% [two] *vs* 2·2% [four]; –1·6 [–4·9 to 0·2]). One death occurred (in the baseline ART group) and was not considered treatment-related. No participants discontinued treatment as a result of protocol-specified declines in CD4 cell or total lymphocyte counts.

Interpretation Doravirine and islatravir is efficacious and well tolerated and would represent the first non-INSTI-based, two-drug regimen for HIV-1 treatment. With increasing concern over the potential development of widespread INSTI resistance, this once-daily, oral, single-tablet regimen could be a potential option for people living with HIV-1 requiring a change to their antiretroviral regimen. The safety and efficacy findings support the ongoing development of islatravir, a drug with long-acting potential.

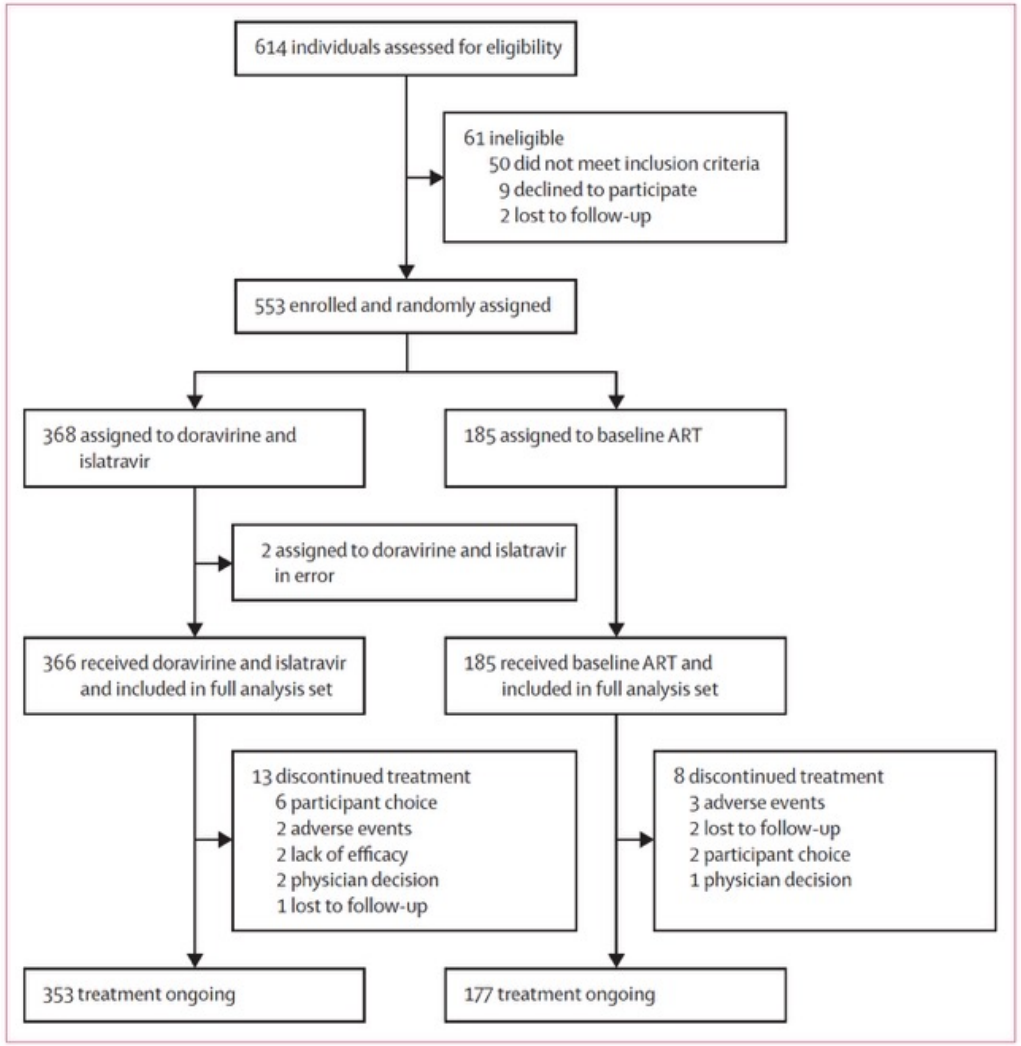


Figure 1: **Trial profile**
ART=antiretroviral therapy.

	Doravirine and islatravir (n=366)	Baseline ART (n=185)
Age, years	51 (41–59)	51 (42–59)
18–49	164 (45%)	86 (46%)
50–64	160 (44%)	85 (46%)
≥65	42 (11%)	14 (8%)
Sex assigned at birth		
Male	214 (58%)	118 (64%)
Female	152 (42%)	67 (36%)
Race		
Black or African American	166 (45%)	84 (45%)
White	141 (39%)	74 (40%)
Asian	18 (5%)	10 (5%)
Other	41 (11%)	17 (9%)
Hispanic, Latino, or Latina ethnicity	54 (15%)	26 (14%)
Region		
North America	126 (34%)	46 (25%)
Europe	83 (23%)	49 (26%)
South America	29 (8%)	12 (6%)
Asia and Pacific Islands	27 (7%)	20 (11%)
Africa	101 (28%)	58 (31%)
BMI, kg/m²	28·0 (24·2–32·1)	27·3 (23·8–31·2)
Anti-HBc-positive at screening	106 (29%)	54 (29%)
CD4 count, cells per μL	697 (525–922)	725 (566–918)
≥500	287 (78%)	154 (83%)
≥350 to <500	45 (12%)	19 (10%)
≥200 to <350	32 (9%)	9 (5%)
<200	2 (1%)	3 (2%)
Time since HIV-1 diagnosis, years	13·3 (7·7–21·2)	13·3 (6·8–19·1)
Time on baseline ART, years	3·7 (2·0–6·3)	3·8 (2·1–6·3)
≥12 months	335 (92%)	172 (93%)
Baseline ART		
INSTI-based regimens (without protease inhibitors)	233 (64%)	121 (65%)
NNRTI-based regimens (non-protease inhibitor, non-INSTI)	111 (30%)	56 (30%)
Protease-inhibitor-based regimens (including with INSTIs)	22 (6%)	8 (4%)

Data are median (IQR) or n (%). Percentages might not total 100 owing to rounding. ART=antiretroviral therapy. INSTI=integrase strand-transfer inhibitor. NNRTI=non-nucleoside reverse transcriptase inhibitor.

Table 1: **Baseline demographic and clinical characteristics of the full analysis set**

	Doravirine and islatravir	Baseline ART	Treatment difference (95% CI)
Full analysis set			
Number of participants	366	185	..
Viral load of HIV-1 RNA ≥50 copies per mL	5 (1·4%)	9 (4·9%)	−3·6 (−7·8 to −0·8)
Viral load ≥50 copies per mL in week 48 window	2 (0·5%)	0	..
Discontinued owing to lack of efficacy	0	1 (0·5%)	..
Discontinued for other reasons and last viral load measurement ≥50 copies per mL	3 (0·8%)	8 (4·3%)	..
Viral load <50 copies per mL	350 (95·6%)	170 (91·9%)	3·8 (−0·3 to 8·9)
No virological data in week-48 window	11 (3·0%)	6 (3·2%)	..
Discontinued owing to adverse event or death and last viral load measurement <50 copies per mL	2 (0·5%)	2 (1·1%)	..
Discontinued for other reasons and last viral load measurement <50 copies per mL	7 (1·9%)	3 (1·6%)	..
On study treatment but missing data in window	2 (0·5%)	1 (0·5%)	..
Viral load <200 copies per mL	350 (95·6%)	177 (95·7%)	−0·1 (−3·5 to 4·2)
Mean change in CD4 count (cells per µL) from baseline (95% CI)*	5·4 (−12·1 to 22·9)	18·2 (−11·8 to 48·3)	−15·4 (−46·3 to 15·5)
Per-protocol population			
Number of participants	328	170	..
Viral load ≥50 copies per mL	5 (1·5%)	7 (4·1%)	−2·6 (−6·9 to 0·2)
Viral load <50 copies per mL	317 (96·6%)	159 (93·5%)	3·2 (−0·6 to 8·2)
Viral load <200 copies per mL	317 (96·6%)	165 (97·1%)	−0·4 (−3·5 to 3·6)

Data are n or n (%) unless otherwise stated. Virological endpoints were assessed according to the US Food and Drug Administration snapshot approach.[22] ART=antiretroviral therapy. *n=352 for the doravirine and islatravir group and n=178 for the baseline ART group.

Table 2: **Efficacy outcomes at week 48**

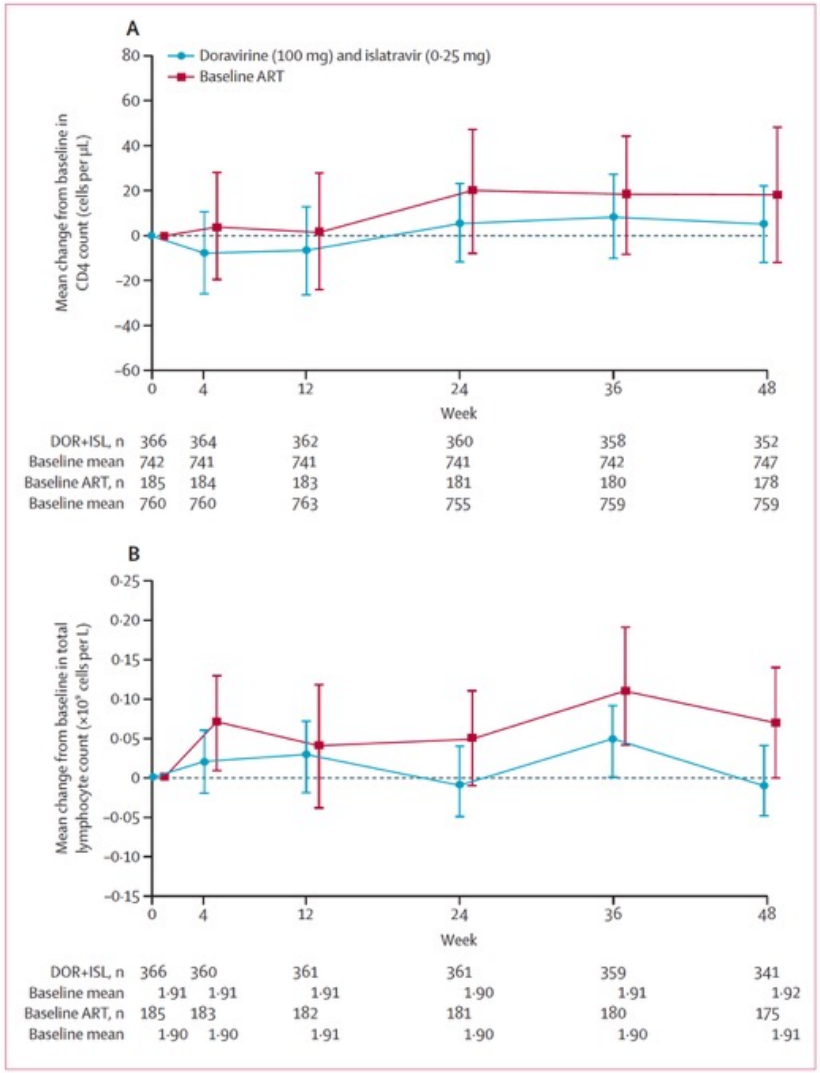


Figure 2: **Mean change in CD4 cell count (A) and total lymphocyte count (B) from baseline to week 48**
Error bars represent the within-group 95% CI. ART=antiretroviral therapy. DOR+ISL=doravirine and islatravir.

	Doravirine and islatravir (n=366)	Baseline ART (n=185)	Treatment difference (95% CI)
Any adverse event	291 (79·5%)	155 (83·8%)	−4·3 (−10·7 to 2·8)
Most common adverse events (≥5% in either group)			
Diarrhoea	29 (7·9%)	3 (1·6%)	6·3 (2·6 to 9·8)
COVID-19	14 (3·8%)	10 (5·4%)	−1·6 (−6·1 to 1·9)
Nasopharyngitis	20 (5·5%)	12 (6·5%)	−1·0 (−5·9 to 2·9)
Upper respiratory tract infection	38 (10·4%)	25 (13·5%)	−3·1 (−9·5 to 2·4)
Arthralgia	16 (4·4%)	14 (7·6%)	−3·2 (−8·2 to 0·8)
Back pain	18 (4·9%)	10 (5·4%)	−0·5 (−5·1 to 3·2)
Headache	19 (5·2%)	14 (7·6%)	−2·4 (−7·5 to 1·7)
Treatment-related* adverse events	44 (12·0%)	9 (4·9%)	7·2 (2·2 to 11·6)
Most common treatment-related* adverse events (≥1% in either group)			
Abdominal distension	6 (1·6%)	0	1·6 (−0·4 to 3·5)
Diarrhoea	12 (3·3%)	0	3·3 (1·2 to 5·6)
Fatigue	7 (1·9%)	1 (0·5%)	1·4 (−1·2 to 3·5)
Increased weight	6 (1·6%)	0	1·6 (−0·4 to 3·5)
Dizziness	7 (1·9%)	1 (0·5%)	1·4 (−1·2 to 3·5)
Headache	6 (1·6%)	2 (1·1%)	0·6 (−2·3 to 2·6)
Grade 3 or 4 adverse events	39 (10·7%)	18 (9·7%)	0·9 (−4·9 to 6·0)
Treatment-related* grade 3 or 4 adverse events	1 (0·3%)	1 (0·5%)	−0·3 (−2·7 to 1·1)
Serious adverse events	23 (6·3%)	9 (4·9%)	1·4 (−3·2 to 5·2)
Treatment-related* serious adverse events	0	1 (0·5%)	−0·5 (−3·0 to 0·5)
Deaths	0	1 (0·5%)	−0·5 (−3·0 to 0·5)
Due to treatment-related* adverse event	0	0	0·0 (−2·0 to 1·0)
Discontinuation due to adverse events	2 (0·5%)	4 (2·2%)	−1·6 (−4·9 to 0·2)
Due to treatment-related* adverse events	1 (0·3%)	2 (1·1%)	−0·8 (−3·6 to 0·6)
Due to serious adverse events	0	2 (1·1%)	−1·1 (−3·9 to 0·0)
Due to treatment-related* serious adverse events	0	1 (0·5%)	−0·5 (−3·0 to 0·5)
Events of clinical interest (potential drug-induced liver injury†)	0	0	0·0 (−2·0 to 1·0)

Data are n (%) unless otherwise indicated. ART=antiretroviral therapy. ULN=upper limit of normal. *Assessed by the investigator to be related to study medication. †Defined as aspartate aminotransferase or alanine aminotransferase concentration ≥3 × ULN, total bilirubin concentration ≥2 × ULN, and alkaline phosphatase concentration <2 × ULN.

Table 3: **Summary of adverse events to week 48 in the safety population**

	Doravirine and islatravir	Baseline ART	Treatment difference (95% CI)	p value
Protease-inhibitor-based regimens (n=10 doravirine and islatravir; n=4 baseline ART)				
LDL cholesterol	−7·1 (−27·1 to 12·9)	−2·8 (−9·9 to 4·4)	−2·2 (−24·9 to 20·5)	0·83
Non-HDL cholesterol	−11·8 (−32·0 to 8·4)	−2·8 (−10·9 to 5·4)	−7·0 (−29·8 to 15·8)	ND
NNRTI-based regimens (n=69 doravirine and islatravir; n=41 baseline ART)				
LDL cholesterol	5·1 (−0·8 to 10·9)	0·3 (−5·9 to 6·5)	3·4 (−5·1 to 12·0)	0·43
Non-HDL cholesterol	5·8 (−0·4 to 12·0)	0·4 (−6·5 to 7·4)	4·0 (−5·2 to 13·2)	ND
INSTI-based regimens (n=156 doravirine and islatravir; n=84 baseline ART)				
LDL cholesterol	2·5 (−0·7 to 5·6)	−0·4 (−5·0 to 4·3)	3·7 (−1·5 to 9·0)	0·16
Non-HDL cholesterol	3·6 (0·1 to 7·1)	3·3 (−5·9 to 12·4)	1·0 (−6·8 to 8·9)	ND

Data are mean (95% CI) unless otherwise indicated. ART=antiretroviral therapy. INSTI=integrase strand-transfer inhibitor. ND=not determined. NNRTI=non-nucleoside reverse transcriptase inhibitor.

Table 4: **Change in fasting LDL cholesterol and non-HDL cholesterol concentrations (mg/dL) from baseline to week 48 in the safety population, excluding participants on lipid-lowering therapy**

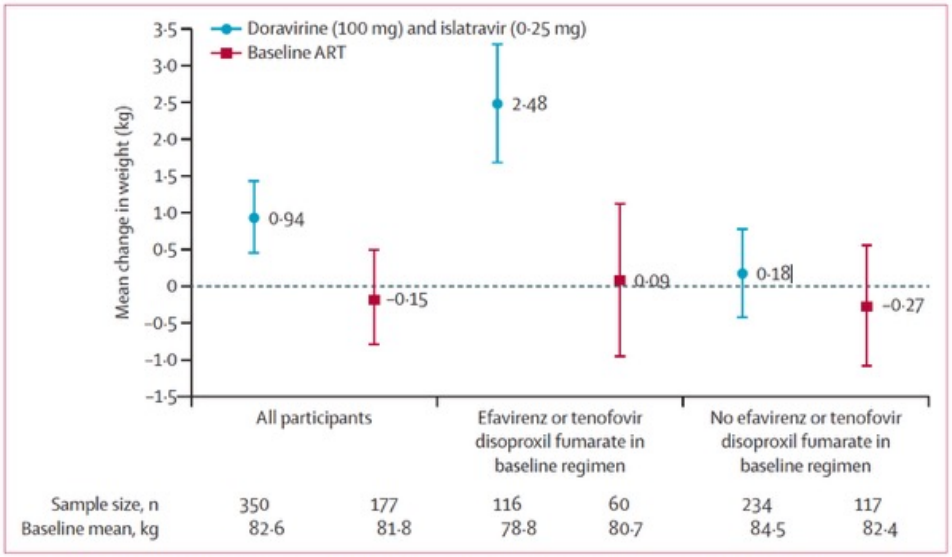


Figure 3: **Mean change in weight from baseline at week 48, overall and by baseline ART subgroup**
Error bars are 95% CI. ART=antiretroviral therapy.

Research in context

Evidence before this study

People living with HIV-1 currently require lifelong antiretroviral therapy (ART). Two-drug or three-drug regimens based on integrase strand-transfer inhibitors (INSTIs) are the current standard of care in first-line and maintenance therapy. However, two-drug regimens form the basis of the HIV development pipeline and currently there are no non-INSTI-based two-drug therapies. The combination of doravirine (an approved non-nucleoside reverse transcriptase inhibitor [NNRTI]) and islatravir (an investigational nucleoside reverse transcriptase translocation inhibitor) is the first non-INSTI-based two-drug oral regimen in development for the treatment of HIV-1. We searched PubMed, with no language restrictions, for articles published between database inception and May 27, 2025 using the search terms (doravirine or rilpivirine or efavirenz or etravirine or nevirapine) and (islatravir or translocation inhibitor) and (phase 3). Our search yielded three reports for doravirine (100 mg) and islatravir (0·75 mg) once daily: two switch trials for virologically suppressed adults and one trial for previously untreated adults with HIV-1. In all three trials, doravirine (100 mg) and islatravir (0·75 mg) was non-inferior to the comparator regimens at week 48; however, development of this combination was discontinued owing to islatravir-related, dose-dependent decreases in CD4 cell and total lymphocyte counts. On the basis of a previous phase 2b trial and modelling and simulation analyses predicting that islatravir 0·25 mg would lead to effective exposures without a decrease in lymphocyte counts, the development of the two-drug combination was transitioned to doravirine (100 mg) and islatravir (0·25 mg) orally once daily.

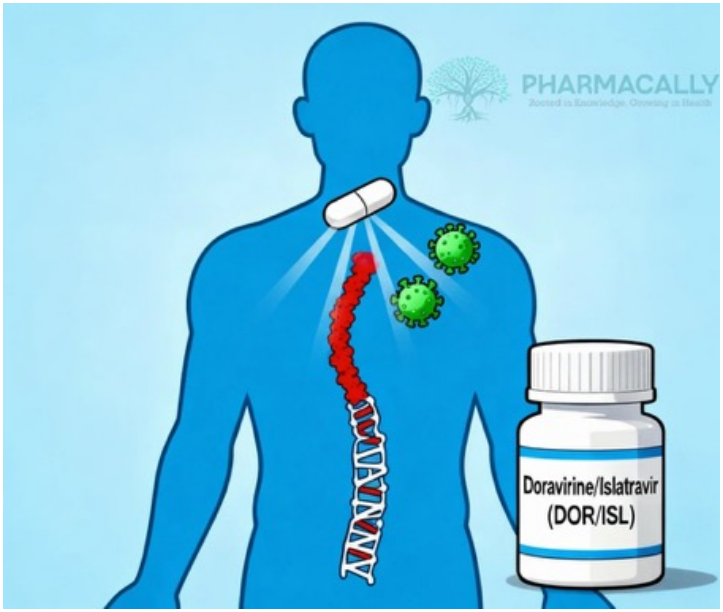
Added value of this study

This randomised, open-label, phase 3 trial in virologically suppressed adults with HIV-1 enrolled participants who were broadly representative of the global population of people living with HIV-1, which is unusual and an improvement for clinical trials in this field. The study showed that switching to doravirine (100 mg) and islatravir (0·25 mg) was non-inferior to continuing on a stable, oral, two-drug or three-drug combination ART regimen in terms of the primary endpoint of an HIV-1 RNA viral load of 50 copies per mL or higher at week 48. No treatment-emergent resistance to doravirine or islatravir was detected, and no clinically significant difference was observed between the treatment groups in the mean change from baseline in CD4 cell or total lymphocyte counts. Treatment-related adverse events were more common in participants who switched to the new regimen than in those who continued on baseline ART, as is often seen in open-label switch studies. Other adverse event rates were similar between the treatment groups, including the low rate of discontinuation due to adverse events.

Implications of all the available evidence

Simplified two-drug regimens can reduce lifetime exposure to antiretrovirals while maintaining the benefits of viral suppression. With the growing concern for the potential development of widespread INSTI resistance in low-resource settings where viral load testing is infrequent and resistance testing is rarely conducted, the development of alternative non-INSTI-based, two-drug, oral and long-acting regimens is important. Doravirine in combination with islatravir is a potential two-drug, once-daily regimen that does not contain an INSTI. The results of this trial and the corresponding double-blind switch trial show that doravirine (100 mg) and islatravir (0·25 mg) is non-inferior to commonly used ART and does not adversely affect CD4 cell or total lymphocyte counts. The doravirine and islatravir once-daily, single-tablet regimen would be the first two-drug, non-INSTI-based treatment option for adults living with HIV-1 who are virologically suppressed but desire or require a regimen change. Islatravir is also being investigated for once-weekly oral treatment of HIV in combination with lenacapavir (a capsid inhibitor) and ulonivirine (an NNRTI). The findings from this study support the continued development of islatravir as part of these once-weekly regimens.

Doravirine und **Islatravir** bilden eine experimentelle, einmal täglich einzunehmende **Zwei-Medikamenten-Kombination** zur Behandlung von HIV-1.
Der aktuelle Stand (Februar 2026)



- **Zulassungsstatus:** Die US-Zulassungsbehörde **FDA** prüft derzeit den Zulassungsantrag (NDA) für dieses Regime. Das Zieldatum für eine Entscheidung (**PDUFA-Datum**) ist der **28.April 2026**.

- **Wirkmechanismus:** Die Kombination nutzt zwei unterschiedliche Wirkstoffklassen:
  - **Doravirine (100 mg):** Ein bereits zugelassener Nicht-nukleosidischer Reverse-Transkriptase-Inhibitor (**NNRTI**).
  - **Islatravir (0,25 mg):** Der erste Wirkstoff einer neuen Klasse, den nukleosidischen Reverse-Transkriptase-Translokations-Inhibitoren (**NRTTIs**).

Switch to fixed-dose doravirine (100 mg) and islatravir (0·25 mg) once daily in virologically suppressed adults with HIV-1 on bictegravir, emtricitabine, and tenofovir alafenamide: 48-week results of a phase 3, multicentre, randomised, controlled, double-blind, non-inferiority trial

Summary

Background The combination of doravirine and islatravir is under investigation as a fixed-dose, single-tablet regimen for the treatment of HIV-1. We aimed to assess the efficacy and safety of switching to doravirine (100 mg) and islatravir (0·25 mg) from bictegravir, emtricitabine, and tenofovir alafenamide in virologically suppressed adults with HIV-1.

INSTI

Methods This phase 3, randomised, controlled, double-blind, non-inferiority trial was conducted at 49 research, community, and hospital-based clinics in six countries: Australia, Chile, Israel, Japan, the UK, and the USA. Adults aged 18 years or older with HIV-1, who were virologically suppressed (with a viral load of HIV-1 RNA <50 copies per mL) for at least 3 consecutive months on bictegravir, emtricitabine, and tenofovir alafenamide and had no history of treatment failure or known resistance to doravirine, were eligible for the study. Participants were randomly assigned, in a 2:1 ratio according to a computer-generated randomisation schedule with a block size of three, to switch to oral doravirine (100 mg) and islatravir (0·25 mg) or to continue bictegravir, emtricitabine, and tenofovir alafenamide, once daily. Participants, investigators, study staff, and sponsor personnel were masked to study treatment; sponsor personnel directly involved in this analysis were unmasked at week 48. The primary endpoint, which was assessed in all randomly assigned participants who received at least one dose of study treatment, was the percentage of participants with a viral load of 50 copies per mL or higher at week 48 according to the US Food and Drug Administration snapshot approach; non-inferiority would be concluded if the upper bound of the multiplicity-adjusted 95% CI for the treatment difference was less than 4%. The trial is registered at ClinicalTrials.gov, NCT05630755, and is ongoing but closed to enrolment.

Findings Between Feb 17 and Nov 17, 2023, 585 individuals were screened, of whom 514 were randomly assigned and 513 treated: 342 participants were switched to doravirine (100 mg) and islatravir (0·25 mg) and 171 continued bictegravir, emtricitabine, and tenofovir alafenamide. The median age of the 513 participants was 47 years (IQR 37–58), 403 (79%) were assigned male and 110 (21%) were assigned female at birth, 158 (31%) were Black or African American, and 117 (23%) were Hispanic, Latino, or Latina. At week 48, doravirine and islatravir showed non-inferiority to bictegravir, emtricitabine, and tenofovir alafenamide (viral load ≥50 copies per mL in five [1·5%] of 342 *vs* one [0·6%] of 171 participants) with a treatment difference of 0·9% (multiplicity-adjusted 95% CI –1·9 to 2·9). The rates of adverse events (74·6% [255 of 342 participants] *vs* 71·3% [122 of 171 participants]; difference 3·2 [95% CI –4·7 to 11·6]), treatment-related adverse events (10·2% [35] *vs* 9·4% [16]; 0·9 [–5·1 to 6·0]), serious adverse events (4·4% [15] *vs* 6·4% [11]; –2·0 [–7·1 to 1·9]), and discontinuations due to adverse events (2·9% [ten] *vs* 1·8% [three]; 1·2 [–2·3 to 3·9]) were similar in the doravirine and islatravir group and the bictegravir, emtricitabine, and tenofovir alafenamide group, and no deaths were reported.

Interpretation The combination of doravirine (100 mg) and islatravir (0·25 mg) has similar efficacy and safety profiles to bictegravir, emtricitabine, and tenofovir alafenamide, and could provide a two-drug, once daily, oral single-tablet option without an integrase strand-transfer inhibitor for adults who are virologically suppressed and want to switch to a different ART regimen.

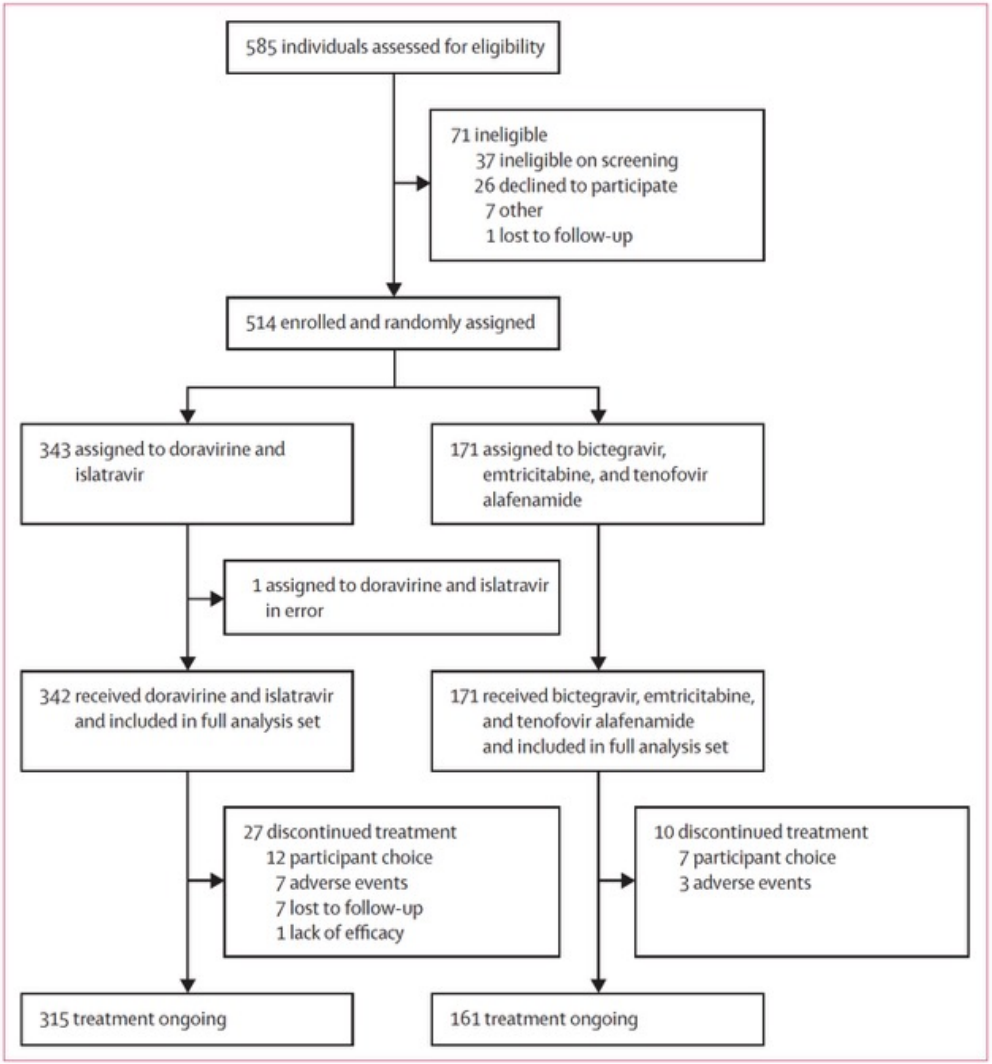


Figure 1: **Trial profile**

	Doravirine and islatravir (n=342)	Bictegravir, emtricitabine, and tenofovir alafenamide (n=171)
Age, years	47 (37–58)	48 (37–60)
18–49	190 (56%)	95 (56%)
50–64	113 (33%)	58 (34%)
≥65	39 (11%)	18 (11%)
Sex assigned at birth		
Male	268 (78%)	135 (79%)
Female	74 (22%)	36 (21%)
Race		
White	206 (60%)	106 (62%)
Black or African American	111 (32%)	47 (27%)
Asian	20 (6%)	10 (6%)
Other	3 (1%)	7 (4%)
Unknown	2 (1%)	1 (1%)
Hispanic, Latino, or Latina ethnicity	73 (21%)	44 (26%)
Region		
North America	228 (66%)	114 (67%)
Europe	35 (10%)	14 (8%)
South America	25 (7%)	15 (9%)
Asia and Pacific Islands	54 (16%)	28 (16%)
BMI, kg/m²	27·3 (24·0–31·0)	27·2 (24·0–32·0)
Anti-HBc-positive at screening	86 (25%)	46 (27%)
CD4 count, cells per μL	681 (497–874)	705 (512–920)
≥500	254 (74%)	130 (76)
≥350 to <500	61 (18%)	21 (12%)
≥200 to <350	21 (6%)	15 (9%)
<200	6 (2%)	5 (3%)
Time since HIV-1 diagnosis, years	11·3 (4·0–19·0)	10·6 (5·0–19·0)
Duration of bictegravir, emtricitabine, and tenofovir alafenamide before enrolment, years	3·3 (2·0–5·0)	3·6 (2·0–5·0)
≥12 months	310 (91%)	154 (90%)
Antiretroviral regimen line of therapy		
First	104 (30%)	54 (32%)
Second	58 (17%)	29 (17%)
Third	61 (18%)	29 (17%)
Fourth or more	119 (35%)	59 (35%)

Data are median (IQR) or n (%). Percentages might not total 100 owing to rounding.

Table 1: **Baseline demographic and clinical characteristics of the full analysis set**

	Doravirine and islatravir	Bictegravir, emtricitabine, and tenofovir alafenamide	Treatment difference (95% CI)
Full analysis set			
Number of participants	342	171	..
Viral load of HIV-1 RNA ≥50 copies per mL	5 (1·5%)	1 (0·6%)	0·9 (−1·9 to 2·9)
Viral load ≥50 copies per mL in week 48 window	2 (0·6%)	1 (0·6%)	..
Discontinued owing to lack of efficacy	1 (0·3 %)	0	..
Discontinued owing to adverse event or death and last viral load measurement ≥50 copies per mL	1 (0·3%)	0	..
Discontinued for other reasons and last viral load measurement ≥50 copies per mL	1 (0·3%)	0	..
Viral load <50 copies per mL	313 (91·5%)	161 (94·2%)	−2·6 (−7·1 to 2·6)
No virological data in week-48 window	24 (7·0%)	9 (5·3%)	..
Discontinued owing to adverse event or death and last viral load measurement <50 copies per mL	6 (1·8%)	3 (1·8%)	..
Discontinued for other reasons and last viral load measurement <50 copies per mL	18 (5·3%)	6 (3·5%)	..
Viral load <200 copies per mL	314 (91·8%)	161 (94·2%)	−2·3 (−7·1 to 1·9)
Mean change in CD4 count (cells per µL) from baseline (95% CI)*	30·4 (11·0 to 49·8)	28·2 (−4·5 to 60·8)	4·9 (−29·9 to 39·6)
Per-protocol population			
Number of participants	288	147	..
Viral load ≥50 copies per mL	4 (1·4%)	1 (0·7%)	0·7 (−2·5 to 3·0)
Viral load <50 copies per mL	267 (92·7%)	139 (94·6%)	−1·9 (−6·4 to 3·6)
Viral load <200 copies per mL	268 (93·1%)	139 (94·6%)	−1·5 (−6·0 to 4·0)

Data are n or n (%) unless otherwise stated. Virological endpoints were assessed according to the US Food and Drug Administration snapshot approach.[22] *n=315 for the doravirine and islatravir group and n=161 for the bictegravir, emtricitabine, and tenofovir alafenamide group.

Table 2: **Efficacy outcomes at week 48**

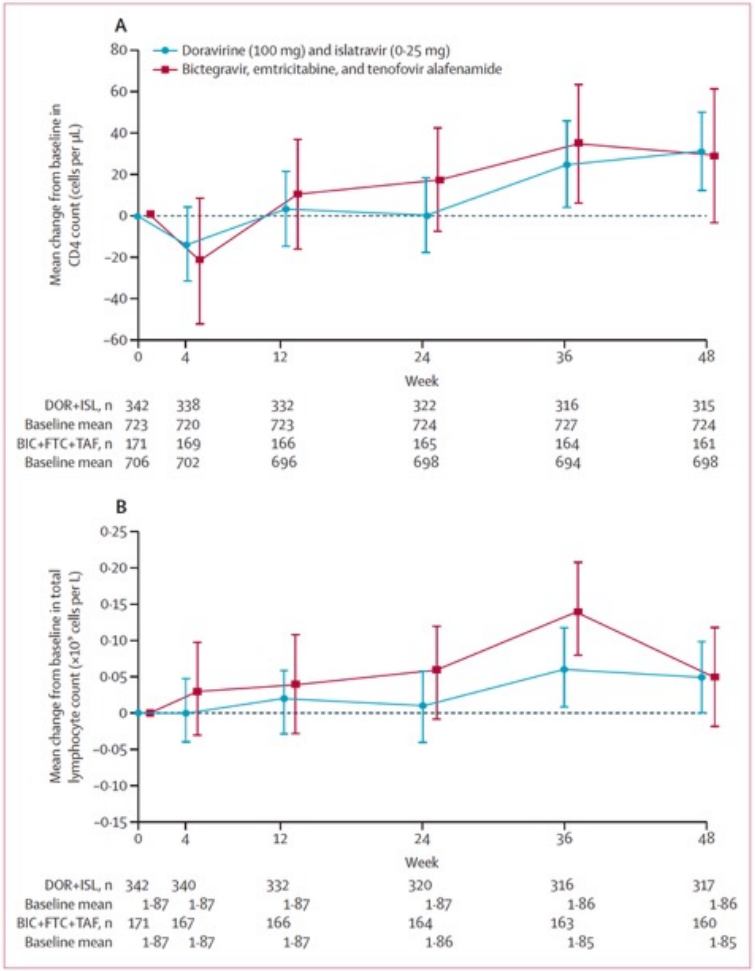


***Figure 2*: Mean change in CD4 cell count (A) and total lymphocyte count (B) from baseline to week 48**
Error bars represent the within-group 95% CIs. BIC+FTC+TAF=bictegravir, emtricitabine, and tenofovir alafenamide. DOR+ISL=doravirine and islatravir.

	Doravirine and islatravir (n=342)	Bictegravir, emtricitabine, and tenofovir alafenamide (n=171)	Treatment difference (95% CI)
Any adverse event	255 (74·6%)	122 (71·3%)	3·2 (−4·7 to 11·6)
Most common adverse events (≥5% in either group)			
Arthralgia	22 (6·4%)	8 (4·7%)	1·8 (−3·0 to 5·7)
COVID-19	21 (6·1%)	9 (5·3%)	0·9 (−4·0 to 4·9)
Nasopharyngitis	21 (6·1%)	13 (7·6%)	−1·5 (−6·9 to 2·9)
Diarrhoea	20 (5·8%)	6 (3·5%)	2·3 (−2·0 to 6·0)
Headache	17 (5·0%)	4 (2·3%)	2·6 (−1·3 to 5·9)
Fatigue	13 (3·8%)	12 (7·0%)	−3·2 (−8·3 to 0·7)
Dizziness	11 (3·2%)	9 (5·3%)	−2·0 (−6·7 to 1·4)
Influenza	9 (2·6%)	9 (5·3%)	−2·6 (−7·3 to 0·7)
Treatment-related* adverse events	35 (10·2%)	16 (9·4%)	0·9 (−5·1 to 6·0)
Most common treatment-related* adverse events (≥1% in either group)			
Diarrhoea	5 (1·5%)	1 (0·6%)	0·9 (−1·9 to 2·9)
Flatulence	4 (1·2%)	1 (0·6%)	0·6 (−2·1 to 2·5)
Headache	4 (1·2%)	0	1·2 (−1·0 to 3·0)
Pruritus	4 (1·2%)	1 (0·6%)	0·6 (−2·1 to 2·5)
Decreased weight	1 (0·3%)	2 (1·2%)	−0·9 (−3·9 to 0·6)
Decreased appetite	1 (0·3%)	2 (1·2%)	−0·9 (−3·9 to 0·6)
Abnormal dreams	1 (0·3%)	2 (1·2%)	−0·9 (−3·9 to 0·6)
Sleep disorder	1 (0·3%)	2 (1·2%)	−0·9 (−3·9 to 0·6)
Grade 3 to 4 adverse events	25 (7·3%)	13 (7·6%)	−0·3 (−5·8 to 4·3)
Treatment-related* grade 3 or 4 adverse events	4 (1·2%)	0	1·2 (−1·0 to 3·0)
Serious adverse events	15 (4·4%)	11 (6·4%)	−2·0 (−7·1 to 1·9)
Treatment-related* serious adverse events	1 (0·3%)	0	0·3 (−1·9 to 1·6)
Deaths	0	0	0·0 (−2·2 to 1·1)
Discontinuation due to adverse events	10 (2·9%)	3 (1·8%)	1·2 (−2·3 to 3·9)
Due to treatment-related* adverse events	4 (1·2%)	2 (1·2%)	0·0 (−3·1 to 2·0)
Due to serious adverse events	1 (0·3%)	0	0·3 (−1·9 to 1·6)
Due to treatment-related* serious adverse events	1 (0·3%)	0	0·3 (−1·9 to 1·6)
Events of clinical interest (potential drug-induced liver injury†)	1 (0·3%)‡	0	0·3 (−1·9 to 1·6)

Data are n (%) unless otherwise indicated. ULN=upper limit of normal. *Considered by the investigator to be related to study treatment. †Defined as aspartate aminotransferase or alanine aminotransferase concentration≥3 × ULN, total bilirubin concentration ≥2 × ULN, and alkaline phosphatase concentration <2 × ULN. ‡Attributed to an acute hepatitis C virus infection and deemed not related to study treatment by the investigator.

***Table 3*: Summary of adverse events to week 48 in the safety population**

	Doravirine and islatravir (n=342)	Bictegravir, emtricitabine, and tenofovir alafenamide (n=171)	Treatment difference (95% CI)
Any adverse event	255 (74·6%)	122 (71·3%)	3·2 (−4·7 to 11·6)
Most common adverse events (≥5% in either group)			
Arthralgia	22 (6·4%)	8 (4·7%)	1·8 (−3·0 to 5·7)
COVID-19	21 (6·1%)	9 (5·3%)	0·9 (−4·0 to 4·9)
Nasopharyngitis	21 (6·1%)	13 (7·6%)	−1·5 (−6·9 to 2·9)
Diarrhoea	20 (5·8%)	6 (3·5%)	2·3 (−2·0 to 6·0)
Headache	17 (5·0%)	4 (2·3%)	2·6 (−1·3 to 5·9)
Fatigue	13 (3·8%)	12 (7·0%)	−3·2 (−8·3 to 0·7)
Dizziness	11 (3·2%)	9 (5·3%)	−2·0 (−6·7 to 1·4)
Influenza	9 (2·6%)	9 (5·3%)	−2·6 (−7·3 to 0·7)
Treatment-related* adverse events	35 (10·2%)	16 (9·4%)	0·9 (−5·1 to 6·0)
Most common treatment-related* adverse events (≥1% in either group)			
Diarrhoea	5 (1·5%)	1 (0·6%)	0·9 (−1·9 to 2·9)
Flatulence	4 (1·2%)	1 (0·6%)	0·6 (−2·1 to 2·5)
Headache	4 (1·2%)	0	1·2 (−1·0 to 3·0)
Pruritus	4 (1·2%)	1 (0·6%)	0·6 (−2·1 to 2·5)
Decreased weight	1 (0·3%)	2 (1·2%)	−0·9 (−3·9 to 0·6)
Decreased appetite	1 (0·3%)	2 (1·2%)	−0·9 (−3·9 to 0·6)
Abnormal dreams	1 (0·3%)	2 (1·2%)	−0·9 (−3·9 to 0·6)
Sleep disorder	1 (0·3%)	2 (1·2%)	−0·9 (−3·9 to 0·6)
Grade 3 to 4 adverse events	25 (7·3%)	13 (7·6%)	−0·3 (−5·8 to 4·3)
Treatment-related* grade 3 or 4 adverse events	4 (1·2%)	0	1·2 (−1·0 to 3·0)
Serious adverse events	15 (4·4%)	11 (6·4%)	−2·0 (−7·1 to 1·9)
Treatment-related* serious adverse events	1 (0·3%)	0	0·3 (−1·9 to 1·6)
Deaths	0	0	0·0 (−2·2 to 1·1)
Discontinuation due to adverse events	10 (2·9%)	3 (1·8%)	1·2 (−2·3 to 3·9)
Due to treatment-related* adverse events	4 (1·2%)	2 (1·2%)	0·0 (−3·1 to 2·0)
Due to serious adverse events	1 (0·3%)	0	0·3 (−1·9 to 1·6)
Due to treatment-related* serious adverse events	1 (0·3%)	0	0·3 (−1·9 to 1·6)
Events of clinical interest (potential drug-induced liver injury†)	1 (0·3%)‡	0	0·3 (−1·9 to 1·6)

Data are n (%) unless otherwise indicated. ULN=upper limit of normal. *Considered by the investigator to be related to study treatment. †Defined as aspartate aminotransferase or alanine aminotransferase concentration≥3 × ULN, total bilirubin concentration ≥2 × ULN, and alkaline phosphatase concentration <2 × ULN. ‡Attributed to an acute hepatitis C virus infection and deemed not related to study treatment by the investigator.

***Table 3*: Summary of adverse events to week 48 in the safety population**

Research in context

Evidence before this study

We searched PubMed, using the terms (doravirine or rilpivirine or efavirenz or etravirine or nevirapine) and (islatravir or translocation inhibitor) and (phase 3), for publications between database inception and May 27, 2025. No language restrictions were applied. This search returned three manuscripts. A phase 3 programme with doravirine (100 mg) and islatravir (0·75 mg) orally once daily was conducted, involving two switch trials and one trial for adults with HIV-1 who had not received previous treatment. In all three trials, doravirine (100 mg) and islatravir (0·75 mg) was non-inferior to comparator regimens at week 48, but development was discontinued owing to islatravir dose-dependent decreases in CD4 cell and total lymphocyte counts. On the basis of a phase 2b trial, as well as modelling and simulation analyses predicting that a 0·25 mg dose of islatravir would result in effective exposures without a decrease in lymphocyte counts, the combination was amended to oral doravirine (100 mg) and islatravir (0·25 mg) once daily for further development.

Added value of this study

This phase 3, randomised, double-blind study in virologically suppressed adults living with HIV-1 compared switching to oral doravirine (100 mg) and islatravir (0·25 mg) once daily with continuing oral bictegravir (50 mg), emtricitabine (200 mg), and tenofovir alafenamide (25 mg)—a once daily, three-drug integrase strand-transfer inhibitor (INSTI)-based regimen. The combination of doravirine and islatravir was non-inferior to the combination of bictegravir, emtricitabine, and tenofovir alafenamide, a preferred antiretroviral regimen, in terms of the primary endpoint of an HIV-1 RNA viral load of 50 copies per mL or higher at week 48. Of the two participants in the doravirine and islatravir group with a confirmed viral load of 200 copies per mL or higher who discontinued study treatment, genotypic and phenotypic testing results were available for one, and no treatment-emergent resistance to doravirine or islatravir was detected. No difference was observed between the treatment groups in the mean change from baseline in CD4 cell counts or total lymphocyte counts. Adverse event rates were similar between treatment groups and discontinuation due to adverse events was rare and occurred at a similar rate in both groups. These findings suggest that, in people living with HIV-1 with virological suppression, doravirine (100 mg) and islatravir (0·25 mg) is an effective and well tolerated option when switching from bictegravir, emtricitabine, and tenofovir alafenamide.

Implications of all the available evidence

Two-drug antiretroviral regimens reduce lifetime exposure to antiretrovirals, polypharmacy, drug–drug interactions, and long-term tolerability issues. Several INSTI-based, two-drug regimens are now recommended in HIV treatment guidelines; however, as concern for the emergence of more widespread INSTI resistance is increasing, two-drug regimens without an INSTI are of interest. The combination of doravirine with islatravir is a potential non-INSTI-based, two-drug, once daily regimen. After dose-dependent decreases in CD4 cell counts and total lymphocyte counts were observed with islatravir 0·75 mg, the phase 3 programme was resumed with islatravir 0·25 mg. The results of this trial, in addition to those of the corresponding open-label switch trial, show that the combination of doravirine (100 mg) and islatravir (0·25 mg) is non-inferior to commonly used ART regimens and does not adversely affect CD4 cell counts or total lymphocyte counts. Doravirine and islatravir is a potential oral, once daily, fixed-dose combination treatment for adults living with HIV-1 who are virologically suppressed on a stable, three-drug or two-drug regimen and would like to switch to an effective two-drug regimen that does not include an INSTI.

Prostate cancer

Prostate cancer poses a substantial clinical challenge and accounts for a large proportion of cancer-related deaths worldwide. The therapeutic landscape has undergone a large transformation in the past 5 years, resulting in improved patient outcomes. In this Seminar, we review the pathology, diagnostic strategies, and treatments for prostate cancer. Active surveillance is the preferred treatment option for patients with indolent prostate cancer. For those requiring treatment, local therapies provide effective cancer control. Systemic treatment is essential for advanced and metastatic cases, and a wide range of therapies are now available, including androgen deprivation therapy, chemotherapy, and emerging targeted agents such as lutetium-177-labelled prostate-specific membrane antigen radioligand therapy and PARP inhibitors. Considering toxicity profiles alongside patient preferences is important to facilitating shared decision making. Further research is needed to establish the most effective sequence and combination of treatments for metastatic prostate cancer.

PARP (Poly(ADP-ribose)-Polymerase)
ist eine Enzymfamilie im Zellkern, die essenziell für die Reparatur von DNA-Einzelstrangbrüchen ist. In der Krebstherapie werden PARP-Inhibitoren eingesetzt, um diese Reparatur zu blockieren, was insbesondere bei Tumoren mit BRCA-Mutationen durch das Prinzip der "synthetischen Letalität" zum Absterben der Krebszellen führt.

Panel: **Overview of the different risk group stratification systems commonly used internationally for prostate cancer**

EAU 2025

Low risk

Clinical tumour stage 1–2a, and PSA less than 10 ng/mL, and ISUP grade group 1.

Favourable intermediate risk

- Clinical tumour stage 1–2b, and PSA concentration less than 10 ng/mL, and ISUP grade group 2
- Clinical tumour stage 1–2b, and PSA concentration of 10–20 ng/mL, and ISUP grade group 1
- Clinical tumour stage 2b, and PSA concentration less than 10 ng/mL, and ISUP grade group 1

Unfavourable intermediate risk

- Clinical tumour stage 1–2b, and PSA concentration of 10–20 ng/mL, and ISUP grade group 2
- Clinical tumour stage 1–2b and ISUP grade group 3

Localised high risk

- Clinical tumour stage 2c
- PSA concentration greater than 20 ng/mL
- ISUP grade group 4–5

Locally advanced high risk

Clinical tumour stage 3–4 or clinical node-positive, or both, with any PSA value and any ISUP grade.

NCCN 2026

Low risk

Clinical tumour stage 1–2a, and PSA concentration less than 10 ng/mL, and ISUP grade group 1.

Favourable intermediate risk

ISUP grade group 1–2, and less than 50% positive biopsy cores, and one intermediate risk factor (eg, clinical tumour stage 2b–2c, PSA concentration of 10–20 ng/mL, or ISUP grade 2–3).

Unfavourable intermediate risk

ISUP grade group 3 and/or 50% or greater positive biopsy cores, and/or two or three intermediate risk factors (eg, clinical tumour stage 2b–2c, PSA concentration of 10–20 ng/mL, or ISUP grade group 2–3).

High risk

One or more high-risk features present but does not meet criteria for very high risk (eg, clinical tumour stage 3–4, PSA concentration greater than 20 ng/mL, or ISUP grade group 4–5).

Very high risk

At least two of the following present:

- Clinical tumour stage 3–4
- PSA concentration greater than 40 ng/mL
- ISUP grade group 4–5

Cambridge Prognostic Group

Group 1

Clinical tumour stage 1–2, and PSA concentration less than 10 ng/mL, and ISUP grade group 1.

Group 2

Clinical tumour stage 1–2 and PSA concentration of 10–20 ng/mL or ISUP grade group 2.

Group 3

- Clinical tumour stage 1–2, and PSA concentration of 10–20 ng/mL, and ISUP grade group 2
- Clinical tumour stage 1–2 and ISUP grade group 3

Group 4

One of the following:

- Clinical tumour stage 3
- PSA concentration greater than 20 ng/mL
- ISUP grade group 4

Group 5

Two or more of the following:

- Clinical tumour stage 3 or 4
- PSA concentration greater than 20 ng/mL
- ISUP grade group 4 or 5

EAU=European Association of Urology. PSA=prostate-specific antigen. ISUP=International Society of Urological Pathology. NCCN=National Comprehensive Cancer Network.

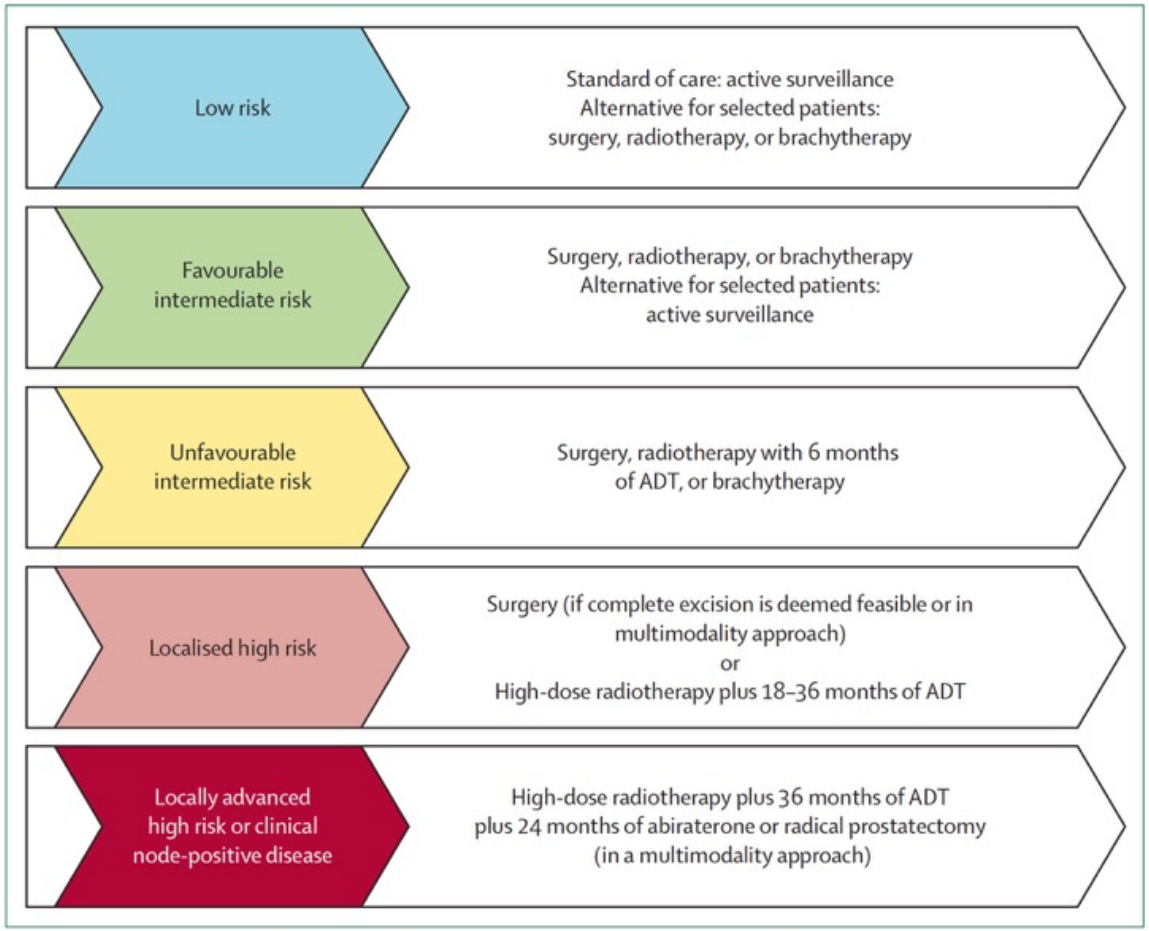


Figure 1: **Localised and locally advanced non-metastatic prostate cancer: different treatment options per risk group**

Treatment options are categorised according to the European Association of Urology's definition of risk group, except for clinical tumour stage 2c disease, which is currently considered to be intermediate-risk prostate cancer rather than localised high-risk prostate cancer. ADT=androgen deprivation therapy.

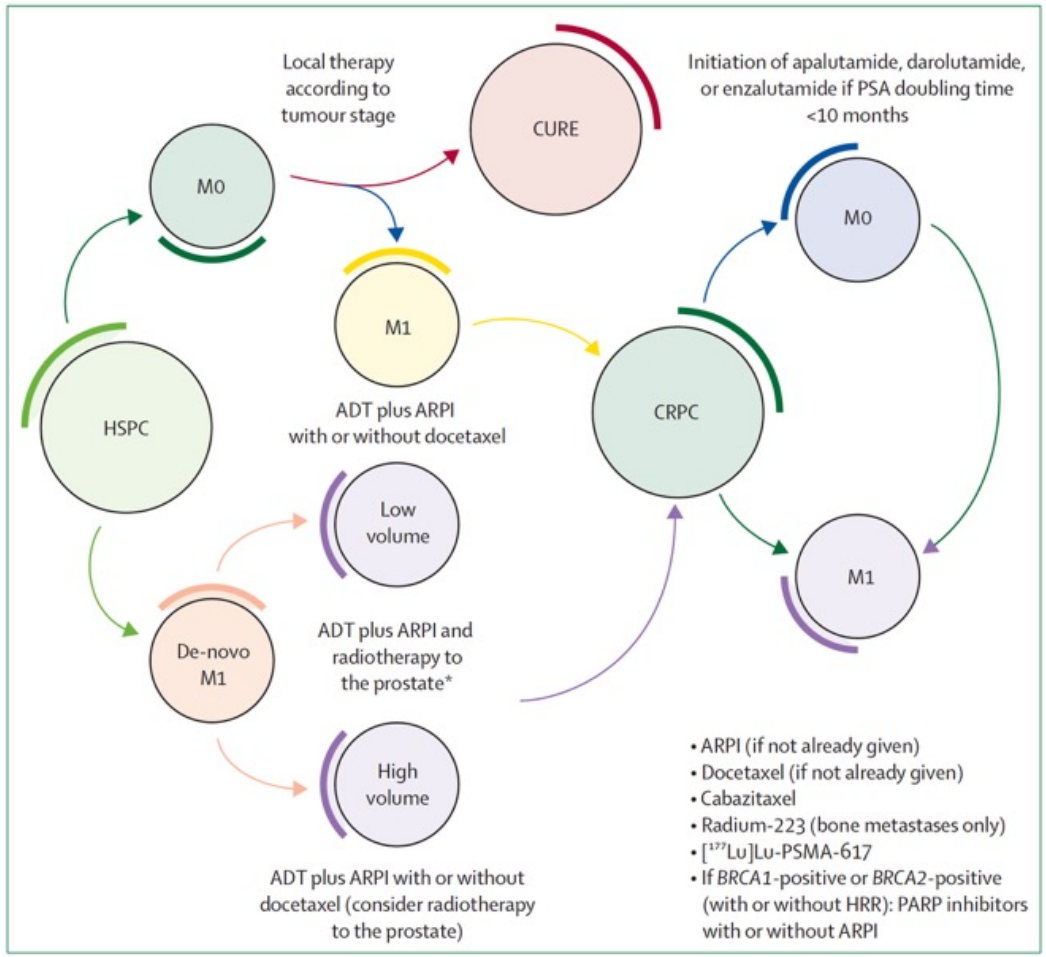


Figure 2: **Treatment options in HSPC and CRPC**

PSA=prostate-specific antigen. M0=non-metastatic disease. M1=metastatic disease. HSPC=hormone-sensitive prostate cancer. CRPC=castration-resistant prostate cancer. ADT=androgen deprivation therapy. ARPI=androgen receptor pathway inhibitor. HRR=homologous recombination repair. [^{177}Lu]Lu-PSMA-617=lutetium-177 prostate-specific membrane antigen-617. *35% of patients in PEACE-1, evaluating triplet therapy, had low-volume disease.

	Treatments	Number of patients in experimental group (control)	Population	Median follow-up (months)	Overall survival	Hazard ratio (95% CI)	Grade 3 or worse adverse events of interest in experimental group
CHAARTED[101]	ADT plus docetaxel vs ADT	397 (393)	mHSPC	53·7	57·6 months vs 47·2 months	0·72 (0·59–0·89)	Neutropenia: 12%; febrile neutropenia: 6%; fatigue: 4%
STAMPEDE[104]	ADT plus docetaxel vs ADT	592 (1184)	High-risk M0 and mHSPC	78·2	63·1 months vs 57·1 months	0·78 (0·66–0·93)	Febrile neutropenia: 15%; neutropenia: 12%; nausea or vomiting: 8%
LATITUDE[102]	ADT plus abiraterone vs ADT	597 (602)	mHSPC	51·8	53·3 months vs 36·5 months	0·66 (0·56–0·78)	Hypertension: 21%; hypokalaemia: 12%; ALT or AST increase: 4%
STAMPEDE[105]	ADT plus abiraterone vs ADT	502 (501)	mHSPC	73·2	66·0 months vs 54·0 months	0·60 (0·5–0·71)	Hypertension: 5%; cardiac disorder: 10%; hepatic disorder: 7%
ARCHES[106]	ADT plus enzalutamide vs ADT (18% of patients had previously received docetaxel)	574 (576)	mHSPC	61·4	NR	0·7 (0·58–0·85)	Hypertension: 3·3%; fatigue: 1·7%; musculoskeletal events: 1·6%
ENZAMET[107]	ADT plus enzalutamide vs ADT (45% of patients received concurrent docetaxel)	563 (562)	mHSPC	98·0	96·0 months vs 69·6 months	0·73 (0·63–0·86)	Hypertension: 8%; febrile neutropenia: 7%; fatigue: 6%
TITAN[108]	ADT plus apalutamide vs ADT (11% of patients had previously received docetaxel)	525 (527)	mHSPC	44·0	NR vs 52·2 months	0·65 (0·53–0·79)	Hypertension: 8·4%; rash: 6% fatigue or asthenia: 3·5%
ARANOTE[109]	ADT plus darolutamide vs ADT	446 (223)	mHSPC	25·3	NR	0·81* (0·59–1·12)	Hypertension: 4·3%; anaemia: 3·1%; AST increase: 2·2
PEACE-1[110]	ADT plus docetaxel plus abiraterone vs ADT plus docetaxel	355 (355)	mHSPC	45·6	NR vs 52·8 months	0·75 (0·55–0·95)	Hypertension: 22%; ALT or AST increase: 6%; febrile neutropenia: 5%
ARASENS[111]	ADT plus docetaxel plus darolutamide vs ADT plus docetaxel	651 (655)	mHSPC	43·7	NR vs 48·9 months	0·68 (0·57–0·80)	Neutropenia: 33·7%; febrile neutropenia: 7·8%; hypertension: 6·4%
AMPLITUDE[112]	ADT plus abiraterone plus niraparib vs ADT plus abiraterone (16% of patients had previously received docetaxel)	348 (348)	mHSPC with HRR alterations	30·8	NR	0·791 (0·59–1·04)	Anaemia: 29%; hypertension: 27%; hypokalaemia: 12%
SPARTAN[113]	ADT plus apalutamide vs ADT plus placebo	806 (401)	nmCRPC	52·0	73·9 months vs 59·9 months	0·78 (0·64–0·96)	Hypertension: 16%; fall: 2·7%; diarrhoea: 1·5%; weight loss: 1·5%; back pain: 1·4%
PROSPER[114]	ADT plus enzalutamide vs ADT plus placebo	933 (468)	nmCRPC	48·0	67·0 months vs 56·3 months	0·73 (0·61–0·89)	Hypertension: 6%; fatigue: 4%; haematuria: 3%; asthenia: 2%; fall: 2%
ARAMIS[115]	ADT plus darolutamide vs ADT plus placebo	955 (554)	nmCRPC	29·0	3-year overall survival: 83% vs 77%	0·69 (0·53–0·88)	Hypertension: 3·5%; coronary artery disorder: 2%; cardiac arrhythmia: 1·8%; bone fracture: 1%
TAX-327[116]	ADT plus docetaxel 3-weekly vs ADT plus docetaxel weekly vs ADT plus mitroxantrone	335 (ADT plus docetaxel 3-weekly); 334 (ADT plus docetaxel weekly); 337 (ADT plus mitroxantrone)	mCRPC	20·8	18·9 months vs 17·4 months vs 16·5 months	Docetaxel 3-weekly: 0·76 (0·62–0·94); docetaxel weekly: 0·91 (0·75–1·11)	Nausea or vomiting: 42%; febrile neutropenia: 3%; peripheral neuropathy: 30%
COU-AA-301[117]	ADT plus abiraterone vs ADT in patients who had previously received docetaxel	797 (398)	mCRPC	20·2	15·8 months vs 11·2 months	0·74 (0·64–0·86)	Fatigue or asthenia: 10%; anaemia: 8%; hypokalaemia: 3%
COU-AA-302[118]	ADT plus abiraterone vs ADT in patients who had not received docetaxel previously	546 (542)	mCRPC	49·2	34·7 months vs 30·3 months	0·81 (0·70–0·93)	Cardiac disorders: 8%; AST or ALT increase: 6%; hypertension: 5%
AFFIRM[119]	ADT plus enzalutamide vs ADT in patients who had previously received docetaxel	800 (399)	mCRPC	14·4	18·4 months vs 13·6 months	0·63 (0·53–0·75)	Fatigue: 6%; AST or ALT increase: 1%; seizures: 0·6%
PREVAIL[120]	ADT plus enzalutamide vs ADT in patients who had not received docetaxel previously	872 (845)	mCRPC	31·0	35·0 months vs 31·0 months	0·77 (0·67–0·88)	Hypertension: 7·2%; cardiac disorder: 3·4%; fatigue or asthenia: 3·5%

(Table 1 continues on next page)

(Continued from previous page)

	Treatments	Number of patients in experimental group (control)	Population	Median follow-up (months)	Overall survival	Hazard ratio (95% CI)	Grade 3 or worse adverse events of interest in experimental group
TROPIC[121]	ADT plus cabazitaxel vs ADT plus mitroxantrone in patients who had previously received docetaxel	378 (377)	mCRPC	12·8	15·1 months vs 12·7 months	0·7 (0·59–0·83)	Anaemia: 11%; febrile neutropenia: 8%; diarrhoea: 6%
CARD[122]	ADT plus cabazitaxel vs ADT plus second ARPI in patients who had previously received docetaxel and ARPIs	129 (126)	mCRPC	9·2	13·6 months vs 11·0 months	0·64 (0·46–0·89)	Infection: 8%; febrile neutropenia: 3·2%; diarrhoea: 3·2%
VISION[123]	ADT plus [^{177}Lu]-Lu-PSMA-617 vs ADT plus SOC in patients who had previously received docetaxel and ARPIs	385 (196)	mCRPC PSMA-PET positive	20·9	15·3 months vs 11·3 months	0·62 (0·52–0·74)	Anaemia: 13%; thrombocytopenia: 8%; lymphopenia: 8%
PSMAfore[124]	ADT plus [^{177}Lu]Lu-PSMA-617 vs ADT plus second ARPI in patients who had previously received ARPIs	234 (234)	mCRPC; PSMA-PET positive	24	23·66 months vs 23·85 months	0·98‡ (0·75–1·28)	Anaemia: 6%; fatigue or asthenia: 2%; dry mouth: 1%
PROFOUND[125]	ADT plus olaparib vs ADT plus second ARPI in patients who had previously received ARPIs	Cohort A: 162 (83); cohort B: 94 (48)	mCRPC with HRR alterations	18·5	Cohort A: 19·1 months vs 14·7 months; cohort B: 14·1 months vs 11·5 months	Cohort A§: 0·69 (0·5–0·97); cohort B§: 0·96 (0·63–1·49)	Anaemia: 23%; nausea, vomiting: 4%; fatigue or asthenia: 3%
TRITON3[126]	ADT plus rucaparib vs ADT plus second ARPI or docetaxel in patients who had previously received ARPIs	270 (135)	mCRPC with *BRCA* or *ATM* alterations	44	*BRCA*: 23·2 months vs 21·2 months	*BRCA*¶: 0·91 (0·68–1·2)	Anaemia: 23·7%; neutropenia: 7·4%; fatigue or asthenia: 7%
PROPEL[127]	ADT plus olaparib plus abiraterone vs ADT plus abiraterone	399 (397)	mCRPC	36·6	42·1 months vs 34·7 months	0·81 (0·67–1·00)	Anaemia: 16%; embolic or thrombotic events: 9%; hypertension: 4%
TALAPRO-2[128,129]	ADT plus talazoparib plus enzalutamide vs ADT plus enzalutamide	402 (403)	mCRPC	52·5	45·8 months vs 37·0 months	0·79 (0·66–0·96)	Anaemia: 45%; neutropenia: 18%; leukopenia: 6·8%
MAGNITUDE[130]	ADT plus niraparib plus abiraterone vs ADT plus abiraterone	212 (211)	mCRPC with HRR alterations	37·3	30·98 months vs 30·96 months	0·93 (0·72–1·20)	Anaemia: 30·7%; hypertension: 16·5%; thrombocytopenia: 8·5%
ALSYMPCA[131]	ADT plus Radium-223 vs ADT plus SOC in patients who had previously received docetaxel	614 (307)	mCRPC	10·4	14·9 months vs 11·3 months	0·7 (0·55–0·88)	Anaemia: 13%; thrombocytopenia: 7%; fatigue or asthenia: 6%
PEACE-3[132]	ADT plus Radium-223 plus enzalutamide vs ADT plus enzalutamide	224 (222)	mCRPC	41·5	42·3 months vs 35·0 months	0·69‖ (0·52–0·90)	Hypertension: 33%; fatigue or asthenia: 7%; anaemia: 4·6%

ADT=androgen deprivation therapy. mHSPC=metastatic hormone-sensitive prostate cancer. M0=non-metastatic disease. ALT=alanine aminotransferase. AST=aspartate aminotransferase. NR=not reported. HRR=homologous recombination repair. nmCRPC=non-metastatic castration-resistant prostate cancer. mCRPC=metastatic castration-resistant prostate cancer. ARPI=androgen receptor pathway inhibitor. [^{177}Lu]Lu-PSMA-617=lutetium-177 prostate-specific membrane antigen-617. SOC=standard of care. PSMA=prostate-specific membrane antigen. *ARANOTE: interim overall survival analysis. †AMPLITUDE: interim overall survival analysis at 50% maturity. ‡PSMAfore: 57% crossover from control to experimental group. §PROFOUND: 66% crossover from control to experimental group. ¶TRITON3: overall survival only reported in *BRCA* subgroup. 52% crossover from control to experimental group. ‖PEACE-5: interim overall survival analysis at 80% maturity.

Table 1: Phase 3 trials that have shaped current practice in mHSPC and CRPC

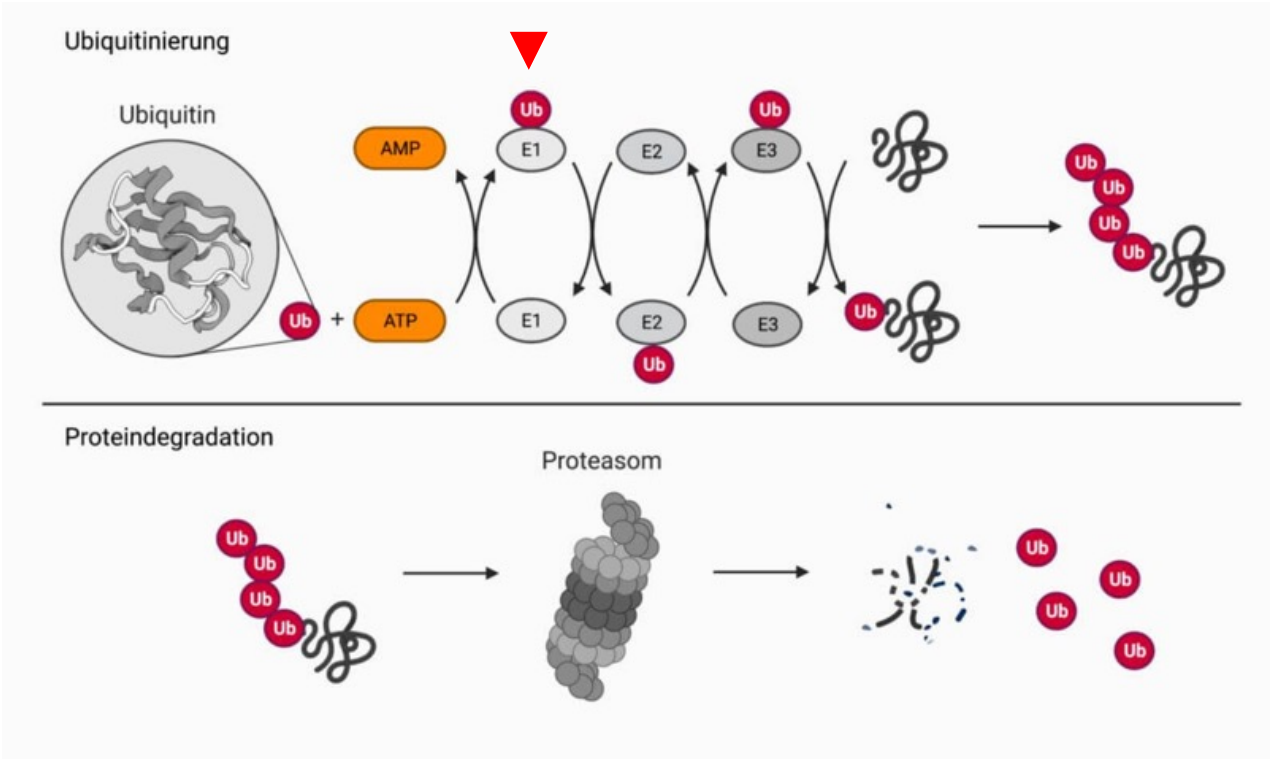
The future

	Acronym	Intervention	Remarks	Outcome
Localised non-metastatic prostate cancer				
NCT05050084	Guidance trial	Therapy based on Decipher score	Intermediate-risk prostate cancer	MFS
NCT02446444	ENZARAD*	EBRT plus ADT plus enzalutamide vs EBRT plus ADT plus conventional non-steroidal anti-androgen	High-risk prostate cancer	OS
NCT02799706	PEGASUS	EBRT plus long-term gonadotropin-releasing hormone antagonist vs gonadotropin-releasing hormone agonist	Very high-risk prostate cancer	PFS
NCT02799706	ALADDIN	EBRT plus ADT plus darolutamide (24 months) vs EBRT plus ADT plus placebo (24 months)	Node-positive disease	FFS
NCT04134260	INNOVATE	EBRT plus ADT (24 months) plus apalutamide vs EBRT plus ADT (24 months) plus placebo	Postoperative setting with pathological node-positive disease	MFS
mHSPC				
NCT04787744	VA STARPORT	Standard systemic therapy with or without PET-directed local therapy	Oligorecurrent prostate cancer	CRPC-free survival
NCT04302454	ADOPT	Metastasis-directed therapy vs metastasis-directed therapy plus ADT (6 months)	Oligometastatic recurrence	MFS
NCT03784755	PLATON	SOC plus radiotherapy to the prostate vs SOC plus ablative radiotherapy to all sites	Metastatic disease with ≤5 metastases	FFS
NCT05956639	NA	ADT plus chemotherapy plus 6-month rezvilutamide vs ADT plus chemotherapy plus long-term rezvilutamide	mHSPC	rPFS
NCT05983783	NA	Rezvilutamide plus ADT plus docetaxel vs rezvilutamide plus ADT	mHSPC	rPFS
NCT06177015	NA	ADT plus docetaxel plus intermittent darolutamide vs ADT plus docetaxel plus long-term darolutamide	mHSPC	rPFS and OS
NCT05884398	LIBERTAS	Apalutamide with continued ADT vs intermittent ADT following prostate-specific antigen response	mHSPC	rPFS
NCT05884398	CYCLONE 3	Abiraterone plus prednisone vs abiraterone plus prednisone plus abemaciclib	high-risk mHSPC	rPFS
NCT03903835	ProBio	Outcome-adaptive randomisation within biomarker signatures	mHSPC and mCRPC	NLCB
NCT04720157	PSMAaddition	SOC plus [^{177}Lu]Lu-PSMA-617 vs SOC alone	mHSPC	rPFS
NCT04821622	TALAPRO-3	Talazoparib plus enzalutamide vs placebo plus enzalutamide	DNA damage response gene-mutated mHSPC	rPFS
NCT04493853	CAPItello-281	Abiraterone acetate plus prednisone plus ADT plus capivasertib vs abiraterone acetate plus prednisone plus ADT plus placebo	mHSPC with *PTEN* deficiency	rPFS
CRPC				
NCT03574571	DORA	Docetaxel vs docetaxel plus radium-223	CRPC	OS
NCT04455750	CASPAR	Enzalutamide plus rucaparib vs enzalutamide plus placebo	CRPC	OS and rPFS
NCT04691804	FUZUPRO	Fuzuloparib plus abiraterone acetate plus prednisone vs placebo plus abiraterone acetate plus prednisone	CRPC	rPFS
NCT04821622	TALAPRO-3	Talazoparib plus enzalutamide vs placebo plus enzalutamide	DNA damage response gene-mutated mCRPC	rPFS
NCT06136624	OMAHA-003	Abiraterone acetate plus prednisone or enzalutamide vs opevesostat	mCRPC	OS and rPFS
NCT06136650	OMAHA-004	Alternative next-generation hormonal agent vs opevesostat	mCRPC after receiving one next-generation hormonal agent	OS and rPFS

MFS=metastasis-free survival. EBRT=external-beam radiotherapy. ADT=androgen deprivation therapy. OS=overall survival. PFS=progression-free survival, FFS=failure-free survival. mHSPC=metastatic hormone-sensitive prostate cancer. CRPC=castration-resistant protate cancer. SOC=standard of care. NA=not available. rPFS=radiographic PFS. mCRPC=metastatic CRPC. NLCB=no longer clinical benefitting. [^{177}Lu]Lu-PSMA-617=lutetium-177 prostate-specific membrane antigen-617. *Data were presented at the European Society for Medical Oncology Congress 2025.

Table 2: **Ongoing phase 3 trials expected to report results within the next 2 years that could influence future treatment strategies**

Das **E1-Enzym** (Ubiquitin-aktivierendes Enzym) ist der zentrale „Torwächter“ des Ubiquitin-Proteasom-Systems (UPS). Es katalysiert den ersten und einzigen **ATP-abhängigen Schritt** der Ubiquitinierung, wodurch es den gesamten Prozess der Proteinmarkierung und des -abbaus in Gang setzt (alles von der Hefe-Forschung).



VEXAS syndrome: a comprehensive review of pathogenesis, clinical spectrum, and therapeutic strategies

Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome is a monogenic disease of adulthood characterised by treatment-refractory systemic inflammation and progressive bone marrow failure. VEXAS syndrome is caused by acquired mutations in the *UBA1* gene that are restricted to haematopoietic cells. Men aged 50 years or older are particularly susceptible to VEXAS syndrome, with prevalence estimates of approximately one in 4000 men. Perturbation of UBA1, the master enzyme of cellular ubiquitination, promotes myeloid-driven inflammation that is difficult to control with medications other than glucocorticoids. Cytokine-directed therapies (ie, IL-6 and JAK inhibitors) might temporise symptoms and allow glucocorticoid reduction. Hypomethylating agents (ie, azacytidine) can induce clinical and molecular remission in some patients, but are associated with substantial toxicities. Haematopoietic cell transplant might be effective treatment in patients who are suitable candidates. The discovery of VEXAS syndrome highlights the potential role of somatic mutations in complex inflammatory diseases.

Bone marrow somatic mutations in *UBA1* that encodes for an E1 ligase

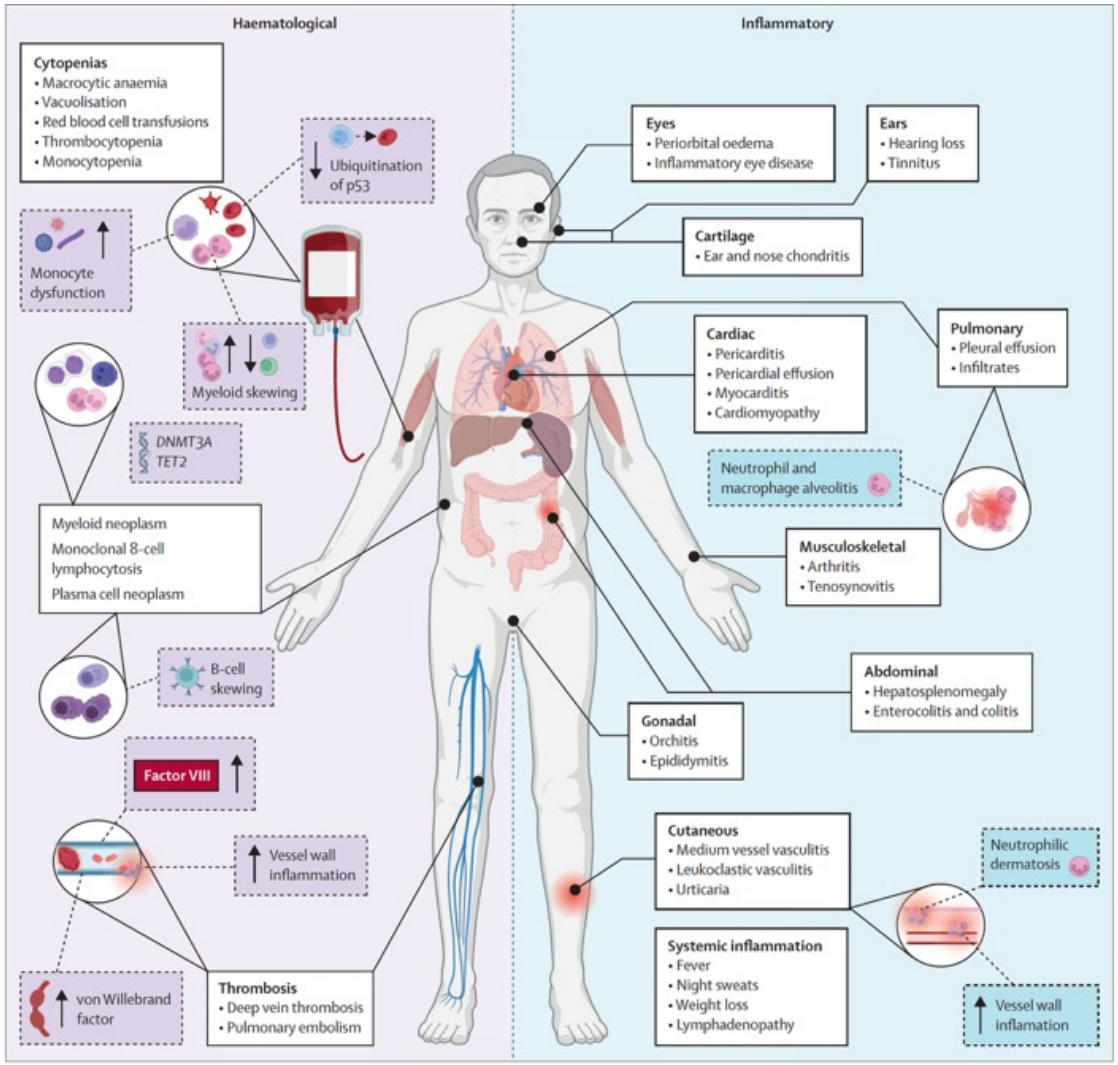


Figure 1: **Overview of VEXAS syndrome**

VEXAS syndrome is a multisystemic disease affecting most organs. The clinical phenotype is expanding and the pathobiology of some manifestations have been elucidated. VEXAS=vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.

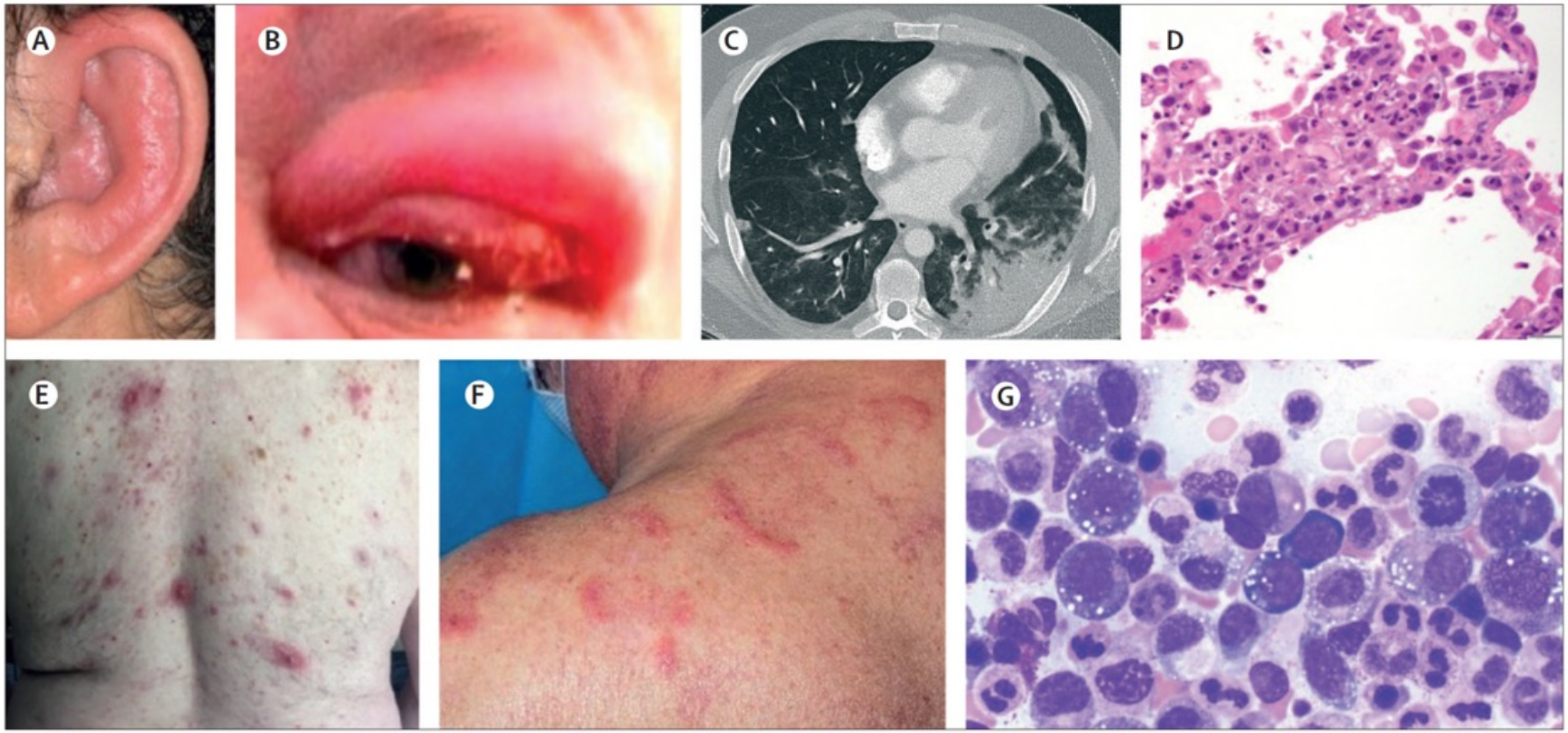


Figure 2: **Clinical images from patients with VEXAS syndrome**
(A) Cartilaginous involvement includes auricular and nasal chondritis. (B) Periorbital inflammation. (C) Pulmonary involvement can manifest as pleural effusion or infiltrates. (D) Histological neutrophilic alveolitis. (E) Cutaneous involvement includes Sweet's syndrome. (F) Characteristic cutaneous arcuate plaques. (G) Bone marrow is typically hypercellular with granulocytic hyperplasia, erythroid hypoplasia, and vacuolisation of myeloid and erythroid precursors. VEXAS=vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.

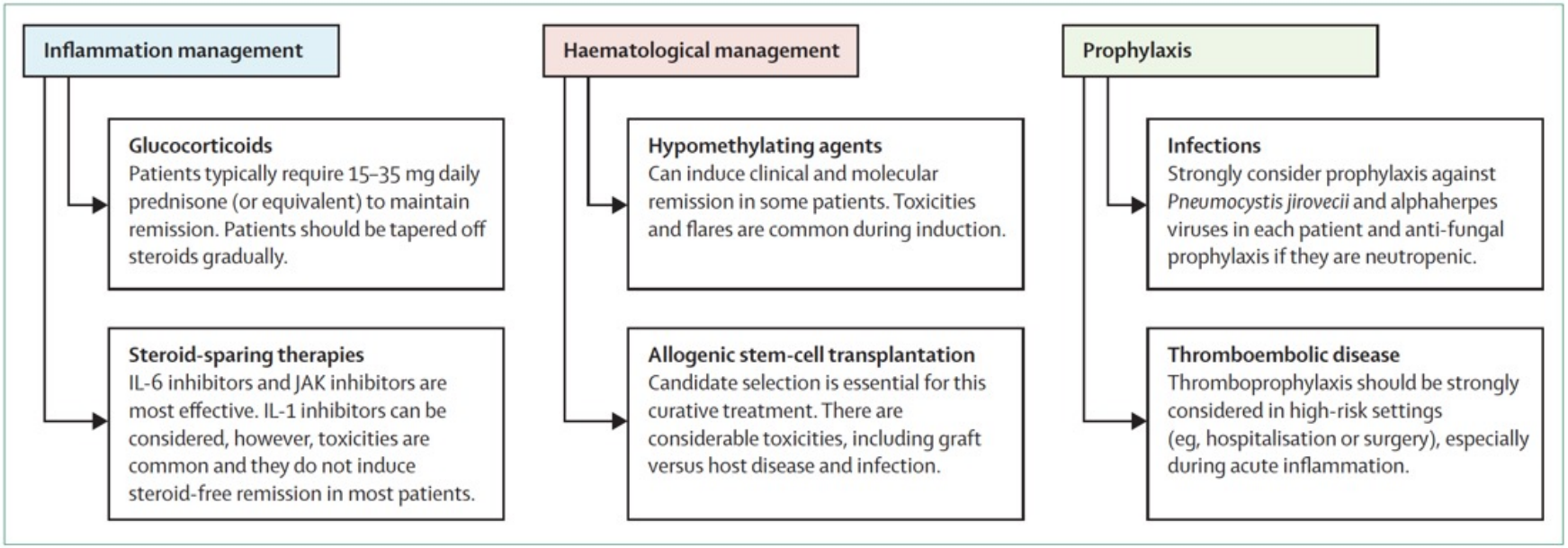


Figure 3: **Management considerations for patients with VEXAS syndrome**
Recommendations to manage the haematological, inflammatory, and prophylactic manifestations of VEXAS syndrome. VEXAS=vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.

	Dosing regimens	Most common or severe toxicities	Management
Azacitidine (hypomethylating agent)[80]	75 mg/m^2 intravenously or subcutaneously for 7 days,[81] consider dose reduction to 75 mg/m^2 intravenously or subcutaneously for 5 days in people who are at high risk or if toxicity is present.[82]	Clinically significant cytopenias (anaemia, thrombocytopenia, and neutropenia); infection; subcutaneous injection site reactions; and disease flare in the first 2–3 cycles.	Closely monitor patients for cytopenias; monitor patients for neutropenia-related and atypical infections; and consider escalation of glucocorticoids for the first 1–3 cycles.
Ruxolitinib (JAK1, JAK2, and TYK2 inhibitors)[83]	5–20 mg twice daily,[84,85] with doses titrated based on haematological toxicity.	Cytopenias (anaemia most common); infection (viral [eg, varicella zoster virus], bacterial, fungal, and atypical mycobacterial); non-melanoma skin cancers; and although thrombosis is not reported, it might be a class effect of JAK inhibitors.	Consider use of erythropoietin if anaemia is dose-limiting; administer antiviral prophylaxis; and monitor for atypical infection.
Anti-IL-6 (tocilizumab[86] or sarilumab)[87]	Tocilizumab: 4–8 mg/kg intravenously every 4 weeks (preferred) or 162 mg weekly subcutaneously; sarilumab: 200 mg subcutaneously every 2 weeks.[2]	Cytopenia (neutropenia and thrombocytopenia); infection (viral [eg, varicella zoster virus], bacterial, fungal, and atypical mycobacterial); infusion and subcutaneous injection site reactions; diverticulitis and bowel perforation; and hepatic toxicity.	A degree of neutropenia (absolute neutrophil count >0·75 × 10^9/L) and thrombocytopenia (platelets 50 × 10^9/L) is tolerated in patients with VEXAS syndrome; consider giving intravenous formulation to avoid subcutaneous reactions; and avoid administering anti-IL-6 if patient has history of diverticulitis.
Anti-IL-1 (anakinra[88] or canakinumab [IL-1b][89])	Canakinumab: 150–300 mg subcutaneous every 4 weeks (preferred);[90] anakinra: 100–200 mg subcutaneous daily[90]	Neutropenia (anakinra); subcutaneous injection site reactions (especially anakinra); infusion reactions; and infection (mainly bacterial and viral, but possibly atypical).	A degree of neutropenia (absolute neutrophil count >0·75 × 10^9/L) is tolerated in patients with VEXAS syndrome. Consider use of canakinumab due to severe subcutaneous reactions with anakinra.
Other JAK inhibitors (upadacitinib [selective JAK1],[91] tofacitinib [JAK1/3],[92] or baricitinib [JAK1/2][93])	Upadacitinib: 15–45 mg daily with a median utilised dose in VEXAS of 15 mg;[85] tofacitinib: 5–10 mg daily;[85] baricitinib: 2 mg daily.[85]	Cytopenias; infection (viral [eg, varicella zoster virus], bacterial, fungal, and atypical mycobacterial); hepatic toxicity; non-melanoma skin cancers; thrombosis; and major adverse cardiovascular events.	Administer antiviral prophylaxis and monitor for atypical infection. Caution to be used if patient has history of thrombosis.

VEXAS=vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.

Table: **Steroid-sparing therapies commonly used for VEXAS syndrome**

Conclusion

Beyond the discovery of a new disease that is remarkably prevalent and life-threatening, VEXAS syndrome illustrates the potential causal role that somatic variants might have in non-malignant conditions. Acquired mutations in blood or solid organs might underlie a spectrum of single-organ and systemic diseases. Defining complex inflammatory diseases based on molecular characterisation of disease rather than patterns of clinical features will likely continue to reshape disease taxonomy in rheumatology and other related medical specialties for many decades.

Although much has been uncovered in the 5 years since the discovery of VEXAS syndrome, there remain many unknowns in terms of pathophysiology, diagnostics, and therapeutics. The origins and clonal selection of *UBA1* mutations, and the precise mechanisms underlying the resultant systemic autoinflammatory effect, remain poorly understood. Most published clinical data are retrospective, and there are currently no approved drugs from a regulatory body for VEXAS syndrome, although there are two prospective clinical trials underway. In August, 2025, the International VEXAS Working Group Expert Panel proposed the first formal international consensus guidance for VEXAS syndrome, incorporating both diagnostics and clinical management.[48] However, overall treatment outcomes remain inadequate with patients remaining dependent on chronic glucocorticoids, highlighting the need for further research.

Softening the blow

Inside the data-driven quest to make football helmets safer

1 Softer shells
Molded from more pliable materials and perforated to allow for flexing, the shell of a modern football helmet bends under a blow, much like a car's crumple zones do. Unlike the car, the helmet returns to its original shape.

2 Bigger helmets
Continuing a decadeslong trend, modern helmets have also gotten bigger. The extra padded space between shell and scalp gives the head more room and time to slow down.

1970–1990s

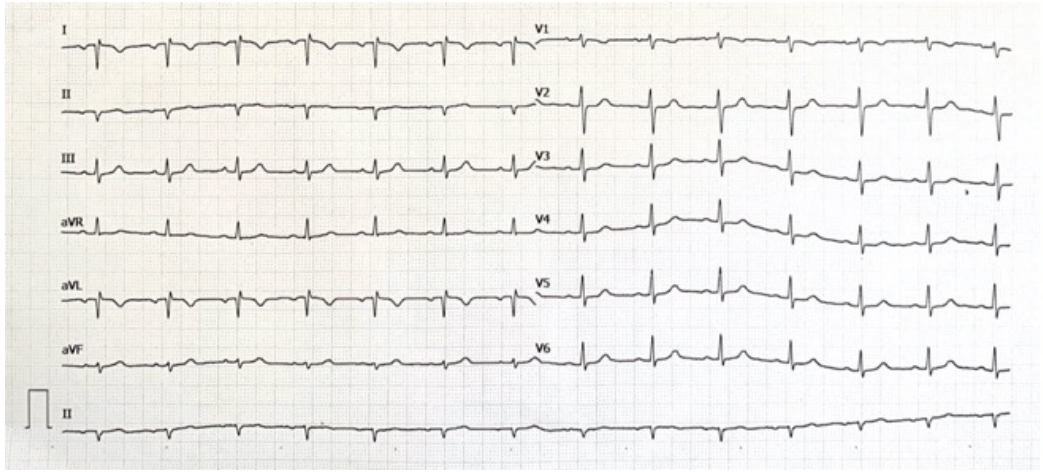
2020s

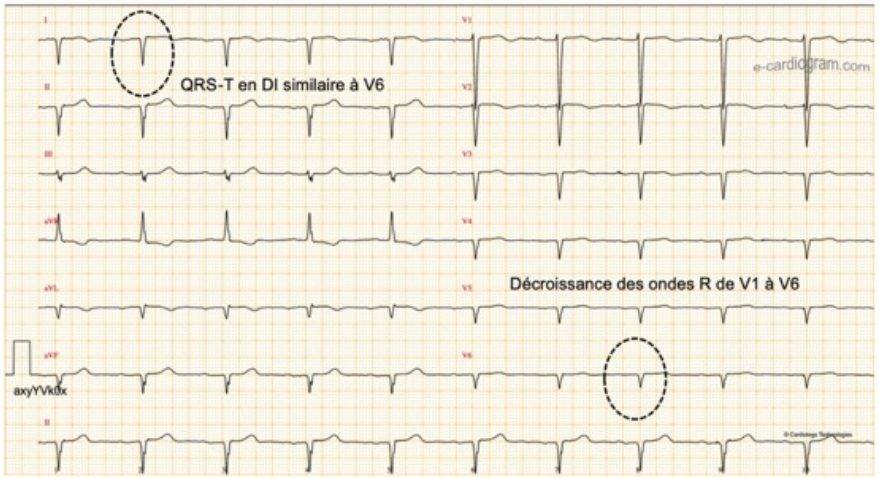
3 3D less-is-more padding
Many modern helmets employ 3D-printed liners, such as the K3D technology from KOLLIDE. Such pads exploit the subtle and tunable physics of crumpling. Made of less material, they can compress to as little as 10% to 20% of their original thickness, as opposed to 40% to 50% for foam.

Action and reaction
As a player's head recoils from a blow, it can undergo straight linear acceleration, twisting rotational acceleration, or both, depending on the blow's direction and location on the helmet.

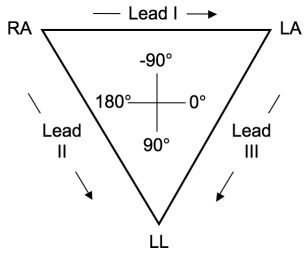
Twisting trauma
Key to concussion, a rotational acceleration can cause the brain to twist and stretch—in some regions, as much as 20%, computer simulations like this one suggest. The stretching appears to set off a cascade of cellular signaling that causes concussion symptoms. Test protocols aim to probe a helmet's ability to reduce both linear and rotational accelerations.

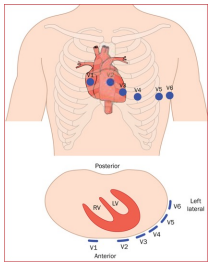
Was ist los bei diesen EKGs?





Arm Ableitungen wurden vertauscht



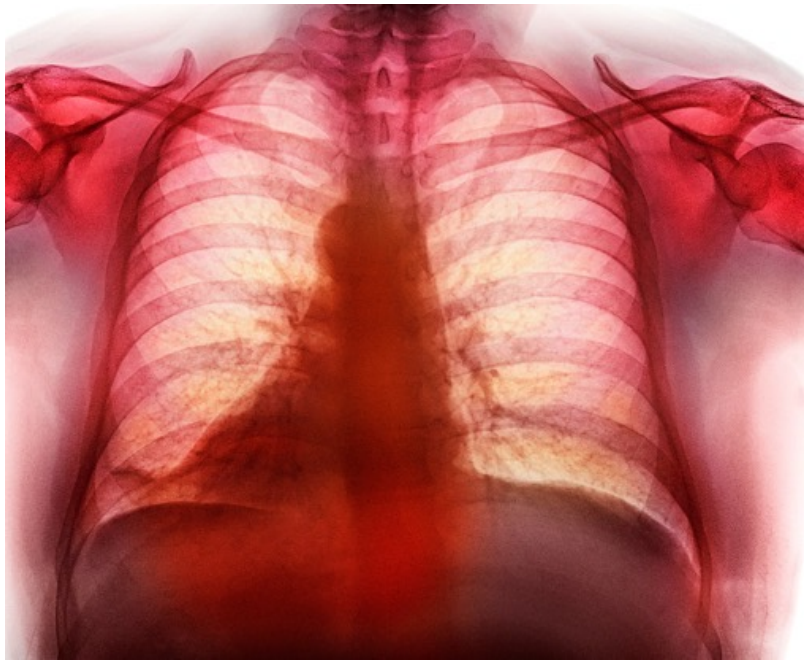


Situs inversus

What to know about the rare condition Catherine O'Hara had

The cause of her death has not yet been confirmed, although O'Hara previously shared she was born with a rare congenital condition called situs inversus that affects roughly 1 in 10,000 people. She reportedly discovered her diagnosis over 20 years ago when undergoing routine medical tests. "When the doctor told us that my heart was on the right side, and my organs were flipped, my husband immediately said, 'No, her head's on backwards,'" O'Hara said during a "Virtual Happy Hour" with Kathryn Hall in 2020.

There is no evidence that situs inversus — a condition in which the internal organs are essentially a mirror image of where they typically occur — contributed to O'Hara's death. However, the condition occasionally co-occurs with a respiratory disorder that impairs lung function. We asked two cardiologists, neither of whom had treated O'Hara, about the causes, symptoms and complications of situs inversus.



PA chest roetgenogram

How is situs inversus diagnosed?

O'Hara said she discovered her internal organs were reversed only when she underwent an electrocardiogram for an unrelated health exam. Small said that most people get diagnosed this way — essentially, by accident. "Someone comes into the emergency room for problem X, Y or Z, and they get a CT scan or X-ray, and the computer will show the heart is on the right side," he said.

What is the life expectancy of someone with situs inversus?

The prognosis for situs inversus varies from person to person, depending on the severity of their condition and the subtype they have. The life expectancy for people with situs inversus totalis is in line with that of the general population. "Because it's a mirror image, everything ends up being hooked up properly," Small said.