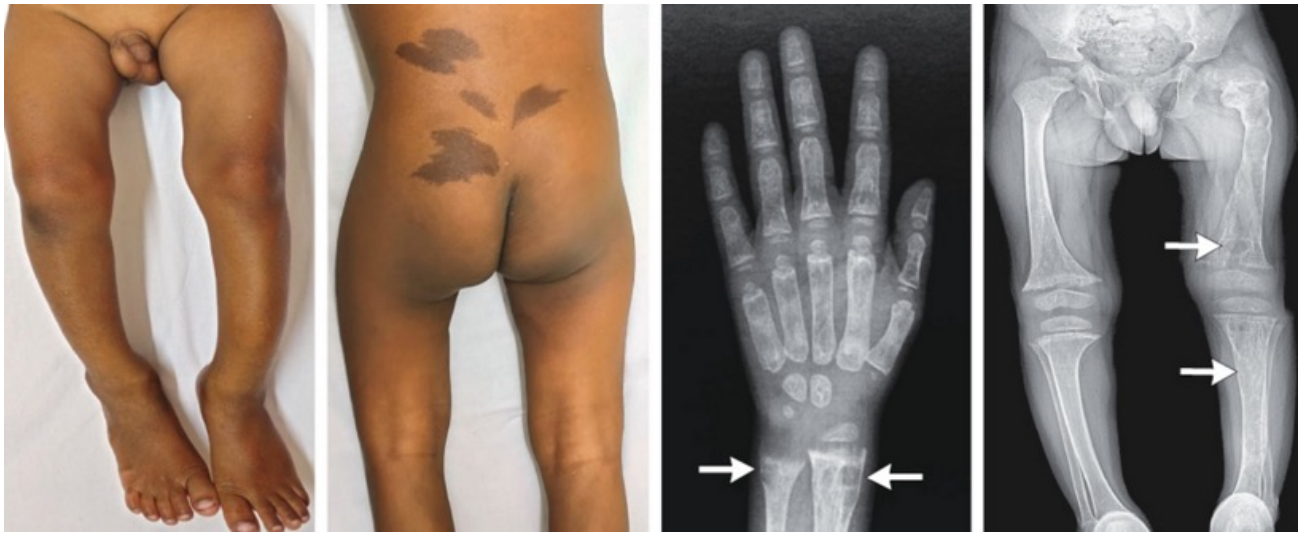
https://www.mdc-berlin.de/de/veroeffentlichungstypen/clinical-journal-club

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 3-year-old boy was brought to the endocrinology department with an 18-month history of bowing of the left leg that had resulted in regression of his ability to walk. On physical examination, there was lateral bowing of the left femur and anterior bowing of the left tibia, as well as testicular enlargement. Café au lait spots were also noted on the lower back, cheek, and neck. Radiographs of the wrist, femur, and tibia on the left side showed fibrous dysplasia (arrows) and rickets. What is the most likely diagnosis in this case?

Carney complex

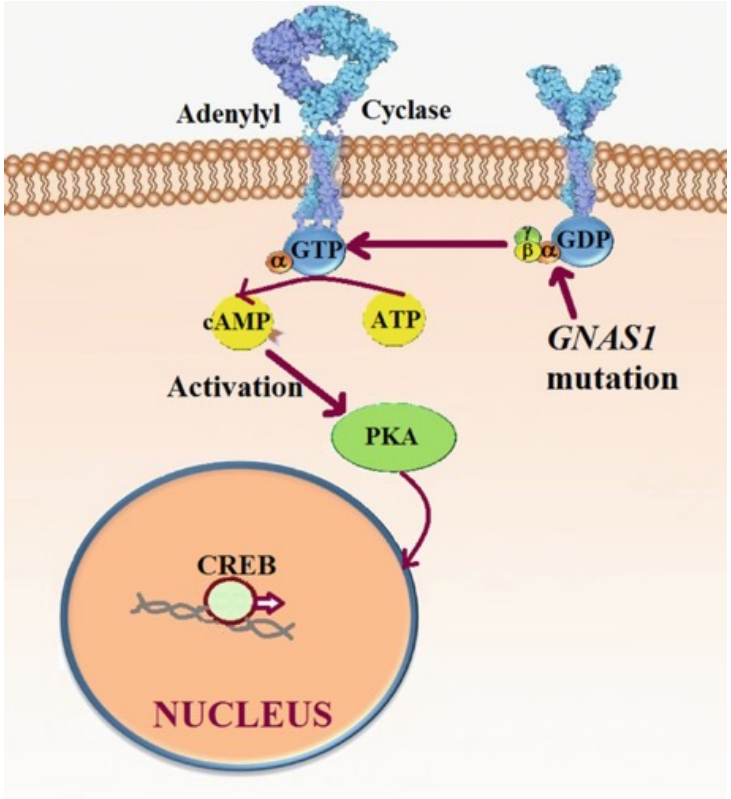
Fanconi anemia

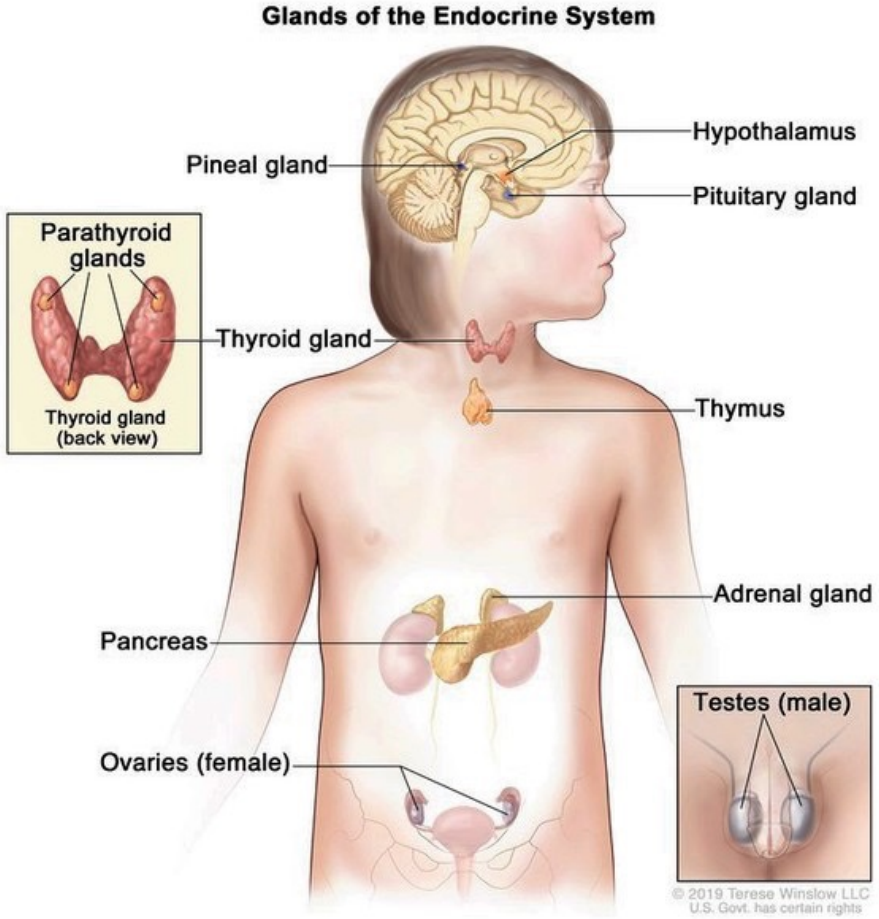
McCune–Albright syndrome

Neurofibromatosis type 1 (NF1)

Osteofibrous dysplasia

On the basis of the findings of café au lait spots, macroorchidism, and fibrous dysplasia, a diagnosis of the McCune–Albright syndrome was made. The McCune–Albright syndrome is caused by a somatic mutation in GNAS that results in stimulation of endocrine function. The patient's parents declined genetic analysis of the affected organs. Treatment with oral phosphate and calcitriol was given.


Adenylyl
Cyclase
GTP
GDP
cAMP
ATP
Activation
GNAS1
mutation
PKA
CREB
NUCLEUS


Glands of the Endocrine System
Pineal gland
Hypothalamus
Pituitary gland
Parathyroid glands
Thyroid gland
Thyroid gland (back view)
Thymus
Adrenal gland
Pancreas
Testes (male)
Ovaries (female)
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Patienten mit McCune-Albright-Syndrom fallen durch eine typische Trias auf:

- Café-au-lait-Flecken
- Pseudopubertas praecox: gonadotropinunabhängige Stimulation der Testosteronbildung
- polyostotische Fibröse Dysplasie mit hypophosphatämischer Rachitis.

Die Café-au-lait-Flecken treten oft nur auf einer Körperseite auf und haben eine flache, irreguläre, ausgefranste Konfiguration, die auch als "Küste von Maine" bezeichnet wird. Dadurch unterscheiden sie sich von den glatt begrenzten Hyperpigmentierungen bei Neurofibromatose ("Küste von Kalifornien").

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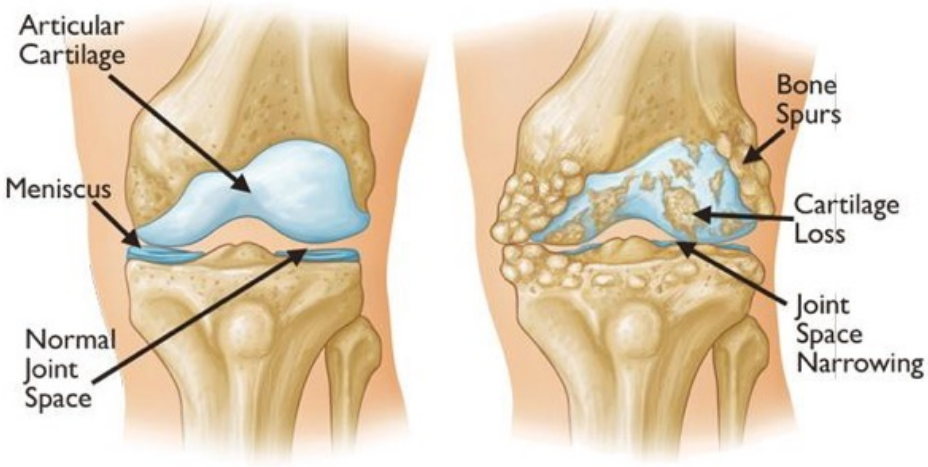
Die polyostotische fibröse Dysplasie betrifft v.a. Oberkiefer, Gesichtsschädel, Rippen, proximales Femur und Tibia. Das Wachstum der Knochenläsion kann zu Schmerzen, Fehlstellungen, Frakturen oder Nervenkompression führen. Die Läsionen bestehen aus mesenchymalen Zellen, die sich nicht zu Osteoblasten weiterentwickeln, und unvollständigem Knochengewebe. An anderen Stellen nehmen fibroblastenähnliche Zellen Eigenschaften von Osteoblasten an und produzieren eine Extrazellularmatrix, die sich zu Geflechtknochen organisiert. Stellenweise kommt es auch zur Verkalkung und Verknorpelung. Eine maligne Transformation ist selten. Bei einigen Patienten führt die Hypophosphatämie und Phosphaturie über die Nieren zu Rachitis und Osteomalazie. Die Hypophosphatämie entsteht durch Bildung von FGF23 im Fasergewebe.

Neben den klassischen Symptomen finden sich bei einigen Patienten auch folgende Symptome:

primäre Hyperthyreose ggf. mit Struma multinodosa
High-T3-Syndrom und T3-Hyperthyreose durch Hyperdeiodierung
ACTH-unabhängiges Cushing-Syndrom durch Nebennierenadenome
Hyperparathyreoidismus durch Nebenschilddrüsenadenome
Akromegalie, Hyperprolaktinämie

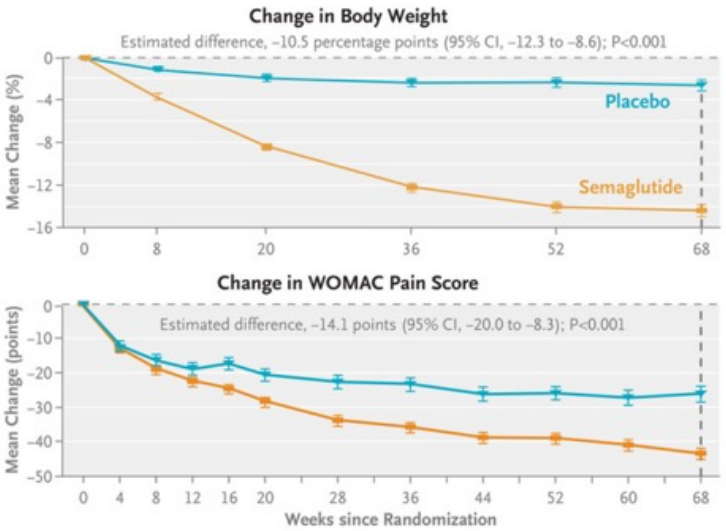
Knee osteoarthritis (OA), also known as degenerative joint disease of the knee, is typically the result of wear and tear and progressive loss of articular cartilage. It is most common in the elderly. Knee osteoarthritis can be divided into two types, primary and secondary.



Semaglutid ist ein Antidiabetikum aus der Gruppe der GLP-1-Rezeptor-Agonisten. Der Arzneistoff wird zur Therapie des Diabetes mellitus Typ 2 und zur Gewichtsreduktion bei Adipositas angewendet.

Once-Weekly Semaglutide in Persons with Obesity and Knee Osteoarthritis

Weight reduction has been shown to alleviate symptoms of osteoarthritis of the knee, including pain. The effect of glucagon-like peptide-1 receptor agonists on outcomes in knee osteoarthritis among persons with obesity has not been well studied. We conducted a 68-week, double-blind, randomized, placebo-controlled trial at 61 sites in 11 countries. Participants with obesity (a body-mass index [BMI; the weight in kilograms divided by the square of the height in meters] of ≥30) and a clinical and radiologic diagnosis of moderate knee osteoarthritis with at least moderate pain were randomly assigned, in a 2:1 ratio, to receive once-weekly subcutaneous semaglutide (2.4 mg) or placebo, in addition to counseling on physical activity and a reduced-calorie diet. The primary end points were the percentage change in body weight and the change in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score (on a scale of 0 to 100, with higher scores reflecting worse outcomes) from baseline to week 68. A key confirmatory secondary end point was the physical-function score on the 36-Item Short Form Health Survey (SF-36), version 2 (on a scale of 0 to 100, with higher scores indicating greater well-being).



Participants

Participants were 18 years of age or older and had obesity (BMI ≥30), a clinical diagnosis of knee osteoarthritis according to American College of Rheumatology criteria (knee pain with three or more of the following factors: an age of >50 years, stiffness for <30 minutes in the morning, crepitus, bony tenderness, bony enlargement, and no palpable warmth), with moderate radiographic changes (Kellgren–Lawrence grade 2 or 3) in the target knee.

Procedures

Participants were randomly assigned in a 2:1 ratio, with the use of an interactive Web-response system, to receive once-weekly subcutaneous semaglutide or visually identical placebo for 68 weeks, followed by a 7-week follow-up period during which the participants did not receive semaglutide or placebo. Semaglutide was initiated at a dose of 0.24 mg, with dose escalation intended to reach the 2.4-mg target at week 16. Participants who had unacceptable side effects with a 2.4-mg dose could continue to receive a lower dose (1.7 mg), provided that the investigator considered the treatment to be safe.

End Points and Assessments

All the end points were assessed from baseline to week 68. The primary end points were the percentage change in body weight and the change in WOMAC pain score. Confirmatory secondary end points were the percentage of participants with a body-weight reduction of at least 5% or at least 10%, the change in the WOMAC physical-function score, and the change in physical-function score on the 36-Item Short Form Health Survey (SF-36), version 2.0.

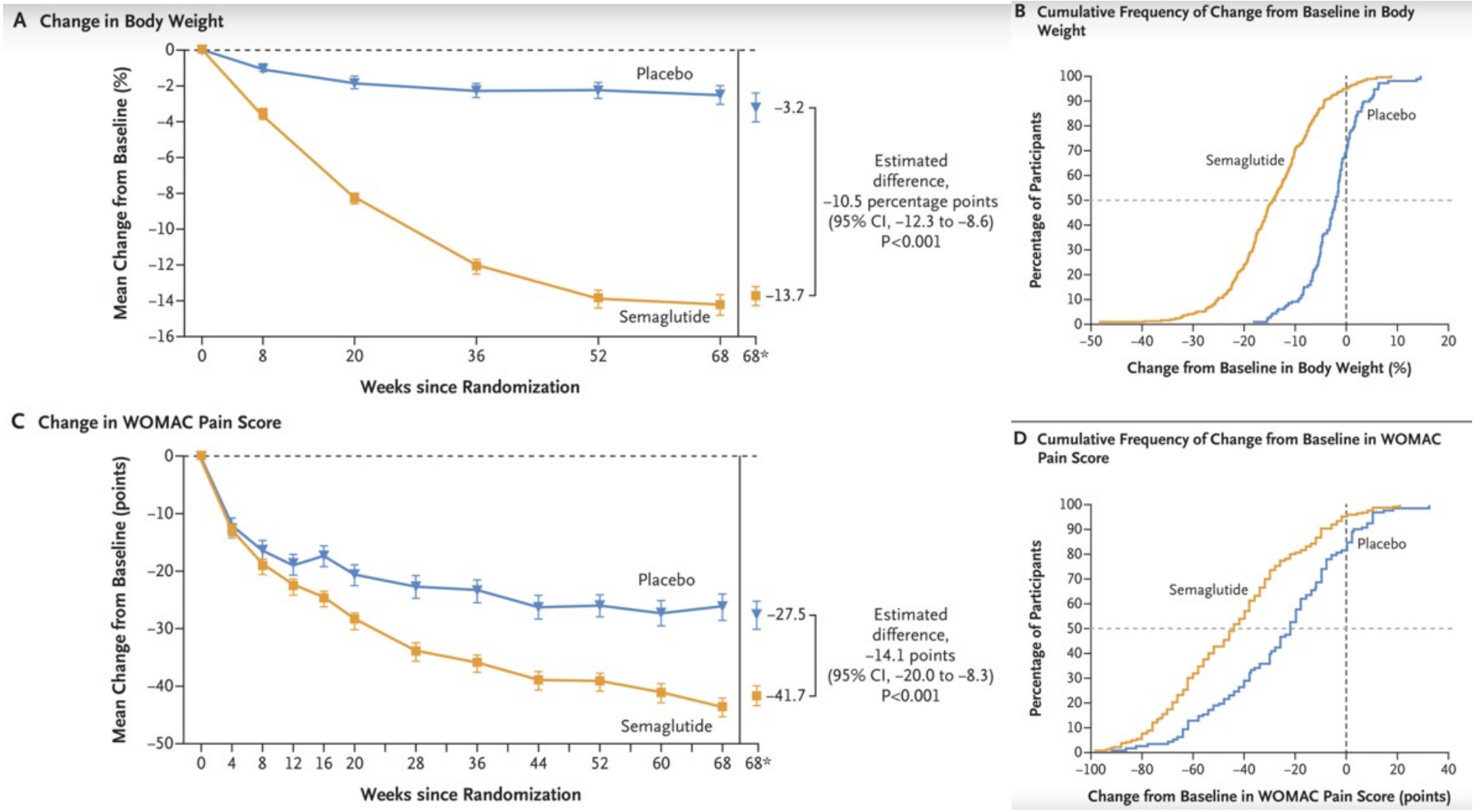
Characteristics of the Participants at Baseline.

Characteristic	Semaglutide (N=271)	Placebo (N=136)	Total (N=407)
Age — yr	56±10	56±10	56±10
Female sex — no. (%)	228 (84.1)	104 (76.5)	332 (81.6)
Race or ethnic group — no. (%)†			
White	168 (62.0)	80 (58.8)	248 (60.9)
Asian	16 (5.9)	6 (4.4)	22 (5.4)
Black	18 (6.6)	13 (9.6)	31 (7.6)
American Indian or Alaska Native	37 (13.7)	11 (8.1)	48 (11.8)
Other	32 (11.8)	26 (19.1)	58 (14.3)
Body weight — kg	108.7±24.1	108.5±24.5	108.6±24.2
Body-mass index			
Mean	40.5±7.3	40.0±7.1	40.3±7.2
Distribution — no. (%)			
<30	0	1 (0.7)	1 (0.2)
30 to <35	67 (24.7)	32 (23.5)	99 (24.3)
35 to <40	84 (31.0)	56 (41.2)	140 (34.4)
≥40	120 (44.3)	47 (34.6)	167 (41.0)
Waist circumference — cm‡	118.3±15.8	119.7±15.9	118.7±15.8
WOMAC pain score§	72.8±15.6	67.2±16.0	70.9±16.0
Systolic blood pressure — mm Hg¶	132±14	131±15	132±15
Diastolic blood pressure — mm Hg¶	82±10	82±10	82±10
Coexisting conditions — no. (%)‖			
Hypertension	128 (47.2)	68 (50.0)	196 (48.2)
Dyslipidemia	80 (29.5)	44 (32.4)	124 (30.5)
Gastroesophageal reflux disease	31 (11.4)	15 (11.0)	46 (11.3)
Asthma	19 (7.0)	19 (14.0)	38 (9.3)
Cardiovascular disease	13 (4.8)	8 (5.9)	21 (5.2)

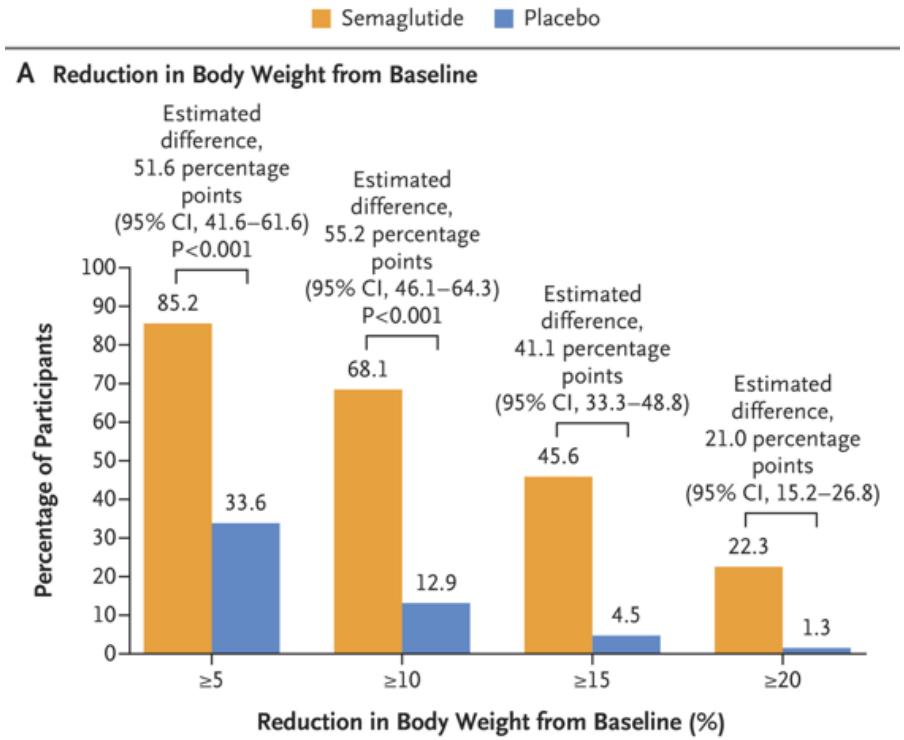
Adverse Events.

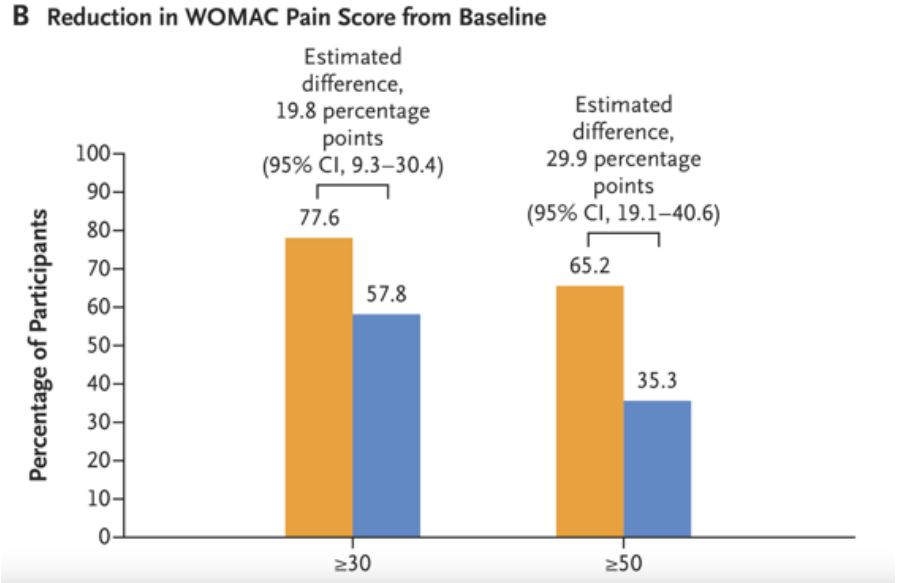
Adverse Event	Semaglutide (N=269)	Placebo (N=135)	Relative Risk (95% CI)	Risk Difference (95% CI)††
	no. of participants (%)			
Any serious adverse event	27 (10.0)	11 (8.1)	1.23 (0.64 to 2.40)	1.9 (−4.7 to 7.3)
Adverse event leading to permanent discontinuation of semaglutide or placebo				
Any event	18 (6.7)	4 (3.0)	2.26 (0.82 to 6.30)	3.7 (−1.3 to 7.7)
Gastrointestinal disorder	6 (2.2)	0	—	2.2 (−0.8 to 4.8)
Fatal event	0	0	—	—
Safety focus areas				
Coronavirus disease 2019	51 (19.0)	32 (23.7)	0.80 (0.54 to 1.19)	−4.7 (−13.7 to 3.4)
Serious neoplasm‡	10 (3.7)	6 (4.4)	0.84 (0.32 to 2.18)	−0.7 (−5.9 to 3.1)
Serious malignant neoplasm‡	8 (3.0)	2 (1.5)	2.01 (0.49 to 8.31)	1.5 (−2.5 to 4.5)
Serious gastrointestinal event‡	4 (1.5)	1 (0.7)	2.01 (0.31 to 13.33)	0.7 (−2.7 to 3.1)
Serious acute gallbladder disease‡	3 (1.1)	1 (0.7)	1.51 (0.22 to 10.49)	0.4 (−3.0 to 2.6)
Serious cardiovascular disorder‡	3 (1.1)	2 (1.5)	0.75 (0.15 to 3.75)	−0.4 (−4.2 to 2.0)
Medication error§	2 (0.7)	4 (3.0)	0.25 (0.05 to 1.16)	−2.2 (−6.7 to 0.4)
Serious acute renal failure‡	0	1 (0.7)	0.00 (0.00 to 1.93)	−0.7 (−4.1 to 0.8)
Serious psychiatric disorder‡	0	1 (0.7)	0.00 (0.00 to 1.93)	−0.7 (−4.1 to 0.8)
Acute pancreatitis	0	0	—	—
Pregnancy or pregnancy-related adverse event‡	0	0	—	—
Joint replacement	2 (0.7)	0	—	—

Changes in Body Weight and WOMAC Pain Score.

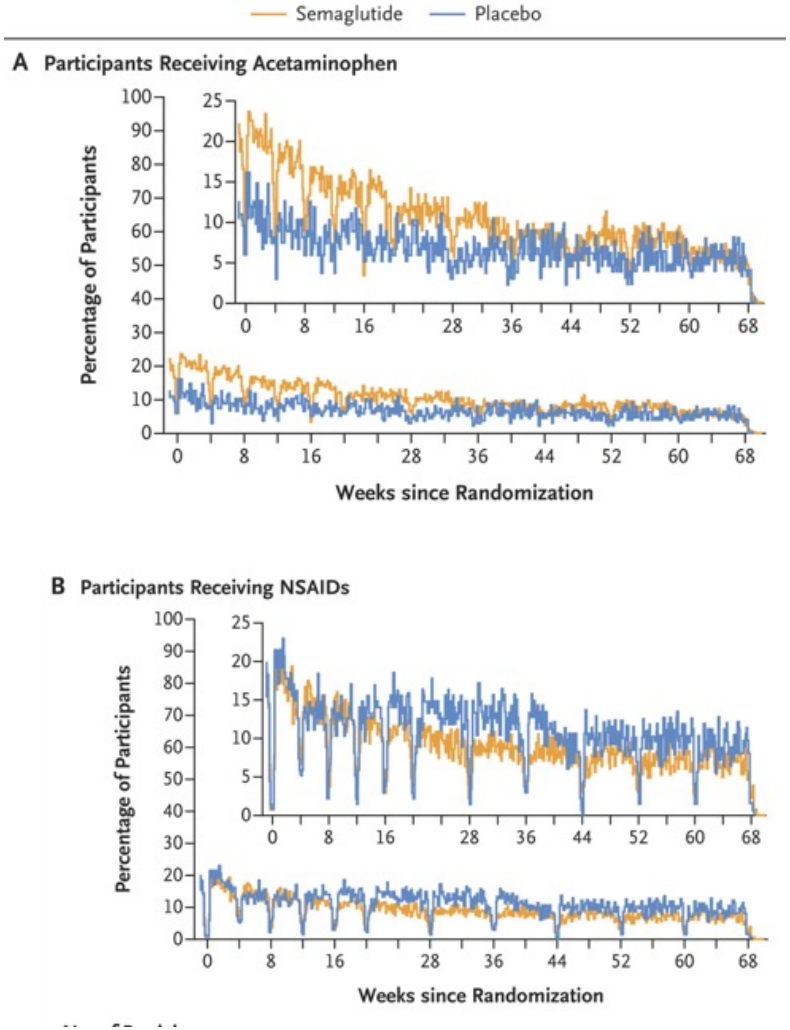


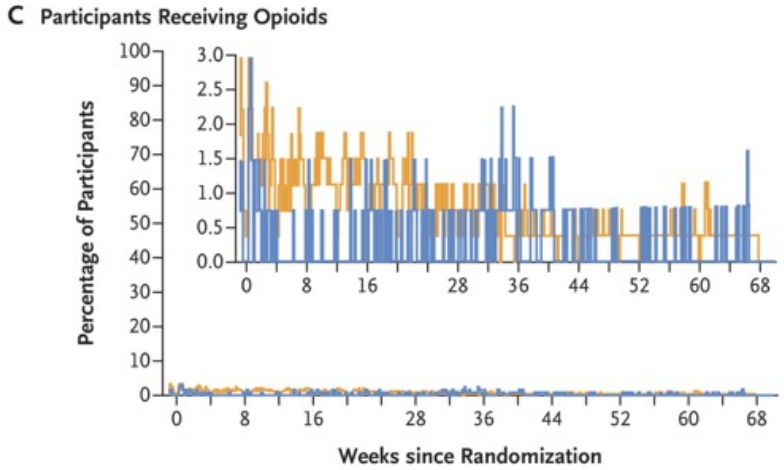
Reduction in Body Weight and WOMAC Pain Score at Week 68.

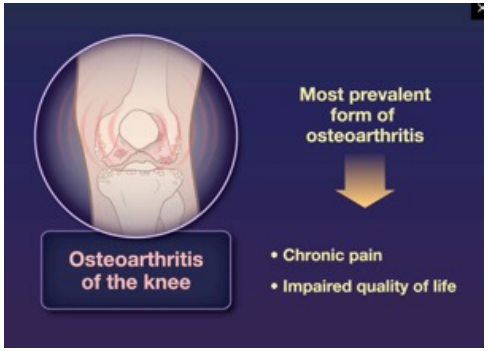




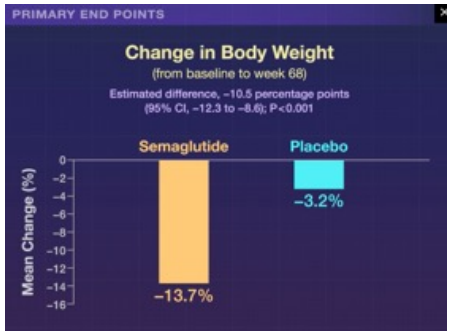
Use of Pain Medication According to Type.

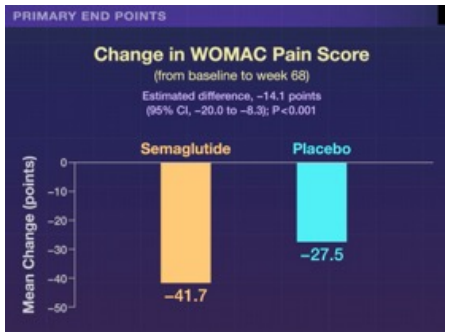


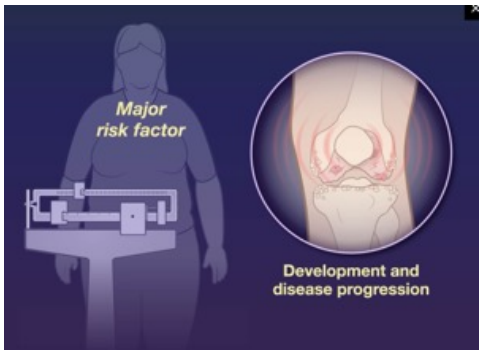


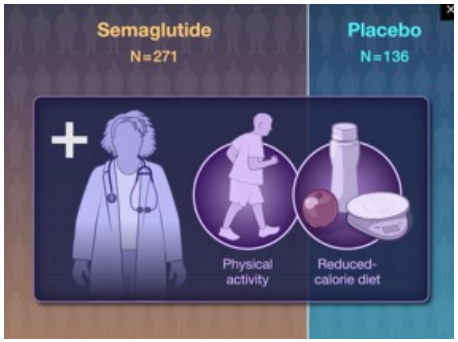

Most prevalent form of osteoarthritis
Osteoarthritis of the knee
• Chronic pain
• Impaired quality of life

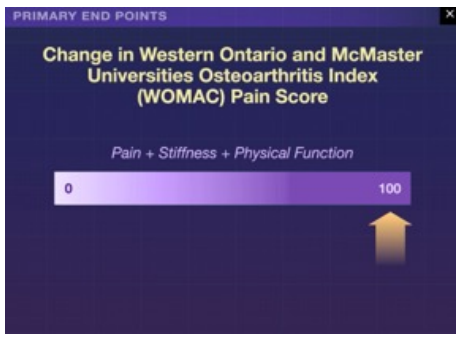

Semaglutide
N=271
Placebo
N=136
2.4 mg

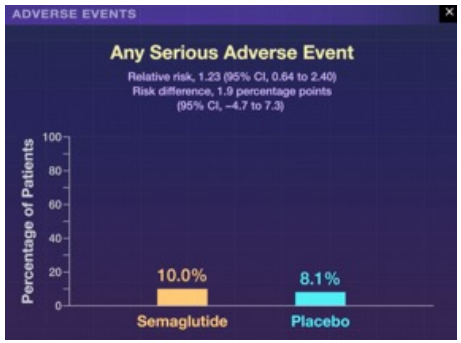

PRIMARY END POINTS
Change in Body Weight
(from baseline to week 68)
Estimated difference, −10.5 percentage points
(95% CI, −12.3 to −8.6); P<0.001
Semaglutide
Placebo
Mean Change (%)
0
−2
−4
−6
−8
−10
−12
−14
−16
−13.7%
−3.2%


PRIMARY END POINTS
Change in WOMAC Pain Score
(from baseline to week 68)
Estimated difference, −14.1 points
(95% CI, −20.0 to −8.3); P<0.001
Semaglutide
Placebo
Mean Change (points)
0
−10
−20
−30
−40
−50
−41.7
−27.5

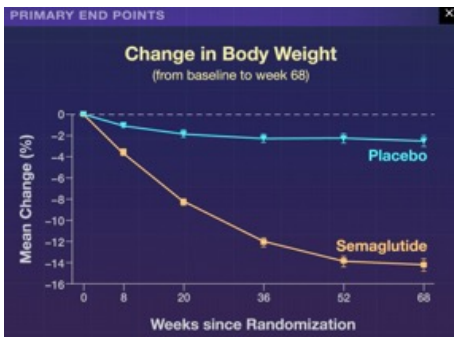

Major risk factor
Development and disease progression

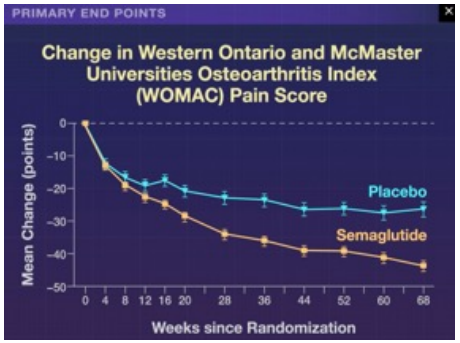

Semaglutide
N=271
Placebo
N=136
Physical activity
Reduced-calorie diet


PRIMARY END POINTS
Change in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain Score
Pain + Stiffness + Physical Function
0
100


ADVERSE EVENTS
Any Serious Adverse Event
Relative risk, 1.23 (95% CI, 0.64 to 2.40)
Risk difference, 1.9 percentage points
(95% CI, −4.7 to 7.3)
Percentage of Patients
100
80
60
40
20
0
10.0%
8.1%
Semaglutide
Placebo

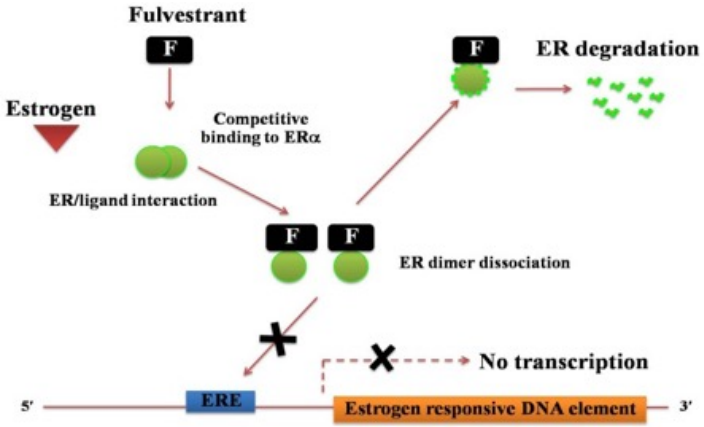

? Superior to placebo
• Body weight
• Knee osteoarthritis–related pain


PRIMARY END POINTS
Change in Body Weight
(from baseline to week 68)
Mean Change (%)
0
−2
−4
−6
−8
−10
−12
−14
−16
Placebo
Semaglutide
0
8
20
36
52
68
Weeks since Randomization

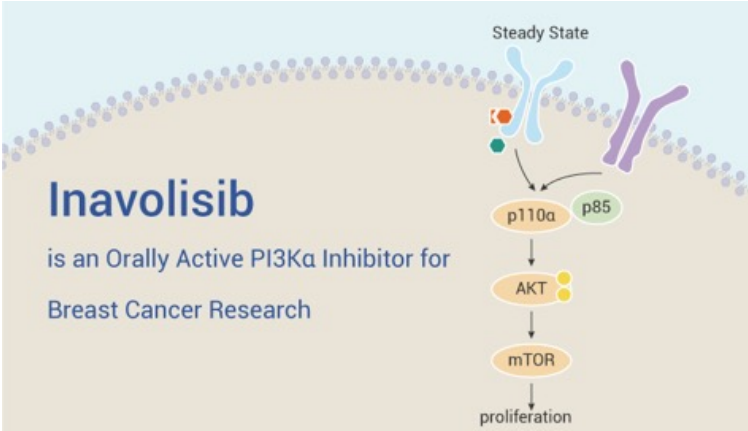

PRIMARY END POINTS
Change in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain Score
Mean Change (points)
0
−10
−20
−30
−40
−50
Placebo
Semaglutide
0
4
8
12
16
20
28
36
44
52
60
68
Weeks since Randomization


Body weight and knee osteoarthritis pain
as compared with placebo

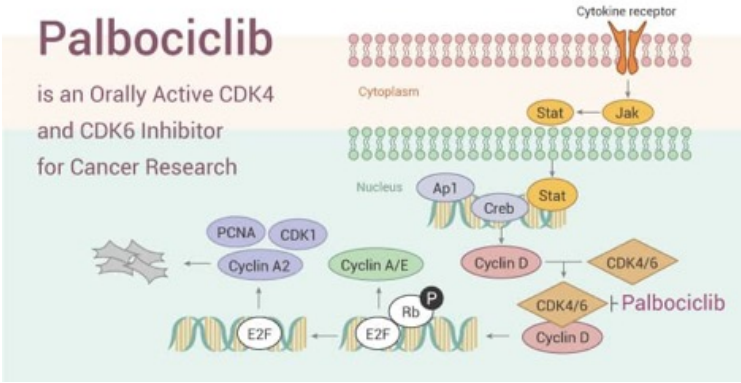
Fulvestrant ist ein Zytostatikum aus der Gruppe der Antiöstrogene und kommt bei der Behandlung des Mammakarzinoms zur Hemmung des Krebswachstums zum Einsatz. Fulvestrant hat - im Gegensatz zu Tamoxifen - keine agonistische Restwirkung an den Östrogenrezeptoren.



Inavolisib, das unter dem Markennamen Itovebi vertrieben wird, ist ein Krebsmedikament zur Behandlung von Brustkrebs. Es ist ein Inhibitor und Abbauer der mutierten Phosphatidylinositol-3-Kinase Alpha.

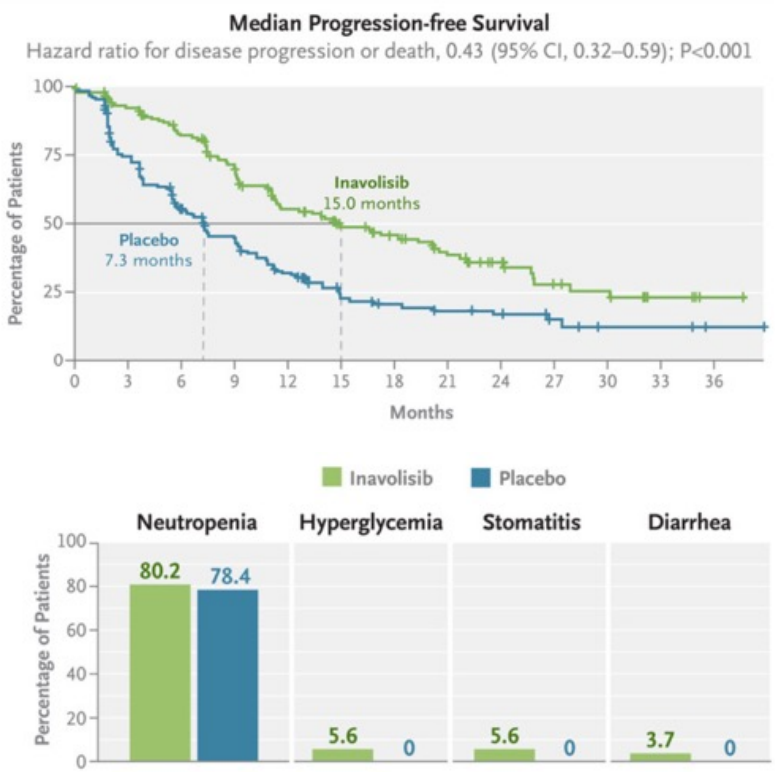


Palbociclib ist ein Arzneistoff zur Behandlung bestimmter Formen des Brustkrebses. Er ist der erste Vertreter der neuen Wirkstoffklasse der Cyclin-abhängige Kinase-Inhibitoren und ist bei peroraler Gabe wirksam.



Inavolisib-Based Therapy in PIK3CA-Mutated Advanced Breast Cancer

Inavolisib is a highly potent and selective inhibitor of the alpha isoform of the p110 catalytic subunit of the phosphatidylinositol 3-kinase complex (encoded by *PIK3CA*) that also promotes the degradation of mutated p110α. Inavolisib plus palbociclib–fulvestrant has shown synergistic activity in preclinical models and promising antitumor activity in early-phase trials. In a phase 3, double-blind, randomized trial, we compared first-line inavolisib (at an oral dose of 9 mg once daily) plus palbociclib–fulvestrant (inavolisib group) with placebo plus palbociclib–fulvestrant (placebo group) in patients with *PIK3CA*-mutated, hormone receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative locally advanced or metastatic breast cancer who had had relapse during or within 12 months after the completion of adjuvant endocrine therapy. The primary end point was progression-free survival as assessed by the investigator.



Activating mutations in *PIK3CA* occur in approximately 35 to 40% of hormone receptor–positive breast cancers. The presence of such mutations is a poor prognostic factor in patients with advanced breast cancer and is a predictive biomarker of response to phosphatidylinositol 3-kinase (PI3K) inhibitors.

Patients

Premenopausal, perimenopausal, or postmenopausal women or men with *PIK3CA*-mutated, hormone receptor–positive, HER2-negative locally advanced or metastatic breast cancer were eligible for enrollment. Additional eligibility criteria included disease recurrence or progression during or within 12 months after the completion of adjuvant endocrine therapy (patients with de novo metastatic breast cancer were excluded), a fasting glucose level of less than 126 mg per deciliter, a glycated hemoglobin level of less than 6.0%, and measurable disease.

Trial Design and Treatment

Patients were randomly assigned in a 1:1 ratio to receive inavolisib (at a dose of 9 mg, administered orally, once daily on days 1 to 28 of each 28-day cycle) or placebo (once daily), each given with palbociclib (at a dose of 125 mg, administered orally, once daily on days 1 to 21 of each 28-day cycle) and fulvestrant (at a dose of 500 mg, administered intramuscularly, on days 1 and 15 of cycle 1 and approximately every 28 days thereafter).

End Points

The primary end point was progression-free survival, defined as the time from randomization to the first occurrence of disease progression (as assessed by the investigator according to RECIST, version 1.1) or death from any cause, whichever occurred first.

Demographic and Clinical

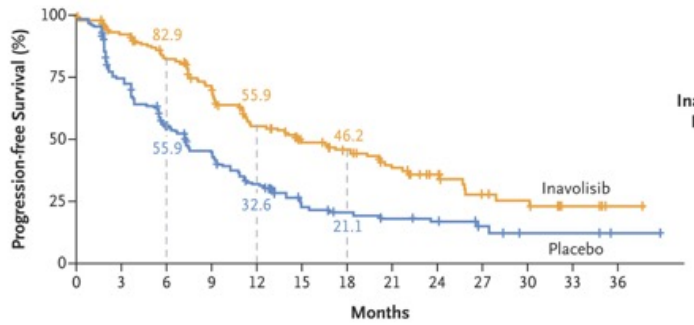
Characteristic	Inavolisib (N=161)	Placebo (N=164)	All Patients (N=325)
Median age (range) — yr	53.0 (27–77)	54.5 (29–79)	54.0 (27–79)
Female sex — no. (%)	156 (96.9)	163 (99.4)	319 (98.2)
Race — no. (%)†			
Asian	61 (37.9)	63 (38.4)	124 (38.2)
Black or African American	1 (0.6)	1 (0.6)	2 (0.6)
White	94 (58.4)	97 (59.1)	191 (58.8)
ECOG performance-status score — no. (%)‡			
0	100 (62.1)	106 (64.6)	206 (63.4)
1	60 (37.3)	58 (35.4)	118 (36.3)
Menopausal status at randomization — no. (%)			
Premenopausal	65 (40.4)	59 (36.0)	124 (38.2)
Postmenopausal	91 (56.5)	104 (63.4)	195 (60.0)
Median weight (range) — kg	62.5 (39–124)	64.0 (38–111)	63.0 (38–124)
Body-mass index — no. (%)§			
<18.5	8 (5.0)	10 (6.1)	18 (5.5)
≥18.5 to <25.0	78 (48.4)	75 (45.7)	153 (47.1)
≥25.0 to <30.0	44 (27.3)	50 (30.5)	94 (28.9)
≥30.0	29 (18.0)	28 (17.1)	57 (17.5)
Missing data	2 (1.2)	1 (0.6)	3 (0.9)
No. of organs with metastases — no. (%)			
1	21 (13.0)	32 (19.5)	53 (16.3)
2	59 (36.6)	46 (28.0)	105 (32.3)
≥3	81 (50.3)	86 (52.4)	167 (51.4)
Site of metastases — no. (%)			
Viscera¶	132 (82.0)	128 (78.0)	260 (80.0)
Liver	77 (47.8)	91 (55.5)	168 (51.7)
Lung	66 (41.0)	66 (40.2)	132 (40.6)
Bone only‖	5 (3.1)	6 (3.7)	11 (3.4)
Hormone-receptor status — no. (%)**			
ER-positive, PR-positive	113 (70.2)	113 (68.9)	226 (69.5)
ER-positive, PR-negative	45 (28.0)	45 (27.4)	90 (27.7)
Other	3 (1.9)	6 (3.7)	9 (2.8)
Resistance to endocrine therapy — no. (%)††			
Primary resistance	53 (32.9)	58 (35.4)	111 (34.2)
Secondary resistance	108 (67.1)	105 (64.0)	213 (65.5)
Missing data	0	1 (0.6)	1 (0.3)
Previous neoadjuvant or adjuvant chemotherapy — no. (%)	132 (82.0)	137 (83.5)	269 (82.8)
Previous neoadjuvant or adjuvant endocrine therapy — no. (%)			
Overall	160 (99.4)	163 (99.4)	323 (99.4)
Aromatase inhibitor only	60 (37.3)	71 (43.3)	131 (40.3)
Tamoxifen only	82 (50.9)	73 (44.5)	155 (47.7)
Aromatase inhibitor and tamoxifen	18 (11.2)	19 (11.6)	37 (11.4)
Previous neoadjuvant or adjuvant CDK4/6 inhibitor — no. (%)	3 (1.9)	1 (0.6)	4 (1.2)

Adverse Events.

Adverse Event	Inavolisib (N=162)		Placebo (N=162)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Neutropenia	144 (88.9)	130 (80.2)	147 (90.7)	127 (78.4)
Thrombocytopenia	78 (48.1)	23 (14.2)	73 (45.1)	7 (4.3)
Stomatitis and mucosal inflammation	83 (51.2)	9 (5.6)	43 (26.5)	0
Anemia	60 (37.0)	10 (6.2)	59 (36.4)	3 (1.9)
Hyperglycemia	95 (58.6)	9 (5.6)	14 (8.6)	0
Diarrhea	78 (48.1)	6 (3.7)	26 (16.0)	0
Nausea	45 (27.8)	1 (0.6)	27 (16.7)	0
Rash	41 (25.3)	0	28 (17.3)	0
Decreased appetite	38 (23.5)	0	14 (8.6)	0
Fatigue	38 (23.5)	0	21 (13.0)	2 (1.2)
Covid-19	37 (22.8)	3 (1.9)	17 (10.5)	1 (0.6)
Headache	34 (21.0)	0	22 (13.6)	0
Leukopenia	28 (17.3)	11 (6.8)	40 (24.7)	17 (10.5)
Ocular toxic effects	36 (22.2)	0	21 (13.0)	0

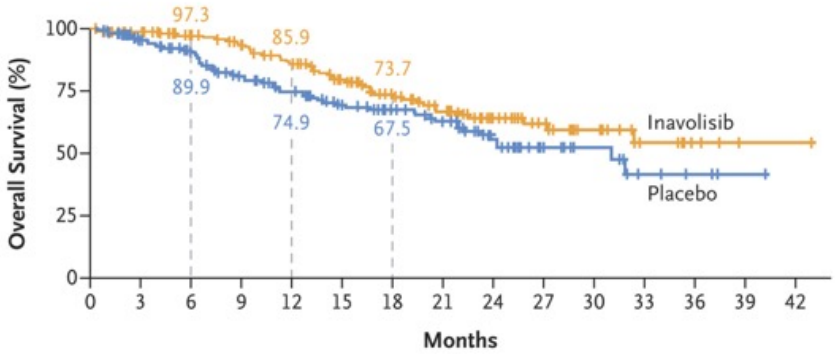
Progression free and overall survival longer

A Progression-free Survival in the Full Analysis Population



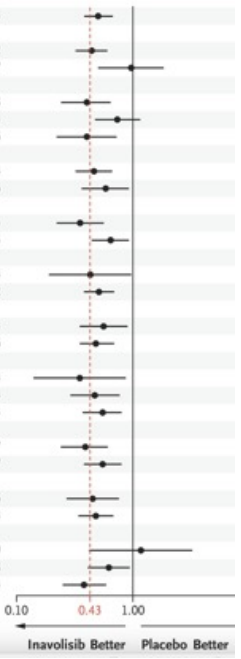
	No. of Events (%)	Median Progression-free Survival (95% CI)
		mo
Inavolisib (N=161)	82 (50.9)	15.0 (11.3–20.5)
Placebo (N=164)	113 (68.9)	7.3 (5.6–9.3)

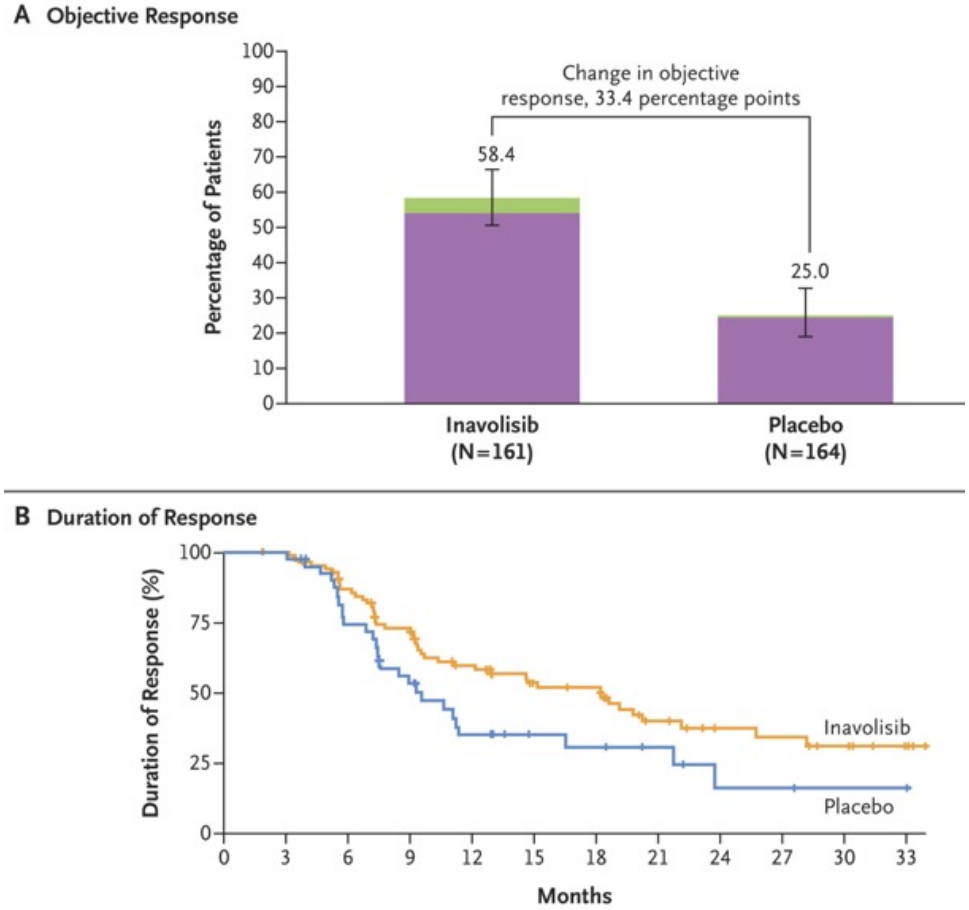
Stratified hazard ratio for disease progression or death, 0.43 (95% CI, 0.32–0.59)
P<0.001



B Analysis of Progression-free Survival in Key Subgroups

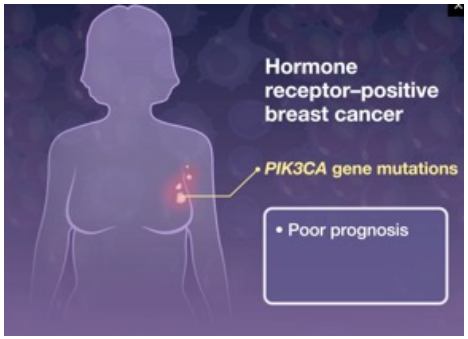
Subgroup	No. of Patients		Median Progression-free Survival		Hazard Ratio for Disease or Death (95% C
	Inavolisib	Placebo	Inavolisib	Placebo	
			mo		
All patients	161	164	15.0	7.3	
Age					
<65 yr	136	130	16.6	7.2	
≥65 yr	25	34	9.3	10.7	
Geographic region					
Asia	56	58	14.6	5.8	
North America or Western Europe	63	64	13.8	9.3	
Other	42	42	21.0	5.6	
ECOG performance-status score at baseline					
0	100	106	16.6	7.4	
1	60	58	11.4	5.6	
Menopausal status at randomization					
Premenopausal	65	59	20.1	6.5	
Postmenopausal	91	104	13.4	7.5	
Visceral disease					
No	29	36	25.8	7.4	
Yes	132	128	13.8	7.2	
Liver metastasis at enrollment					
No	84	73	24.2	11.3	
Yes	77	91	11.0	5.6	
No. of organs with metastases at enrollment					
1	21	32	20.2	7.4	
2	59	46	18.2	7.4	
≥3	81	86	14.1	7.3	
Resistance to endocrine therapy					
Primary	53	58	11.4	3.7	
Secondary	108	105	18.2	9.7	
Hormone receptor status					
ER-positive, PR-negative	45	45	11.1	5.6	
ER-positive, PR-positive	113	113	18.2	7.4	
Previous endocrine therapy					
Aromatase inhibitor and tamoxifen	18	19	11.0	12.9	
Aromatase inhibitor only	60	71	10.9	5.8	
Tamoxifen only	82	73	21.0	7.4	

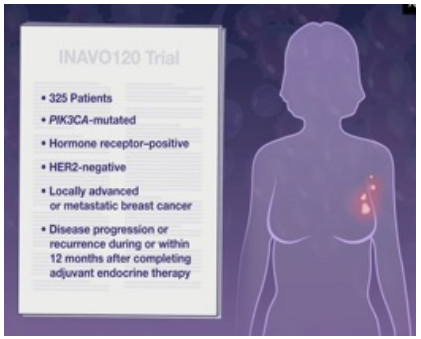


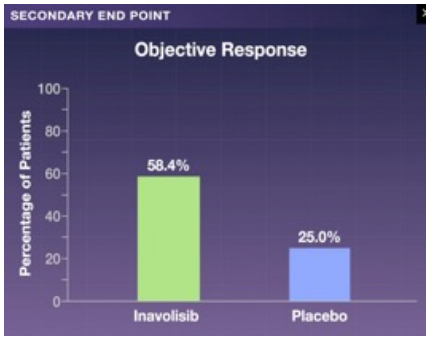


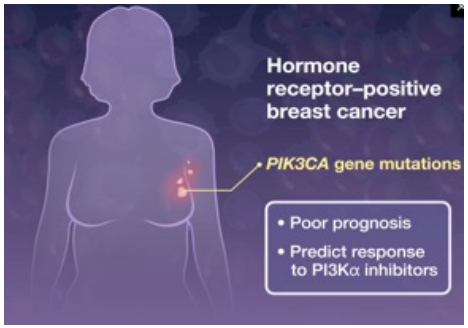
Objective Response and Response Duration.

Panel A shows the percentage of patients with an objective response as assessed by the investigator according to RECIST, version 1.1.[27] In the inavolisib group, 7 patients had a complete response, 87 had a partial response, 46 had stable disease, 7 had progressive disease, and 14 had missing data. In the placebo group, 1 patient had a complete response, 40 had a partial response, 79 had stable disease, 34 had progressive disease, and 10 had missing data. Data are for the full analysis population. Panel B shows the duration of response as assessed by the investigator according to RECIST, version 1.1.

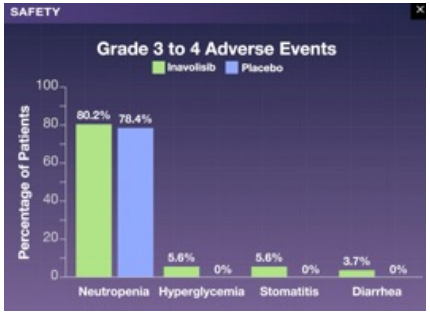

Hormone receptor–positive breast cancer
PIK3CA gene mutations
• Poor prognosis


INAVO120 Trial
• 325 Patients
• PIK3CA-mutated
• Hormone receptor–positive
• HER2-negative
• Locally advanced or metastatic breast cancer
• Disease progression or recurrence during or within 12 months after completing adjuvant endocrine therapy


SECONDARY END POINT
Objective Response
Percentage of Patients
100
80
60
40
20
0
58.4%
25.0%
Inavolisib
Placebo


Hormone receptor–positive breast cancer
PIK3CA gene mutations
• Poor prognosis
• Predict response to PI3Kα inhibitors

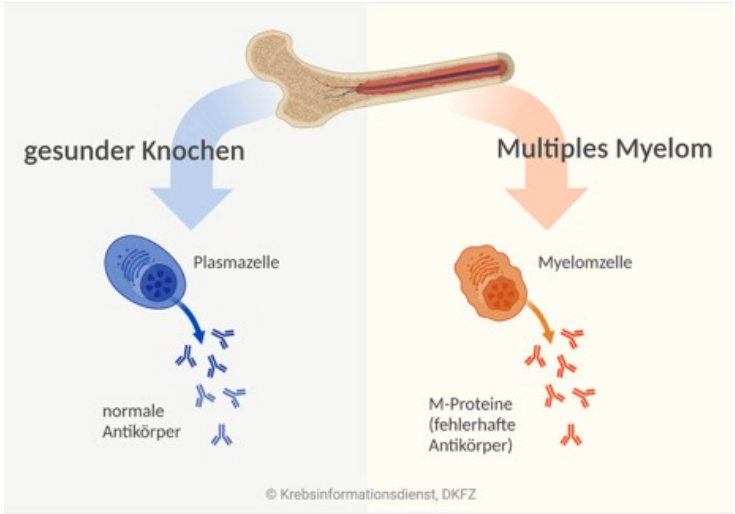

Inavolisib
(N=161)
Placebo
(N=164)
Inavolisib
Placebo
In addition to palbociclib plus fulvestrant

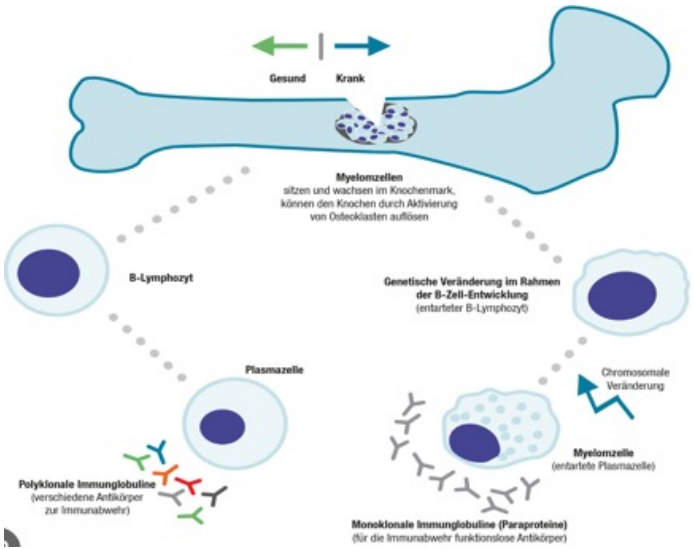

SAFETY
Grade 3 to 4 Adverse Events
Inavolisib
Placebo
Percentage of Patients
100
80
60
40
20
0
80.2%
78.4%
5.6%
0%
5.6%
0%
3.7%
0%
Neutropenia
Hyperglycemia
Stomatitis
Diarrhea

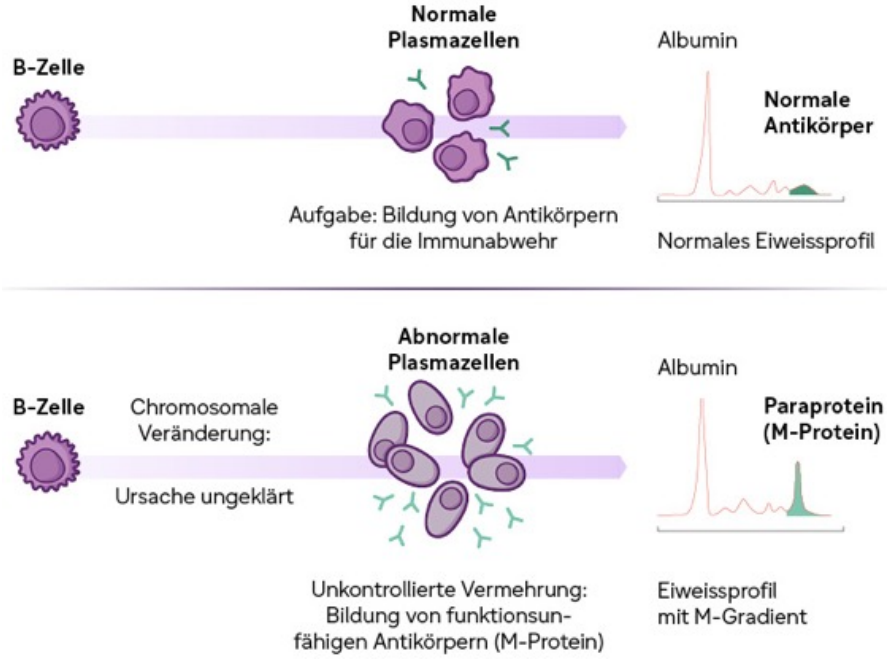

Improve outcomes
INAVO120 Trial
PI3Kα
Inavolisib
+
Palbociclib
Fulvestrant


PRIMARY END POINT
Median Progression-free Survival
Hazard ratio for disease progression or death, 0.43
(95% CI, 0.32 to 0.59); P<0.001
Percentage of Patients
100
75
50
25
0
Inavolisib
(95% CI, 11.3 to 20.5)
Placebo
(95% CI, 5.6 to 9.3)
7.3
0 3 6 9 12 15 18 21 24 27 30 33 36
Months


PI3Kα Inhibitor
Inavolisib
+
Palbociclib
Fulvestrant
Improved progression-free survival

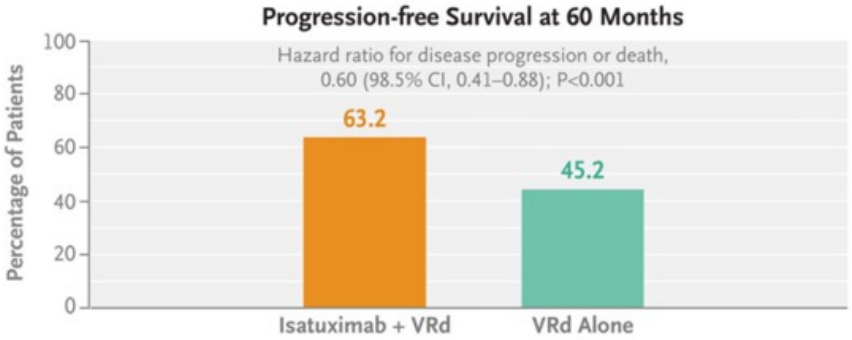

gesunder Knochen
Multiples Myelom
Plasmazelle
Myelomzelle
normale Antikörper
M-Proteine (fehlerhafte Antikörper)
© Krebsinformationsdienst, DKFZ

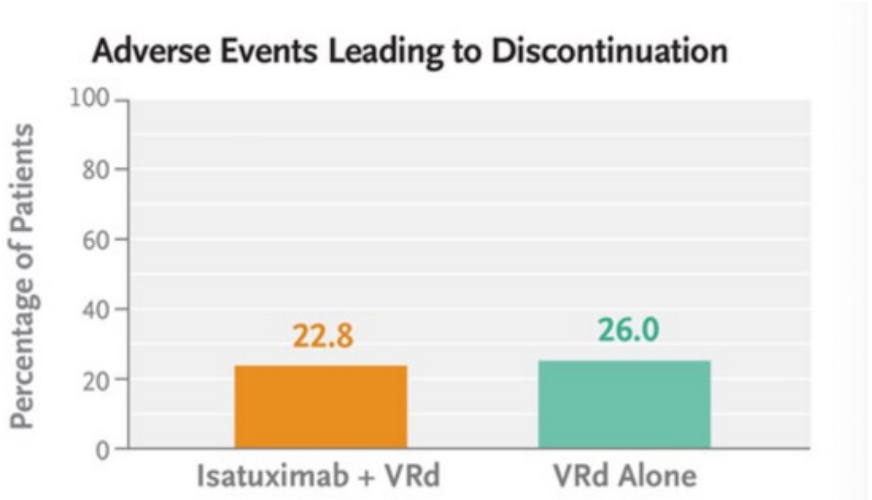

Gesund
Krank
Myelomzellen
sitzen und wachsen im Knochenmark, können den Knochen durch Aktivierung von Osteoklasten auflösen
B-Lymphozyt
Genetische Veränderung im Rahmen der B-Zell-Entwicklung
(entarteter B-Lymphozyt)
Plasmazelle
Chromosomale Veränderung
Myelomzelle
(entartete Plasmazelle)
Polyklonale Immunglobuline
(verschiedene Antikörper zur Immunabwehr)
Monoklonale Immunglobuline (Paraproteine)
(für die Immunabwehr funktionslose Antikörper)


B-Zelle
Normale Plasmazellen
Albumin
Normale Antikörper
Aufgabe: Bildung von Antikörpern für die Immunabwehr
Normales Eiweissprofil
B-Zelle
Chromosomale Veränderung:
Ursache ungeklärt
Abnormale Plasmazellen
Albumin
Paraprotein (M-Protein)
Unkontrollierte Vermehrung: Bildung von funktionsunfähigen Antikörpern (M-Protein)
Eiweissprofil mit M-Gradient

Isatuximab, Bortezomib, Lenalidomide, and Dexamethasone for Multiple Myeloma

Bortezomib, lenalidomide, and dexamethasone (VRd) is a preferred first-line treatment option for patients with newly diagnosed multiple myeloma. Whether the addition of the anti-CD38 monoclonal antibody isatuximab to the VRd regimen would reduce the risk of disease progression or death among patients ineligible to undergo transplantation is unclear. In an international, open-label, phase 3 trial, we randomly assigned, in a 3:2 ratio, patients 18 to 80 years of age with newly diagnosed multiple myeloma who were ineligible to undergo transplantation to receive either isatuximab plus VRd or VRd alone. The primary efficacy end point was progression-free survival. Key secondary end points included a complete response or better and minimal residual disease (MRD)–negative status in patients with a complete response.





Treatment with triplet therapies has historically improved outcomes in patients with newly diagnosed multiple myeloma, providing deep, durable disease control in most patients and delaying disease relapse. The SWOG S0777 trial established bortezomib–lenalidomide–dexamethasone (VRd) as a standard, first-line treatment for patients with myeloma, regardless of their eligibility for transplantation, and is commonly used in clinical practice. Older patients with multiple myeloma benefit most when efficacious regimens are used early, given that some do not receive any subsequent lines of therapy after first-line treatment.

Patients

We enrolled patients 18 years of age or older with symptomatic previously untreated myeloma (according to International Myeloma Working Group [IMWG] criteria) and measurable disease who were ineligible to undergo transplantation owing to an age of 65 years or older or to coexisting conditions. Key exclusion criteria were an age of more than 80 years, an Eastern Cooperative Oncology Group (ECOG) performance-status score of more than 2 (on a 5-point scale, with higher scores indicating greater disability), or an estimated glomerular filtration rate (GFR) of less than 30 ml per minute per 1.73 m^2 of body-surface area.

End Points and Assessments

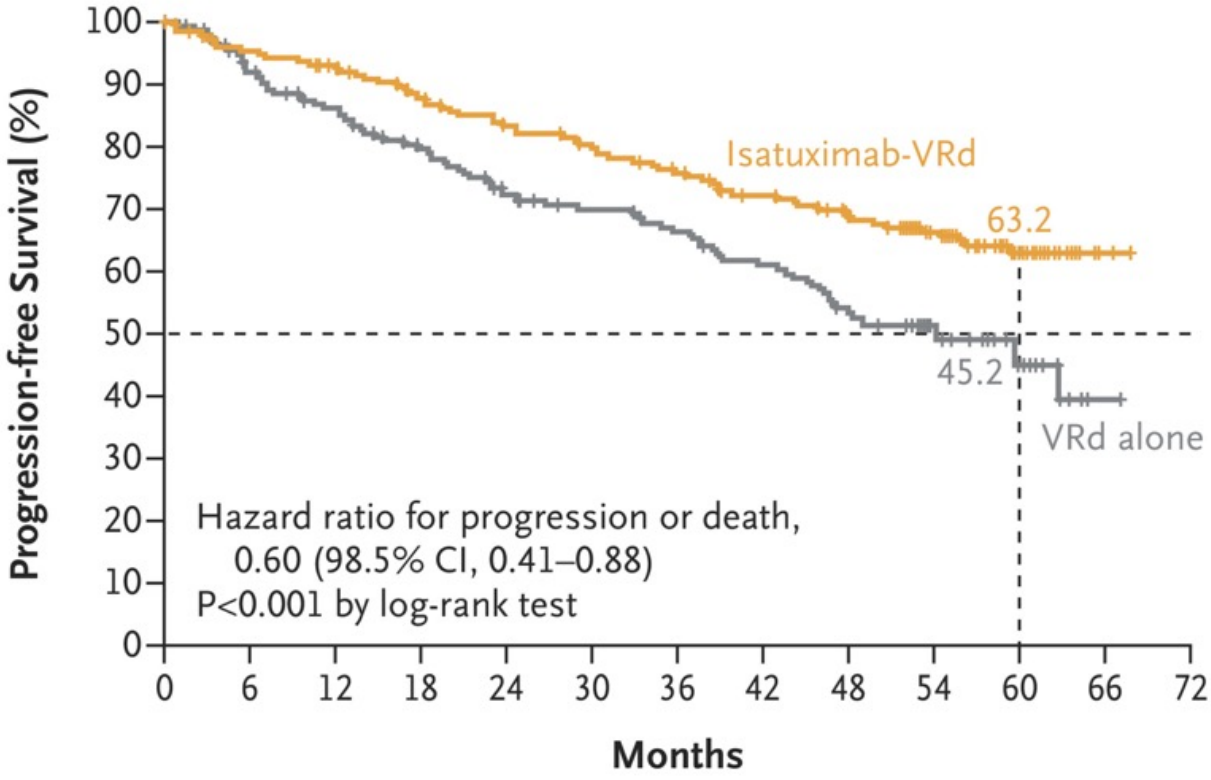
The primary end point was progression-free survival, which was defined as the time from randomization to the first documented disease progression (on the basis of assessment by the independent review committee) or death, whichever occurred first.

Characteristic	Isatuximab-VRd (N=265)	VRd (N=181)
Age		
Median (range) — yr	72 (60–80)	72 (55–80)
Distribution — no. (%)		
<65 yr	8 (3.0)	9 (5.0)
65–69 yr	73 (27.5)	47 (26.0)
70–74 yr	115 (43.4)	68 (37.6)
75–80 yr	69 (26.0)	57 (31.5)
Sex		
Female	122 (46.0)	87 (48.1)
Male	143 (54.0)	94 (51.9)
Race or ethnic group†		
American Indian or Alaska Native	4 (1.5)	1 (0.6)
Asian	31 (11.7)	17 (9.4)
Black	2 (0.8)	2 (1.1)
Native Hawaiian or other Pacific Islander	1 (0.4)	1 (0.6)
White	192 (72.5)	131 (72.4)
Not reported or missing data	35 (13.2)	29 (16.0)
ECOG performance-status score — no. (%)‡		
0 or 1	235 (88.7)	162 (89.5)
>1	30 (11.3)	19 (10.5)
Estimated GFR <60 ml/min/1.73 m^2 — no. (%)§	66 (24.9)	62 (34.3)
Extramedullary disease at trial enrollment — no. (%)¶	18 (6.8)	6 (3.3)
Median duration since initial diagnosis of multiple myeloma (range) — mo	1.2 (0.3–48.9)	1.2 (0.3–37.7)
Type of myeloma at baseline — no. (%)		
IgG	171 (64.5)	115 (63.5)
Non-IgG	94 (35.5)	66 (36.5)
IgA	57 (21.5)	41 (22.7)
Light chain only‖	32 (12.1)	21 (11.6)
R-ISS stage at baseline — no. (%)**		
Stage I or II	234 (88.3)	157 (86.7)
Stage III	29 (10.9)	21 (11.6)
Not classified	2 (0.8)	3 (1.7)
Cytogenetic risk at baseline — no. (%)		
Standard	207 (78.1)	140 (77.3)
High††	40 (15.1)	34 (18.8)
Unknown or missing data	18 (6.8)	7 (3.9)
High-risk chromosomal abnormalities and 1q21+ — no. (%)‡‡	19 (7.2)	15 (8.3)
Chromosomal abnormality — no. (%)§§		
1q21+	95 (35.8)	70 (38.7)
Amplification 1q21	32 (12.1)	23 (12.7)
Del(17p) with a 50% cutoff	15 (5.7)	9 (5.0)

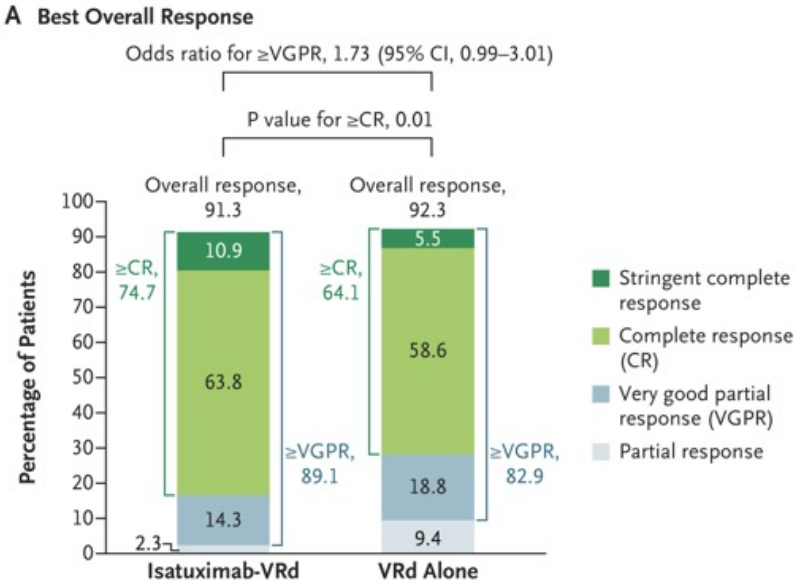
Hematologic Laboratory Abnormalities, Adverse Events of Any Grade, and Second Primary Cancers (Safety Population).

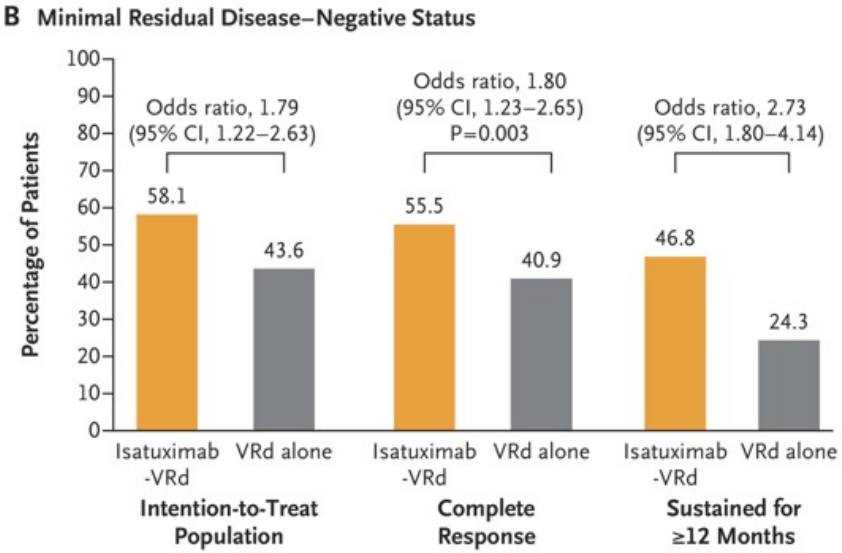
Event	Isatuximab-VRd (N=263)		VRd (N=181)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Hematologic laboratory abnormalities†				
Anemia	260 (98.9)	46 (17.5)	177 (97.8)	29 (16.0)
Lymphopenia	251 (95.4)	158 (60.1)	167 (92.3)	96 (53.0)
Neutropenia	230 (87.5)	143 (54.4)	145 (80.1)	67 (37.0)
Leukopenia	256 (97.3)	83 (31.6)	160 (88.4)	30 (16.6)
Thrombocytopenia	251 (95.4)	79 (30.0)	153 (84.5)	50 (27.6)
Nonhematologic adverse events				
Infection‡				
Pneumonia	79 (30.0)	53 (20.2)	35 (19.3)	23 (12.7)
Bronchitis	58 (22.1)	7 (2.7)	32 (17.7)	3 (1.7)
Upper respiratory tract infection	90 (34.2)	2 (0.8)	61 (33.7)	2 (1.1)
Diarrhea	144 (54.8)	20 (7.6)	88 (48.6)	15 (8.3)
Peripheral sensory neuropathy	143 (54.4)	19 (7.2)	110 (60.8)	11 (6.1)
Cataract	100 (38.0)	41 (15.6)	46 (25.4)	20 (11.0)
Constipation	94 (35.7)	6 (2.3)	74 (40.9)	3 (1.7)
Fatigue	91 (34.6)	21 (8.0)	48 (26.5)	12 (6.6)
Peripheral edema	86 (32.7)	0	59 (32.6)	2 (1.1)
Infusion-related reaction	62 (23.6)	1 (0.4)	2 (1.1)	0
Covid-19§	78 (29.7)	23 (8.7)	37 (20.4)	12 (6.6)
Insomnia	59 (22.4)	10 (3.8)	44 (24.3)	4 (2.2)
Back pain	58 (22.1)	9 (3.4)	31 (17.1)	3 (1.7)
Asthenia	57 (21.7)	7 (2.7)	44 (24.3)	4 (2.2)
Invasive second primary cancer¶				
Solid tumor‖	22 (8.4)	14 (5.3)	8 (4.4)	6 (3.3)
Hematologic cancer	3 (1.1)	1 (0.4)	2 (1.1)	2 (1.1)

Progression-free Survival (Intention-to-Treat Population).

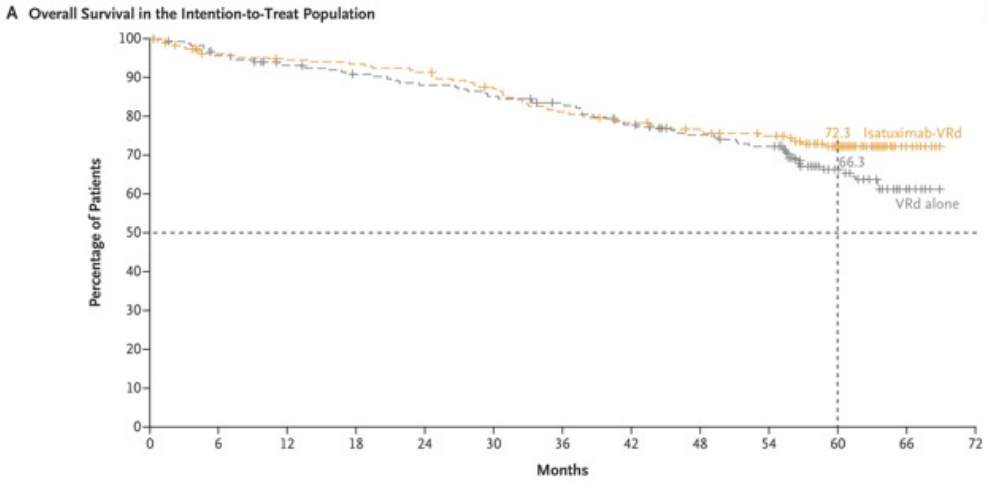


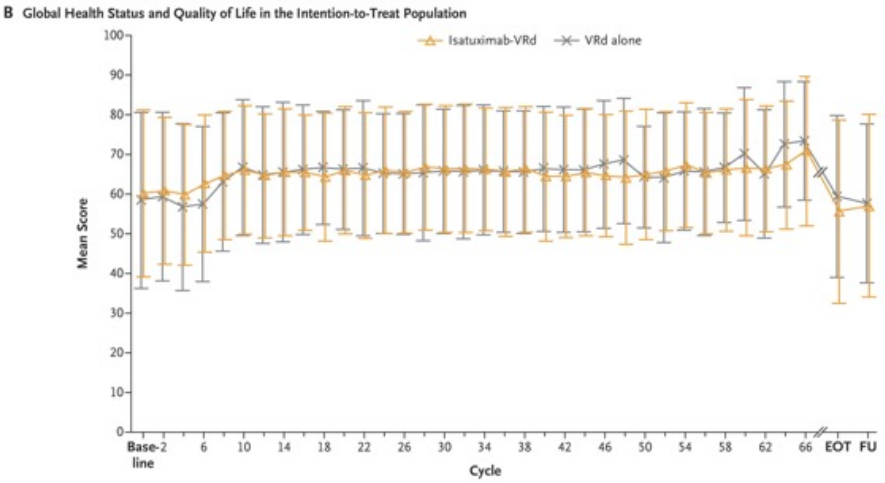
Summary of Responses and Minimal Residual Disease Status (Intention-to-Treat Population).

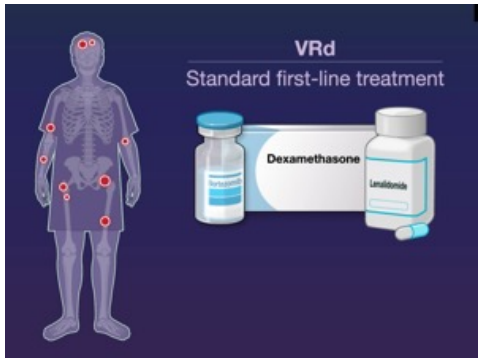




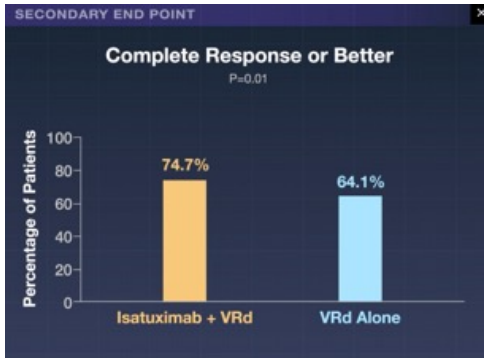
Overall Survival and Quality of Life (Intention-to-Treat Population).



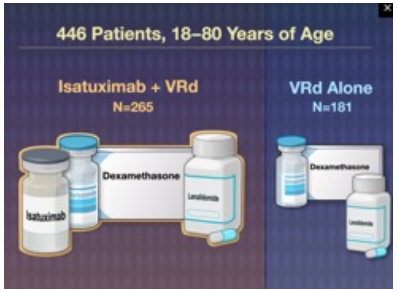


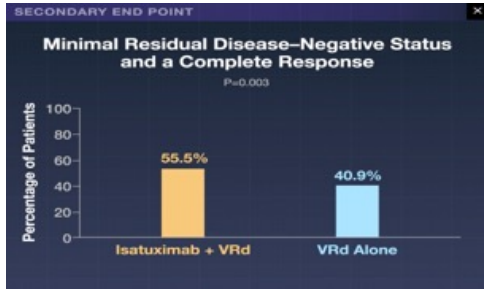

VRd
Standard first-line treatment
Dexamethasone
Lenalidomide

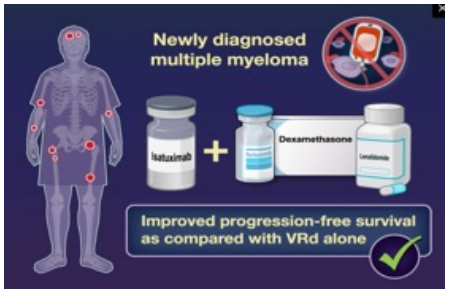

Efficacy and Safety
Isatuximab
Dexamethasone
Lenalidomide
Anti-CD38 Monoclonal Antibody
VRd
In patients with multiple myeloma


SECONDARY END POINT
Complete Response or Better
P=0.01
Percentage of Patients
100
80
60
40
20
0
74.7%
64.1%
Isatuximab + VRd
VRd Alone

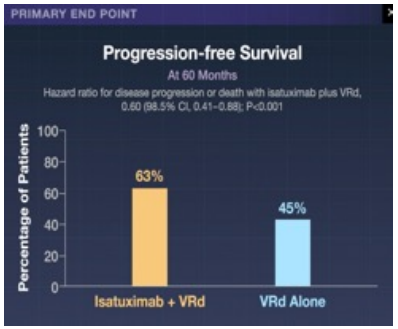

Adding Anti-CD38 Therapy
Anti-CD38
Dexamethasone
Lenalidomide
Patients who are eligible for transplantation

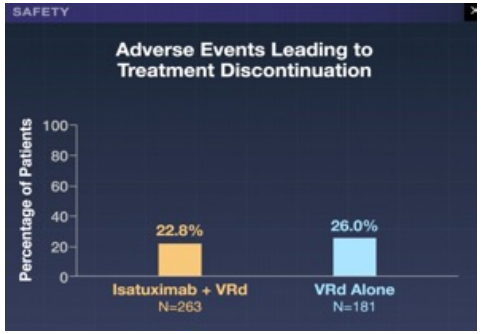

446 Patients, 18–80 Years of Age
Isatuximab + VRd
N=265
VRd Alone
N=181
Isatuximab
Dexamethasone
Lenalidomide


SECONDARY END POINT
Minimal Residual Disease–Negative Status and a Complete Response
P=0.003
Percentage of Patients
100
80
60
40
20
0
55.5%
40.9%
Isatuximab + VRd
VRd Alone


Newly diagnosed multiple myeloma
Isatuximab
Dexamethasone
Lenalidomide
Improved progression-free survival as compared with VRd alone

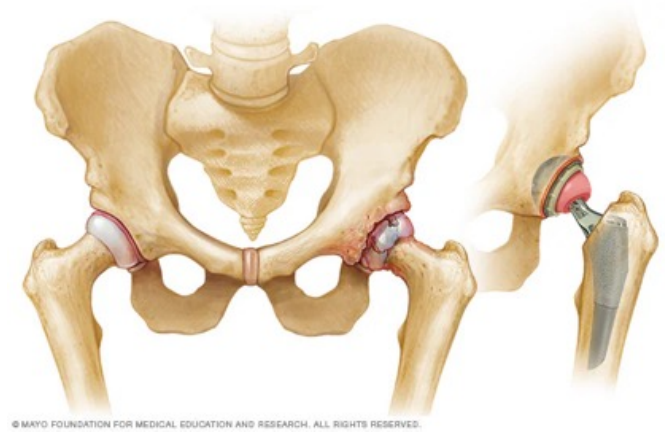

Adding Anti-CD38 Therapy
Anti-CD38
Dexamethasone
Lenalidomide
Transplantation ineligible patients

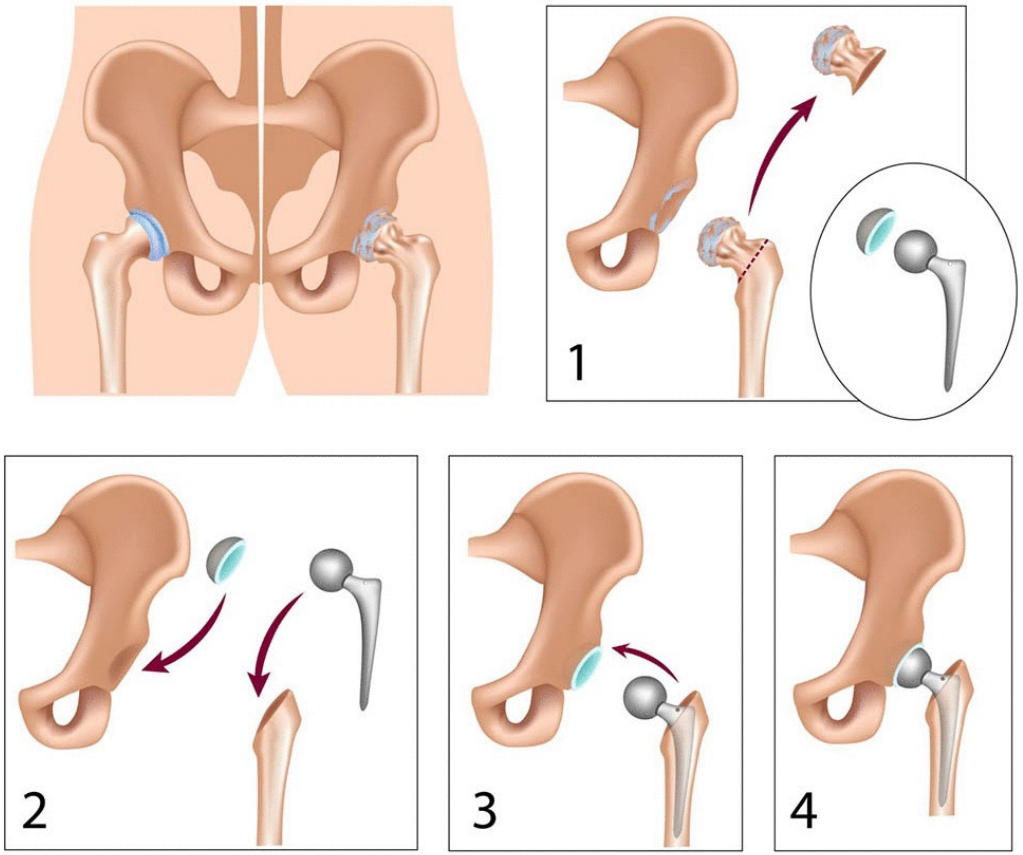

PRIMARY END POINT
Progression-free Survival
At 60 Months
Hazard ratio for disease progression or death with isatuximab plus VRd, 0.60 (98.5% CI, 0.41–0.88); P<0.001
Percentage of Patients
100
80
60
40
20
0
63%
45%
Isatuximab + VRd
VRd Alone


SAFETY
Adverse Events Leading to Treatment Discontinuation
Percentage of Patients
100
80
60
40
20
0
22.8%
26.0%
Isatuximab + VRd
N=263
VRd Alone
N=181

Artificial hip

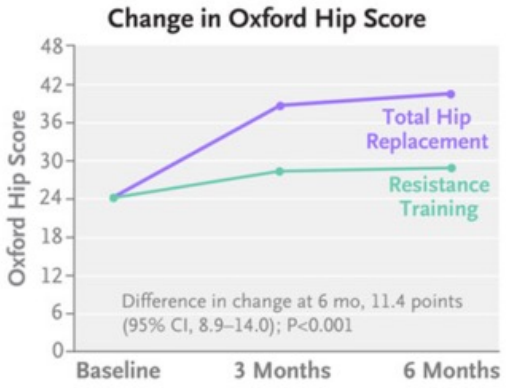
Hip prostheses are designed to mimic the ball-and-socket action of your hip joint. During hip replacement surgery, your surgeon removes the diseased or damaged parts of your hip joint and inserts the artificial joint.

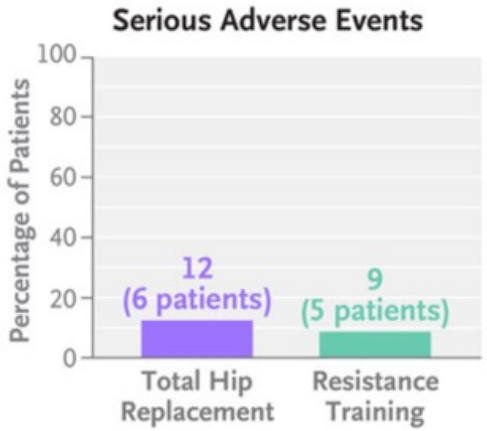




Total Hip Replacement or Resistance Training for Severe Hip Osteoarthritis

Total hip replacement is routinely recommended for severe hip osteoarthritis, but data from randomized trials are lacking regarding comparison of the effectiveness of this procedure with that of nonsurgical treatment such as resistance training. We conducted a multicenter, randomized, controlled trial to compare total hip replacement with resistance training in patients 50 years of age or older who had severe hip osteoarthritis and an indication for surgery. The primary outcome was the change in patient-reported hip pain and function from baseline to 6 months after the initiation of treatment, assessed with the use of the Oxford Hip Score (range, 0 to 48, with higher scores indicating less pain and better function). Safety was also assessed.





Hip osteoarthritis is a substantial contributor to disability, affecting 33 million persons worldwide. Across Europe and Australia, the lifetime likelihood of undergoing total hip replacement is 8 to 16%. This procedure effectively alleviates hip pain, reduces functional impairment, and improves quality of life, with up to 86% of patients reporting satisfaction with outcomes 6 months after surgery. More than 1 million total hip replacements are performed yearly worldwide, with the annual rate predicted to increase by 284% in the United States by 2040 as compared with 2014, a situation that highlights a greater future burden on health care systems.

Patients

Patients 50 years of age or older who had severe hip osteoarthritis and an indication for total hip replacement on the basis of hip pain, clinical presentation, and radiographic imaging, as assessed by a specialist in orthopedic surgery at one of four public orthopedic departments in Denmark, were considered to be eligible for trial enrollment.

Trial Procedures

After the baseline assessment, patients were randomly assigned to undergo total hip replacement (hip-replacement group) or to participate in resistance training (resistance-training group).

Outcomes

We assessed outcome measures for pain, function, and serious adverse events according to current recommendations. The primary outcome was the change in patient-reported hip pain and function from baseline to 6 months as assessed by means of the Oxford Hip Score.

PROHIP

The Progressive Resistance Training Versus Total Hip Arthroplasty Trial

WARM UP – STATIONARY ERGOMETER CYCLING (10 MIN)

PROHIP

The Progressive Resistance Training Versus Total Hip Arthroplasty Trial

EXERCISE #1 – LEG PRESS

PROHIP

The Progressive Resistance Training Versus Total Hip Arthroplasty Trial

EXERCISE #2 – HIP EXTENSION (CABLE)

PROHIP

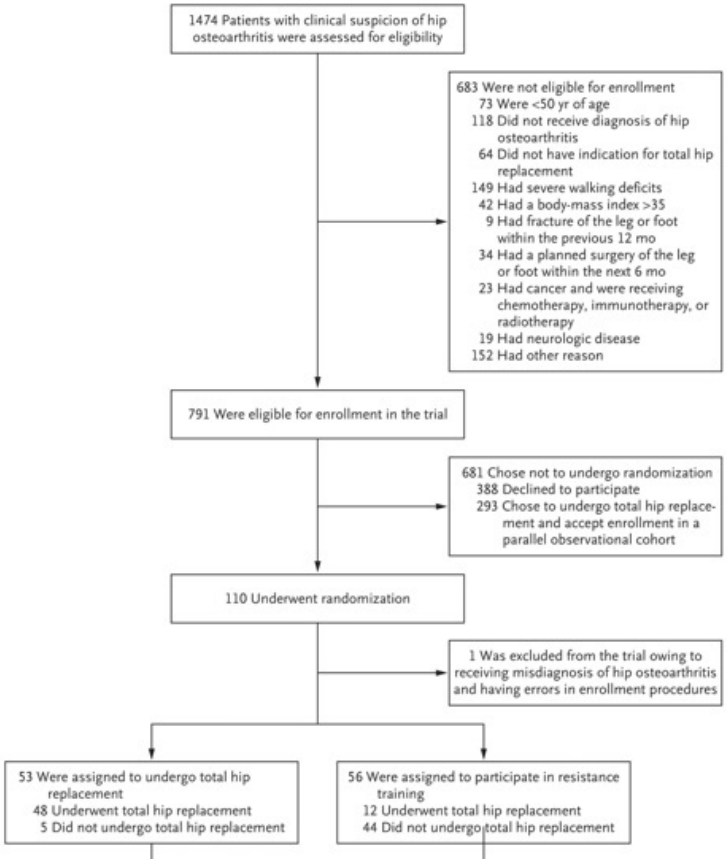
The Progressive Resistance Training Versus Total Hip Arthroplasty Trial

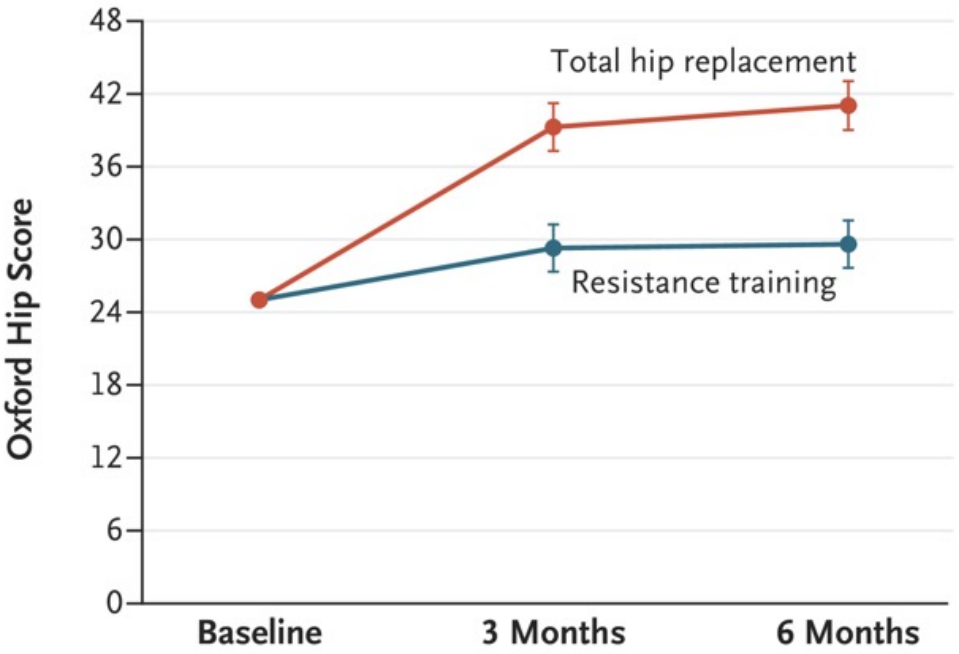
EXERCISE #3 – HIP FLEXION (CABLE)

Characteristic	Total Hip Replacement (N=53)	Resistance Training (N=56)
Age — yr	67.5±7.3	67.6±7.1
Female sex — no. (%)	26 (49)	28 (50)
Body-mass index	27.9±3.9	28.2±3.8
Educational level above high school — no. (%)	29 (55)	28 (50)
Employment status — no. (%)		
Employed for wages or self-employed	19 (36)	16 (29)
On sick leave	1 (2)	2 (4)
Retired	32 (60)	38 (68)
Other	1 (2)	0
Current smoking — no. (%)	1 (2)	4 (7)
Alcohol intake of >10 units/wk — no. (%)†	6 (11)	7 (12)
Median duration of hip symptoms (IQR) — yr	2.0 (1.0–3.0)	1.5 (0.7–4.0)
Previous total hip arthroplasty — no. (%)	2 (4)	9 (16)
Previous total knee arthroplasty — no. (%)	1 (2)	1 (2)
Previous treatment for hip-related pain — no. (%)		
Supervised exercise	14 (26)	17 (30)
Manual or passive treatment	7 (13)	10 (18)
Glucocorticoid injection	1 (2)	2 (4)
Other nonsurgical treatment	5 (9)	8 (14)
Use of analgesic agents for hip-related pain — no. (%)		
Acetaminophen	38 (72)	45 (80)
Nonsteroidal antiinflammatory drug	22 (42)	17 (30)
Opioid	5 (9)	3 (5)
Other analgesic agent	5 (9)	4 (7)
Oxford Hip Score‡	25.4±6.2	24.8±5.6
Hip Disability Osteoarthritis Outcome Score subscales§		
Pain	49.7±13.4	46.0±16.3
Symptoms	47.7±18.5	44.0±16.8
Function in activities of daily living	55.8±17.1	52.5±17.7
Hip-related quality of life	34.0±16.0	34.0±15.0
Function in sports and recreation	32.0±19.3	31.1±20.4
UCLA activity score¶	5.3±1.8	5.1±1.7
Gait speed in the 40-m fast-paced walk test — m/sec	1.5±0.3	1.4±0.3
No. of repetitions in the 30-sec sit-to-stand test	11.1±3.6	10.6±3.4

Outcomes at 6 Months (Intention-to-Treat Population).

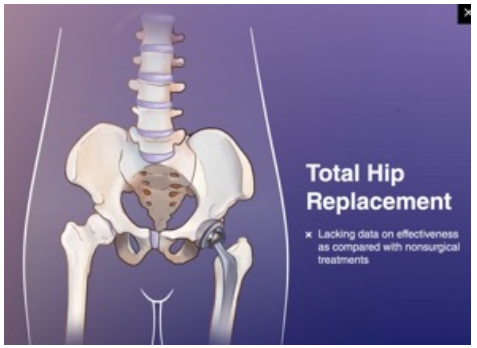
Outcome	Change from Baseline to 6 Mo		Adjusted Mean Difference (95% CI)	P Value
	Total Hip Replacement (N=53)	Resistance Training (N=56)		
Primary outcome				
Oxford Hip Score	15.9±1.0	4.5±1.0	11.4 (8.9 to 14.0)	<0.001
Secondary outcomes				
Hip Disability Osteoarthritis Outcome Score subscales				
Pain	39.2±2.4	15.0±2.3	24.2 (18.2 to 30.2)	<0.001
Symptoms	39.3±2.5	13.6±2.4	25.7 (19.5 to 31.8)	<0.001
Function in activities of daily living	32.9±2.2	12.1±2.1	20.8 (15.2 to 26.3)	<0.001
Hip-related quality of life	43.5±3.1	10.7±3.0	32.7 (25.0 to 40.4)	<0.001
Function in sports and recreation	41.0±2.8	9.2±2.7	31.8 (24.9 to 38.8)	<0.001
UCLA activity score	1.2±0.2	0.5±0.2	0.7 (0.1 to 1.3)	0.02
Median gait speed in the 40-m fast-paced walk test (IQR) — m/sec†	0.15 (0.05 to 0.33)	0.06 (−0.05 to 0.19)	0.10 (0.03 to 0.17)	0.009
Median no. of repetitions in the 30-sec sit-to-stand test (IQR)†	1 (0 to 4)	1 (0 to 3)	0 (−1 to 2)	0.36
Treatment response				
Met minimal clinically important change criteria for Oxford Hip Score — no. (%)‡	40 (75)	21 (38)	38 (21 to 55)	
Met OMERACT-OARSI criteria — no. (%)§	41 (77)	21 (38)	40 (23 to 57)	

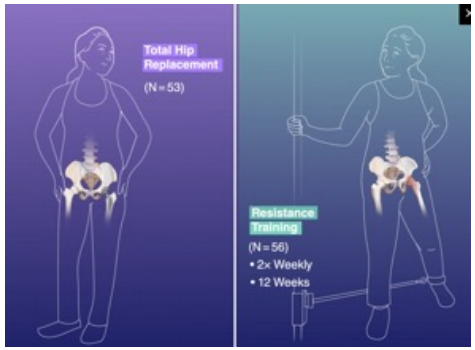

1474 Patients with clinical suspicion of hip osteoarthritis were assessed for eligibility
683 Were not eligible for enrollment
73 Were <50 yr of age
118 Did not receive diagnosis of hip osteoarthritis
64 Did not have indication for total hip replacement
149 Had severe walking deficits
42 Had a body-mass index >35
9 Had fracture of the leg or foot within the previous 12 mo
34 Had a planned surgery of the leg or foot within the next 6 mo
23 Had cancer and were receiving chemotherapy, immunotherapy, or radiotherapy
19 Had neurologic disease
152 Had other reason
791 Were eligible for enrollment in the trial
681 Chose not to undergo randomization
388 Declined to participate
293 Chose to undergo total hip replacement and accept enrollment in a parallel observational cohort
110 Underwent randomization
1 Was excluded from the trial owing to receiving misdiagnosis of hip osteoarthritis and having errors in enrollment procedures
53 Were assigned to undergo total hip replacement
48 Underwent total hip replacement
5 Did not undergo total hip replacement
56 Were assigned to participate in resistance training
12 Underwent total hip replacement
44 Did not undergo total hip replacement

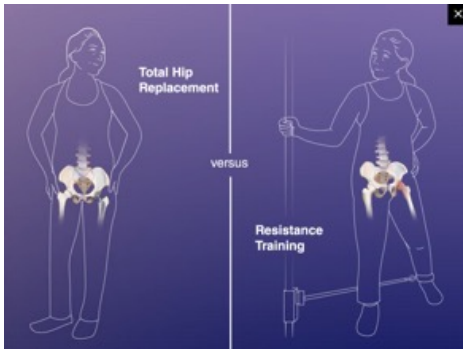

Oxford Hip Score
48
42
36
30
24
18
12
6
0
Total hip replacement
Resistance training
Baseline
3 Months
6 Months

Serious Adverse Events at 6 Months of Follow-up (Safety Population).

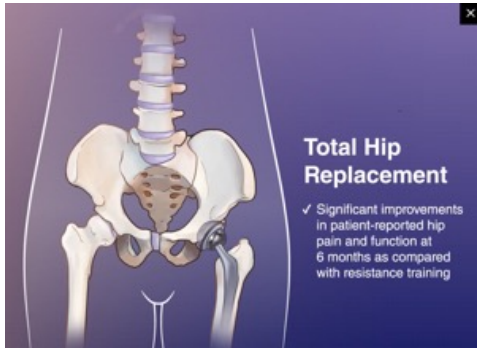
Event	Total Hip Replacement (N=48)	Resistance Training (N=55)
	number (percent)	
Musculoskeletal event		
Prosthetic joint infection	1 (2)	0
Hip dislocation	1 (2)	1 (2)†
Revision surgery	2 (4)	0
Pelvic fracture and distal radius fracture	0	1 (2)‡
Total shoulder replacement	0	1 (2)§
Cardiovascular event: atrial fibrillation	0	1 (2)¶
Nervous system event: drop foot	1 (2)	0
Gastrointestinal event: reflux	1 (2)	0
Renal event: urinary tract infection and kidney infection	0	1 (2)
Discontinuation due to serious adverse event	0	1 (2)†
Any serious adverse event	6 (12)	5 (9)

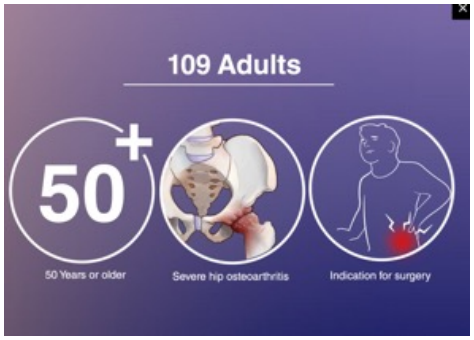

Total Hip Replacement
× Lacking data on effectiveness as compared with nonsurgical treatments

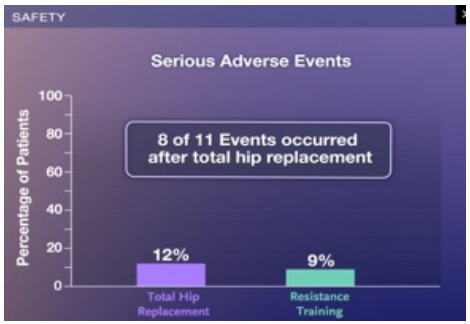

Total Hip Replacement
(N = 53)
Resistance Training
(N = 56)
• 2x Weekly
• 12 Weeks

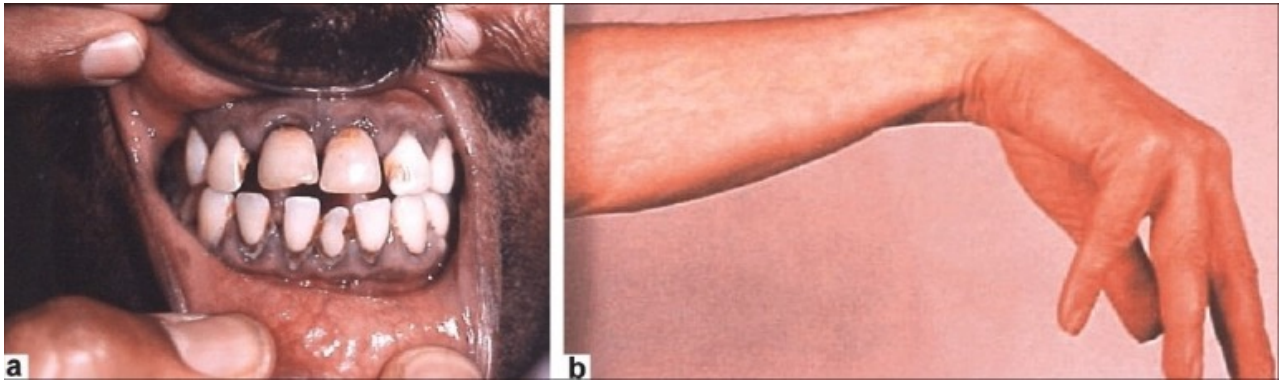

Total Hip Replacement
versus
Resistance Training

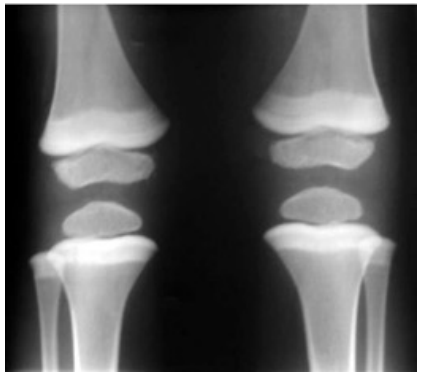

PRIMARY OUTCOME
Change from Baseline to 6 Months in Patient-Reported Hip Pain and Function
Oxford Hip Score
48
42
36
30
24
18
12
6
0
Less pain and better function
Total Hip Replacement
15.9
4.5
Resistance Training
Difference: 11.4 points (95% CI, 8.9-14.0); P<0.001
Baseline
3 Months
6 Months

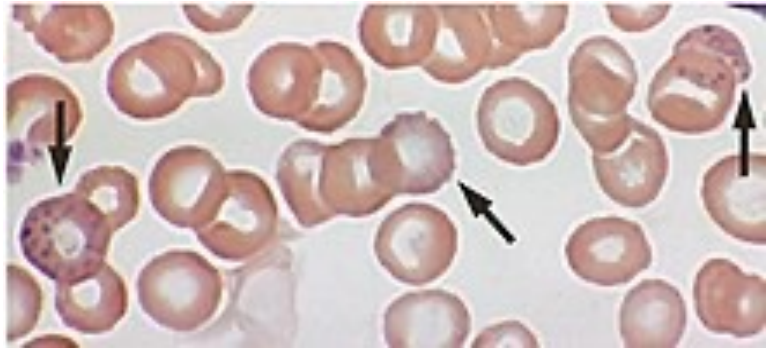

Total Hip Replacement
✓ Significant improvements in patient-reported hip pain and function at 6 months as compared with resistance training

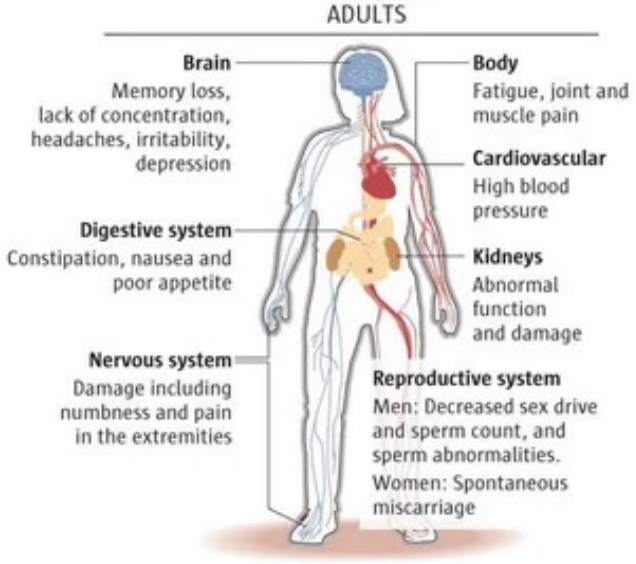

109 Adults
50+
50 Years or older
Severe hip osteoarthritis
Indication for surgery

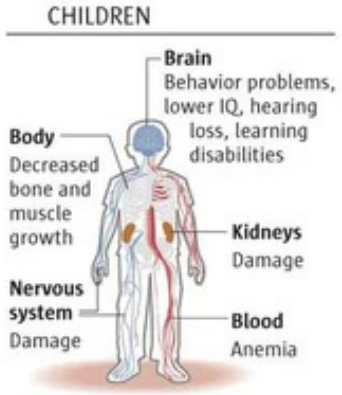

SAFETY
Serious Adverse Events
Percentage of Patients
100
80
60
40
20
0
8 of 11 Events occurred after total hip replacement
12%
9%
Total Hip Replacement
Resistance Training


a
b






ADULTS
Brain
Memory loss, lack of concentration, headaches, irritability, depression
Body
Fatigue, joint and muscle pain
Cardiovascular
High blood pressure
Digestive system
Constipation, nausea and poor appetite
Kidneys
Abnormal function and damage
Nervous system
Damage including numbness and pain in the extremities
Reproductive system
Men: Decreased sex drive and sperm count, and sperm abnormalities.
Women: Spontaneous miscarriage


CHILDREN
Brain
Behavior problems, lower IQ, hearing loss, learning disabilities
Body
Decreased bone and muscle growth
Kidneys
Damage
Nervous system
Damage
Blood
Anemia

REVIEW ARTICLE

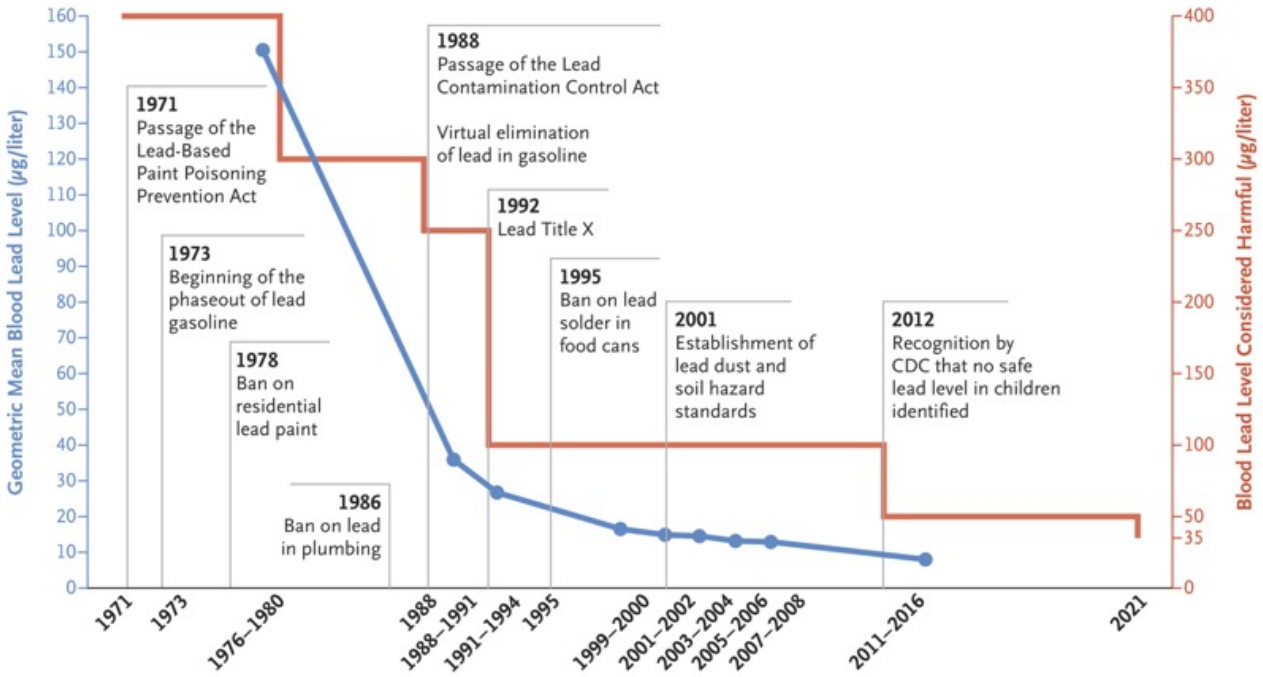
Lead Poisoning

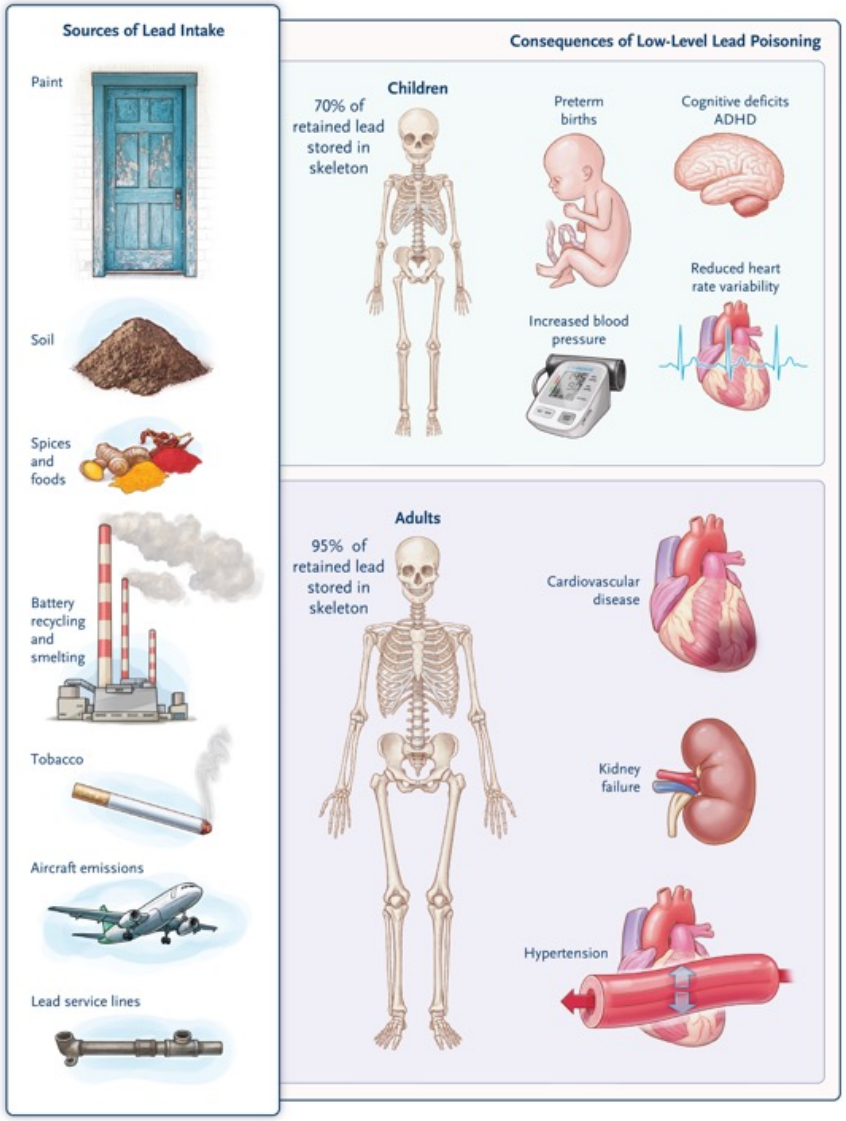
KEY POINTS

LEAD POISONING

- Lead exposure among people in the United States has declined by more than 95% since the 1970s, but the body lead burden is still 10 to 100 times as high as the lead burden in humans who lived in preindustrial times.
- Studies conducted over the past 40 years have established that chronic, low-level lead poisoning is a major risk factor for cardiovascular disease in adults and cognitive deficits in children, even at levels previously thought to be safe or innocuous.
- Lead exposure is a risk factor for chronic kidney disease and preterm births at concentrations commonly found in people today.
- In 2019, lead exposure accounted for 5.5 million deaths from cardiovascular disease and an annual loss of 765 million IQ points in children globally.
- The steep decrease in IQ and the sharp increase in the risk of death from cardiovascular disease, even at the lowest measurable blood lead concentrations, coupled with ubiquitous exposure, indicate that population strategies are critical for eliminating lead poisoning.

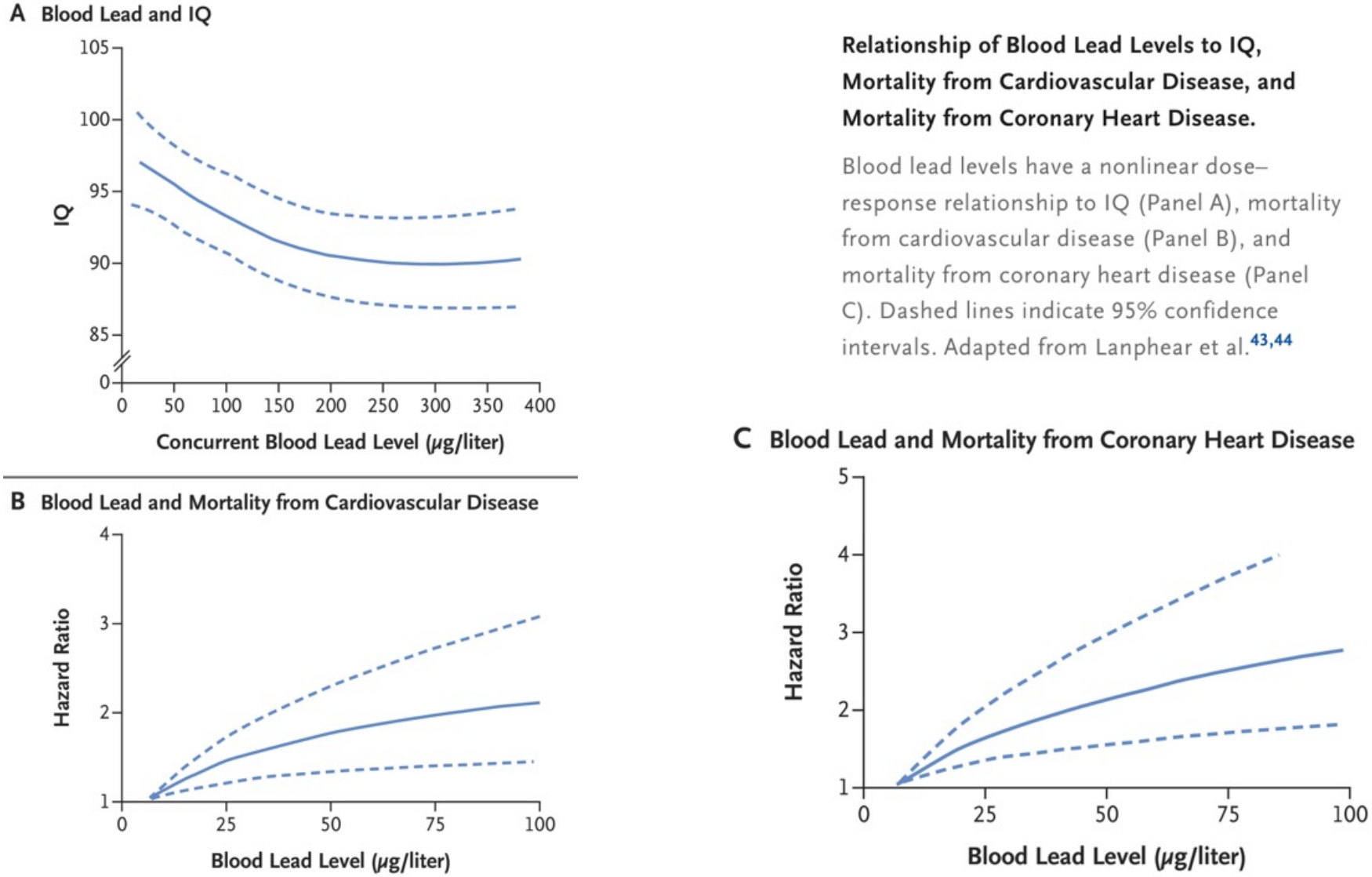
Mean Blood Lead Levels in U.S. Children between 1 and 5 Years of Age, Blood Lead Levels Considered Elevated in Children, and Regulations Reducing Lead Exposure.





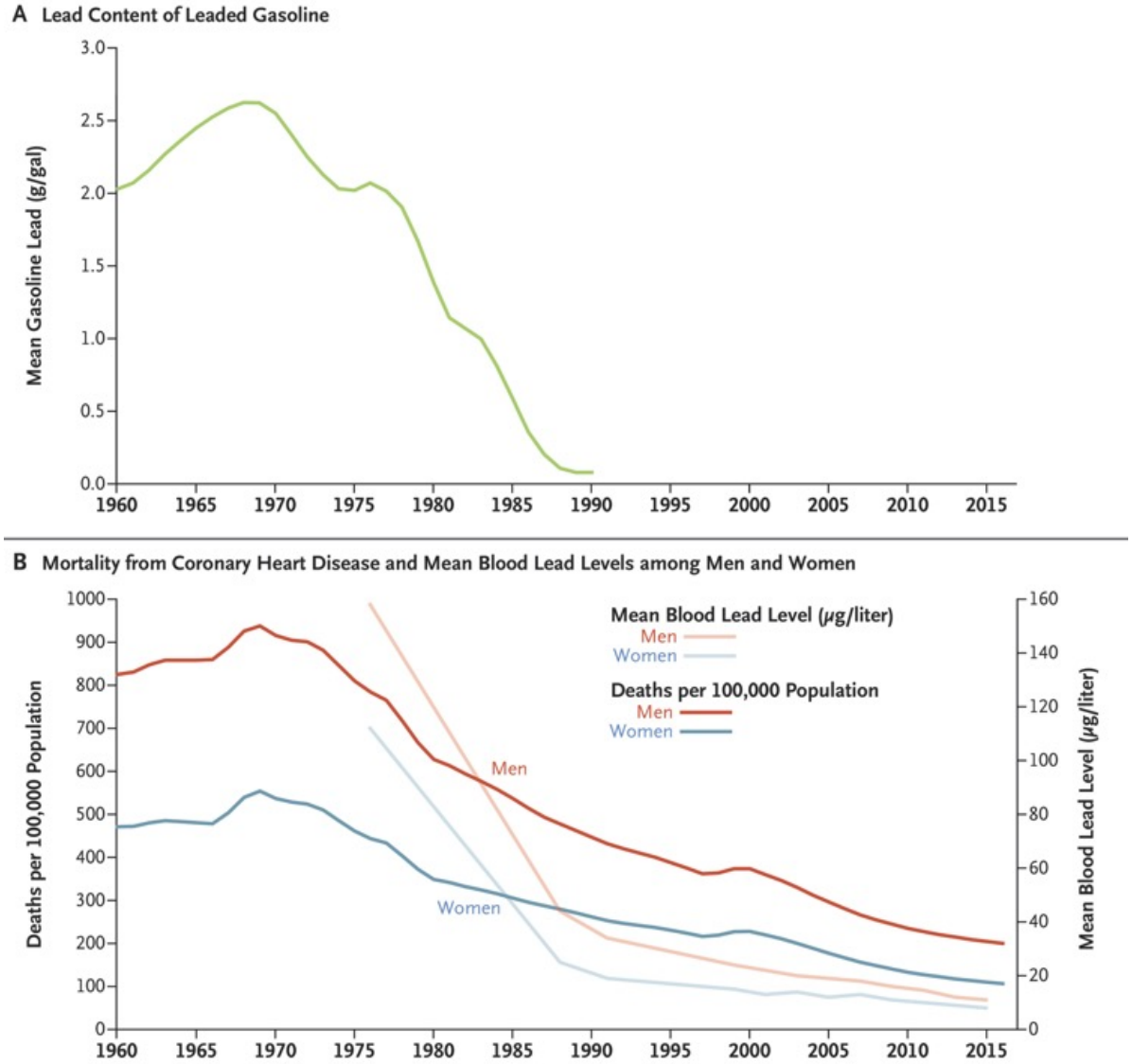
Sources of Lead Exposure and Health Effects of Lead Poisoning.

Many historical and current sources of lead continue to contribute to lead poisoning today. Most of the lead in human bodies is stored in bones, and long-term exposure increases the risk of preterm birth, learning and behavioral problems, hypertension, kidney failure, and coronary heart disease.



Relationship of Blood Lead Levels to IQ, Mortality from Cardiovascular Disease, and Mortality from Coronary Heart Disease.

Blood lead levels have a nonlinear dose–response relationship to IQ (Panel A), mortality from cardiovascular disease (Panel B), and mortality from coronary heart disease (Panel C). Dashed lines indicate 95% confidence intervals. Adapted from Lanphear et al.[43,44]



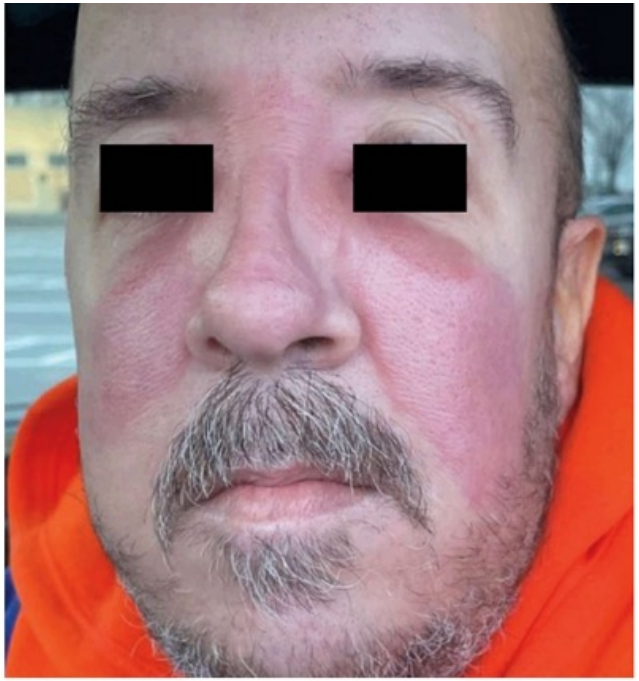
Lead Content in Leaded Gasoline (1960–1990), Mean Blood Lead Levels in U.S. Adults (1976–2015), and Mortality from Coronary Heart Disease among Men and Women (1960–2016).

Panel A shows the average lead content in gasoline in the United States from 1960 through 1990. Panel B shows geometric mean blood lead levels in U.S. adults enrolled in the National Health and Nutrition Examination Survey (NHANES) from 1976 to 2016 and age-standardized mortality from coronary heart disease from 1960 through 2016 among men and women over the age of 25 years. Blood lead levels were stratified and weighted according to survey year and adjusted for age. Adapted from Pirkle et al.,[67] Muntner et al.,[68] and Wang et al.[69]

Prevention of Lead Poisoning

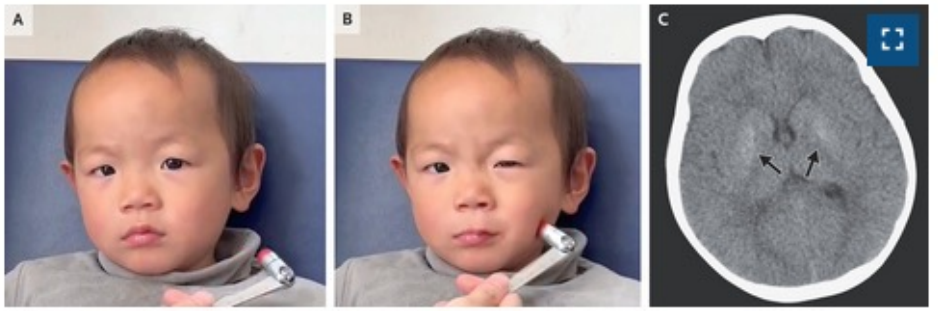
The lead pandemic — the largest mass poisoning in history — is a humbling reminder that widespread exposure to an ancient metal, rarely found in high concentrations on the surface of the earth before human activity, has resulted in a staggering number of deaths and disabilities. The failure to prevent this century-long pandemic, despite early warnings, exposes an anemic regulatory system ill-suited to protect the public from industry-orchestrated campaigns and regulatory delays.[5,6] In 1925, Yandell Henderson warned, "This is probably the greatest single question in the field of public health that has ever faced the American public. It is the question whether scientific experts are to be consulted, and the action of Government guided by their advice; or whether, on the contrary, commercial interests are to be allowed to subordinate every other consideration to that of profit."[6]

Erysipelas



A 44-year-old man with Crohn's disease that was being treated with infliximab presented to the primary care clinic with a 2-day history of a rash on his face. In the week before presentation, his daughter had had a sore throat and his mother had had a similar rash on her face. His heart rate was 96 beats per minute, and his temperature was 36.6°C (97.9°F). Physical examination was notable for well-demarcated, warm, erythematous, confluent plaques across the cheeks, nose, and glabella, with a dimpled (*peau d'orange*) appearance of the skin. The pharynx was normal, and no cervical lymphadenopathy was observed. A diagnosis of erysipelas — a skin infection that involves the upper dermis — was made. Erysipelas typically manifests as a bright-red rash — often on the malar region of the face — with raised, distinct borders. Most cases can be managed with oral antibacterial agents in the outpatient setting. Blood cultures, which are not usually required for this diagnosis, were obtained in this case owing to the patient's immunosuppression. The blood cultures grew *Streptococcus pyogenes*, so the patient was admitted to the hospital. Treatment was changed from oral cephalexin to a 2-week course of intravenous penicillin G potassium. After 5 days of antibacterial therapy, the patient's rash resolved.

Chvostek's Sign in Familial Hypoparathyroidism



A previously healthy 2-year-old boy was brought to the emergency department after he had had four generalized seizures in the previous week. After his second seizure, he had been taken to another hospital, where he had received treatment for a low serum calcium level. At the current presentation, physical examination was notable for brisk tendon reflexes in all four limbs. Involuntary twitching of the muscles of the face was observed after tapping of the ipsilateral facial nerve (Panels A and B and video), a finding known as Chvostek's sign that indicates neuromuscular irritability. Laboratory studies were notable for low total calcium, magnesium, and parathyroid hormone levels and an elevated phosphorus level. Computed tomography of the head showed patchy hyperdensities in the basal ganglia (Panel C, arrows), a finding consistent with chronic hypoparathyroidism. Owing to concern for a genetic cause of hypoparathyroidism, whole-exome sequencing was performed, which revealed one de novo variant allele in *GCM2*. A diagnosis of familial isolated hypoparathyroidism type 2 was made. The patient was treated with intravenous and oral calcium, and the seizures resolved. Long-term treatment with calcitriol and calcium supplementation was initiated. At the 3-month follow-up, the patient was seizure-free and had a low-normal serum calcium level.

VIDEO

Chvostek's Sign 0m 15s

Case 34-2024: A 69-Year-Old Man with Dyspnea after Old Myocardial Infarction

A 69-year-old man with a history of myocardial infarction, ischemic cardiomyopathy, and an implantable cardioverter–defibrillator (ICD) was evaluated because of dyspnea during an urgent visit at an outpatient primary care clinic affiliated with this hospital.

The patient had been in his usual state of health until 2 days before the current presentation, when he felt unwell while working. He had dyspnea on exertion (while moving and stocking boxes and when walking home from work), with baseline exertional dyspnea that occurred after ascending two to three flights of stairs. The next day, the patient had palpitations and felt lightheaded throughout the day. The palpitations continued, and he was evaluated by his primary care physician at an outpatient primary care clinic affiliated with this hospital.

On a review of systems, the patient reported nausea with intermittent retching, anorexia (eating only a slice of cheese for the day), and fatigue. He stated that his right eye was “out of focus,” but he also noted that he had had this symptom in the past. He reported no chest pain or pressure. Although he had often had angina in the past, the patient noted that he had not had any episodes in the past 2 years and that he had had only one episode of substernal discomfort, which occurred while he was walking and had lasted 45 seconds. In addition, he had had no presyncope or loss of consciousness, ICD discharge, edema, orthopnea, paroxysms of nocturnal dyspnea, fever, known sick contacts, diarrhea, weight change, abdominal pain or bloating, dysuria, myalgia, arthralgia, rash, bleeding symptoms, or focal neurologic symptoms. He had not missed any doses of medications, and his last ICD check was 3 months before the current presentation.

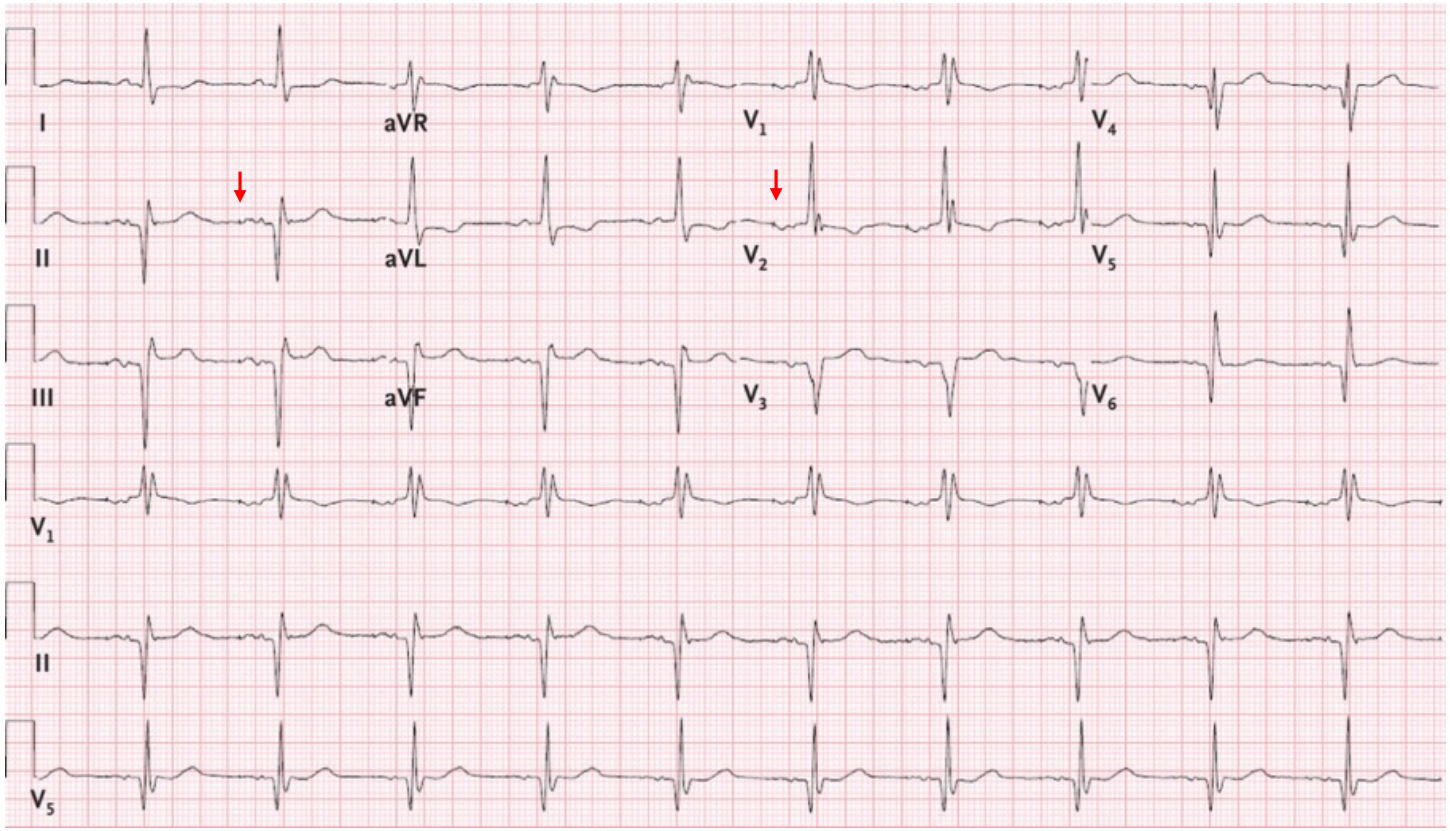
The patient’s medical history was notable for premature coronary artery disease, with a first occurrence of myocardial infarction in his third decade of life. In his fifth decade of life, he had undergone coronary-artery bypass grafting (CABG) and subsequent stenting of the native left anterior descending coronary artery. Coronary angiography, which was performed 2 years earlier for evaluation of angina, showed that the bypass graft and stent were patent but that severe native coronary disease was present (and was unchanged from an earlier study).

The patient's medical history also included ischemic cardiomyopathy with chronically reduced ejection fraction and scarring of the inferior and inferoposterior left ventricle, and ventricular tachycardia that had been treated with antiarrhythmic medication and an ICD. The ICD had been placed 3 years before the current presentation during an admission at this hospital for syncope that was followed by in-hospital cardiac arrest due to ventricular tachycardia, which required multiple external defibrillations. Thereafter, the patient received treatment with oral amiodarone; however, device interrogation revealed intermittent ventricular tachycardia at rates of 109 to 117 beats per minute that persisted over the next 8 months, and he underwent endocardial ablation of ventricular tachycardia in the scar of the mid-inferior wall. Six months after ablation, he was readmitted to this hospital because of nausea and dizziness that were due to recurrent sustained slow ventricular tachycardia (110 beats per minute), for which he was treated with intravenous lidocaine and antitachycardia pacing.

In addition, the patient's medical history included bioprosthetic mitral valve replacement concurrent with CABG, which had been complicated by prosthetic valve deterioration with mixed stenosis and mitral regurgitation, and culminated in transcatheter valve-in-valve replacement 2.5 years before the current presentation. He also had a history of hypertension, pulmonary embolism (4 years before the current presentation), iron-deficiency anemia, a colonic polyp, and prolonged encephalopathy after CABG. Medications included aspirin, coumadin, furosemide, metoprolol, lisinopril, dapagliflozin, ranolazine, atorvastatin, ferrous gluconate, paroxetine, and clonazepam. Treatment with amiodarone had previously been associated with elevations in liver-function test results. At the patient's last office visit with an electrophysiologist 6 months before the current presentation, device interrogation showed no ventricular tachycardia and the heart rate was 60 beats per minute; treatment with amiodarone was discontinued.

A transthoracic echocardiogram obtained at the same office visit with the electrophysiologist showed a left ventricular ejection fraction of 31% with inferior, posterior, and apical territory dysfunction; right ventricular hypokinesis; a left-to-right interatrial shunt; trace-to-mild aortic insufficiency; a well-seated mitral valve prosthesis with no regurgitation and a mean transmitral gradient of 5 mm Hg; and a right ventricular systolic pressure of 31 mm Hg.
At a primary care visit 5 months before the current presentation, the patient reported bloating. The heart rate was 62 beats per minute and the blood pressure 104/64 mm Hg. The thyrotropin level was normal, the N-terminal pro–B-type natriuretic peptide (NT-proBNP) level 646 pg per milliliter (reference value, <900), the hematocrit level 40.9% (reference range, 41.0 to 53.0), and the low-density lipoprotein cholesterol level 74 mg per deciliter (1.92 mmol per liter; reference range, 50 to 129 mg per deciliter [1.29 to 3.34 mmol per liter]).
The patient had had a routine office visit with his cardiologist 18 days before the current presentation, during which the heart rate was 63 beats per minute and the blood pressure 111/69 mm Hg; the weight was 83 kg. No changes were made to his medications.

At the current presentation, the temporal temperature was 35.7°C, the heart rate 124 beats per minute and regular, the blood pressure 84/59 mm Hg while the patient was sitting and 99/67 mm Hg while he was in the supine position, and the oxygen saturation 99% while he was breathing ambient air. The weight was 83 kg. The patient appeared diaphoretic and clammy, and the skin was warm to the touch. He was alert, oriented, and lucid. The previous sternotomy and ICD sites were intact. There was no heart murmur; however, a possible S3 heart sound and minimal basilar rales were observed. The jugular venous pulse was difficult to visualize. A healed appendectomy scar was present, but the abdomen was nontender, the liver was nonpulsatile, and there was no fluid wave. The legs were warm with mild, symmetric pedal edema.
Laboratory test results were obtained 2 weeks before the current presentation. The sodium level was 139 mmol per liter (reference range, 135 to 145), the potassium level 4.1 mmol per liter (reference range, 3.4 to 5.0), the creatinine level 0.91 mg per deciliter (80.44 µg per liter; reference range, 0.80 to 1.30 mg per deciliter [70.72 to 114.92 µg per liter]), the hematocrit 44.0%, the NT-proBNP 669 pg per milliliter, and the international normalized ratio (INR) 2.9 (reference range, 0.9 to 1.1).



Initial Electrocardiogram.

The initial electrocardiogram, which was obtained 18 days before the current presentation, shows atrial pacing, first-degree atrioventricular delay, right bundle-branch block, and evidence of old inferior, apical, and posterior myocardial infarctions.

Diagnostic Approach in the Primary Care Clinic

As a general internist seeing this patient in a time-pressured urgent care visit, I would be daunted by this complicated myocardial and electrophysiologic disease. My initial concern would be that the primary care clinic environment lacked the appropriate tools to manage unstable cardiac conditions, and I would quickly determine whether triage is needed for treatment in the emergency department.

My attention would be drawn to this patient's history of ventricular tachycardia and ischemic cardiomyopathy — two dynamic and dangerous conditions. However, I would also be resistant to anchoring only on these alarming features. At this point, I would pause to consider other diagnostic possibilities.

Acute Dyspnea

The differential diagnosis of acute dyspnea is extensive in a patient of this age with known systolic heart failure, malignant arrhythmias, pulmonary embolism, iron-deficiency anemia, and valve replacements. The causes of dyspnea usually fall into one of the following categories: cardiac, pulmonary, hematologic, metabolic, and other causes. On initial review of this patient's case, many possibilities on the differential diagnosis remain, with the exception of chronic obstructive pulmonary disease and smoking-related lung disease.

Physical Examination

The physical examination is useful for investigating specific diagnostic hypotheses. In this case, given the patient's elevated heart rate and low blood pressure, I would start the examination by assessing overall hemodynamic stability. This patient was lucid, a finding that suggests adequate cerebral perfusion. In addition, he had no signs of peripheral hypoperfusion, with warm skin and without a narrow pulse pressure, and there were few indications of substantial volume overload with minimal leg edema and minimal rales.

Recent Cardiac Studies

The ECG obtained 18 days before the patient's current presentation showed atrial pacing with evidence of extensive myocardial damage from previous infarctions.

Alternative Diagnoses

The patient's cardiac history could lead a clinician to ignore nonspecific symptoms such as nausea and unfocused vision. It is therefore important to explore other explanations that might account for these symptoms.

The patient had a history of vague gastrointestinal upset, including bloating. At the current evaluation, he presented with acute gastrointestinal symptoms of nausea, retching, and loss of appetite. We also learned that he had had nausea and dizziness that was associated with an episode of slow ventricular tachycardia. It is important to keep in mind the possibility of smoldering intestinal disease. If a repeat ECG were to show sinus tachycardia, this would increase the relevance of these symptoms. However, in the absence of abdominal pain, weight loss, jaundice, or abnormal findings on abdominal examination, it is unlikely that this presentation could be explained by gastrointestinal disease.

The patient's report of his right eye being "out of focus" is an intriguing symptom on first evaluation as a potentially specific clue that leads to a unifying diagnosis (e.g., transient ischemic attack from prosthetic valve endocarditis or thrombus or Graves' ophthalmopathy). The fact that this was a chronic symptom suggests that it is unrelated to the current presentation. An eye out of focus is not a common description associated with amaurosis fugax or retinal emboli. Moreover, the patient had no signs of acute mitral valve dysfunction or murmur or other inflammatory or autoimmune findings that would suggest acute or subacute bacterial endocarditis.

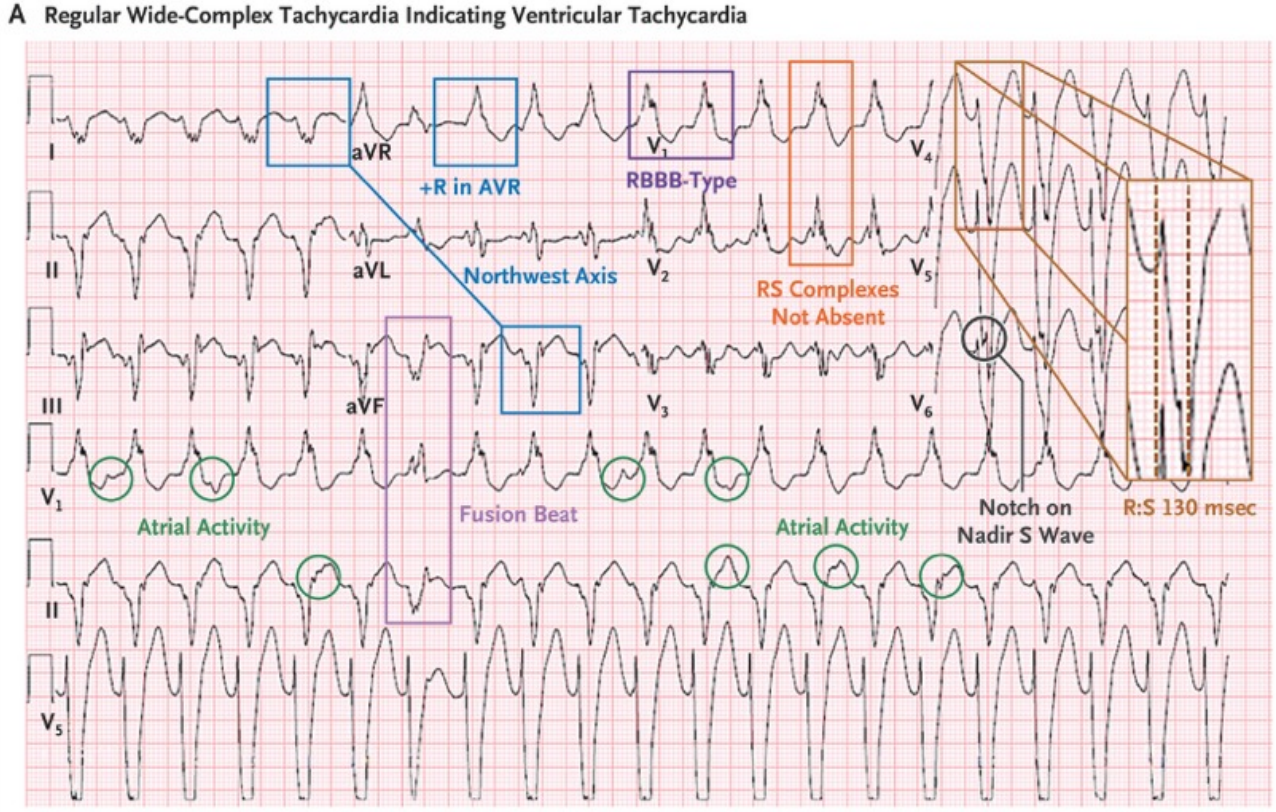
After considering alternative diagnoses that could explain this patient's presenting symptoms, I suspect the most likely diagnosis is slow ventricular arrhythmia.

Dr. Kevin Heaton's Diagnosis

Slow ventricular arrhythmia.

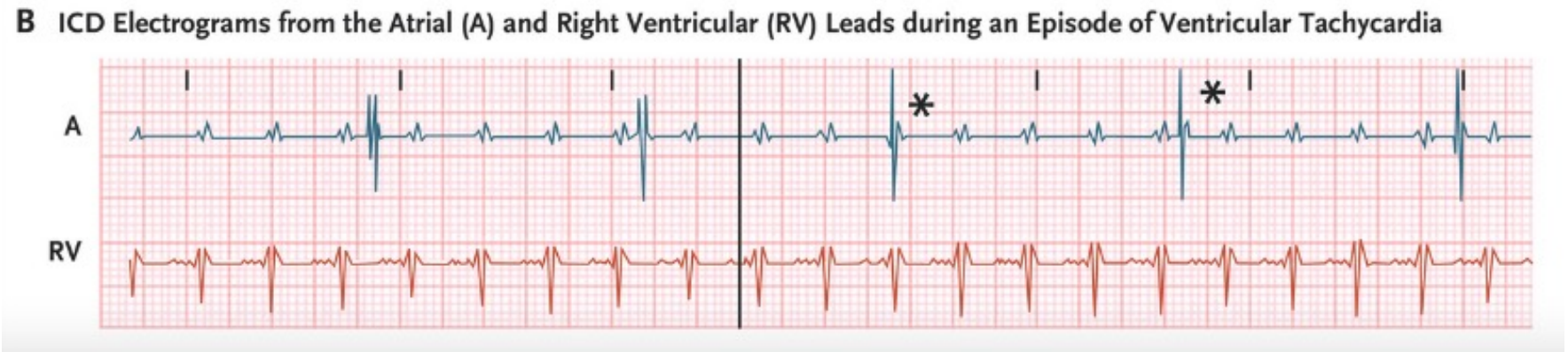
ECG Assessment and Diagnostic Testing

ECG was performed during the patient's urgent visit at the primary care clinic. The ECG findings contribute to establishing the electrophysiologic diagnosis of ventricular tachycardia. On the basis of the patient's history, the pretest probability of ventricular tachycardia is high. Given his history of old myocardial infarctions and a wide-complex tachycardia, our presumptive diagnosis must be ventricular tachycardia until proved otherwise.



Electrocardiogram Obtained at the Primary Care Clinic.

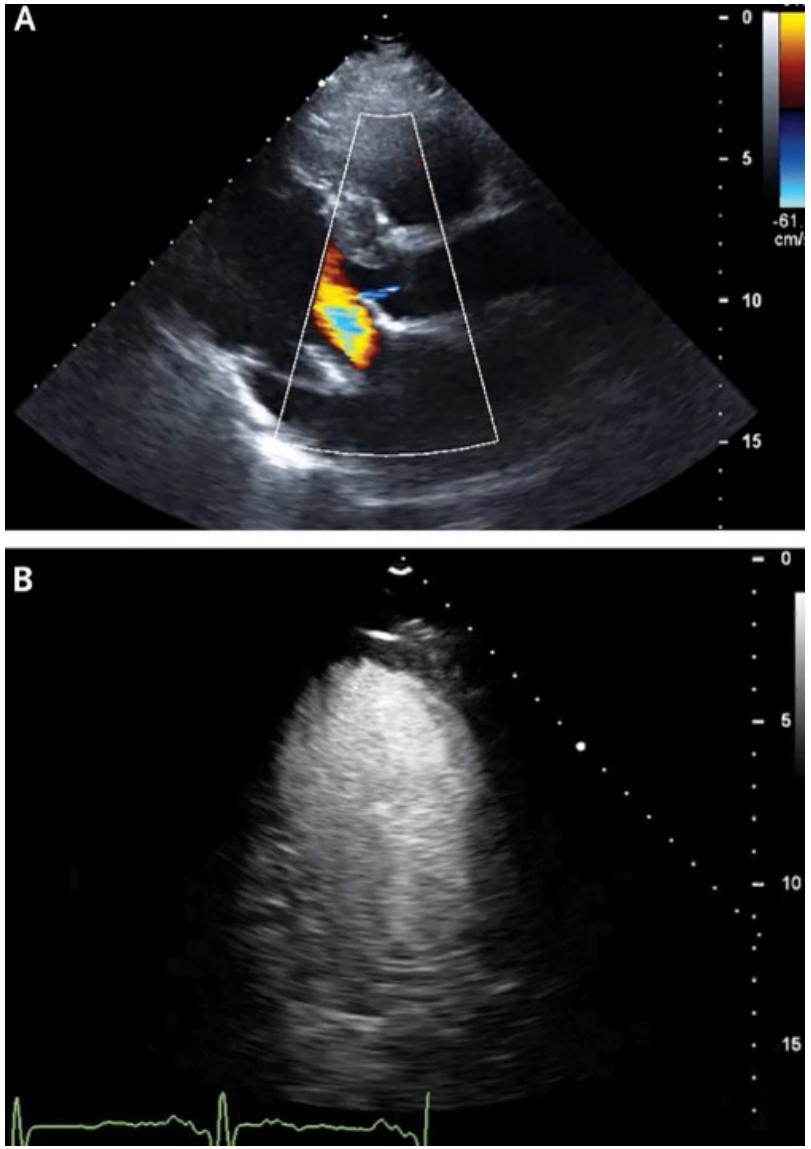
An electrocardiogram obtained at the time of the primary care clinic visit (Panel A) shows a predominantly regular wide-complex tachycardia that is consistent with ventricular tachycardia. The QRS morphologic feature, also see in the baseline electrocardiogram (ECG), is a right bundle-branch block (RBBB)–type morphology (dark purple box), but the QRS morphology has changed and the duration has increased from 120 to 200 msec from the baseline ECG. The seventh beat in the tracing indicates a fusion beat (Panel A, light purple box), in which there is contemporaneous activation of the ventricular myocardium by the ventricular tachycardia, as well as a sinus beat propagating through the atrioventricular node and His–Purkinje system. The first Brugada criterion is not satisfied because RS complexes are present in precordial leads (Panel A, orange box).



This is easily seen during a subsequent and faster episode of ventricular tachycardia on intracardiac electrograms that were obtained from implantable cardioverter–defibrillator (ICD) interrogation (Panel B). This shows sinus rhythm (*) at about 50 beats per minute on the atrial channel with more rapid electrograms during ventricular tachycardia on the RV channel. This atrioventricular dissociation is consistent with those seen on the ECG, albeit at different rates. In addition, the QRS morphologic feature is not the more typical finding of rSR' in a true RBBB, but rather RSr', which is a more common finding in patients with ventricular tachycardia (Panel A, dark purple box); this morphologic feature fulfills the fourth Brugada criterion. Other features consistent with ventricular tachycardia include the extreme (northwest) axis (blue boxes indicate negative QRS in leads I and aVF, with northwest axis triangulation, which is corroborated by the tall positive R wave in lead aVR) and the notching of the nadir of the S wave (Panel A, gray circle).

The ICD did not deliver therapies; does this mean that the ICD was not working or that the patient did not have ventricular tachycardia? Before this admission, the patient's ICD had been programmed to deliver therapies for the treatment of ventricular tachycardia at a rate above 124 beats per minute, so the ICD would not have delivered therapies for the wide-complex tachycardia of the patient's rate on presentation.

We then performed an electrophysiologic study, which confirmed that the patient had a postmyocardial infarction (scar-related) reentrant ventricular tachycardia. After electrophysiologic mapping and pacing maneuvers with an ablation catheter on the inferior wall of the left ventricle were performed, a critical isthmus of myocardium was identified that was responsible for maintenance of ventricular tachycardia circuits. Catheter ablation was performed at this site, resulting in the successful termination of ventricular tachycardia. Moreover, the patient had no inducible ventricular tachycardia with aggressive pacing maneuvers at the end of the ablation and electrophysiologic study procedure. In addition to catheter ablation, successful long-term management of arrhythmia in patients with ischemic cardiomyopathy also requires meticulous management of the patient's heart-failure therapy..



Echocardiogram Obtained before Electrophysiologic Catheter Ablation.
A transthoracic echocardiogram was obtained during hospital admission as part of the evaluation of ventricular tachycardia and for procedural planning; during the imaging study, the patient was in sinus rhythm. The left ventricular ejection fraction was 28% with akinesis of the inferior, inferoposterior, and apical walls; the left ventricle was dilated. In a parasternal long-axis view (Panel A), a bioprosthetic mitral valve shows with no regurgitation and normal transmitral gradients; trace aortic insufficiency is present. No substantial change is observed in left ventricular global or regional function, as compared with the previous transthoracic echocardiogram obtained 6 months before the current presentation. Contrast-enhanced echocardiography was performed 1 day later. An apical four-chamber view (Panel B) shows no echocardiographic evidence of left ventricular thrombus.

Although the patient in this case had an ICD placed for secondary prevention after a cardiac arrest due to ventricular tachycardia, device therapies such as ICDs should be considered for primary prevention of sudden cardiac death due to arrhythmias for patients with a left ventricular ejection fraction of 35% or less. Cardiac resynchronization therapy should be reserved for patients with heart failure who have a left ventricular ejection fraction of 35% or less and left bundle-branch block characterized by wide QRS intervals. Patients who have signs and symptoms of progressive heart failure despite receiving appropriate guideline-directed medical therapy, as well as those who have recurrent hospitalizations related to heart failure or ventricular arrhythmias that are not amenable to conventional treatments, would benefit from a discussion with their cardiologist about therapies for advanced heart failure, such as heart transplantation.

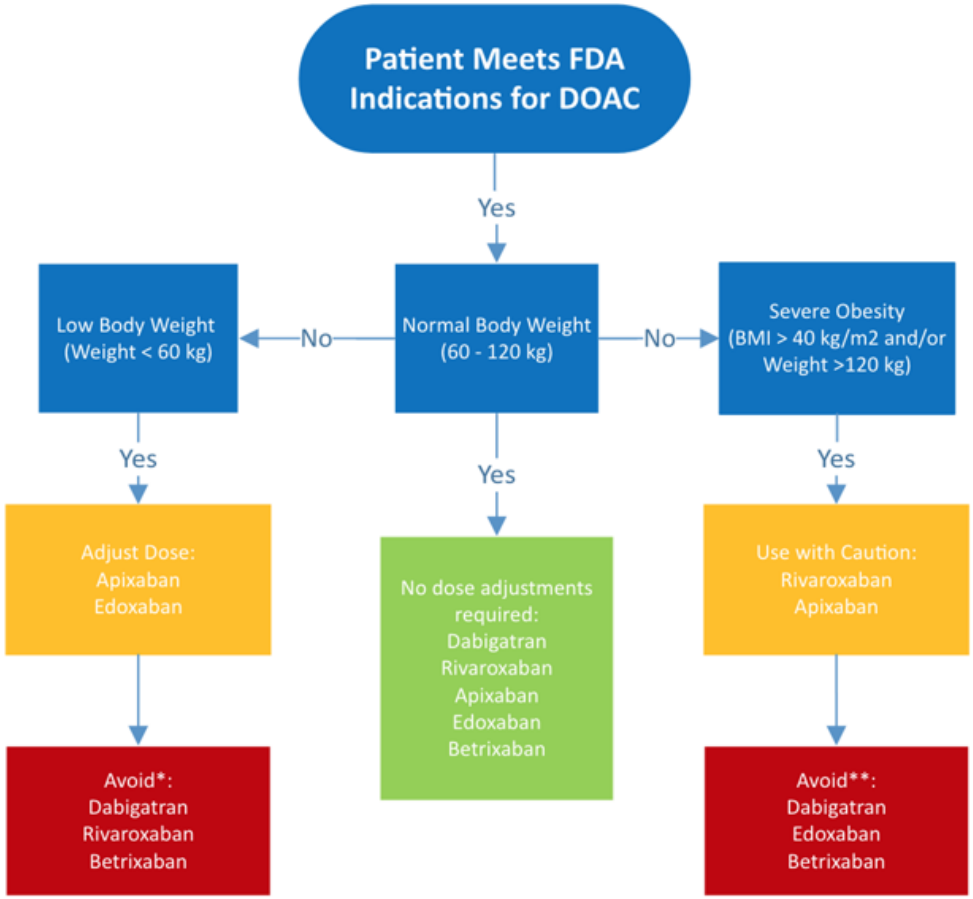
After ablation of the ventricular tachycardia, the patient had no additional ventricular arrhythmias during hospitalization. At hospital discharge approximately 1 week after admission, treatment with mexiletine was started. At a follow-up primary care visit 2.5 weeks later, he reported 1 second of palpitations but no recurrence of dyspnea or chest discomfort.

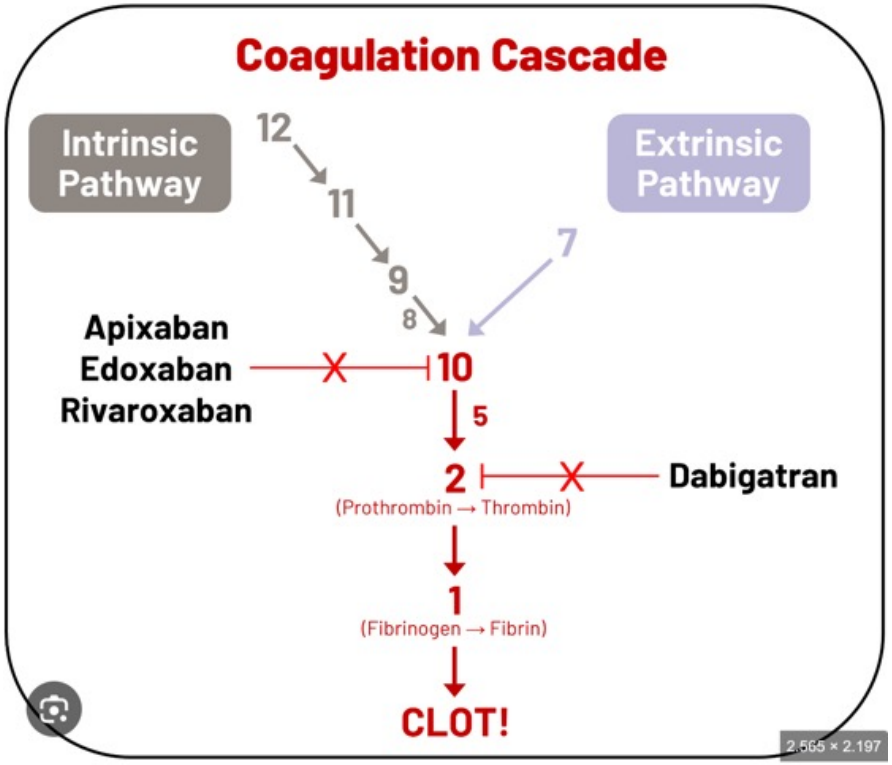
The patient continued treatment with mexiletine for 2 years. Four years after the procedure, the patient reported feeling well, he had a stable weight, and was no longer receiving diuretic therapy. His current treatment regimen includes standard, four-pillar guideline-directed medical therapy with a beta-blocker, an angiotensin receptor–neprilysin inhibitor, a mineralocorticoid receptor antagonist, and an SGLT2 inhibitor. Recent device interrogation revealed a single episode of nonsustained ventricular tachycardia at a rate of approximately 150 beats per minute that lasted for 10 beats.

Final Diagnosis

Postmyocardial infarction (scar-related) reentrant ventricular tachycardia.

Direkte orale Antikoagulanzien, kurz DOAK, ist der Oberbegriff für eine Gruppe von gerinnungshemmenden Arzneistoffen, die direkt gegen bestimmte Gerinnungsfaktoren wirken und oral eingenommen werden können.





Optimal timing of anticoagulation after acute ischaemic stroke with atrial fibrillation (OPTIMAS): a multicentre, blinded-endpoint, phase 4, randomised controlled trial

Summary

Background The optimal timing of anticoagulation for patients with acute ischaemic stoke with atrial fibrillation is uncertain. We investigated the efficacy and safety of early compared with delayed initiation of direct oral anticoagulants (DOACs) in patients with acute ischaemic stroke associated with atrial fibrillation.

Methods We performed a multicentre, open-label, blinded-endpoint, parallel-group, phase 4, randomised controlled trial at 100 UK hospitals. Adults with atrial fibrillation and a clinical diagnosis of acute ischaemic stroke and whose physician was uncertain of the optimal timing for DOAC initiation were eligible for inclusion in the study. We randomly assigned participants (1:1) to early (ie, ≤4 days from stroke symptom onset) or delayed (ie, 7–14 days) anticoagulation initiation with any DOAC, using an independent online randomisation service with random permuted blocks and varying block length, stratified by stroke severity at randomisation. Participants and treating clinicians were not masked to treatment assignment, but all outcomes were adjudicated by a masked independent external adjudication committee using all available clinical records, brain imaging reports, and source images. The primary outcome was a composite of recurrent ischaemic stroke, symptomatic intracranial haemorrhage, unclassifiable stroke, or systemic embolism incidence at 90 days in a modified intention-to-treat population. We used a gatekeeper approach by sequentially testing for a non-inferiority margin of 2 percentage points, followed by testing for superiority. OPTIMAS is registered with ISRCTN (ISRCTN17896007) and ClinicalTrials.gov (NCT03759938), and the trial is ongoing.

Findings Between July 5, 2019, and Jan 31, 2024, 3648 patients were randomly assigned to early or delayed DOAC initiation. 27 participants did not fulfil the eligibility criteria or withdrew consent to include their data, leaving 3621 patients (1814 in the early group and 1807 in the delayed group; 1981 men and 1640 women) in the modified intention-to-treat analysis. The primary outcome occurred in 59 (3·3%) of 1814 participants in the early DOAC initiation group compared with 59 (3·3%) of 1807 participants in the delayed DOAC initiation group (adjusted risk difference [RD] 0·000, 95% CI –0·011 to 0·012). The upper limit of the 95% CI for the adjusted RD was less than the non-inferiority margin of 2 percentage points ($p_{non\text{-}inferiority}$=0·0003). Superiority was not identified ($p_{superiority}$=0·96). Symptomatic intracranial haemorrhage occurred in 11 (0·6%) participants allocated to the early DOAC initiation group compared with 12 (0·7%) participants allocated to the delayed DOAC initiation group (adjusted RD 0·001, –0·004 to 0·006; p=0·78).

Interpretation Early DOAC initiation within 4 days after ischaemic stroke associated with atrial fibrillation was non-inferior to delayed initiation for the composite outcome of ischaemic stroke, intracranial haemorrhage, unclassifiable stroke, or systemic embolism at 90 days. Our findings do not support the current common and guideline-supported practice of delaying DOAC initiation after ischaemic stroke with atrial fibrillation.

	Early initiation (n=1814)	Delayed initiation (n=1807)	Total (n=3621)
Age, years	78·5 (9·9)	78·5 (9·9)	78·5 (9·9)
Sex			
Female	810 (44·7%)	830 (45·9%)	1640 (45·3%)
Male	1004 (55·3%)	977 (54·1%)	1981 (54·7%)
Ethnicity			
White	1690 (93·2%)	1703 (94·2%)	3393 (93·7%)
Black, Black British, Caribbean, or African	31 (1·7%)	27 (1·5%)	58 (1·6%)
South Asian	30 (1·7%)	30 (1·7%)	60 (1·7%)
East Asian or southeast Asian	23 (1·3%)	17 (0·9%)	40 (1·1%)
Mixed ethnicity, other, not disclosed, or missing	40 (2·2%)	30 (1·7%)	70 (1·9%)
Anticoagulant agent taken before ischaemic stroke			
Vitamin K antagonist	61 (3·4%)	53 (2·9%)	114 (3·1%)
DOAC	582 (32·1%)	584 (32·3%)	1166 (32·2%)
Antiplatelet agent taken before ischaemic stroke	213 (11·7%)	194 (10·7%)	407 (11·2%)
Antiplatelet agent taken after ischaemic stroke	1489 (82·1%)	1546 (85·6%)	3035 (83·8%)
DOAC initiated after ischaemic stroke			
Apixaban	1142 (63·0%)	1106 (61·2%)	2248 (62·1%)
Dabigatran	38 (2·1%)	31 (1·7%)	69 (1·9%)
Edoxaban	537 (29·6%)	508 (28·1%)	1045 (28·9%)
Rivaroxaban	78 (4·3%)	87 (4·8%)	165 (4·6%)
Did not commence DOAC	19 (1·0%)	75 (4·2%)	94 (2·6%)
Intravenous thrombolysis treatment	421 (23·2%)	377 (20·9%)	798 (22·0%)
Endovascular treatment	131 (7·2%)	135 (7·5%)	266 (7·3%)
Hypercholesterolaemia	620 (34·2%)	568 (31·4%)	1188 (32·8%)
Diabetes type 1 or 2, known before ischaemic stroke or diagnosed during admission	392 (21·6%)	376 (20·8%)	768 (21·2%)
Hypertension	1205 (66·4%)	1229 (68·0%)	2434 (67·2%)
Chronic kidney disease	271 (14·9%)	272 (15·1%)	543 (15·0%)
Dementia or cognitive impairment	121 (6·7%)	127 (7·0%)	248 (6·8%)
Smoking status			
Current smoker	144 (7·9%)	129 (7·1%)	273 (7·5%)
Ex-smoker	502 (27·7%)	517 (28·6%)	1019 (28·1%)
Never smoked	946 (52·1%)	970 (53·7%)	1916 (52·9%)
Not known	222 (12·2%)	191 (10·6%)	413 (11·4%)
Current alcohol intake >14 units per week	213 (11·7%)	189 (10·5%)	402 (11·1%)
Myocardial infarction	162 (8·9%)	174 (9·6%)	336 (9·3%)
Coronary revascularisation	109 (6·0%)	120 (6·6%)	229 (6·3%)
Congestive heart failure	210 (11·6%)	173 (9·6%)	383 (10·6%)
History of angina	139 (7·7%)	123 (6·8%)	262 (7·2%)
Peripheral arterial disease	30 (1·7%)	48 (2·7%)	78 (2·2%)
Previous ischaemic stroke	295 (16·3%)	242 (13·4%)	537 (14·8%)
Previous intracranial haemorrhage	35 (1·9%)	28 (1·5%)	63 (1·7%)
Atrial fibrillation known before ischaemic stroke	917 (50·6%)	919 (50·9%)	1836 (50·7%)

(Table 1 continues on next page)

	Early initiation (n=1814)	Delayed initiation (n=1807)	Total (n=3621)
(Continued from previous page)			
Type of atrial fibrillation			
Paroxysmal	468 (25·8%)	498 (27·6%)	966 (26·7%)
Persistent	1297 (71·5%)	1264 (70·0%)	2561 (70·7%)
Atrial flutter	48 (2·6%)	44 (2·4%)	92 (2·5%)
Missing	1 (0·1%)	1 (0·1%)	2 (0·1%)
Previous hospitalisation for extracranial haemorrhage	38 (2·1%)	30 (1·7%)	68 (1·9%)
NIHSS score at admission			
0–4	723 (39·9%)	762 (42·2%)	1485 (41·0%)
5–10	616 (34·0%)	612 (33·9%)	1228 (33·9%)
11–15	237 (13·1%)	200 (11·1%)	437 (12·1%)
16–21	165 (9·1%)	152 (8·4%)	317 (8·8%)
>21	65 (3·6%)	72 (4·0%)	137 (3·8%)
Missing	8 (0·4%)	9 (0·5%)	17 (0·5%)
NIHSS score at randomisation			
0–4	1039 (57·3%)	1044 (57·8%)	2083 (57·5%)
5–10	505 (27·8%)	505 (27·9%)	1010 (27·9%)
11–15	147 (8·1%)	135 (7·5%)	282 (7·8%)
16–21	90 (5·0%)	88 (4·9%)	178 (4·9%)
>21	33 (1·8%)	35 (1·9%)	68 (1·9%)
NIHSS score at admission	6 (3–11)	5 (3–10)	5 (3–10)
NIHSS score at randomisation	4 (2–7)	4 (2–7)	4 (2–7)

Data are mean (SD), n (%), and median (IQR). DOAC=direct oral anticoagulant. NIHSS=National Institutes of Health Stroke Scale.

Table 1: **Participant characteristics at randomisation, by treatment group**

	Early initiation (n=1814)	Delayed initiation (n=1807)	Adjusted risk difference (95% CI)	p value
Primary outcome*	59 (3·3%)	59 (3·3%)	0·000 (–0·011 to 0·012)	0·96
Recurrent ischaemic stroke	44 (2·4%)	42 (2·3%)	–0·001 (–0·011 to 0·009)	0·84
Symptomatic intracranial haemorrhage	11 (0·6%)	12 (0·7%)	0·001 (–0·004 to 0·006)	0·78
Systemic embolism	2 (0·1%)	4 (0·2%)	0·001 (–0·002 to 0·004)	0·40
Unclassifiable stroke	3 (0·2%)	2 (0·1%)	–0·001 (–0·003 to 0·002)	0·66
All-cause mortality	159 (8·8%)	160 (8·9%)	0·002 (–0·015 to 0·019)	0·83
Primary outcome and mortality	196 (10·8%)	190 (10·5%)	–0·001 (–0·021 to 0·018)	0·88
Major extracranial bleeding	7 (0·4%)	13 (0·7%)	0·004 (–0·001 to 0·009)	0·16
Non-major extracranial bleeding	45 (2·5%)	37 (2·0%)	–0·004 (–0·014 to 0·006)	0·42
All major bleeding (extracranial and intracranial)	18 (1·0%)	25 (1·4%)	0·004 (–0·003 to 0·011)	0·24
Venous thromboembolism	7 (0·4%)	10 (0·6%)	0·002 (–0·003 to 0·006)	0·46

Data are n (%) unless otherwise specified. Risk difference estimates and p values are adjusted for stroke severity (assessed with National Institutes of Health Stroke Scale score) at randomisation. *Composite of recurrent ischaemic stroke, unclassifiable stroke, symptomatic intracranial haemorrhage, and systemic embolism at 90 days.

Table 2: **First occurrence of outcome events during follow-up in the modified intention-to-treat population**

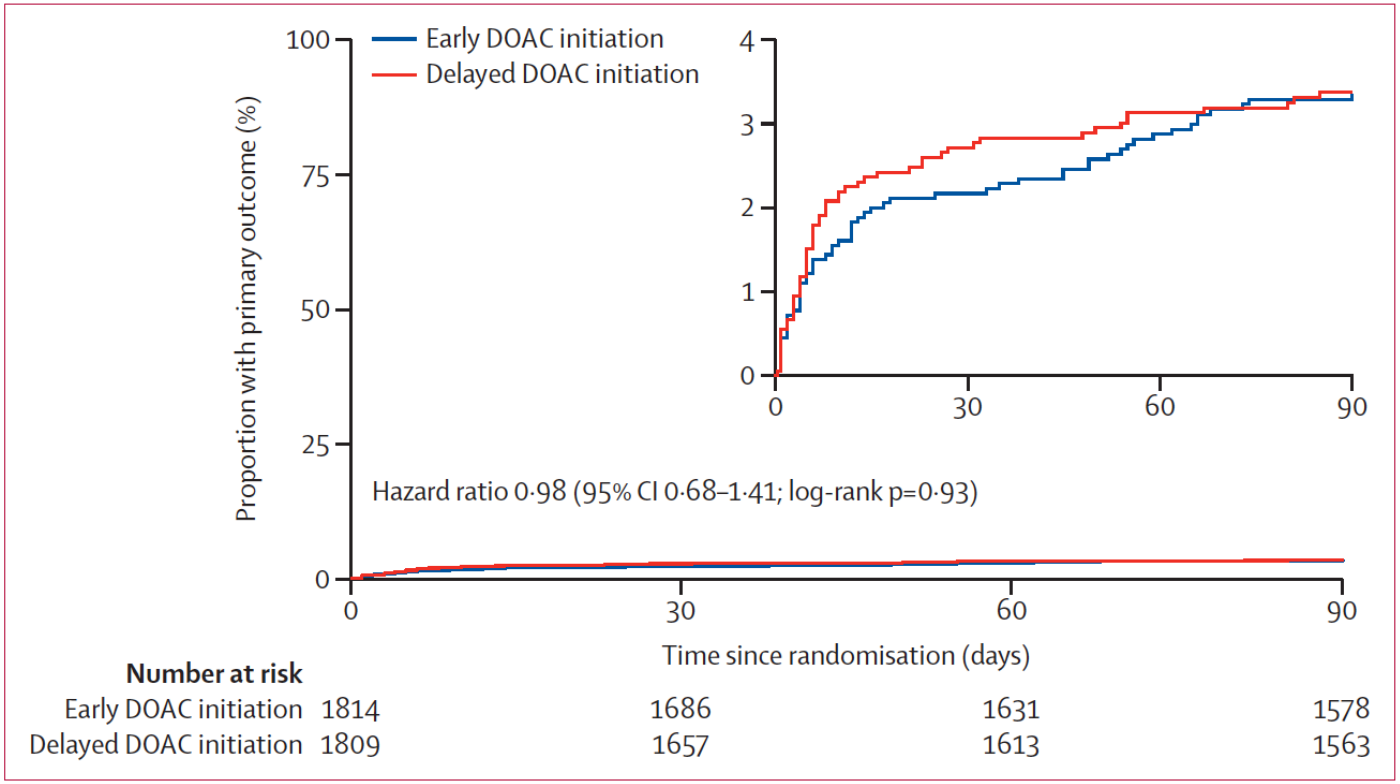


Figure 2: **Time-to-event curves of the primary composite outcome of recurrent ischaemic stroke, symptomatic intracranial haemorrhage, unclassifiable stroke, or systemic embolism at 90 days**
Hazard ratio adjusted for stroke severity (National Institutes of Health Stroke Scale score) at randomisation. DOAC=direct oral anticoagulant.

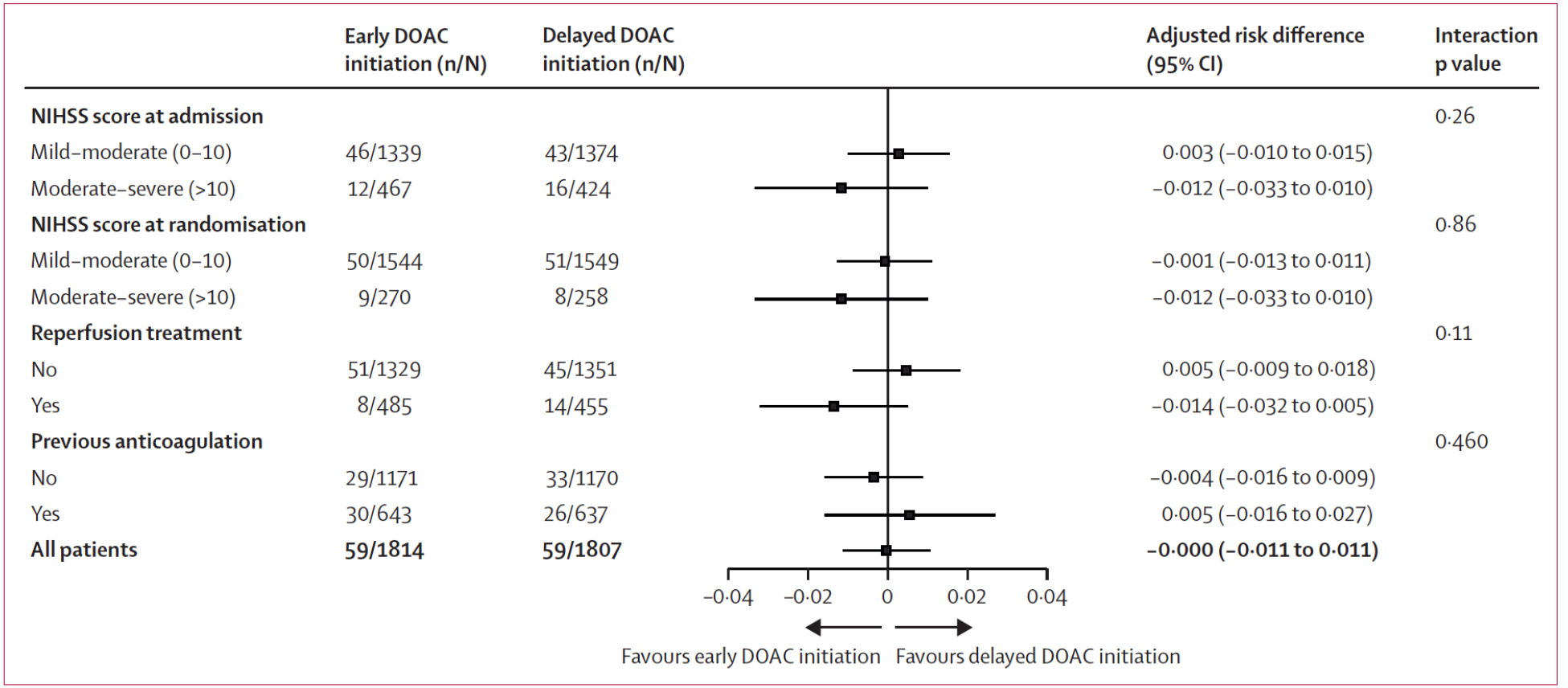


Figure 3: **Forest plot for the primary outcome according to clinically relevant subgroups**

Risk difference was adjusted for stroke severity (based on National Institutes of Health Stroke Scale score at randomisation). p values refer to interaction terms between subgroup characteristics and the DOAC timing with respect to the primary outcome. DOAC=direct oral anticoagulant. NIHSS=National Institutes of Health Stroke Scale.

Research in context

Evidence before this study

We searched the electronic databases PubMed, Embase, and the Cochrane Central Register of Controlled Trials for randomised controlled trials published in English from inception to May 16, 2024, comparing different timings of direct oral anticoagulant (DOAC) initiation for adult patients (aged ≥18 years) with a clinical diagnosis of acute ischaemic stroke and atrial fibrillation. We identified two published studies (TIMING and ELAN) and one study published in abstract form (START). TIMING, an open-label, non-inferiority trial, which randomly assigned participants to early (ie, ≤4 days after stroke onset) or delayed (ie, 5–10 days after stroke onset) DOAC initiation, recruited 888 of 3000 planned participants. The primary outcome, a composite of recurrent ischaemic stroke, symptomatic intracerebral haemorrhage, or all-cause mortality at 90 days, occurred in 31 (6·89%) of 450 patients assigned to early initiation and in 38 (8·68%) of 438 patients assigned to delayed direct oral anticoagulant initiation (absolute risk difference −1·79%, 95% CI −5·31 to 1·74; $p_{non\text{-}inferiority}$=0·004). The risk of ischaemic stroke was 3·11% in patients who started anticoagulation early, compared with 4·57% in patients who started later, with no intracerebral haemorrhages. In the ELAN trial, in which participants were randomly assigned to early (ie, ≤48 h after stroke onset in participants with minor or moderate stroke or on day 6 or 7 in those with major stroke) or later DOAC initiation (ie, on day 3 or 4 in participants with minor stroke, day 6 or 7 in those with moderate stroke, or day 12, 13, or 14 in those with major stroke), the primary outcome (ie, a composite of symptomatic intracranial haemorrhage, major extracranial bleeding, recurrent ischaemic stroke, systemic embolism, or vascular death within 30 days) occurred in 29 (2·9%) of 1006 participants in the early treatment group and 41 (4·1%) of 1007 participants in the delayed treatment group (risk difference −1·18 percentage points, 95% CI −2·84 to 0·47). Recurrent ischaemic stroke occurred in 14 (1·4%) participants in the early treatment group and 25 (2·5%) participants in the delayed treatment group (odds ratio 0·57, 95% CI 0·29 to 1·07), and symptomatic intracranial haemorrhage occurred in four participants in the study (two in each treatment group [0·2%]).

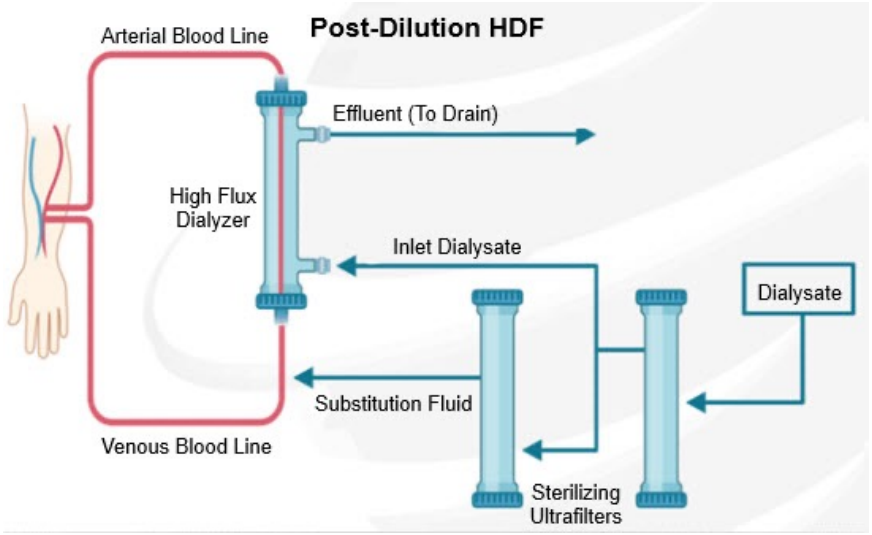
Added value of this study

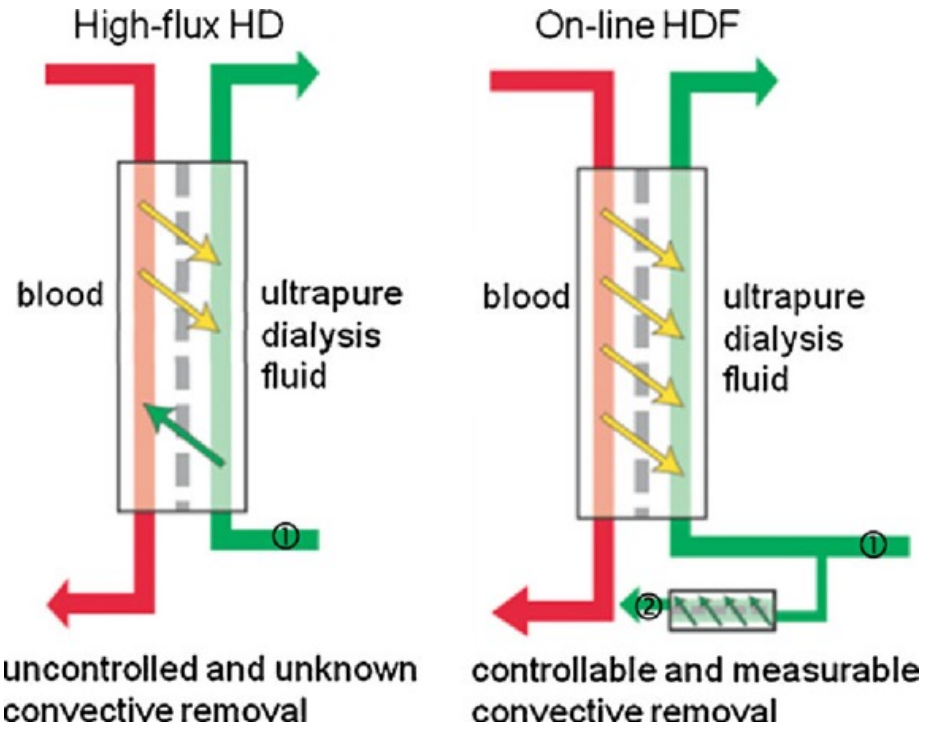
OPTIMAS is the largest trial of DOAC initiation timing in patients with acute ischaemic stroke with atrial fibrillation, providing more precise estimates than previous trials of early DOAC initiation on recurrent ischaemic stroke and the risk of intracranial haemorrhage in a broad patient population. We included many people with moderate-to-severe stroke (528 [14·6%] of 3621 participants with a National Institutes of Health Stroke Scale score of >10 at randomisation), in whom there is greater concern about intracranial haemorrhage than for people with less severe stroke. Our findings provide reassurance that early DOAC initiation is non-inferior to delayed DOAC initiation for a composite outcome of recurrent ischaemic stroke, symptomatic intracranial haemorrhage, unclassified stroke, or systemic embolism. We identified no evidence for heterogeneity of the effect of anticoagulation timing in participants with moderate-to-severe stroke, patients who received acute reperfusion treatments (ie, intravenous thrombolysis, mechanical thrombectomy, or both), or those who were already taking an anticoagulant, providing reassurance that early DOAC initiation does not carry a high risk of symptomatic intracranial haemorrhage in these patient groups.

Implications of all the available evidence

The available evidence indicates that early DOAC initiation is non-inferior to delayed initiation after ischaemic stroke with atrial fibrillation and does not support the common and guideline-recommended practice of delaying treatment due to concerns about intracranial haemorrhage, irrespective of baseline stroke severity. A planned individual participant data meta-analysis will provide additional information on the benefits and risks of early DOAC initiation following acute ischaemic stroke associated with atrial fibrillation.

Hemodiafiltration (HDF) is a form of kidney replacement therapy (KRT) that utilizes convective in combination with diffusive clearance. Compared with conventional hemodialysis, HDF removes more middle-molecular-weight solutes.





Konvektion oder Strömungstransport ist der Transport physikalischer Größen in strömenden Gasen oder Flüssigkeiten.

Haemodiafiltration versus haemodialysis for kidney failure: an individual patient data meta-analysis of randomised controlled trials

Summary

Background High-dose haemodiafiltration has been shown, in a randomised clinical trial, to result in a 23% lower risk of mortality for patients with kidney failure when compared with conventional high-flux haemodialysis. Nevertheless, whether treatment effects differ across subgroups, whether a dose–response relationship with convection volume exists, and the effects on cause-specific mortality remain unclear. The aim of this individual patient data meta-analysis was to compare the effects of haemodiafiltration and standard haemodialysis on all-cause and cause-specific mortality.

Methods On July 17, 2024, we searched MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials for randomised controlled trials, published from database inception, comparing online haemodiafiltration versus haemodialysis designed to measure mortality outcomes. The primary outcome was all-cause mortality. Hazard ratios were generated using Cox proportional hazards regression models reporting hazard ratios and 95% CIs. Subgroup analyses based on predefined patient characteristics and dose–response analyses using natural splines for convection volume were performed. This analysis is registered with PROSPERO (CRD42024511514).

Findings Five trials (n=4153 patients; 2070 receiving haemodialysis and 2083 receiving haemodiafiltration) were eligible for inclusion in this analysis. After a median follow-up of 30 months (IQR 24–36), all-cause mortality occurred in 477 patients (23·3%) treated with haemodiafiltration compared with in 559 patients (27·0%) treated with haemodialysis (hazard ratio 0·84 [95% CI 0·74–0·95]). No evidence of a differential effect across subgroups was noted. A graded relationship between convection volume and mortality risk was apparent: as the volume increased, the mortality risk decreased.

Interpretation Compared with haemodialysis, online haemodiafiltration reduces all-cause mortality in people with kidney failure. Results do not differ across patient and treatment characteristics and the risk reduction appears to be dose-dependent. In conclusion, the present analysis strengthens the notion that haemodiafiltration can be considered as a superior alternative to the present standard (ie, haemodialysis).

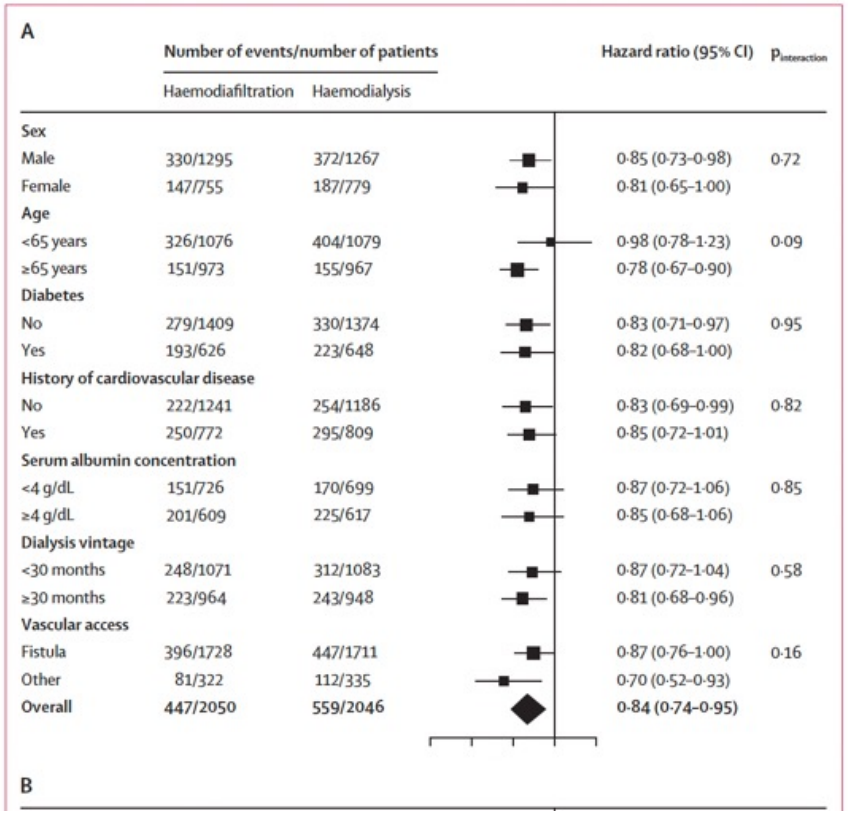
	CONTRAST (n=714)	CONVINCE (n=1360)	ESHOL (n=906)	French study (n=391)	Turkish study (n=782)
Number of patients treated with haemodiafiltration	358 (50·1%)	683 (50·2%)	456 (50·3%)	195 (49·9%)	391 (50·0%)
Number of patients treated with haemodialysis	356 (49·9%)	677 (49·8%)	450 (49·7%)	196 (50·1%)	391 (50·0%)
Age, years	66·8 (54·9–74·8)	64·0 (54·0–72·0)	68·0 (56·0–77·0)	76·2 (71·2–81·1)	58·1 (48·1–67·1)
Female	269 (37·7%)	504 (37·1%)	300 (33·1%)	154 (39·4%)	322 (41·2%)
Male	445 (62·3%)	856 (62·9%)	606 (66·9%)	237 (60·6%)	460 (58·8%)
History of cardiovascular disease	313 (43·8%)	612 (45·0%)	298 (32·9%)	196 (50·1%)	182 (23·3%)
Diabetes	170 (23·8%)	481 (35·4%)	226 (24·9%)	146 (37·3%)	272 (34·8%)
Dialysis vintage, months	24·0 (12·0–48·0)	32·6 (15·1–71·6)	28·0 (12·0–59·0)	37·7 (17·0–70·6)	49·7 (24·3–83·2)
Systolic blood pressure, mm Hg	147·8 (21·6)	141·4 (22·1)	136·4 (23·9)	138·1 (22·8)	128·2 (16·0)
Diastolic blood pressure, mm Hg	75·7 (12·2)	72·7 (14·7)	72·0 (15·1)	65·1 (14·6)	78·1 (8·2)
Vascular access, arteriovenous fistula	567 (79·4%)	1115 (82·0%)	779 (86·0%)	283 (72·4%)	747 (95·5%)
Duration of dialysis session, min	240·0 (210·0–240·0)	240·0 (240·0–246·0)	240·0 (235·0–240·0)	240·0 (240·0–240·0)	239·8 (234·5–240·0)
Blood flow, mL per min	300·0 (280·0–325·0)	360·0 (350·0–400·0)	380·0 (350·0–400·0)	338·0 (300·0–358·0)	290·0 (266·7–319·1)
Dialysis single-pool, Kt/V	1·39 (0·22)	1·64 (0·31)	1·66 (0·31)	1·59 (0·34)	1·43 (0·27)
Haemoglobin, g/dL	11·80 (1·25)	11·28 (1·21)	11·98 (1·43)	11·61 (1·30)	11·43 (1·49)
Phosphorus, mg/dL	5·08 (1·53)	4·92 (1·47)	4·66 (1·47)	4·46 (1·36)	4·83 (1·46)
B-2 microglobulin, mg/L	31·78 (14·69)	..	24·26 (9·67)	26·99 (7·38)	26·36 (8·72)
BMI after dialysis, kg/m²	25·39 (4·80)	27·41 (5·65)	24·95 (4·53)	26·29 (4·89)	24·91 (4·76)
Body surface area, m²	1·85 (0·21)	1·86 (0·22)	1·73 (0·19)	1·76 (0·19)	1·74 (0·18)
Albumin, g/dL	4·04 (0·38)	..	4·09 (0·43)	3·90 (0·39)	3·84 (0·37)
C-reactive protein, mg/L	3·93 (1·38–10·36)	4·5 (2·0–10·4)	6·30 (4·90–13·00)	5·00 (1·85–12·60)	0·87 (0·37–1·90)
Pre-dialysis creatinine, mg/dL	9·74 (2·89)	8·36 (2·31)	8·02 (2·37)	7·64 (1·75)	8·05 (2·17)
Cholesterol, mmol/L	3·68 (0·96)	..	..	4·14 (1·63)	4·50 (1·09)
Convection volume, L per session*	19·8 (17·2–23·0)	24·9 (23·5–27·0)	24·2 (22·3–26·0)	19·9 (16·8–24·0)	19·6 (18·7–20·6)

Data are n (%), median (IQR), or mean (SD). *Only for patients receiving haemodiafiltration.

Table 1: **Baseline characteristics of study participants**

	Haemodialysis			Haemodiafiltration			Hazard ratio (95% CI) for haemodiafiltration *vs* haemodialysis
	n	Events	Events per 100 person-years	n	Events	Events per 100 person-years	
All-cause mortality (primary outcome)	2046	559	11·18	2050	477	9·37	0·84 (0·74–0·95)
Cardiovascular mortality	1979	202	4·04	1972	160	3·14	0·78 (0·64–0·96)
Cardiac causes	1979	117	2·34	1972	80	1·57	0·67 (0·50–0·89)
Non-cardiac causes	1979	32	0·64	1972	39	0·77	1·20 (0·75–1·91)
Unclassified	1979	53	1·06	1972	41	0·83	0·78 (0·52–1·17)
Infection-related mortality, including COVID-19	1677	118	2·36	1691	96	1·89	0·80 (0·61–1·04)
Infection-related mortality, excluding COVID-19	1677	97	1·94	1691	81	1·59	0·82 (0·61–1·10)
Sudden death	1979	98	1·96	1972	84	1·65	0·84 (0·63–1·12)
Transplantation	2070	162	2·80	2083	193	2·98	1·14 (0·92–1·41)

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



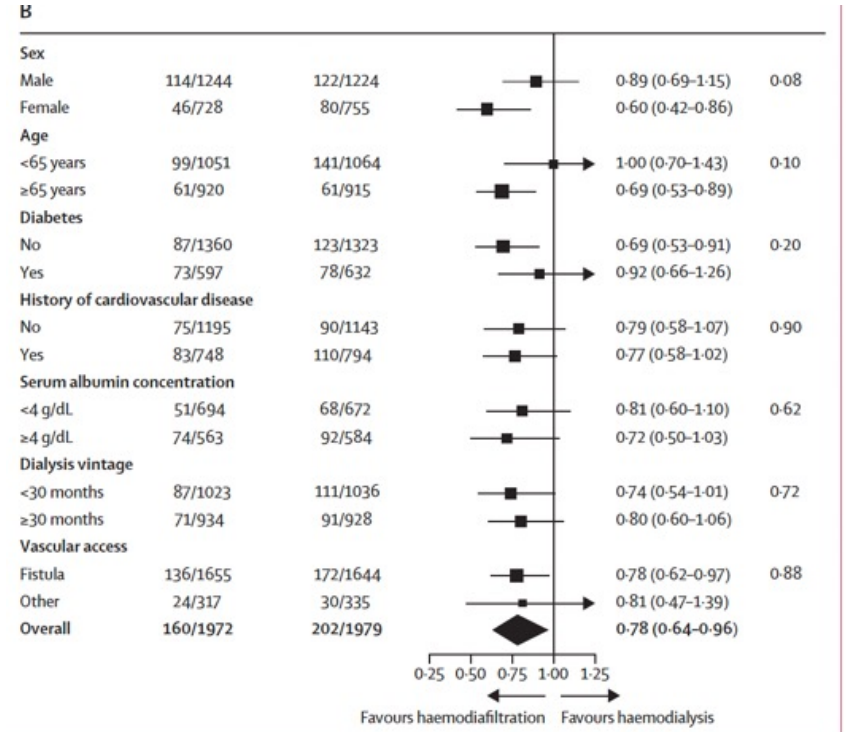


Figure 2: All-cause mortality (A) and cardiovascular mortality (B) in patients treated with online haemodiafiltration versus haemodialysis

	Standard haemodialysis n=2070	Haemodiafiltration convection volume, L per session		
		<19 (n=370)	19–23 (n=641)	>23 (n=959)
All-cause mortality				
Unadjusted	Reference	0·92 (0·74–1·15)	0·93 (0·78–1·11)	0·70 (0·59–0·83)
Adjusted*	Reference	0·85 (0·67–1·08)	1·06 (0·87–1·29)	0·63 (0·50–0·79)
Cardiovascular mortality				
Unadjusted	Reference	0·98 (0·68–1·41)	0·76 (0·56–1·04)	0·74 (0·55–0·98)
Adjusted*	Reference	0·99 (0·68–1·44)	0·84 (0·60–1·16)	0·58 (0·40–0·85)
Cardiac cardiovascular death				
Unadjusted	Reference	0·71 (0·39–1·28)	0·58 (0·37–0·92)	0·74 (0·52–1·06)
Adjusted*	Reference	0·75 (0·41–1·37)	0·65 (0·40–1·04)	0·62 (0·40–0·97)
Infection-related mortality, including COVID-19				
Unadjusted	Reference	1·14 (0·70–1·85)	0·95 (0·63–1·44)	0·57 (0·39–0·82)
Adjusted*	Reference	1·02 (0·59–1·77)	1·22 (0·73–2·03)	0·51 (0·28–0·93)
Infection-related mortality, excluding COVID-19				
Unadjusted	Reference	1·21 (0·74–1·99)	1·04 (0·68–1·61)	0·51 (0·34–0·78)
Adjusted*	Reference	1·02 (0·59–1·77)	1·22 (0·73–2·03)	0·51 (0·28–0·93)

*Adjusted for age, sex, creatinine, history of cardiovascular disease, and history of diabetes.

Table 3: **All-cause and cause-specific mortality by convection volume (with standard haemodialysis as a reference)**

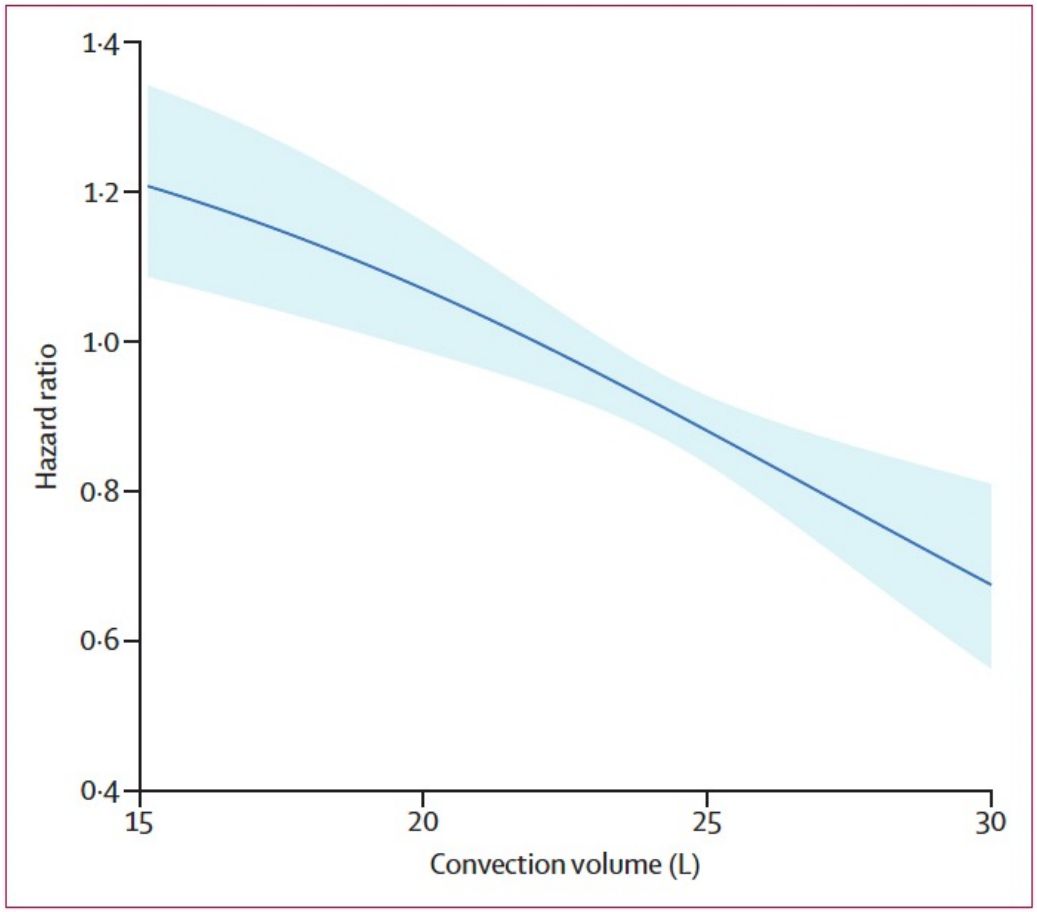


Figure 3: **Dose–response curve of the relation between convection volume plotted against hazard ratios of all-cause mortality, based on data from patients treated with haemodiafiltration**

The shaded area represents the 95% CI.

Research in context

Evidence before this study

Haemodialysis for kidney failure is associated with a mortality rate of approximately 50% at 5 years. Previous evidence on clinical outcomes from haemodiafiltration compared with haemodialysis reported divergent results on all-cause mortality, and only limited conclusions could be drawn on subgroup effects or dose–response relationships. In 2023, the CONVINCE trial reported a reduction in all-cause mortality in favour of high-dose haemodiafiltration, raising questions around implications for clinical practice, but clinical implementation should not be viewed based on the results of a single trial, and rather on all available evidence.

Added value of this study

This collaborative individual patient data meta-analysis of five large randomised controlled trials, including more than 4000 patients, showed that online haemodiafiltration, compared with conventional haemodialysis, reduces all-cause mortality and cardiovascular mortality, in particular cardiac mortality. This effect does not change with patient or treatment characteristics. A graded relationship between achieved haemodiafiltration convection volume and mortality risk was apparent: the higher the convection volume, the greater the benefit.

Implications of all the available evidence

Online haemodiafiltration reduces the risk of all-cause mortality, cardiovascular mortality, and cardiac mortality. When updated evidence on cost-effectiveness and on patient-reported outcomes is added to this information, it then proves a solid basis for recommendations for a change in clinical practice.

STEP 1:

Implanted similar to drug-eluting stent

STEP 2:

Drug elutes over 3 months

STEP 3:

Polymer coating resorbs over 6 months

STEP 4:

Uncaging elements release once coating is resorbed

Bioadaptor implant versus contemporary drug-eluting stent in percutaneous coronary interventions in Sweden

Summary

Background Persistent non-plateauing adverse event rates in patients who underwent percutaneous coronary intervention (PCI) remain a challenge. A bioadaptor is a novel implant that addresses this issue by restoring the haemodynamic modulation of the artery, allowing cyclic pulsatility, vasomotion, and adaptative remodelling, by unlocking and providing dynamic support to the artery. We aimed to assess outcomes with the device versus a contemporary drug-eluting stent (DES) in a representative PCI population.

Methods INFINITY-SWEDEHEART is a single-blind, non-inferiority, registry-based, randomised controlled study conducted in 20 hospitals in Sweden. Patients aged 18–85 years, with chronic or acute coronary syndrome ischaemic heart disease, with an indication for PCI, with up to three de novo lesions suitable for implantation with one single device per lesion, and successful pre-dilatation were identified via the Swedish Coronary Angiography and Angioplasty Registry and eligible for enrolment. Participants were randomly assigned (1:1), using block randomisation with random variation in block size and stratified by site, to either the DynamX bioadaptor (Elixir Medical, Milpitas, CA, USA) or a zotarolimus-eluting DES (Resolute Onyx and Onyx Trustar, Medtronic, Minneapolis, MN, USA). The primary endpoint was the device-oriented clinical endpoint of target lesion failure at 12 months (a composite of cardiovascular death, target vessel myocardial infarction, and ischaemia-driven target lesion revascularisation), assessed in the intention-to-treat (ITT) population (ie, all patients randomly assigned to treatment, regardless of treatment received) who had either experienced an event up to 12 months or completed the trial up to 12 months. Non-inferiority was established if the upper limit of the two-sided 95% CI for the absolute risk difference was less than 4·2%. Powered secondary endpoints were landmark analyses from 6 months onwards for target lesion failure, target vessel failure (composite of cardiovascular death, target vessel myocardial infarction, and ischaemia-driven target vessel revascularisation), and target lesion failure for patients with acute coronary syndrome assessed in the ITT population). This study is registered with ClinicalTrials.gov, NCT04562805, and follow-up to 5 years is ongoing.

Findings Between Sept 30, 2020, and July 11, 2023, 2399 patients were randomly assigned to receive the bioadaptor (n=1201) or DES (n=1198; ITT population). Median age was 69·5 years (IQR 61·2–75·6), 575 (24·0%) of 2399 patients were female, and 1824 (76·0%) were male (data on race and ethnicity were not collected), and 1838 (76·6%) patients presented with acute coronary syndrome. The primary endpoint of 12-month target lesion failure occurred in 28 (2·4%) of 1189 assessable patients in the bioadaptor group versus 33 (2·8%) of 1192 assessable patients in the DES group, with a risk difference of –0·41% (95% CI –1·94 to 1·11; $p_{non\text{-}inferiority}<0·0001$). In the prespecified landmark analysis from 6 months to 12 months, the Kaplan–Meier estimates of target lesion failure were 0·3% (with events in three of 1170 patients) in the bioadaptor group versus 1·7% (with events in 16 of 1176 patients) in the DES group (hazard ratio 0·19 [95% CI 0·06 to 0·65]; p=0·0079), of target vessel failure were 0·8% (events in eight of 1167) versus 2·5% (events in 23 of 1174; 0·35 [0·16 to 0·79]; p=0·011), and of target lesion failure in patients with acute coronary syndrome were 0·3% (events in two of 906) versus 1·8% (events in 12 of 895; 0·17 [0·04 to 0·74]; p=0·018). The rate of definite or probable device thrombosis, which was recorded as a safety outcome, was low and did not differ between groups (eight [0·7%] of 1201 in the bioadaptor group *vs* six [0·5%] of 1198 in the DES group; difference in event rates of 0·16% [95% CI –0·50 to 0·83]).

Interpretation Among patients with coronary artery disease, including those with acute coronary syndrome, treatment with the bioadaptor was non-inferior to contemporary DES, showing potential to mitigate non-plateauing device-related events and improving outcomes in patients undergoing PCI. The additional planned follow-up will help to reinforce the clinical significance of the 1-year findings.

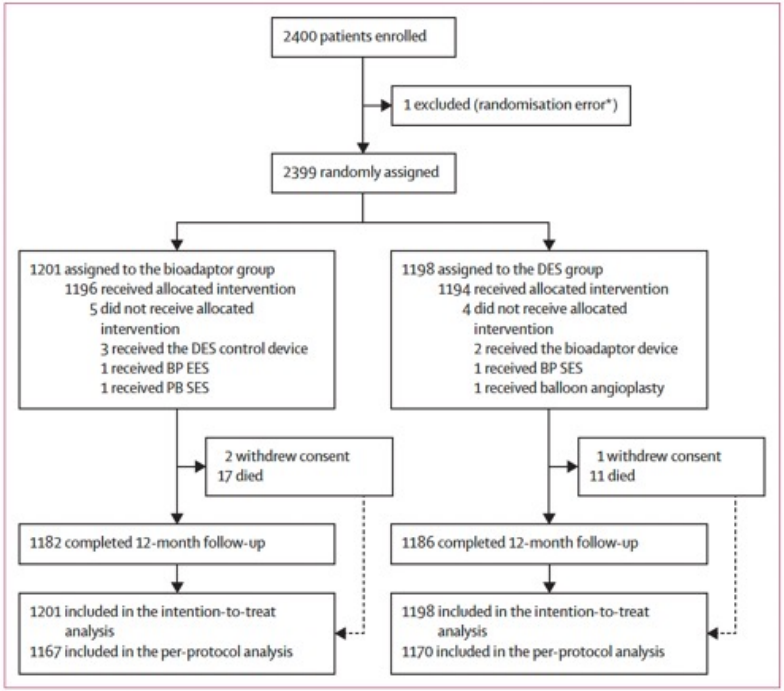


Figure 1: **Trial profile**
BP EES=biodegradable polymer everolimus-eluting stent. BP SES=biodegradable polymer sirolimus-eluting stent. DES=drug-eluting stent. *The randomisation error was of a patient who did not sign consent, and so was not included in the intention-to-treat population.

	Bioadaptor group (N=1201; 1419 lesions)	Drug-eluting stent group (N=1198; 1431 lesions)
Age, years	69·7 (61·2–75·7)	69·3 (61·5–75·6)
BMI, kg/m²	27·1 (24·6–30·1)	27·1 (24·8–30·1)
Sex		
Male	911/1201 (75·9%)	913/1198 (76·2%)
Female	290/1201 (24·1%)	285/1198 (23·8%)
Current smoking	164/1155 (14·2%)	187/1158 (16·1%)
Diabetes	231/1196 (19·3%)	198/1191 (16·6%)
Hypertension	722/1194 (60·5%)	710/1186 (59·9%)
Hyperlipidaemia	544/1194 (45·6%)	492/1186 (41·5%)
Previous myocardial infarction	144/1192 (12·1%)	141/1189 (11·9%)
Previous PCI	176/1196 (14·7%)	165/1191 (13·9%)
Previous CABG	12/1196 (1·0%)	8/1191 (0·7%)
Angina or ischaemia status		
CCS	276/1201 (23·0%)	285/1198 (23·8%)
Acute coronary syndrome	925/1201 (77·0%)	913/1198 (76·2%)
STEMI	282/1201 (23·5%)	317/1198 (26·5%)
NSTEMI	458/1201 (38·1%)	437/1198 (36·5%)
Unstable angina	185/1201 (15·4%)	159/1198 (13·3%)
Number of target lesions per patient		
1	1009/1200 (84·1%)	987/1195 (82·6%)
≥2	191/1200 (15·9%)	208/1195 (17·4%)
Number of target vessels per patient		
1	1071/1200 (89·3%)	1050/1195 (87·9%)
≥2	129/1200 (10·8%)	145/1195 (12·1%)
Non-target lesion treated	146/1200 (12·2%)	153/1195 (12·8%)
Target vessel		
LAD	726/1419 (51·2%)	728/1431 (50·9%)
LCX	365/1419 (25·7%)	384/1431 (26·8%)
RCA	327/1419 (23·0%)	318/1431 (22·2%)
LMCA	1/1419 (0·1%)	1/1431 (0·1%)
Lesion classification		
A	160/1408 (11·4%)	170/1426 (11·9%)
B1	639/1408 (45·4%)	666/1426 (46·7%)
B2/C	609/1408 (43·3%)	590/1426 (41·4%)
Bifurcation	165/1400 (11·8%)	161/1420 (11·3%)
Calcified lesion (moderate to severe)	239/1417 (16·9%)	204/1431 (14·3%)
Tortuous lesion (moderate to severe)	109/1417 (7·7%)	105/1431 (7·3%)
Reference vessel diameter, mm	3·2 (0·5)	3·2 (0·5)
Lesion lengths, mm	24·4 (9·1)	24·7 (9·4)
Diameter stenosis, %	87·0% (12·1)	87·3% (11·7)

Data are mean (SD), median (IQR), or n/N (%), where N is either number of participants with available data or number of lesions with available data. CABG=coronary artery bypass graft. CCS=chronic coronary syndrome (stable angina, chronic angina, or chronic coronary artery disease). LAD=left anterior descending artery. LCX=left circumflex artery. LMCA=left main coronary artery. NSTEMI=non-ST-elevation myocardial infarction. PCI=percutaneous coronary intervention. RCA=right coronary artery. STEMI=ST-elevation myocardial infarction.

Table 1: **Baseline demographic and clinical characteristics, intention-to-treat population**

	(N=1201; 1419 lesions)	(N=1198; 1431 lesions)
Age, years	69·7 (61·2–75·7)	69·3 (61·5–75·6)
BMI, kg/m²	27·1 (24·6–30·1)	27·1 (24·8–30·1)
Sex		
Male	911/1201 (75·9%)	913/1198 (76·2%)
Female	290/1201 (24·1%)	285/1198 (23·8%)
Current smoking	164/1155 (14·2%)	187/1158 (16·1%)
Diabetes	231/1196 (19·3%)	198/1191 (16·6%)
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Acute coronary syndrome	925/1201 (77·0%)	913/1198 (76·2%)
STEMI	282/1201 (23·5%)	317/1198 (26·5%)
NSTEMI	458/1201 (38·1%)	437/1198 (36·5%)
Unstable angina	185/1201 (15·4%)	159/1198 (13·3%)
Number of target lesions per patient		
1	1009/1200 (84·1%)	987/1195 (82·6%)
≥2	191/1200 (15·9%)	208/1195 (17·4%)
Number of target vessels per patient		
1	1071/1200 (89·3%)	1050/1195 (87·9%)
≥2	129/1200 (10·8%)	145/1195 (12·1%)
Non-target lesion treated	146/1200 (12·2%)	153/1195 (12·8%)
Target vessel		
LAD	726/1419 (51·2%)	728/1431 (50·9%)
LCX	365/1419 (25·7%)	384/1431 (26·8%)
RCA	327/1419 (23·0%)	318/1431 (22·2%)
LMCA	1/1419 (0·1%)	1/1431 (0·1%)
Lesion classification		
A	160/1408 (11·4%)	170/1426 (11·9%)
B1	639/1408 (45·4%)	666/1426 (46·7%)
B2/C	609/1408 (43·3%)	590/1426 (41·4%)
Bifurcation	165/1400 (11·8%)	161/1420 (11·3%)
Calcified lesion (moderate to severe)	239/1417 (16·9%)	204/1431 (14·3%)
Tortuous lesion (moderate to severe)	109/1417 (7·7%)	105/1431 (7·3%)
Reference vessel diameter, mm	3·2 (0·5)	3·2 (0·5)
Lesion lengths, mm	24·4 (9·1)	24·7 (9·4)
Diameter stenosis, %	87·0% (12·1)	87·3% (11·7)

Data are mean (SD), median (IQR), or n/N (%), where N is either number of participants with available data or number of lesions with available data. CABG=coronary artery bypass graft. CCS=chronic coronary syndrome (stable angina, chronic angina, or chronic coronary artery disease). LAD=left anterior descending artery. LCX=left circumflex artery. LMCA=left main coronary artery. NSTEMI=non-ST-elevation myocardial infarction. PCI=percutaneous coronary intervention. RCA=right coronary artery. STEMI=ST-elevation myocardial infarction.

Table 1: **Baseline demographic and clinical characteristics, intention-to-treat population**

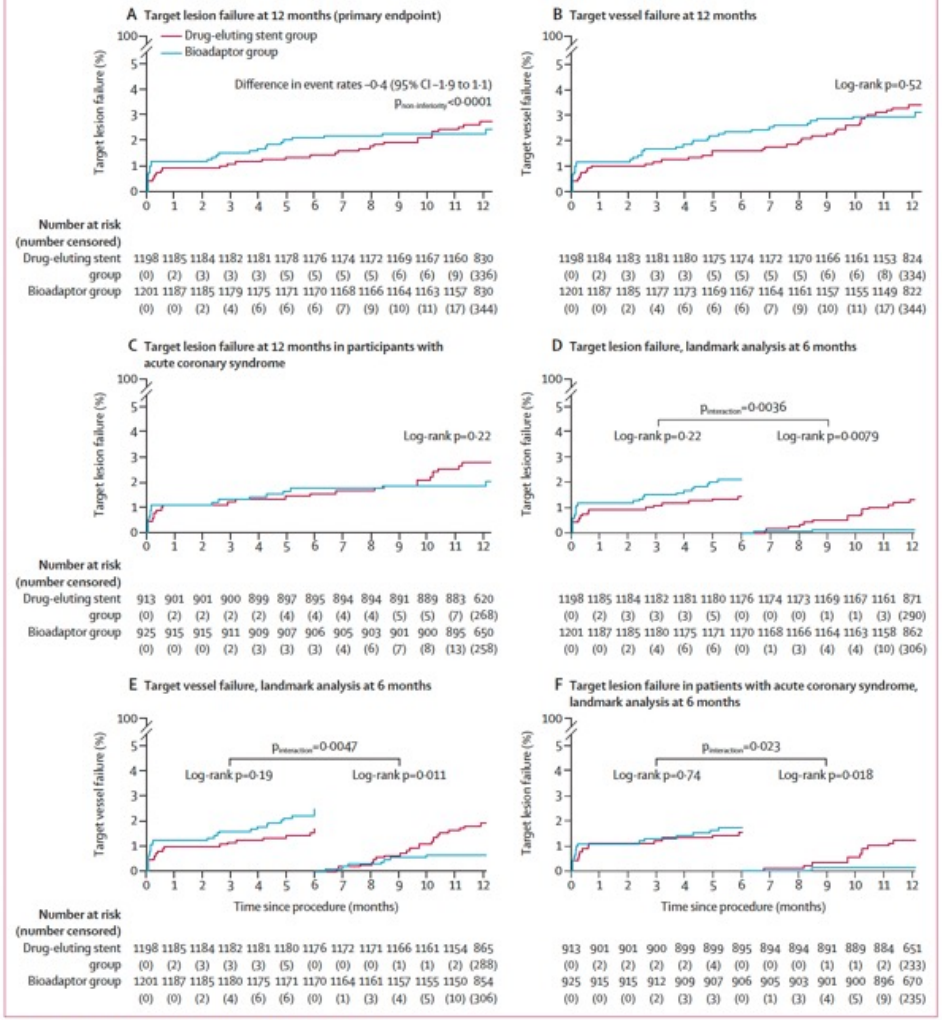


Figure 2: **Primary endpoint (A) and secondary outcomes (B–F)**
(A) Cumulative event estimates for the primary outcome (12-month target lesion failure). (B) Cumulative event estimates for the secondary composite outcome of target vessel failure at 12 months. (C) Cumulative event estimates for the secondary composite outcome of target lesion failure in patients with acute coronary syndrome at 12 months. Event estimates were calculated via the Kaplan-Meier method. All three prespecified powered landmark analysis at 6 months are shown: target lesion failure (D), target vessel failure (E), and target lesion failure in patients with acute coronary syndrome (F). Log-rank p values and p values for interactions

	Bioadaptor group (n=1201)	Drug-eluting stent group (n=1198)	Hazard ratio (95% CI)	p value
POCE (composite of all-cause mortality, any stroke, any myocardial infarction, and any revascularisation)	78 (6·6%)	63 (5·8%)	1·25 (0·90–1·74)	0·19
Composite of cardiovascular death, myocardial infarction, and any revascularisation	62 (5·3%)	49 (4·6%)	1·28 (0·88–1·86)	0·20
Cardiovascular death or myocardial infarction	37 (3·1%)	26 (2·5%)	1·43 (0·87–2·37)	0·16
All-cause death or myocardial infarction	47 (4·0%)	31 (2·9%)	1·53 (0·97–2·40)	0·067
All-cause death, myocardial infarction, or target vessel revascularisation	61 (5·2%)	49 (4·6%)	1·26 (0·86–1·83)	0·24
All-cause death	17 (1·4%)	11 (1·3%)	1·55 (0·73–3·32)	0·26
Cardiovascular death	7 (0·6%)	6 (0·8%)	1·18 (0·40–3·52)	0·76
Myocardial infarction	31 (2·6%)	21 (1·8%)	1·48 (0·85–2·58)	0·16
Q-wave myocardial infarction	8 (0·7%)	3 (0·3%)	2·66 (0·71–10·0)	0·15
Non-Q-wave myocardial infarction	20 (1·7%)	16 (1·4%)	1·25 (0·65–2·42)	0·50
Non-target vessel myocardial infarction	11 (0·9%)	2 (0·2%)	5·52 (1·22–24·9)	0·026
All revascularisations	44 (3·8%)	41 (3·6%)	1·08 (0·71–1·65)	0·72
Target lesion revascularisation	17 (1·5%)	25 (2·1%)	0·68 (0·37–1·26)	0·22
Target vessel revascularisation	24 (2·1%)	34 (3·0%)	0·71 (0·42–1·19)	0·19
Non-target vessel revascularisation	23 (1·9%)	13 (1·3%)	1·78 (0·90–3·51)	0·10
Ischaemia-driven non-target-vessel revascularisation	23 (1·9%)	13 (1·3%)	1·78 (0·90–3·51)	0·10
Stroke	7 (0·6%)	10 (0·8%)	0·70 (0·27–1·83)	0·47

Data are n (%), with the proportion calculated via the Kaplan–Meier method, unless otherwise indicated. Odds ratio comparisons of binary events are shown in the appendix (p 8). POCE=patient-oriented composite endpoint.

Table 3: **Additional secondary endpoints up to 12 months, intention-to-treat population**

Research in context

Evidence before this study

Drug-eluting stents have reduced event rates within the first year after implantation, but are associated with persistent non-plateauing events thereafter. The aim of the bioadaptor implant is to address this non-plateauing event rate. To retrieve previous studies conducted with the bioadaptor, we did a literature search on PubMed on Sept 19, 2024, using the search string "DynamX bioadaptor". The search produced seven results, including the study design paper of INFINITY-SWEDEHEART, and publications related to the BIOADAPTOR-RCT and a mechanistic study. We also identified one computational model and one mention of the mechanistic study in a summary of key clinical trials in 2020, but these were excluded. Outcomes consistently showed that the bioadaptor can restore haemodynamic modulation of the artery, including cyclic pulsatility, vasomotion, adaptive remodelling, and vessel compliance; the BIOADAPTOR RCT additionally reported non-inferior 12-month target lesion failure rates compared with a contemporary drug-eluting stents (DES) and superior imaging outcomes.

Added value of this study

INFINITY-SWEDEHEART is a trial conducted with the bioadaptor that includes a general percutaneous coronary intervention (PCI) population. It shows non-inferiority of the bioadaptor to DES in terms of low rates of 12-month target lesion failure in a representative PCI population and lower target lesion failure and target vessel failure rates from 6 months to 12 months in landmark analyses for the overall population, as well as in high-risk subgroups.

Implications of all the available evidence

The available evidence suggests that the bioadaptor might become a promising treatment option in patients with de novo lesions with the potential to mitigate the high occurrence of stent-related events, which should be confirmed during long-term follow-up.

Embolic stroke and patent foramen ovale in a 43-year-old fan chanting during a football match

A 43-year-old man who developed numbness and impaired fine motor skills in his left arm lasting approximately 10 min while chanting during a football match, attended our emergency room. The patient, who was visiting Germany for the UEFA European Football Championship, explained that the problems started at the end of the first half. He said he had been chanting continuously during the game. Despite complete resolution of the symptoms, he was concerned enough to seek help, and at half-time he came to our hospital by ambulance. We decided to admit him to our stroke unit for further investigations. He had no medical history; he said he had consumed a moderate amount of alcohol. He was a non-smoker.

On examination the patient was generally fit and well; his pulse was 92 beats per min, blood pressure was 140/90 mm Hg, and his oxygen saturation was 94%. Physical examination found no abnormalities.

Laboratory investigations showed a mildly elevated LDL cholesterol (142 mg/dL; normal range <115). A coagulopathy was excluded: clotting factors II and V were within normal range, tests for antiphospholipid syndrome were negative, antithrombin III activity was in normal range, and protein S and C levels were normal. The patient's homocysteine serum concentration was slightly elevated (15 µmol/L; typical range 3·7–13·9), genotyping found the wild-type variant of the *MTHFR* gene.

MRI showed a small acute embolic ischaemic lesion in the postcentral gyrus of the right hemisphere (figure 1); doppler and duplex sonography of extracranial and intracranial vessels and multimodal imaging—including magnetic resonance angiography—ruled out any atherosclerotic plaques, dissection, or vasculitis (figure 1). Electrocardiogram monitoring during more than 72 h of telemetry found no abnormalities.

Transoesophageal echocardiography showed a patent foramen ovale (PFO) with spontaneous passage of bubbles and accentuation with Valsalva manoeuvre; no septal aneurysm was seen (figure 2). Atrial size and valvular structures were normal, and no intracardiac thrombi were seen. The Risk of Paradoxical Embolism score was 8—indicating an 84% chance that a stroke is PFO-related. Venous ultrasound imaging showed no deep vein thromboses in the legs, pelvis, or vena cava. The patient left the hospital after 3 days with a prescription for an antithrombotic treatment. He took a flight back to his home country a day later.

The role of a PFO in young patients with acute ischaemic stroke has been the subject of much debate: several studies have shown PFO closure may reduce risk of recurrent strokes in young patients with cryptogenic stroke. A possible pathophysiologic mechanism is paradoxical embolism through the PFO facilitated by intrathoracic pressure elevation during pressing or coughing. We hypothesise that a paradoxical embolism in our patient was possibly provoked by continuous chanting—a provoking factor not previously reported—and we therefore advised him to avoid intensive chanting until interventional PFO closure.

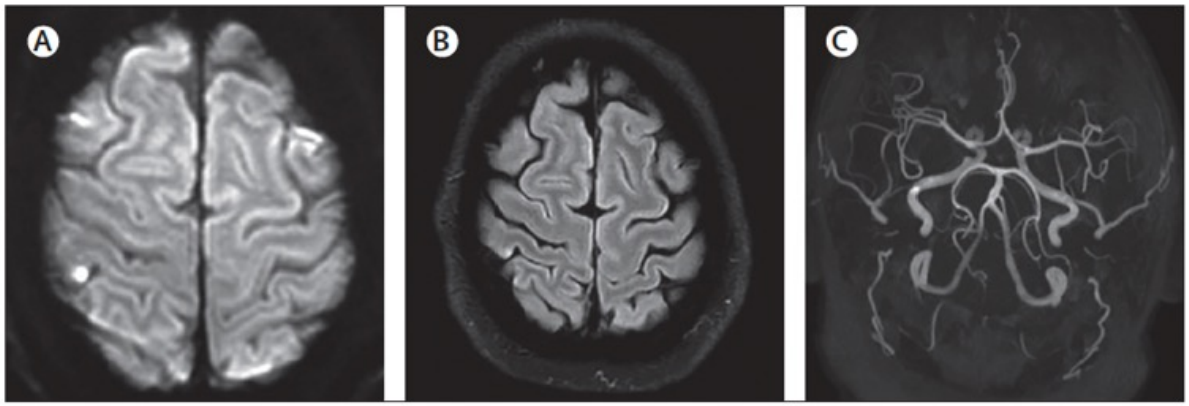


Figure 1: **Embolic stroke and patent foramen ovale in a 43-year-old fan chanting during a football match: MRIs**
MRIs show an acute ischaemic lesion in the post-central gyrus of the right hemisphere on diffusion weighted sequence (A) and FLAIR sequence (B). (C) Time-of-flight magnetic resonance angiography shows unremarkable vessels.

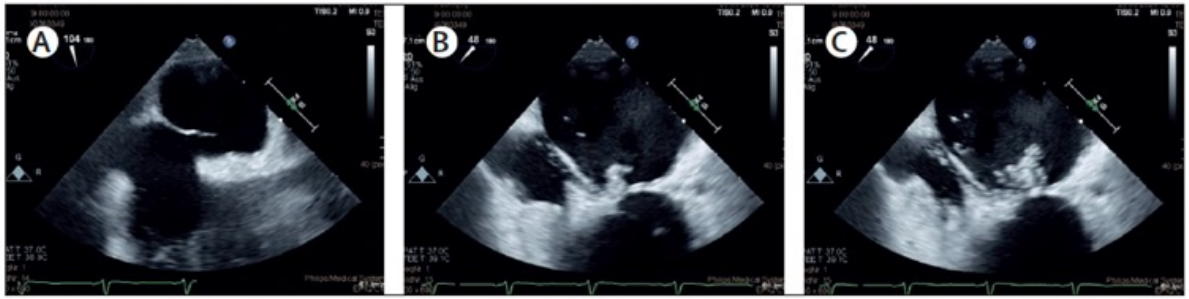
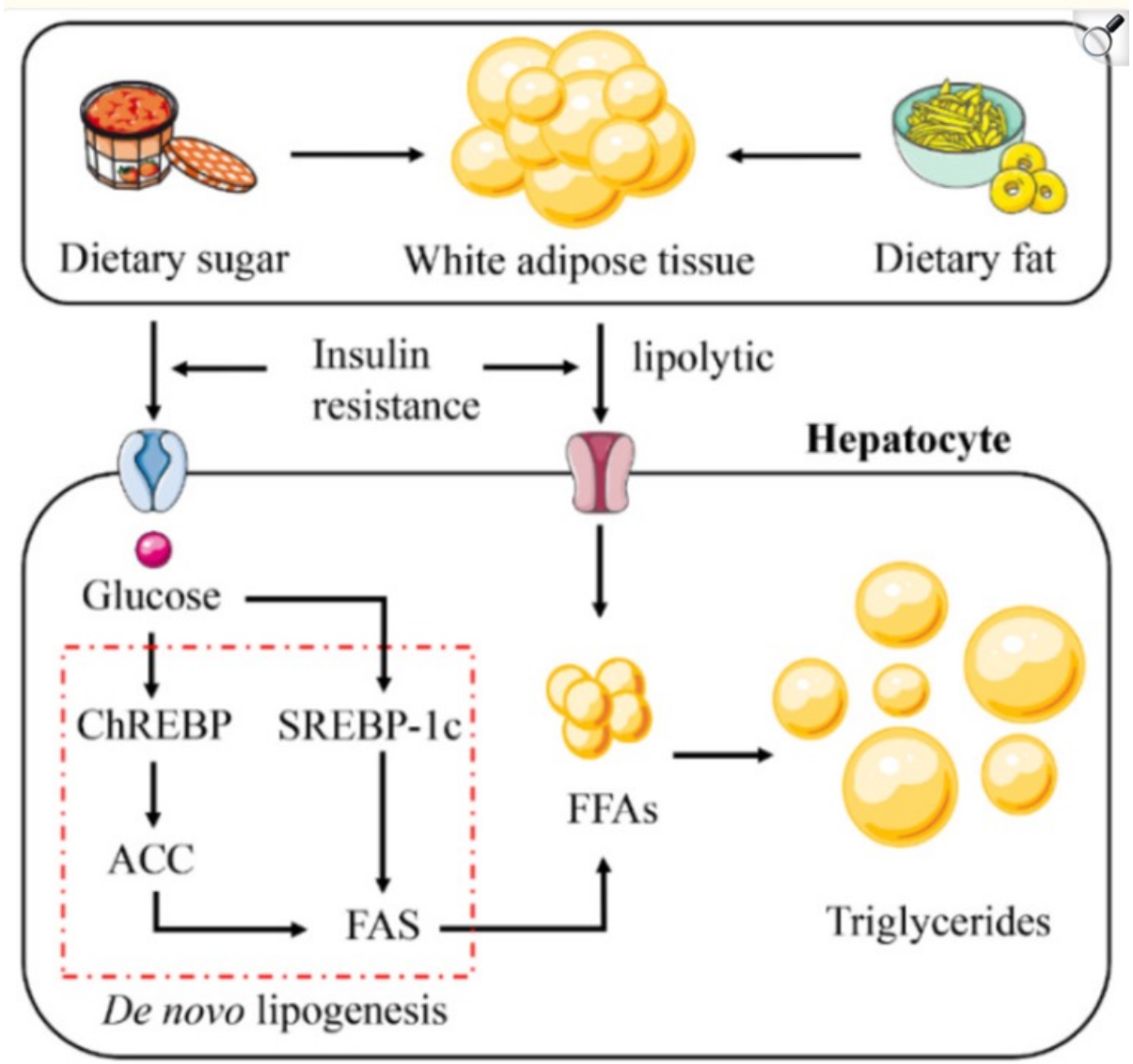


Figure 2: **Embolic stroke and patent foramen ovale in a 43-year-old fan chanting during a football match: transoesophageal echocardiography**
Transoesophageal echocardiography shows the opening of the patent foramen ovale during the Valsalva manoeuvre (A) and subsequent passage of bubbles through the patent foramen ovale (B; C).



Abnormal lipid accumulation in NAFLD. The increase in hepatic lipid accumulation is due to the absorption of large amounts of free fatty acids (FFAs) synthesized triglycerides by the liver from white adipose tissue (WAT), high-fat and high-sugar foods, and de novo lipogenesis (DNL). Insulin resistance plays a vital role in this process. Insulin resistance promotes glucose absorption and enhances the lipolysis of WAT. This leads to the activation of the DNL pathway. Abbreviations: ChREBP, carbohydrate response element binding protein; SREBP-1c, sterol regulatory element binding protein 1c; ACC, acetyl-CoA carboxylase; FAS, fatty acid synthase.

Steatotic liver disease

Steatotic liver disease is the overarching term for conditions characterised by abnormal lipid accumulation in the liver (liver or hepatic steatosis). Steatotic liver disease encompasses what was previously termed non-alcoholic fatty liver disease (NAFLD), which is now called metabolic dysfunction-associated steatotic liver disease (MASLD). Additionally, steatotic liver disease includes alcohol-related liver disease (ALD) and MetALD, the new classification for the overlap between MASLD and ALD, and rare causes of liver steatosis. Cirrhosis is globally the 11th leading cause of death, and steatotic liver disease has become the leading cause of cirrhosis in the EU and USA. Steatotic liver disease affects around 30% of the global population and is mainly driven by obesity, type 2 diabetes, and alcohol intake, but only a minor proportion with steatotic liver disease progress to cirrhosis. The presence and progression of liver fibrosis led by hepatic inflammation is the main predictor of liver-related death across the entire spectrum of steatotic liver diseases. A combination of recent advancements of widely available biomarkers for early detection of liver fibrosis together with considerable advancements in therapeutic interventions offer the possibility to reduce morbidity and mortality in patients with steatotic liver disease. This Seminar covers the recent reclassification of steatotic liver disease and how it reflects clinical practice and prognosis. For early detection of liver fibrosis, we propose a collaborative diagnostic framework between primary care and liver specialists. Lastly, we discuss current best practices for managing steatotic liver disease, we explore therapeutic targets across the spectrum of steatotic liver diseases, and we review the pipeline of drugs in development for MASLD.

Panel 1: Liver steatosis and chronic liver disease

Liver steatosis is defined as the accumulation of lipids in liver parenchymal cells. Alcohol intake has long been recognised as a cause of liver steatosis, yet there are reports of cases of liver steatosis in people not consuming alcohol that date from the 19th century, and some of these reports even already linked the disease to obesity and diabetes.[8] In 1980, Ludwig and colleagues described a series of patients with liver steatosis not consuming alcohol and proposed the term non-alcoholic fatty liver disease (NAFLD) so as to oppose it to the well-known cause of alcohol intake.[9] Since then, NAFLD has been linked to metabolic dysfunction characterised mainly by obesity and diabetes.[10] NAFLD was redefined in 2023 and integrated in the spectrum of steatotic liver disease based on a global consensus process and is now endorsed by more than 75 societies across the world. The clinical significance of liver steatosis remains debated; however, the factors that contribute to steatosis (obesity, diabetes, and alcohol) can also trigger hepatic inflammation and fibrosis. Over time, progression of liver fibrosis can lead to cirrhosis and its complications associated with significant mortality. Therefore, the detection of liver fibrosis, rather than steatosis, is the cornerstone of most initiatives aimed at identifying, intervening in, and preventing symptomatic steatotic liver disease.

Panel 2: Global prevalence of risk factors for steatotic liver disease

- 43% have overweight
- 16% live with obesity
- 6% live with type 2 diabetes
- 50% consume alcohol regularly
- 20% drink heavily at least once a month
- 16% engage in harmful alcohol consumption
- 25% carry genetic risk alleles in *PNPLA3*

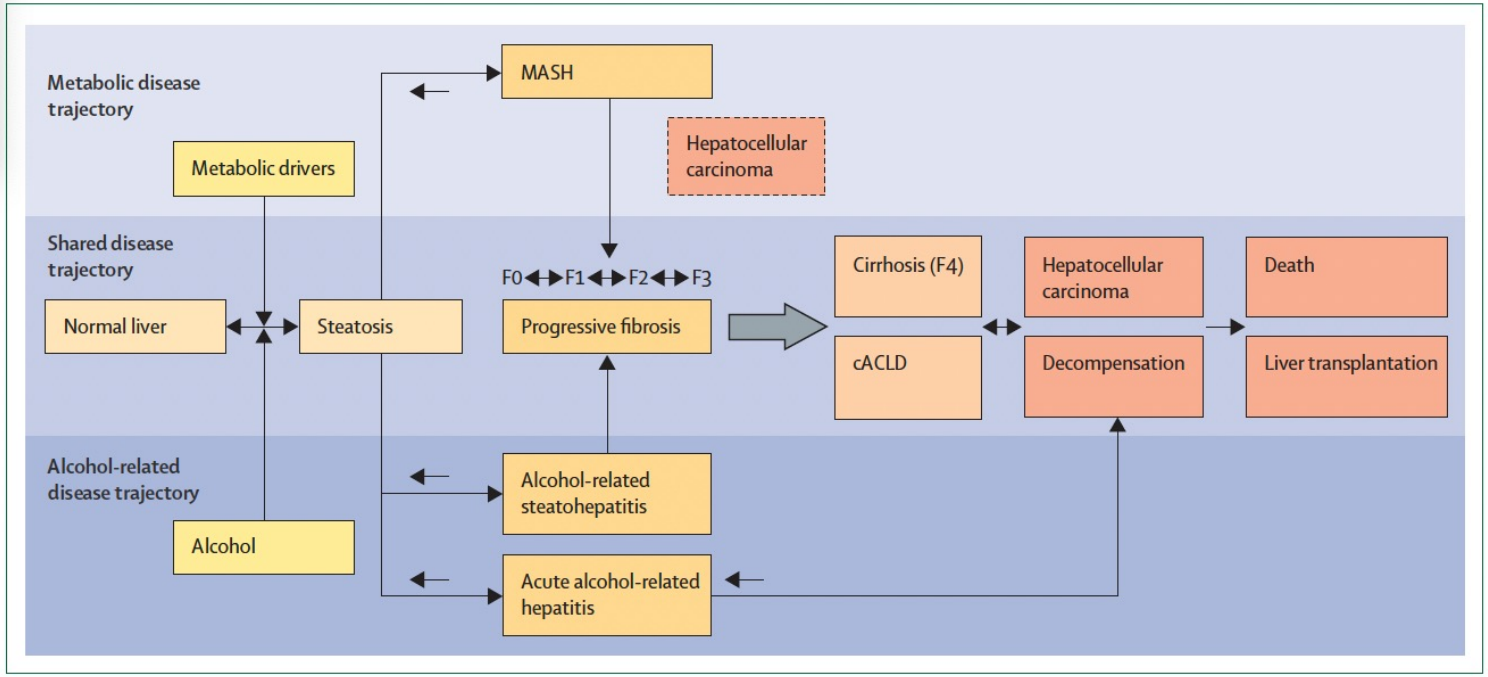


***Figure 1*: The natural history of steatotic liver disease**

In MASLD only, starting from a normal liver and depending on the balance between metabolo-inflammatory drivers and defence mechanisms, steatosis will be accompanied by steatohepatitis, which can result in progressive fibrosis ultimately leading to cirrhosis and the complications.[32,33] Given the disease continuum and some intrahepatic heterogeneity, the concept of cACLD might better reflect the transition from advanced fibrosis (F3) to cirrhosis (F4), as this is a gradual shift in severity. Hepatocellular carcinoma can develop at any stage, although the risk is probably the highest in the cirrhotic stage and ill-defined in earlier stages.[34] At any stage, disease regression is possible pending improvements in the cardiometabolic milieu. Alcohol exposure induces steatosis and various degrees of hepatocyte damage depending on several risk factors.[35] Continuous exposure in susceptible people will lead to progressive fibrosis, the pattern of which might be somewhat different from MASLD, but uses the same staging system. Episodes of acute severe alcohol-related hepatitis can accelerate disease progression or even lead by itself to liver decompensation. The occurrence of hepatocellular carcinoma is usually restricted to the cirrhotic stage. The natural history of people combining risk factors for MASLD and alcohol consumption is ill-defined, but they might reinforce each other with an accelerated disease course and an increased risk of complications. cACLD=compensated advanced chronic liver disease. MASH=metabolic dysfunction-associated steatohepatitis. MASLD=metabolic dysfunction-associated steatotic liver disease.

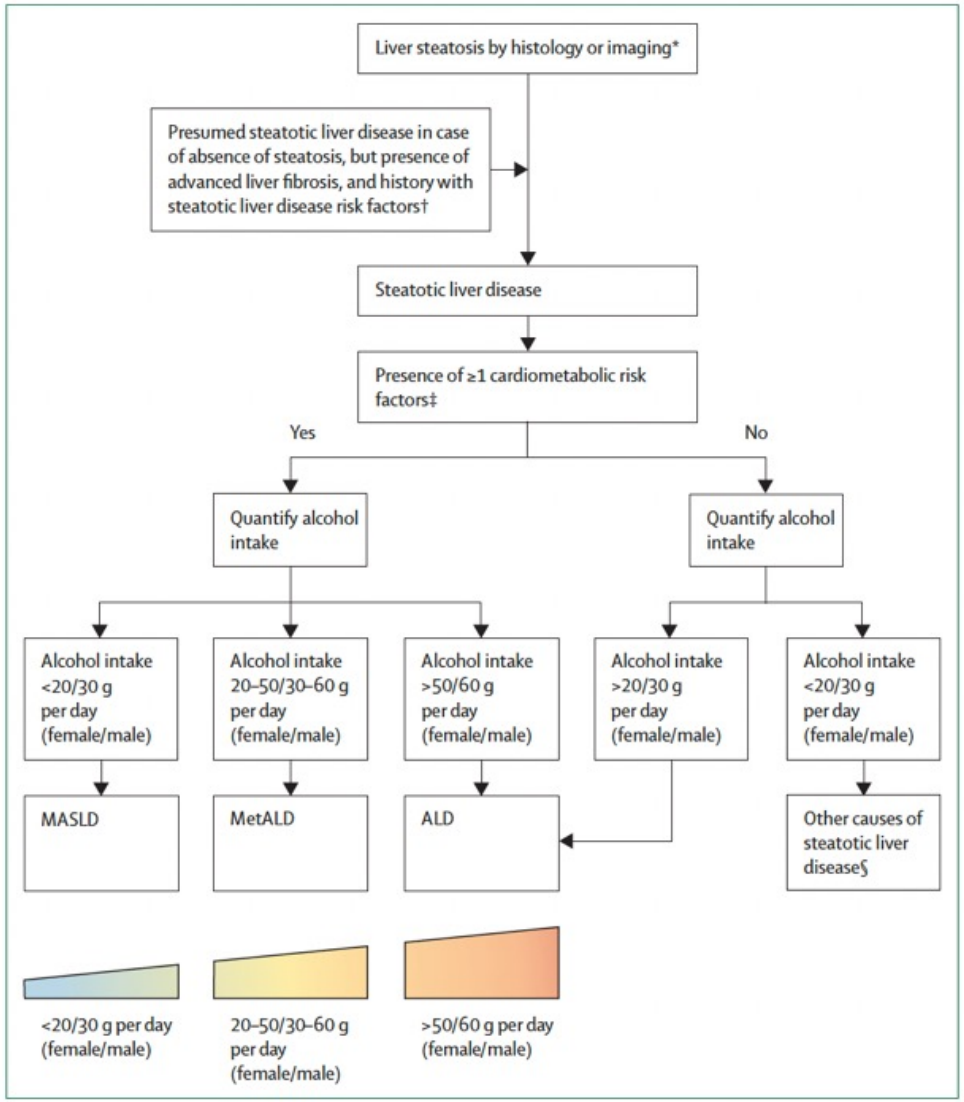


Figure 2: **Flowchart showing classification and subclassification of steatotic liver disease**
Classification based on the diagnostic criteria for steatotic liver disease nomenclature as established by the multi-society Delphi consensus statement in 2023.[1] ALD=alcohol-related liver disease. MASLD=metabolic dysfunction-associated steatotic liver disease. MetALD=metabolic dysfunction and alcohol-related liver disease. *Liver steatosis is defined histologically as the presence of lipid vacuoles in 5% and more of hepatocytes.[41] Imaging including standard ultrasound and MRI-proton density fat fraction can be used as non-invasive assessments for steatosis. †Absence of steatosis can be observed if steatotic liver disease risk factors are eliminated or reduced, or when extensive liver fibrosis is predominant in some cases of severe cirrhosis. However, other lesions, particularly fibrosis, are less dynamic and can persist. In cases of fibrosis without steatosis, a history of previous steatotic liver disease risk factors could justify a diagnosis of presumed steatotic liver disease, which includes cases with histologically confirmed advanced fibrosis (stages F3 and F4), or a corresponding liver stiffness measurement (transient elastography >12 kPa). In these cases, other causes of chronic liver disease should be carefully considered. ‡The criteria for cardiometabolic risk factors used in the definition of steatotic liver disease: (1) BMI of ≥25 kg/m² (adjusted based on ethnicity), or a waist circumference ≥80 cm for women and ≥94 cm for men; (2) fasting serum glucose levels of ≥5·6 mmol/L (100 mg/dL), 2-hour post-load glucose concentrations of ≥7·8 mmol/L (140 mg/dL), glycated haemoglobin of ≥5·7% (39 mmol/mol), presence of type 2 diabetes, or treatment for type 2 diabetes; (3) blood pressure of ≥130/85 mm Hg, or the use of specific antihypertensive drugs; (4) plasma triglycerides of ≥1·70 mmol/L (150 mg/dL), or undergoing lipid-lowering treatment; and (5) plasma HDL-cholesterol levels of ≤1·3 mmol/L (40 mg/dL) for women and ≤1·0 mmol/L (50 mg/dL) for men, or receiving lipid-lowering treatment. §Drug-induced liver injury, monogenic diseases (eg, lysosomal acid lipase deficiency), Wilson's disease, hypobetalipoproteinaemia, inborn errors of metabolism, and miscellaneous liver disease (eg, genotype 3 hepatitis C virus infection, malnutrition, celiac disease, and HIV infection).

Panel 3: **Changes in terminology to reduce stigma**

- Fatty liver disease changed to steatotic liver disease (SLD)
- Non-alcoholic fatty liver disease (NAFLD) changed to metabolic dysfunction-associated steatotic liver disease (MASLD)
- Non-alcoholic steatohepatitis (NASH) changed to metabolic dysfunction-associated steatohepatitis (MASH)
- Metabolic and alcohol-related liver disease (MetALD) newly defined
- Alcoholic liver disease (ALD) changed to alcohol-related liver disease (ALD)
- Alcoholic cirrhosis changed to alcohol-related cirrhosis
- Alcoholic changed to person with alcohol-use disorder (AUD)
- Alcoholic hepatitis (AH) changed to alcohol-related or alcohol-associated hepatitis (AH)
- Alcoholism changed to alcohol-use disorder (AUD)

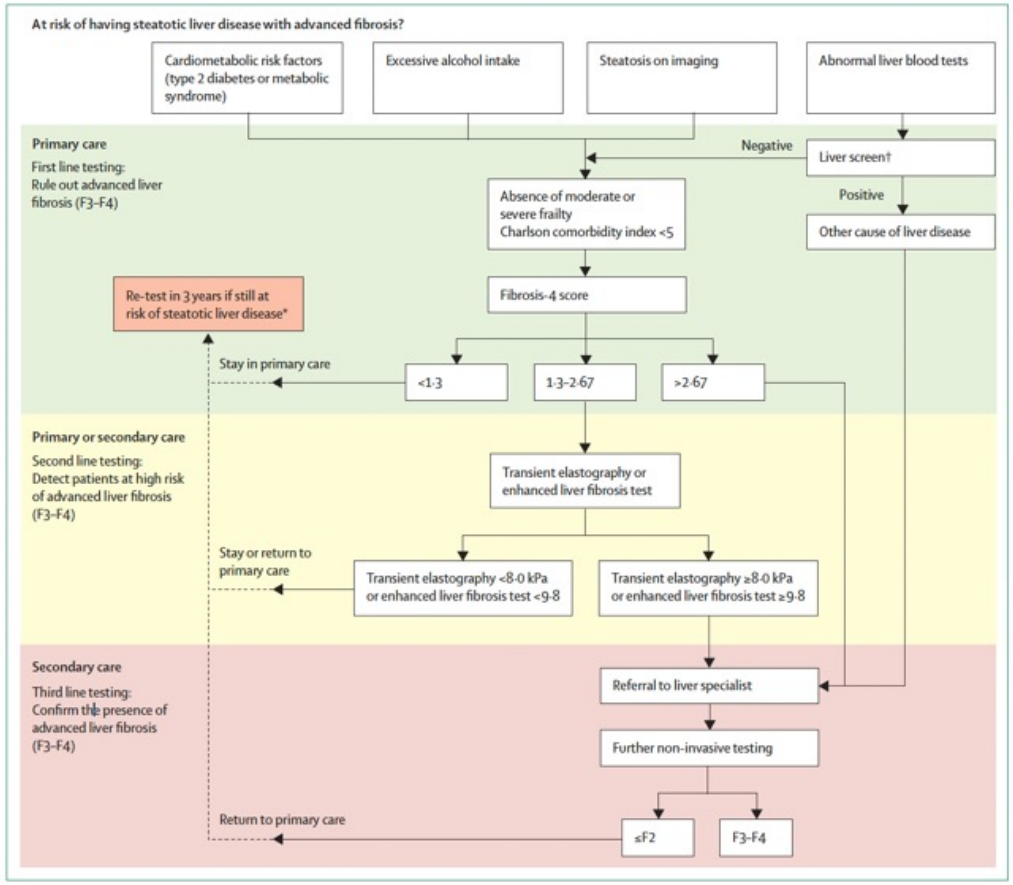


***Figure 3*: Diagnostic framework for early detection of advanced liver fibrosis in steatotic liver disease**

The framework is validated[68] and structured around a three-tier testing process,[69] each with its specific purpose. First-line testing uses affordable, accessible index tests (eg, Fibrosis-4) in primary care to rule out advanced liver fibrosis, emphasising a high sensitivity and negative predictive value to limit further testing. Second-line testing is conducted in primary or secondary care depending on the health-care system's structure. These more costly, specialised tests (eg, transient elastography or enhanced liver fibrosis) aim to detect patients at high risk of advanced fibrosis. Third-line testing is performed by liver specialists to confirm the presence of advanced liver fibrosis and plan a treatment strategy. Confirmation can involve further non-invasive testing or a liver biopsy, particularly in cases of discordant non-invasive test results. In this diagnostic framework, we propose ways to rationalise testing and reduce the burden for health-care systems by using the frailty and the Charlson comorbidity index to select people who would benefit most.[70] ≤F2=absence of advanced fibrosis. F3–F4=presence of advanced fibrosis. *Patients who are classified as not having advanced fibrosis should return to primary care or their already ongoing non-hepatology specialised care. Risk factors for steatotic liver disease should be managed at these levels according to standard guidelines (panel 4). If risk factors for steatotic liver disease persist, patients should be re-tested after 3 years. Due to the slow fibrosis progression in MASLD, re-testing can be omitted in patients with MASLD older than 65 years, as the 10-year risk of developing decompensated liver disease or hepatocellular carcinoma is less than 0·5% in patients with MASLD and without advanced fibrosis.[33] †Liver screen refers to the recommended investigation of an individual with prolonged abnormal liver blood tests.[71] In adults, a standard liver aetiology screen should include an abdominal ultrasound scan, hepatitis B surface antigen, hepatitis C antibody (with follow-on PCR if positive), anti-mitochondrial antibody, anti-smooth muscle antibody, antinuclear antibody, serum immunoglobulins, ceruloplasmin levels in people younger than 40 years, alpha 1-antitrypsin levels, and simultaneous serum ferritin and transferrin saturation. In this context, a negative liver screen means that no other cause for the abnormal liver blood tests has been identified other than the risk factors for steatotic liver disease. In the case of a negative liver screen, patients should be evaluated for liver fibrosis according to this diagnostic framework. A positive liver screen indicates that another cause for the abnormal liver blood tests has been found, and individuals should be referred directly to a liver specialist. Although significant fibrosis would be a reasonable target, the diagnostic accuracy of existing non-invasive tests is suboptimal and we therefore focus on advanced liver fibrosis.[19,69]

	Components	Setting	Cut-offs	Diagnostic accuracy for advanced fibrosis (AUROC)	Prognostic Discrimination (hazard ratio)	Comments
LiverRisk score	Age, sex, glucose, cholesterol, AST, ALT, GGT, and platelet count	First line testing	6, 10, 15	NA	471 for the high-risk group	Derived in the general population
Fibrosis-4 test	Age, AST, ALT, and platelet count	First line testing	<1·3, >2·67	0·76	18·76 for high cut-off	Not useful in people younger than 35 years; age adjusted cut-off proposed for those older than 65 years
Non-alcoholic fatty liver disease fibrosis score	Age, BMI, AST, ALT, type 2 diabetes, platelet count, and albumin	First line testing	<–1·5, >0·67	0·73	18·51 for high cut-off	Only validated in metabolic dysfunction-associated steatotic liver disease; performs worse than Fibrosis-4 test
Enhanced liver fibrosis test	Tissue inhibitor of metalloproteinases 1, aminoterminal propeptide of type III procollagen, and hyaluronic acid	Second line testing	9·8	0·83	16·94 for >10·5 in alcohol-related liver disease	Also increased in extra-hepatic fibrotic conditions; influenced by age
ADAPT	Pro-C3 (N-terminal type III collagen propeptide), age, diabetes, and platelet count	Second line testing	6·32	0·85	NA	Less well validated in steatotic liver disease
Transient elastography	Imaging	Second line testing	<8 KPa, >12 KPa	0·85	HR 10·65 for >20 KPa	Needs to be performed in a fasting state; requires a trained operator
2D shear wave elastography	Imaging	Second line testing	<8 KPa, >12 KPa	0·85	21·6 for >16·4 KPa in alcohol-related liver disease	Needs to be performed in a fasting state; requires a trained operator
Magnetic resonance elastography	Imaging	Second or third line testing	3·5 KPa	0·92	NA	Not widely available

The diagnostic accuracy and prognostic discrimination data presented derive from published studies.[12,70,71,73-77] The diagnostic accuracy data refer to the diagnosis of advanced fibrosis. The prognostic discrimination refers to liver-related mortality. When dual cut-offs are presented, the low cut-off is used to rule out and the high cut-off to diagnose advanced fibrosis. Values for cut-offs, diagnostic accuracy, and prognostic discrimination are based on data from meta-analyses or studies with validation. Diagnostic accuracy refers to fibrosis stage ≥F3 (advanced fibrosis). Prognostic discrimination refers to the development of liver-related events. ALT=alanine aminotransferase. AST=aspartate aminotransferase. AUROC=area under the receiver operating curve. GGT=gamma glutamyl transpeptidase. NA=not applicable.

Table 1: **The commonest biomarkers for fibrosis assessment and prognostication in steatotic liver disease**

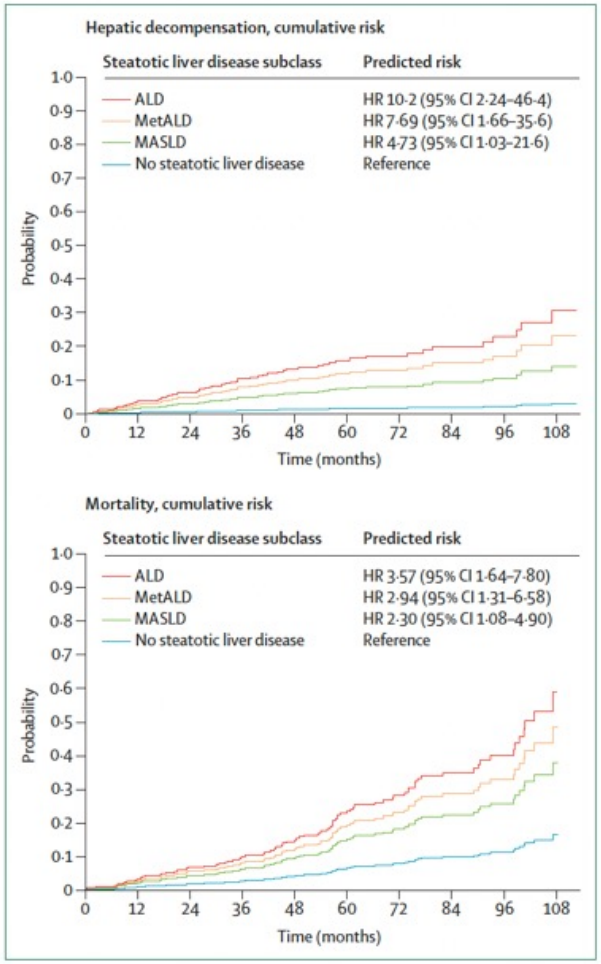


Figure 4: **Predicted cumulative hazard risk curves showing distinct prognoses for the common subclasses of steatotic liver disease**
Models are adjusted for age, sex, and liver stiffness and based on data from the study by Israelsen and colleagues.[47] ALD=alcohol-related liver disease. HR=hazard ratio. MASLD=metabolic dysfunction-associated steatotic liver disease. MetALD=metabolic dysfunction and alcohol-related liver disease.

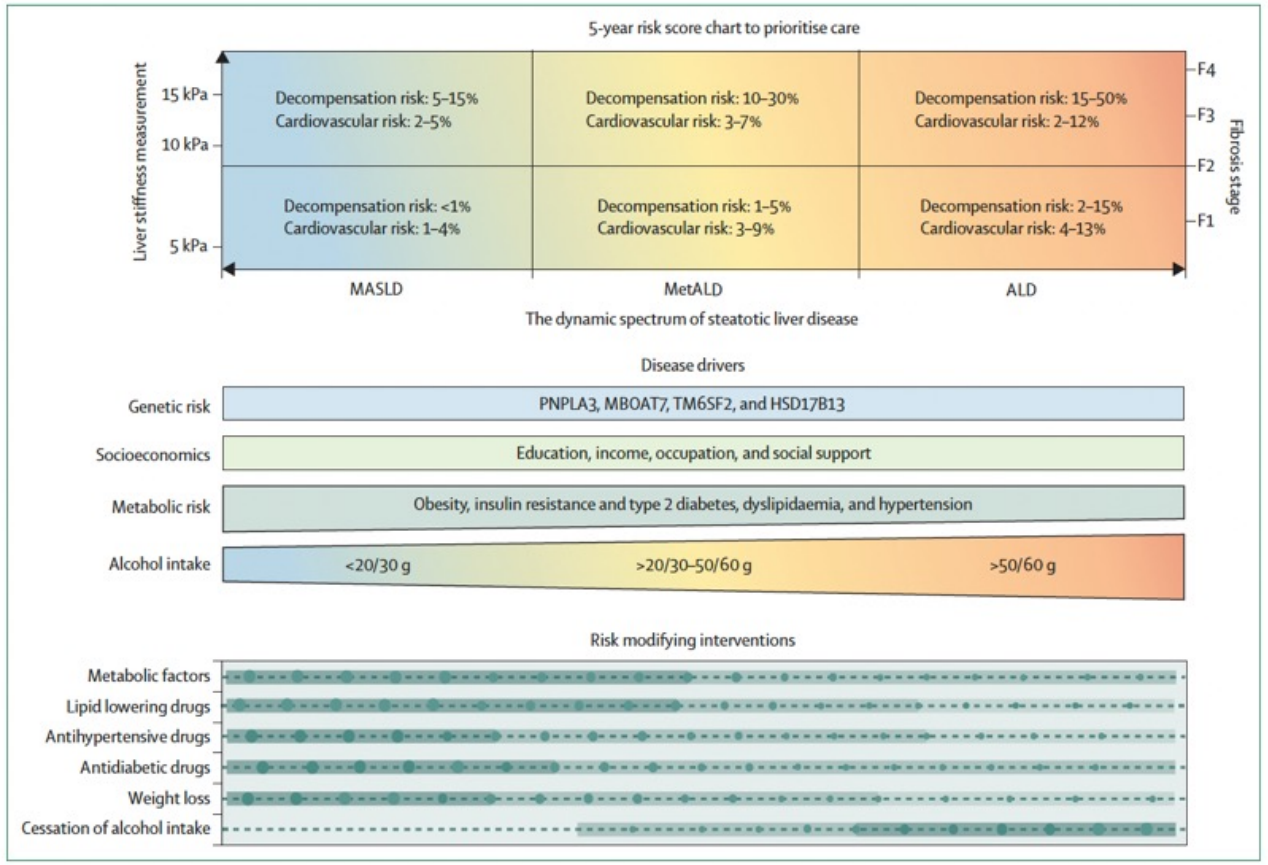


Figure 5: **How to evaluate patients with steatotic liver disease in specialised liver units**
Based on the primary evaluation of a patient with steatotic liver disease, the 5-year risk of progression to clinically significant hepatic and cardiovascular disease can be estimated. This estimation should be considered when planning follow-up care for each patient with steatotic liver disease in alignment with current guidelines.[6,27,76–78] The specified values for liver stiffness measurement refer to measurements conducted with FibroScan. The figure is inspired by the figure by Israelsen and colleagues[100] with an expansion on risk modifying interventions across the spectrum of steatotic liver disease and data on cardiovascular risk for patients with steatotic liver disease.[31] Risk estimates for hepatic decompensation and cardiovascular risk are based on published studies.[12,13,47,101–106] ALD=alcohol-related liver disease. F1=mild fibrosis. F2=moderate fibrosis. F3=severe fibrosis. F4=cirrhosis. MASLD=metabolic dysfunction-associated steatotic liver disease. MetALD=metabolic dysfunction and alcohol-related liver disease.

Panel 4: Standard treatments for cardiometabolic risk factors and alcohol intake

Overweight or obesity

The target is at least 7–10% weight loss with a staged approach. Treatment should start with counselling for lifestyle modification, diet, and exercise. GLP1 receptor agonists or dual agonists or bariatric surgery should be considered if lifestyle modifications are unsuccessful in patients who fulfil the criteria for these treatments (eg, weight lowering drugs usually BMI >30 kg/m² or >35 kg/m² with comorbidities, and surgery BMI >40 kg/m² or >35 kg/m² and comorbidities).

Type 2 diabetes

Preference for drugs that might affect liver inflammation or liver fibrosis, such as GLP1 receptor agonists, SGLT2 inhibitors, or pioglitazone. The choice depends on BMI and comorbidities.

Hyperlipidaemia

Patients can be offered statins for primary or secondary prevention of cardiovascular events according to guidelines and treatment thresholds.

Hypertension

Start patients on treatment if blood pressure above 140/90 mm Hg or 130/80 mm Hg in patients with type 2 diabetes who are at higher cardiovascular risk. There is no preference for a particular drug class.

Smoking

Smoking cessation should be encouraged and pharmacotherapy can be offered if required.

Sleep apnoea

Evaluate patients for sleep apnoea and continuous positive airway pressure can be offered if required.

Alcohol intake

Any reduction at any stage of disease improves outcomes. Patients with advanced fibrosis or cirrhosis should be advised to complete abstinence. Binge drinking should be avoided. A combination of behavioural motivational modalities and relapse prevention medication, such as acamprosate or naltrexone is recommended. Individuals with alcohol-use disorder should be referred to specialised community programmes.

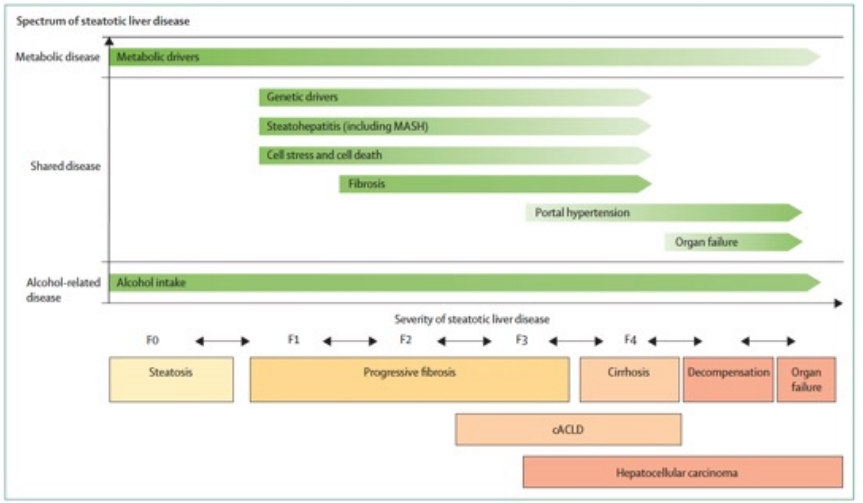


Figure 6: **Drug targets along the spectrum and severity of steatotic liver disease**

Along the spectrum and severity of steatotic liver disease, the role and target of different factors contribute to disease progression. Alcohol-related damage is a driver often at all severity stages of steatotic liver disease. For metabolic disease (ie, MASLD), metabolic drivers play a dominant role. Across the spectrum of steatotic liver disease, metabolic drivers and alcohol lead to steatosis and steatohepatitis. Steatohepatitis has its own intrahepatic mechanisms and drives fibrogenesis and progression towards advanced chronic liver disease and portal hypertension, and ultimately organ failure.[10] Although, in more advanced disease stages and even in cirrhosis and portal hypertension, metabolic factors and intrahepatic mechanisms of cell damage and inflammation, cell stress, and cell death might still play a role, even though they tend to diminish and disappear, and portal hypertension becomes a predominant driver of disease. The green arrows illustrate where drug targets are relevant along the spectrum and the severity of steatotic liver disease. Less colour intensity of the arrows symbolises less relevance of a given drug target. Drugs targeting metabolic drivers or intrahepatic mechanisms are more relevant at earlier time points in the disease severity and are less likely to be efficacious in the advanced stages, where drugs tackling fibrogenesis and the (vascular) mechanisms underlying portal hypertension are could be of clinical benefit.[148] Changing lifestyle is crucial at all stages and might be supported by pharmacotherapy in the context of addiction management. cACLD=compensated advanced chronic liver disease. F0=no fibrosis. F1=mild fibrosis. F2=moderate fibrosis. F3=severe fibrosis. F4=cirrhosis. MASH=metabolic dysfunction-associated steatohepatitis.

	Mode of action	Estimated patient enrolment	Fibrosis stage	Study duration	Endpoints	Sponsor	Clinical trial number
Semaglutide	GLP-1 receptor agonist	1200	F2–F3	Up to 5 years, interim analysis at 72 weeks	Clinical outcomes; histological for interim analysis	Novo Nordisk	NCT04822181
Resmetirom*	THRb agonist	1759 (actual)	F2–F3	Up to 5 years, interim analysis at 52 weeks	Clinical outcomes; histological for interim analysis	Madrigal Pharmaceuticals	NCT03900429
Resmetirom	THRb agonist	700	F4	Up to 3 years	Clinical outcomes	Madrigal Pharmaceuticals	NCT05500222
Lanifibranor	Pan-PPAR agonist	1000	F2–F3	72 weeks, with a further 48 week follow up for safety	Histological	Inventiva	NCT04849728
Pegozafermin	FGF21 analogue	1050	F2–F3	88 weeks, interim analysis at 52 weeks	Clinical outcomes; histological for interim analysis	89Bio	NCT06318169
Efruxifermin	FGF21 analogue	1000	F2–F3	Unknown, interim analysis at 52 weeks	Clinical outcomes; histological for interim analysis	Akero Therapeutics	NCT06215716
Efruxifermin	FGF21 analogue	600	MASLD or MASH based on biopsy or non-invasive testing	52 weeks	Safety and tolerability	Akero Therapeutics	NCT06161571
Denifanstat	FASN inhibitor	1260	F2–F3	Up to 4·5 years, interim analysis at 52 weeks	Clinical outcomes; histological for interim analysis	Sagimet	NCT06594523
Survodutide	Glucagon receptor and GLP-1 receptor agonist (dual)	1800	F2–F3	Up to 7 years, interim analysis at 52 weeks	Clinical outcomes; histological for interim analysis	Boehringer Ingelheim	NCT06632444
Survodutide	Glucagon receptor and GLP-1 receptor agonist (dual)	1590	F4	Up to 4 years	Combined clinical and biochemical outcome	Boehringer Ingelheim	NCT06632457

F2=moderate fibrosis. F3=severe fibrosis. F4=cirrhosis. FASN=fatty acid synthase. FGF21=fibroblast growth factor 21. GLP-1=glucagon-like peptide 1. MASH=metabolic dysfunction-associated steatohepatitis. MASLD=metabolic dysfunction-associated steatotic liver disease. PPAR=peroxisome proliferator-activated receptor. THRb=thyroid hormone receptor b. *Results have been published.[134]

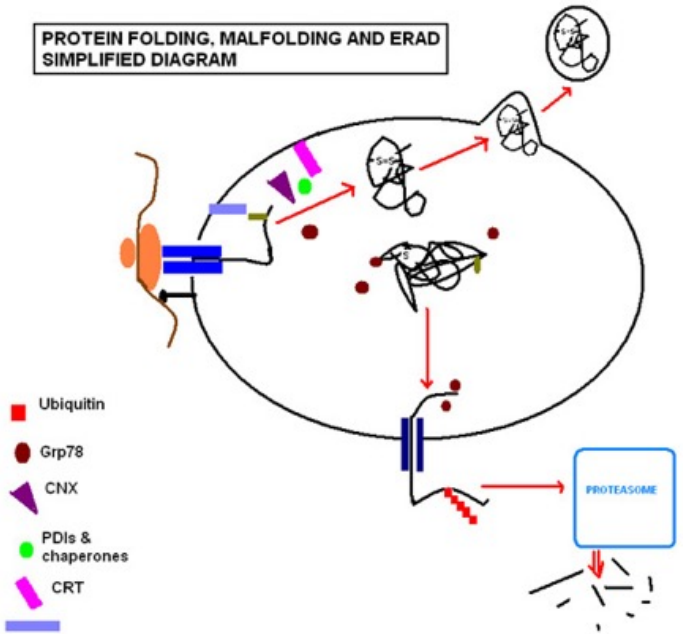
Table 2: **Current phase 3 drug trials in MASLD**

Conclusion

There is a growing focus on advancing liver health with awareness and policy measures led by the European Association for the Study of the Liver, the American Association for the Study of Liver Disease, the *Lancet*, and WHO.[7,161,162] The overall aim is to combat steatotic liver disease with prevention and early detection and to inform policy measures to mitigate the structural determinants of poor liver health. Therefore, steatotic liver disease should be included as part of the WHO programme on fighting non-communicable diseases.[24,161,162]

A key aspect for improving global liver health will be to change the dialogue around liver diseases to reduce stigma by shifting the narrative and adopting terminology that more accurately represents their multifactorial nature, recognising that factors beyond CMRF and alcohol contribute to steatotic liver disease, and promoting more open discussions about this.[30] Furthermore, there is the need to foster a deeper understanding of steatotic liver disease among health-care professionals, patients, and the broader public.[145] On a structural level, there is a need for a unified global effort to integrate liver health into broader health policy frameworks, including prevention and enhancing early diagnosis and treatment access.[24] Such structural improvements should aim to address not only liver health, but also related metabolic and alcohol-use disorders as part of a comprehensive approach to reduce non-communicable diseases on a broader scale.

The unfolded protein response (UPR) is a cellular stress response related to the endoplasmic reticulum (ER) stress. It has been found to be conserved between mammalian species, as well as yeast and worm organisms.
The UPR is activated in response to an accumulation of unfolded or misfolded proteins in the lumen of the endoplasmic reticulum. In this scenario, the UPR has three aims: initially to restore normal function of the cell by halting protein translation, degrading misfolded proteins, and activating the signaling pathways that lead to increasing the production of molecular chaperones involved in protein folding. If these objectives are not achieved within a certain time span or the disruption is prolonged, the UPR aims towards apoptosis. Endoplasmic reticulum associated protein degradation = ERAD.

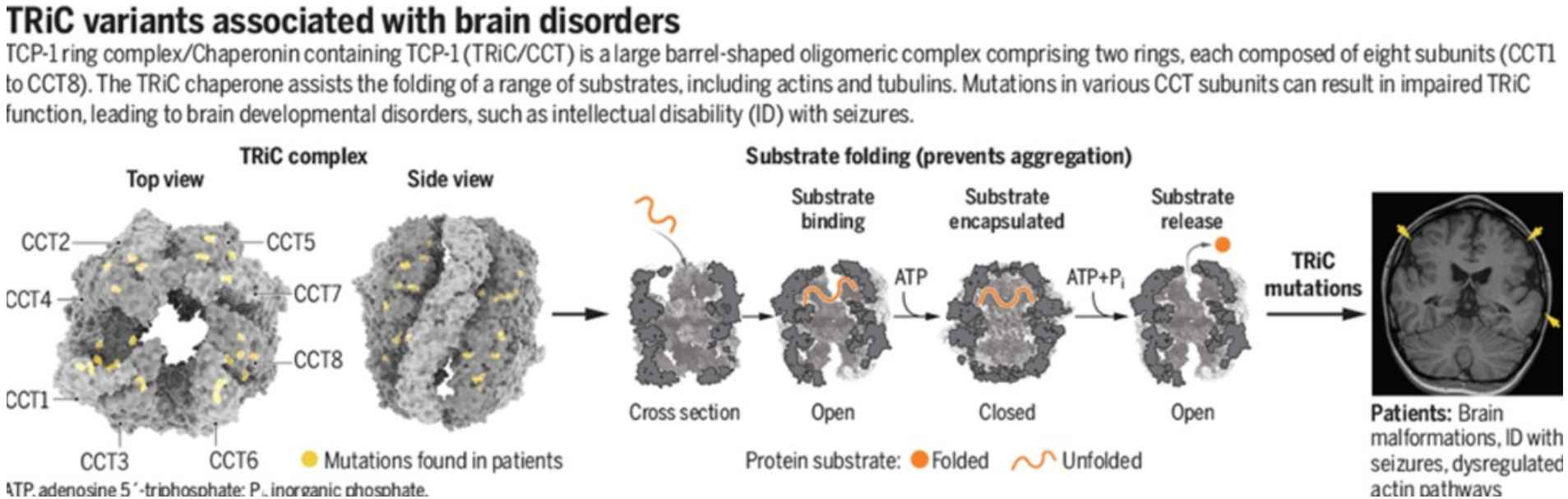


A simplified diagram of the processes involved in protein folding. The polypeptide is translated from its ribosome directly into the ER, where it is glycosylated and guided through modification steps to reach its desired conformation. It is then transported from the ER to the Golgi apparatus for final modifications. Where misfolding proteins continually breach quality control, chaperones including Grp78 facilitate its removal from the ER through retrotranslocation, where it is broken down by the ubiquitin-proteasome pathway as part of the ERAD system.

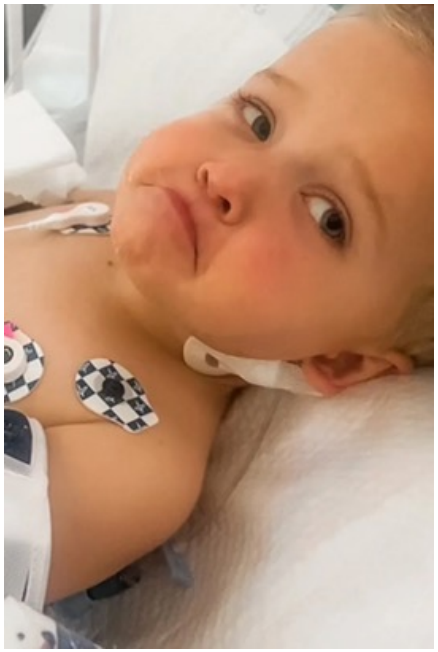
Mutations that impair a protein-folding chaperone can lead to brain malformations

Adequate folding of proteins into their genetically encoded three-dimensional structures allows them to carry out precise interactions and activities. Therefore, proteostasis, or maintenance of the proteome (all proteins expressed in a cell, tissue, or organism at a specific time) in a functionally folded state, is essential to life. Several chaperones, including TCP-1 ring complex/chaperonin containing TCP-1 (TRiC/CCT), assist with protein folding and unfolding to sustain proteostasis. Kraft *et al.* present evidence that multiple TRiC variants are associated with brain disorders in humans and characterize the effect of these disease-linked mutations on TRiC function across several model species. The findings identify a new class of pathologies associated with chaperone defects (chaperonopathies) and support the notion that TRiC function is indispensable for normal brain development.

Proteostasis involves many stages of conformational quality control, such as folding during mRNA translation into protein, the maintenance of conformation, and degradation of misfolded proteins. At every step, chaperones augment the pool of functionally folded proteins by optimizing the biophysical environment for folding nascent proteins, refolding misfolded proteins, and detecting misfolded proteins to be destined for degradation. Chaperones consist of several protein families that act by different yet overlapping mechanisms. For example, heat shock proteins (HSPs) include Hsp70 and Hsp90 chaperone families that bind to substrates in an adenosine 5′-triphosphate (ATP)–dependent manner, Hsp40 co-chaperones, and small HSPs that stabilize their substrates and reduce aggregation through ATP-independent mechanisms.



A child needed antivenom for a snakebite. It cost more than $200,000.



Manufacturing, which hasn't fundamentally changed since antivenom was developed more than a century ago, does not explain the high price. Venomous creatures are milked, then a small, non-harmful amount of toxin is injected into animals like horses or sheep. Antibodies are extracted from their blood and processed to make antivenom.

The final bill

It was $297,461, which included two ambulance rides, an emergency room visit and a couple of days in pediatric intensive care. Antivenom alone accounts for $213,278.80 of the total bill.

The billing problem

The Centers for Disease Control and Prevention estimates venomous snakes bite 7,000 to 8,000 people in the United States every year. About five people die. That number would be higher, the agency says, if not for medical treatment.

Many snakebites happen far from medical care, and not all emergency rooms keep costly antivenom in stock, which can add big ambulance bills to already expensive care.

For instance, Medicare — the government program for those who are at least 65 or disabled — pays about $2,000 for a vial of Anavip. On average, Dusetzina said, that is the price hospitals pay for it.