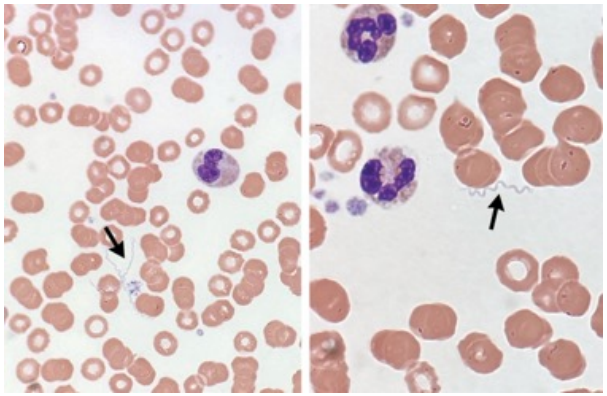
https://www.mdc-berlin.de/de/veroeffentlichungstypen/clinical-journal-club

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 74-year-old man presented to the hospital for the third time in three weeks with recurrent fever, muscle aches, and vomiting. In the prior two hospitalizations, symptoms had self-resolved and broad work-up was unremarkable. He had traveled to Yosemite National Park one week prior to symptom onset. Physical examination was notable for rigors and diaphoresis. Peripheral blood smears are shown. What is the most likely diagnosis?

Babesiosis

Leptospirosis

Rocky Mountain spotted fever

Secondary syphilis

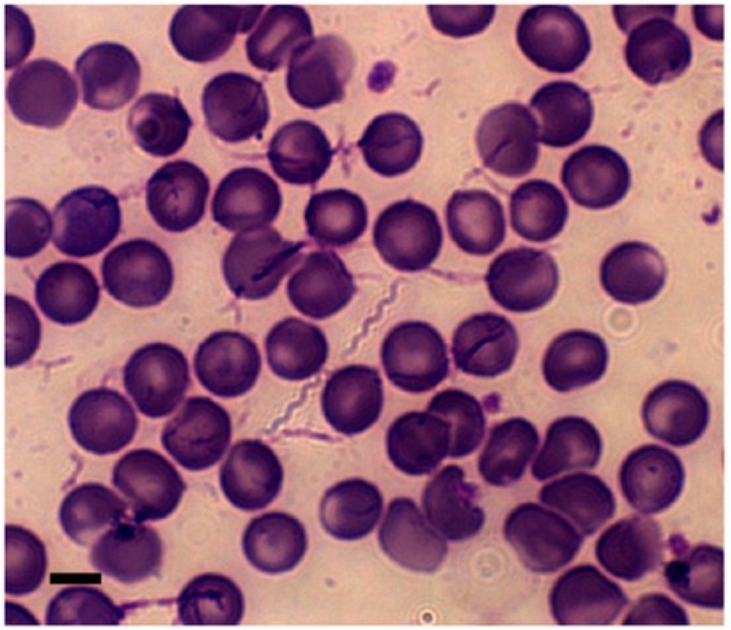
Soft tick relapsing fever (Zeckenrückfallfieber)

Soft tick relapsing fever is a recurrent febrile syndrome caused by transmission of certain borrelia species during the bite of a soft-bodied tick. Peripheral blood smears with Wright's staining showed spirochetes. Polymerase-chain-reaction assay of a peripheral venous blood was positive for borrelia species. In the Sierra Nevada mountain range, Ornithodoros hermsi ticks transmit Borrelia hermsii, the presumptive pathogen in this case. The patient was treated with doxycycline and monitored for a Jarisch-Herxheimer reaction.

Die **Soft tick relapsing fever** heißt auf Deutsch **Zeckenrückfallfieber** (oder durch Lederzecken übertragenes Rückfallfieber). Es ist eine durch *Borrelia*-Bakterien (z.B. *B. duttoni*) verursachte Infektionskrankheit, die von Lederzecken (Gattung *Ornithodoros*) übertragen wird und durch phasenweise-wiederkehrendes, hohes Fieber, Schüttelfrost und Kopfschmerzen gekennzeichnet ist.

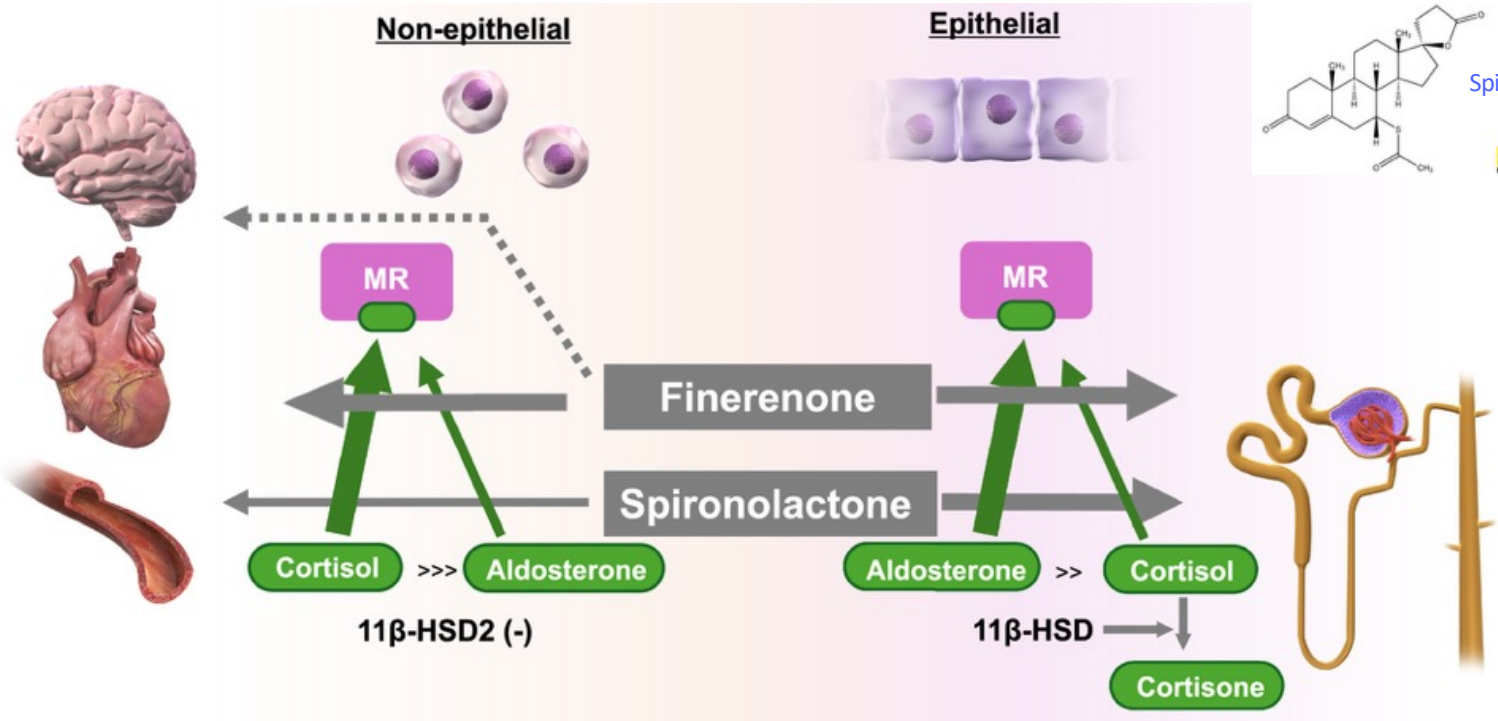
Wichtige Fakten zum Zeckenrückfallfieber:

- **Überträger:** Die Erreger werden nicht von den in Deutschland üblichen Schildzecken, sondern von **Lederzecken** (Soft ticks, Gattung *Ornithodoros*) übertragen.
- **Vorkommen:** Endemisch in tropischen/subtropischen Regionen, Südeuropa (Spanien, Portugal), Nord-/Mittelamerika und dem südlichen Afrika.
- **Symptome:** Plötzlich auftretendes Fieber, Schüttelfrost, Kopfschmerzen, Muskel- und Gelenkschmerzen.
- **Verlauf:** Nach wenigen Tagen abrupte Fieberfreiheit, gefolgt von mehreren Rückfällen.
- **Unterschied zur Lyme-Borreliose:** Es ist eine andere Art von Borreliose als die in Mitteleuropa häufige Lyme-Borreliose.
- **Behandlung:** Erfolgt mit Antibiotika (Doxycyclin).



Borrelia recurrentis

Finerenone is a first-in-class non-steroidal mineralocorticoid receptor antagonist (MRA) approved to reduce the risk of chronic kidney disease (CKD) progression, kidney failure, and cardiovascular events in adults with Type 2 Diabetes (T2DM). It acts by reducing inflammation and fibrosis, offering kidney protection beyond RAS blockade, typically in patients with albuminuria and adequate potassium levels.

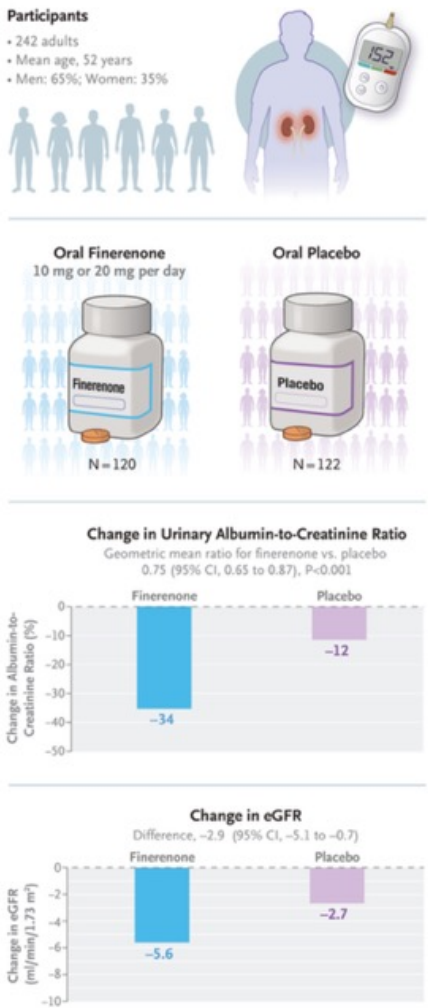


Spironolacton seit 1959

Finerenone in Type 1 Diabetes and Chronic Kidney Disease

The nonsteroidal mineralocorticoid receptor antagonist finerenone has been reported to improve kidney and cardiovascular outcomes in persons with type 2 diabetes and chronic kidney disease (CKD). The efficacy and safety of finerenone in persons with type 1 diabetes and CKD are unknown.

We conducted a phase 3 trial involving adults who had type 1 diabetes, CKD (estimated glomerular filtration rate [eGFR], 25 to <90 ml per minute per 1.73 m^2 of body-surface area), and albuminuria (urinary albumin-to-creatinine ratio [with albumin measured in milligrams and creatinine measured in grams], 200 to <5000) and were receiving an angiotensin-converting–enzyme (ACE) inhibitor or an angiotensin-receptor blocker. Participants were randomly assigned to receive finerenone (10 or 20 mg per day, depending on the eGFR) or matching placebo. The primary outcome was the relative change in the urinary albumin-to-creatinine ratio over a period of 6 months.



Therapies for the management of kidney and cardiovascular disease have emerged for persons with type 2 diabetes and CKD, including sodium–glucose cotransporter 2 (SGLT2) inhibitors, the nonsteroidal mineralocorticoid receptor antagonist finerenone, and the glucagon-like peptide-1 (GLP-1) receptor agonist semaglutide. However, these agents have not been evaluated in rigorous clinical outcome trials involving persons with type 1 diabetes and CKD. To date, the treatment of CKD in persons with type 1 diabetes has focused on optimizing lifestyle, blood glucose levels, and blood pressure, preferably with renin–angiotensin system (RAS) inhibitors on the basis of studies conducted more than three decades ago. Although these interventions are effective in reducing CKD progression, they do not fully halt it. Thus, new therapeutic approaches for persons with type 1 diabetes and CKD would seem indicated.

Studies have suggested that overactivation of the mineralocorticoid receptor and excess aldosterone in the kidneys promote sodium and water reabsorption, stimulate proinflammatory and profibrotic pathways, and contribute to albuminuria development and CKD progression in persons with either type 1 or type 2 diabetes. The nonsteroidal mineralocorticoid receptor antagonist finerenone has been shown to decrease the risk of kidney failure and cardiovascular events in persons with type 2 diabetes and CKD. The current trial, FINE-ONE (Finerenone Efficacy and Safety in Chronic Kidney Disease and Type One Diabetes), assessed the efficacy and safety of finerenone in persons with type 1 diabetes and CKD, with albuminuria as a surrogate outcome.

Participants

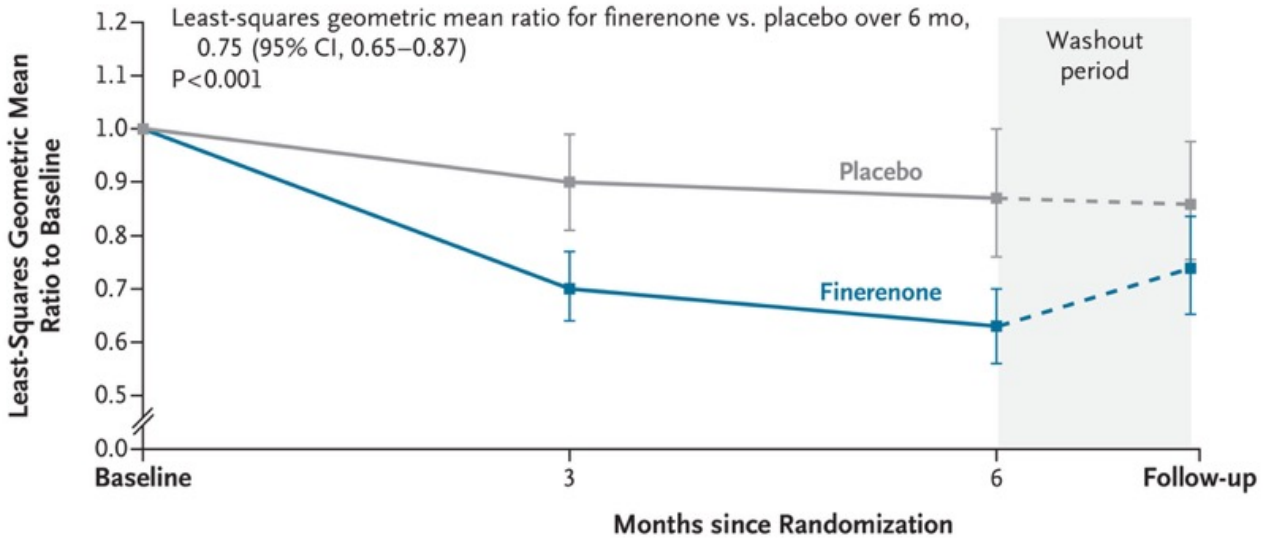
Eligible participants were 18 years of age or older with type 1 diabetes and CKD, defined as an estimated glomerular filtration rate (eGFR) of 25 to less than 90 ml per minute per 1.73 m^2 of body-surface area, and albuminuria, defined as a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of 200 to less than 5000, with documentation of frank albuminuria or proteinuria for at least 3 months before screening. Participants had a glycated hemoglobin level of less than 10% and a serum potassium level of 4.8 mmol per liter or less at screening, and they had received a stable dose of an angiotensin-converting–enzyme (ACE) inhibitor or an angiotensin-receptor blocker for at least 4 weeks before screening. Exclusion criteria were CKD with a known cause other than type 1 diabetes, or previous kidney transplantation. Participants with symptomatic heart failure with a reduced ejection fraction and those who had received an SGLT2 inhibitor or a GLP-1 receptor agonist within 8 weeks before or at screening were also excluded.

Characteristic	Finerenone (N=120)	Placebo (N=122)
Age — yr	51.3±14.2	51.9±13.2
Sex — no. (%)		
Female	41 (34.2)	43 (35.2)
Male	79 (65.8)	79 (64.8)
Race or ethnic group — no. (%)†		
White	85 (70.8)	90 (73.8)
Black	9 (7.5)	6 (4.9)
Asian	23 (19.2)	25 (20.5)
Other or missing	3 (2.5)	1 (0.8)
Body-mass index‡	27.7±5.4	27.3±6.6
Blood pressure — mm Hg		
Systolic	136.5±15.8	134.2±17.7
Diastolic	78.5±10.4	76.7±11.2
Biochemical measurements		
Glycated hemoglobin		
Mean — %§	7.8±1.1	7.5±1.0
Distribution — no. (%)		
≤7.5%	54 (45.0)	70 (57.4)
>7.5%	66 (55.0)	50 (41.0)
Data missing	0	2 (1.6)
Urinary albumin-to-creatinine ratio¶		
Median (IQR)	574.6 (315.8–1224.9)	506.4 (288.2–1182.3)
Distribution — no. (%)		
<300	29 (24.2)	35 (28.7)
300 to 1000	57 (47.5)	54 (44.3)
>1000	34 (28.3)	33 (27.0)
Estimated glomerular filtration rate		
Mean — ml/minute/1.73 m²	59.0±19.5	58.8±19.0
Distribution — no. (%)		
<45 ml/minute/1.73 m²	32 (26.7)	31 (25.4)
45 to <60 ml/minute/1.73 m²	32 (26.7)	30 (24.6)
≥60 ml/minute/1.73 m²	56 (46.7)	61 (50.0)
Mean serum potassium — mmol/liter	4.6±0.4	4.6±0.4
Medical history		
Duration of diabetes — yr	32.0±14.1	32.0±14.4
History of cardiovascular disease — no. (%)‖	35 (29.2)	26 (21.3)
History of hypertension — no. (%)	104 (86.7)	103 (84.4)
Medication use — no./total no. (%)**		
ACE inhibitor	59/119 (49.6)	52/122 (42.6)
Angiotensin-receptor blocker	60/119 (50.4)	68/122 (55.7)
Diuretic	43/119 (36.1)	45/122 (36.9)

Adverse events

Adverse Event	Finerenone (N=119)	Placebo (N=122)
	no. of participants (%)	
Any adverse event	56 (47.1)	60 (49.2)
Related to trial regimen	19 (16.0)	14 (11.5)
Leading to permanent discontinuation of trial regimen	3 (2.5)	3 (2.5)
Any serious adverse event	14 (11.8)	14 (11.5)
Related to trial regimen	3 (2.5)	0
Leading to permanent discontinuation of trial regimen	3 (2.5)	1 (0.8)
Leading to hospitalization	12 (10.1)	10 (8.2)
Life-threatening†	3 (2.5)‡	1 (0.8)§
Leading to death	0	1 (0.8)
Any hyperkalemia¶	12 (10.1)	4 (3.3)
Related to trial regimen	11 (9.2)	4 (3.3)
Leading to permanent discontinuation of trial regimen	2 (1.7)	0
Any serious hyperkalemia	2 (1.7)	0
Related to trial regimen	2 (1.7)	0
Leading to hospitalization	2 (1.7)	0
Life-threatening	0	0
Leading to death	0	0
Serum potassium level — no./total no. (%)		
>5.5 mmol/liter	13/118 (11.0)	4/115 (3.5)
>6.0 mmol/liter	2/119 (1.7)	1/117 (0.9)

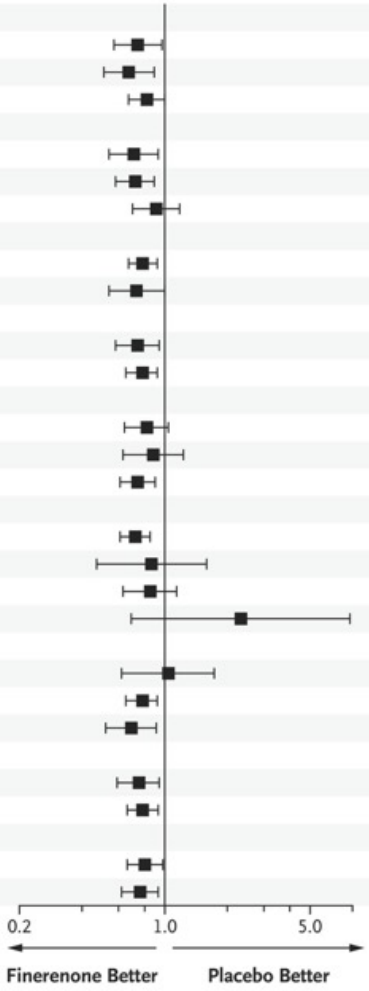
SGLT2 inhibitors are not FDA-approved for type 1 diabetes (T1D) due to a 2–10 fold increased risk of diabetic ketoacidosis (DKA), specifically euglycemic DKA where blood sugar remains normal.



Change in the Urinary Albumin-to-Creatinine Ratio.

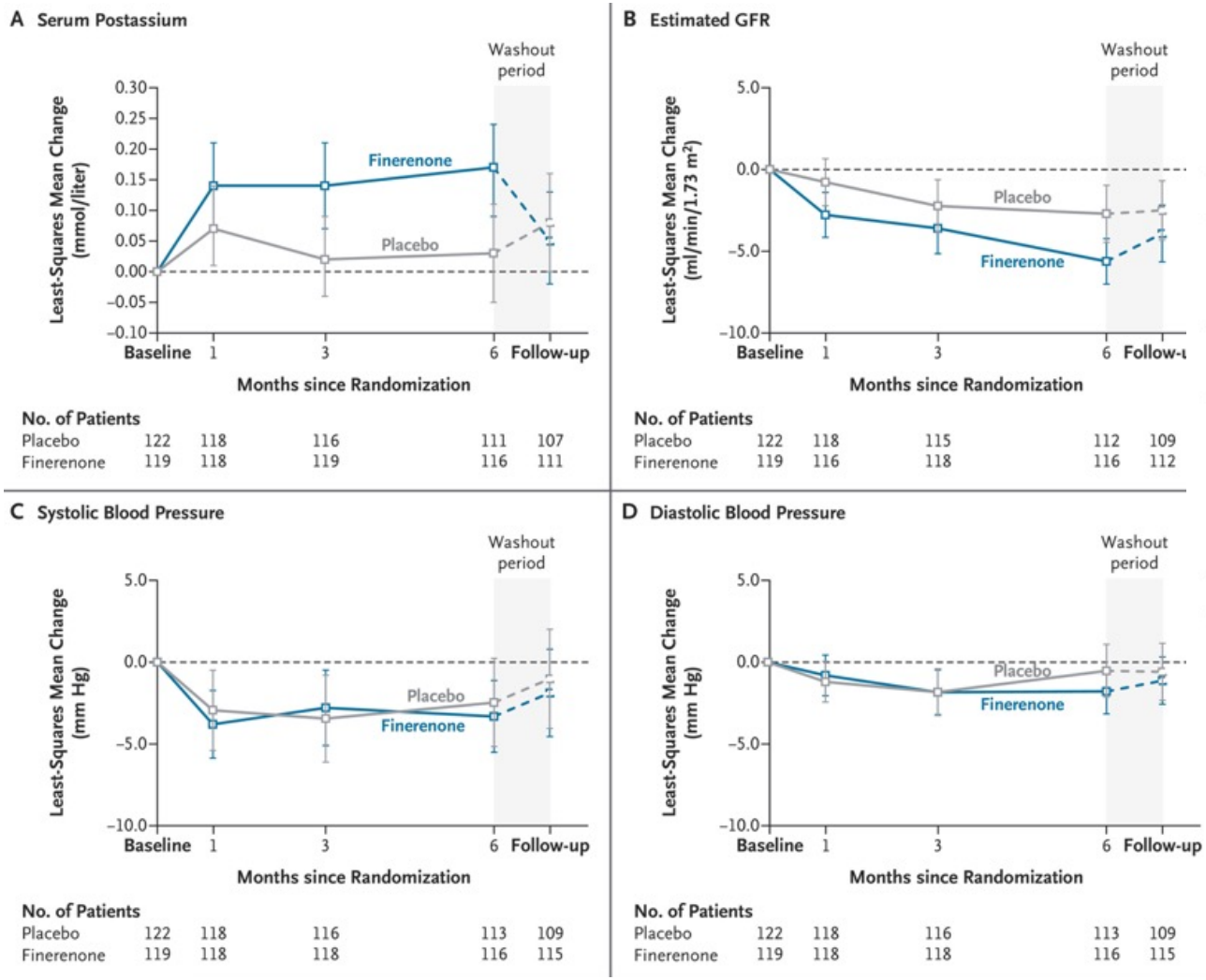
Up to three daily measures of the urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) were combined into a geometric mean urinary albumin-to-creatinine ratio before the analysis of the ratio to the baseline value. The least-squares geometric mean ratio for finerenone as compared with placebo over the trial period was an average of the geometric mean of the treatment effect at the month 3 visit and the month 6 visit. Assessment of data for the washout period was conducted with the use of an analysis-of-covariance model for the ratio to baseline at follow-up, with the model including trial group and log-transformed baseline urinary albumin-to-creatinine ratio. Follow-up was at 30 days (with a window of ±7 days) after the last dose of finerenone or placebo. I bars indicate 95% confidence intervals. Confidence intervals are unadjusted and should not be used for inference.

Subgroup	No. of Patients		Least-Squares Geometeric Mean Ratio to Baseline		Least-Squares Geometeric Mean Ratio for Finerenone vs. Placebo
	Finerenone (N=120)	Placebo (N=122)	Finerenone (N=120)	Placebo (N=122)	
Estimated GFR					
<45 ml/min/1.73 m^2	32	29	0.77	1.04	0.74 (0.57–0.97)
45 to <60 ml/min/1.73 m^2	32	27	0.63	0.93	0.67 (0.51–0.89)
≥60 ml/min/1.73 m^2	54	59	0.63	0.77	0.82 (0.67–1.00)
Urinary ACR					
<300	29	33	0.62	0.87	0.71 (0.54–0.93)
300 to 1000	55	50	0.63	0.87	0.72 (0.58–0.89)
>1000	34	32	0.77	0.85	0.91 (0.70–1.18)
Age					
<65 yr	92	94	0.69	0.89	0.78 (0.67–0.92)
≥65 yr	26	21	0.57	0.78	0.73 (0.54–1.00)
Sex					
Female	40	36	0.69	0.93	0.74 (0.58–0.94)
Male	78	79	0.65	0.84	0.78 (0.65–0.92)
Geographic region					
North America	36	40	0.73	0.89	0.82 (0.64–1.04)
Asia	16	23	0.90	1.02	0.88 (0.63–1.23)
Europe	66	52	0.59	0.79	0.74 (0.61–0.90)
Race or ethnic group					
White	84	84	0.61	0.85	0.72 (0.61–0.85)
Black	8	5	0.71	0.83	0.86 (0.47–1.59)
Asian	23	25	0.82	0.97	0.85 (0.63–1.14)
Other	3	1	1.23	0.53	2.32 (0.69–7.78)
Serum potassium					
<4.0 mmol/liter	10	7	0.60	0.58	1.04 (0.62–1.73)
4.0 to 4.8 mmol/liter	76	82	0.68	0.88	0.78 (0.65–0.92)
>4.8 mmol/liter	32	26	0.65	0.95	0.69 (0.52–0.91)
Systolic blood pressure					
<130 mm Hg	39	42	0.77	1.03	0.75 (0.59–0.94)
≥130 mm Hg	79	73	0.62	0.79	0.78 (0.66–0.93)
Glycated hemoglobin					
≤7.5%	53	67	0.74	0.92	0.80 (0.66–0.98)
>7.5%	65	46	0.61	0.80	0.76 (0.62–0.93)



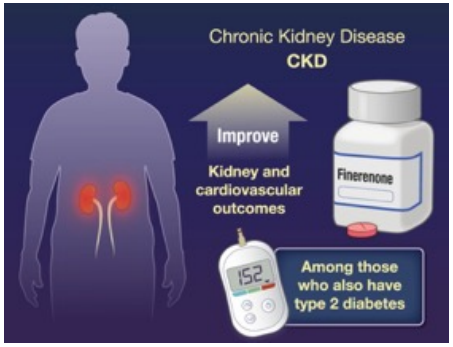
Change in the Urinary Albumin-to Creatinine Ratio According to Subgroup.

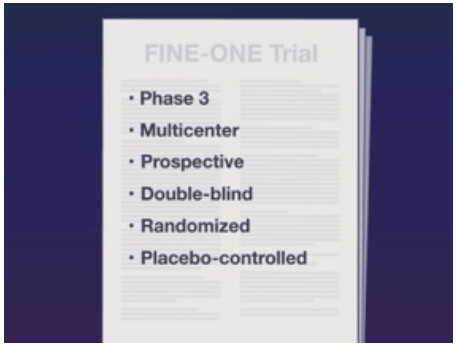
Race or ethnic group was reported by the participants. Two participants in the finerenone group were Native American or Native Alaskan, and race or ethnic group was not reported for one participant in each group. Confidence intervals are unadjusted and should not be used for inference. ACR denotes albumin-to-creatinine ratio, and GFR glomerular filtration rate.

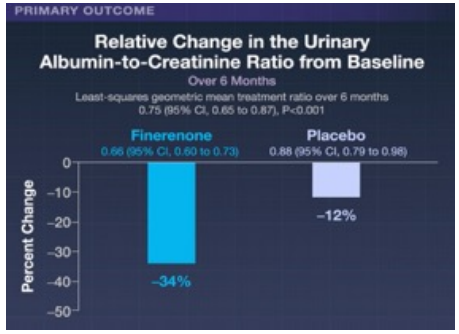


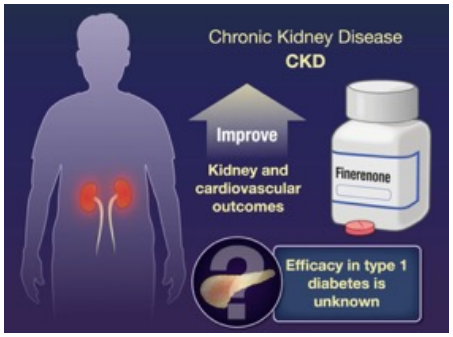
Changes in Serum Potassium Level, Estimated GFR, and Systolic and Diastolic Blood Pressure.

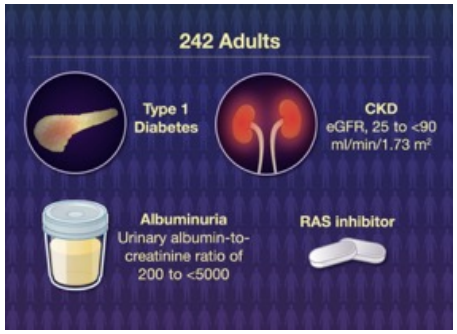
All variables were analyzed with the use of a mixed model for repeated measures with the following factors included as covariates: trial group, visit, trial-group-by-visit interaction, baseline value of variable of interest, and baseline-value-by-visit interaction. Follow-up was at 30 days (with a window of ±7 days) after the last dose of finerenone or placebo. I bars indicate 95% confidence intervals. Confidence intervals are unadjusted and should not be used for inference.

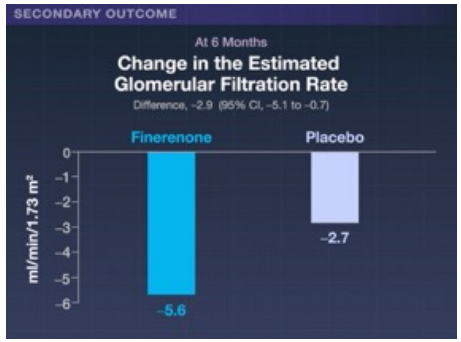


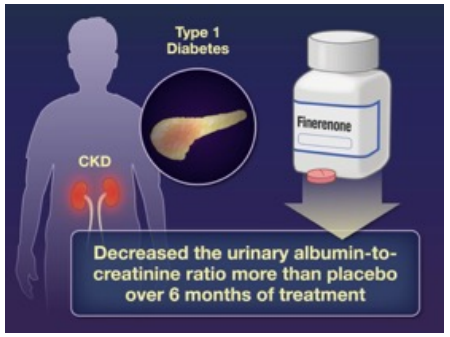


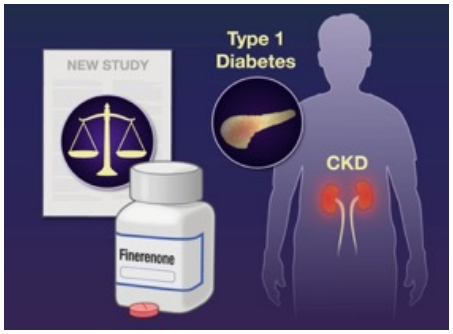


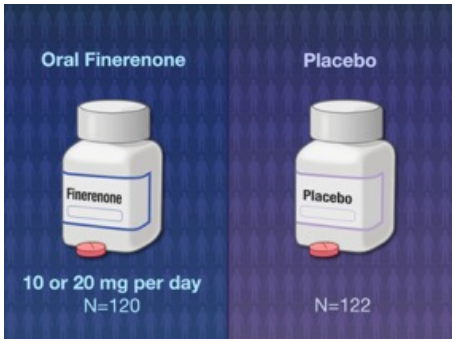


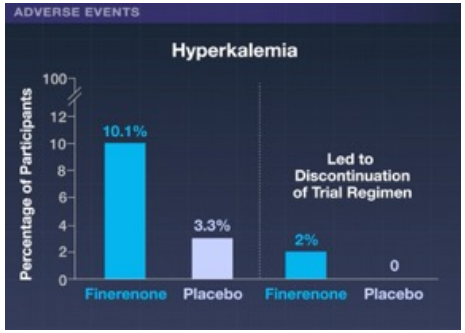












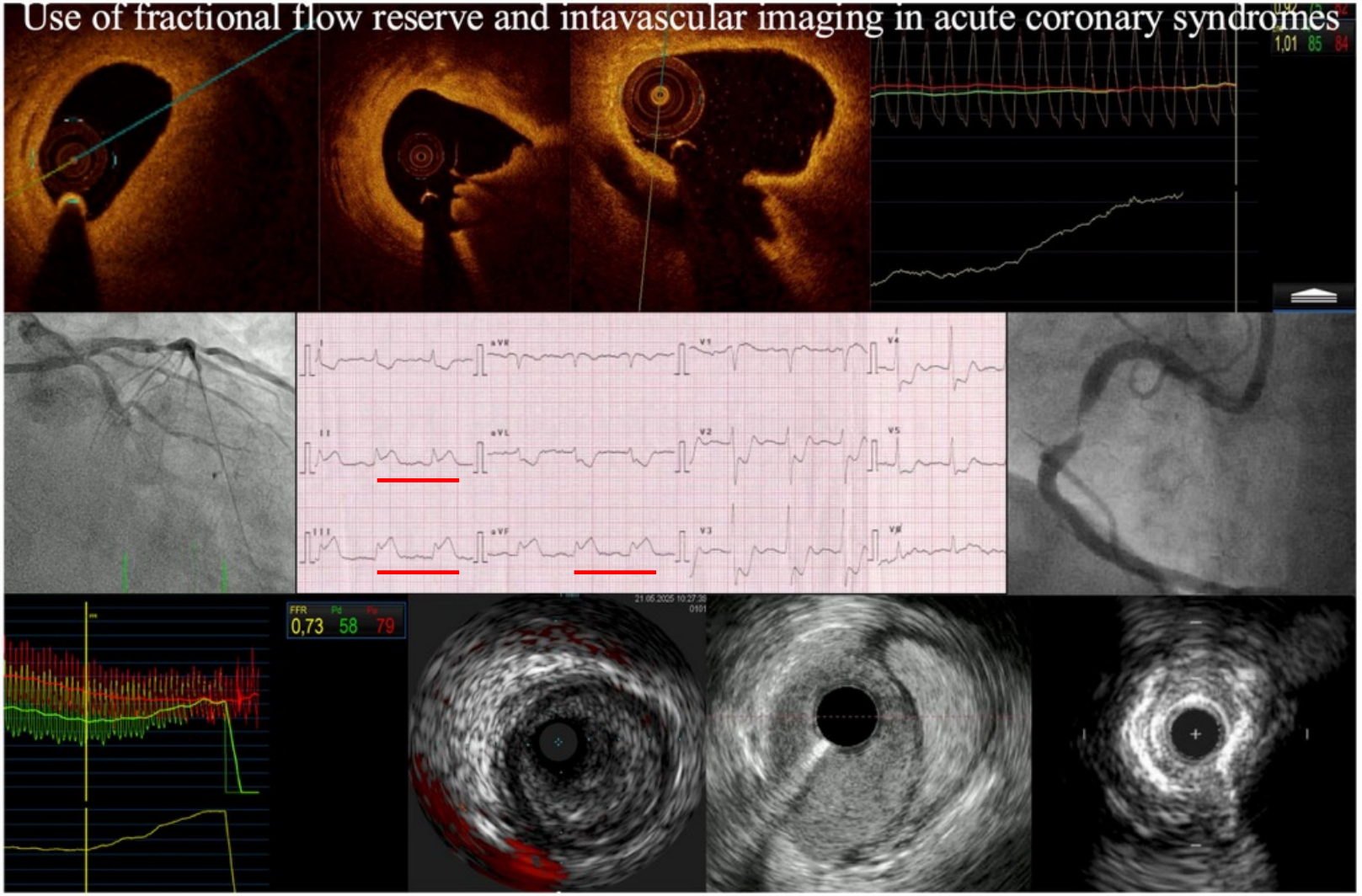
Finerenon (Kerendia 10/20 mg, 98 Stk.): Kostet oft über 200 € bis hin zu ca. 2,33 € pro Tablette.
Spironolacton (50 mg, 100 Stk.): Ist sehr günstig. 100 Tabletten kosten oft nur etwa 20 € - 25 € (ca. 0,20 € - 0,25 € pro Tablette).

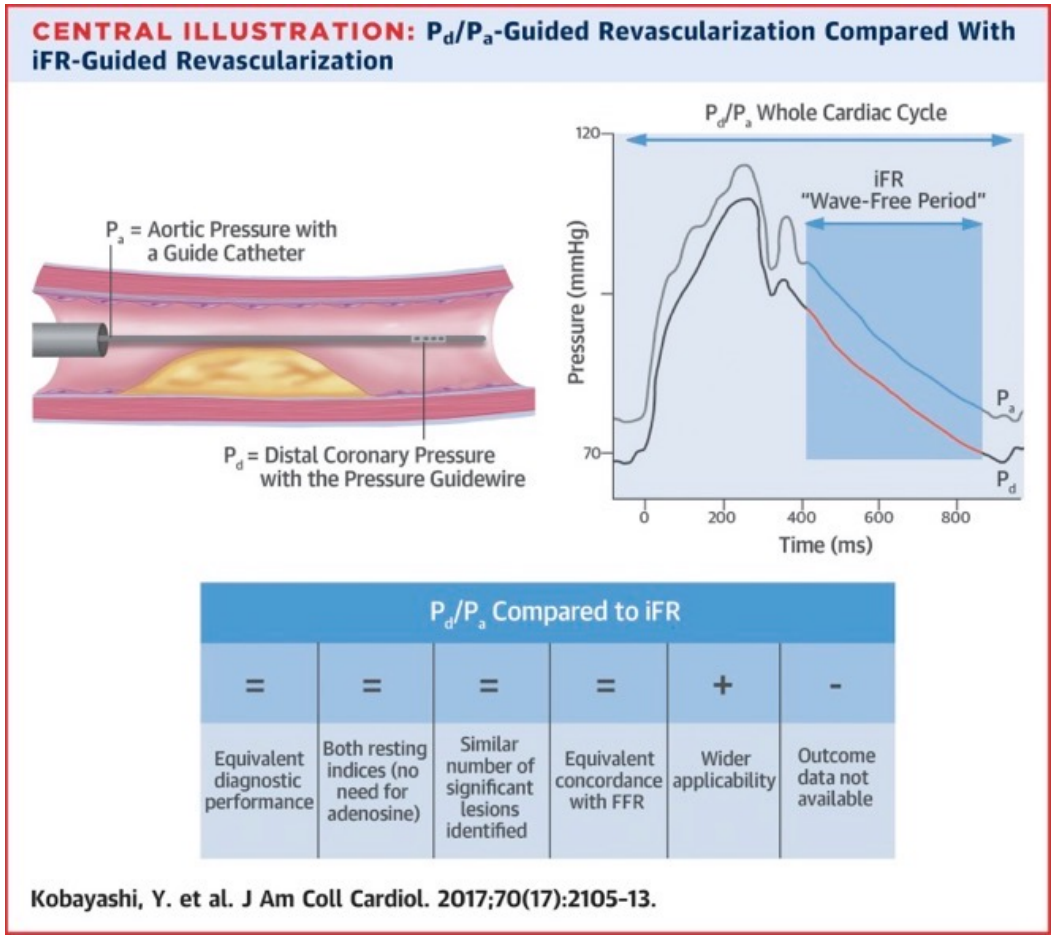
ST-Hebungsinfarkt Stent-Leitlinien heute

In der modernen Kardiologie bezeichnet eine **Non-Culprit-Läsion** eine atherosklerotische Verengung in einem Herzkranzgefäß, die *nicht* unmittelbar für den aktuellen Herzinfarkt verantwortlich ist. Während die **"Schuldner-Läsion"** (Culprit Lesion) sofort behandelt werden muss, war das Vorgehen bei weiteren Engstellen lange umstritten.
Aktuelle Leitlinien und Studien (wie **COMPLETE** oder **MULTISTARS AMI**) haben die Behandlungsstrategie grundlegend verändert:
Aktuelle Empfehlungen

- **Komplette Revaskularisation**: Bei Patienten mit einem ST-Hebungs-Infarkt (STEMI) wird heute die vollständige Behandlung aller signifikanten Engstellen empfohlen, da dies das Risiko für erneute Infarkte und kardiale Todesfälle senkt.
- **Zeitpunkt (Timing)**: Die Behandlung der Non-Culprit-Läsionen kann entweder **sofort** während des Ersteingriffs oder **stadiengerecht (staged)** innerhalb von 45 Tagen (oft noch während des Krankenhausaufenthalts) erfolgen.
- **Indikation**: Eine PCI ist meist angezeigt, wenn die Stenose visuell >70% beträgt oder durch funktionelle Messungen (z.B. FFR/iFR) als bedeutsam eingestuft wird.

Use of fractional flow reserve and intavascular imaging in acute coronary syndromes



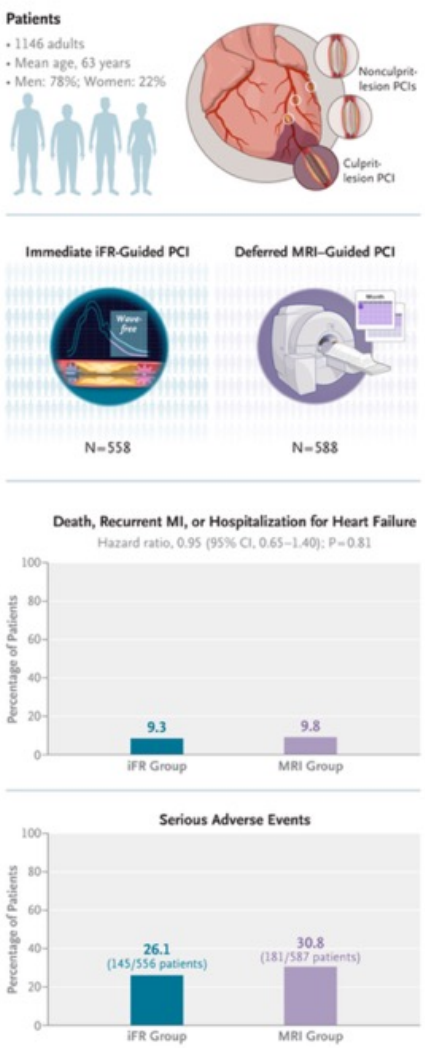


Invasive coronary physiological measurements and core laboratory assessments

All coronary physiological parameters were measured by using a 0.014-inch pressure sensor guidewire and console (PressureWire and QUANTIEN System). After equalization to the guide catheter pressure with the sensor positioned at the ostium of the coronary artery, the pressure guidewire was advanced down the target coronary artery. First, simultaneous recording of the aortic pressure with the guide catheter and the distal coronary pressure with the pressure guidewire was performed for at least 1 min to record resting physiological variables. In addition to contrast and adenosine hyperemic measurements not relevant to this substudy, a second assessment of resting physiological variables was performed before starting intravenous adenosine hyperemia. After all lesion assessments, an optional but encouraged drift check was performed by returning the pressure sensor to the position during equalization.

Immediate or Deferred Nonculprit-Lesion PCI in Myocardial Infarction

The preferred timing of treatment of nonculprit lesions in patients with ST-segment elevation myocardial infarction (STEMI) remains uncertain. A comparison of immediate percutaneous coronary intervention (PCI) guided by instantaneous wave-free ratio (iFR) and deferred PCI guided by cardiac stress magnetic resonance imaging (MRI) in patients with STEMI and multivessel disease is warranted. In this international, investigator-initiated, open-label, randomized, controlled trial, patients with STEMI and at least one nonculprit lesion who had undergone successful primary PCI were randomly assigned in a 1:1 ratio to immediate iFR-guided PCI (in lesions with >50% stenosis and an iFR of ≤0.89 [normal value, >0.89]) or deferred cardiac stress MRI–guided PCI within 6 weeks after randomization. The primary end point was a composite of death from any cause, recurrent myocardial infarction, or hospitalization for heart failure at 3-year follow-up.



Current guidelines recommend revascularization of nonculprit coronary-artery lesions in patients who have ST-segment elevation myocardial infarction (STEMI) and multivessel disease. In previous trials, this strategy was associated with improved survival and a reduction in recurrent myocardial infarction as compared with percutaneous coronary intervention (PCI) performed only in culprit lesions. The guidelines also suggest the performance of nonculprit-lesion PCI during the initial revascularization procedure on the basis of results from two previous trials and a meta-analysis. These trials were designed as noninferiority trials and included unplanned revascularization as a primary end point, which may be considered a subjective end point. Hence, current guideline recommendations for immediate PCI of nonculprit lesions in patients with STEMI need further confirmation.

We compared immediate PCI of nonculprit coronary-artery lesions guided by instantaneous wave-free ratio (iFR) with deferred PCI guided by cardiac stress magnetic resonance imaging (MRI) in patients with STEMI and multivessel disease with respect to the occurrence of death from any cause, recurrent myocardial infarction, or hospitalization for heart failure. We hypothesized that immediate iFR-guided nonculprit-lesion PCI would be associated with fewer events at 3 years than deferred cardiac stress MRI–guided nonculprit-lesion PCI (endpoint Superiority).

Trial Population

Patients with STEMI were eligible if they were 18 years of age or older, had undergone successful primary PCI (leading to Thrombolysis in Myocardial Infarction grade 3 flow and minimal residual stenosis of the culprit lesion) within 12 hours after symptom onset, and had one or more nonculprit lesions in a non–infarct-related artery that had a stenosis diameter of more than 50% and that were amenable to PCI.

Informed Consent and Randomization

After giving verbal consent during the index procedure, patients provided written consent in agreement with the principles of the Declaration of Helsinki. During the initial procedure, patients were randomly assigned in a 1:1 ratio to undergo either immediate iFR-guided nonculprit-lesion PCI or deferred cardiac stress MRI–guided nonculprit-lesion PCI; the deferred PCI was performed within 6 weeks after the index event. Randomization was performed with randomly permuted blocks. Stratification was performed according to the presence or absence of nonculprit-lesion stenosis in segment 6 or segment 7 of the left anterior descending artery.

Immediate iFR-Guided Assessment of Nonculprit Lesions

In patients assigned to the iFR group, assessment of iFR with a pressure wire (Philips Volcano) was performed at the time of the primary PCI procedure in all nonculprit lesions with stenosis of more than 50%. In the case of stenosis of more than 90%, PCI without iFR measurement was allowed, according to the trial protocol. PCI was performed in all nonculprit lesions with an iFR value of 0.89 or lower (normal value, >0.89).

Characteristics of the Patients at Baseline.

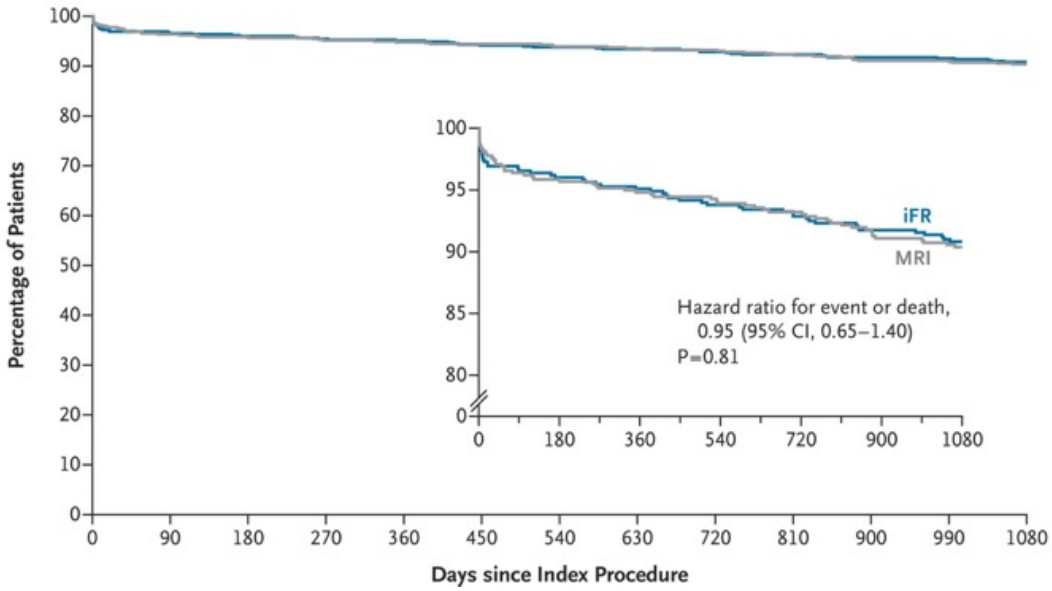
Characteristic	iFR (N=556)	MRI (N=587)
Age — yr	62.7±11.3	62.7±11.0
Male sex — %	77.8	77.6
Body-mass index†		
No. of patients assessed	468	528
Mean	27.4±4.5	27.2±4.3
Obesity — no./total no. (%)‡	122/468 (26.1)	109/528 (20.6)
Hypertension — no./total no. (%)	207/554 (37.4)	228/585 (39.0)
Hyperlipidemia — no./total no. (%)	151/554 (27.3)	180/585 (30.8)
Peripheral vascular disease — no./total no. (%)	13/554 (2.3)	22/585 (3.8)
Diabetes mellitus — no./total no. (%)	73/554 (13.2)	90/585 (15.4)
Smoking history — no./total no. (%)	369/533 (69.2)	363/569 (63.8)
History of stroke — no./total no. (%)	16/554 (2.9)	16/584 (2.7)
Chronic kidney disease — no./total no. (%)	8/554 (1.4)	10/585 (1.7)
Estimated glomerular filtration rate — no./total no. (%)		
<30 ml/min/1.73 m²	1/554 (0.2)	4/579 (0.7)
30–59 ml/min/1.73 m²	55/554 (9.9)	52/579 (9.0)
60–90 ml/min/1.73 m²	281/554 (50.7)	260/579 (44.9)
>90 ml/min/1.73 m²	206/554 (37.2)	248/579 (42.8)
Chronic obstructive pulmonary disease — no./total no. (%)	26/554 (4.7)	29/585 (5.0)
No or mild left ventricular dysfunction on echocardiography — no./total no. (%)	331/398 (83.2)	346/413 (83.8)

Procedural Characteristics.

Characteristic	iFR (N=556)	MRI (N=587)
Primary PCI		
Radial-artery access — no./total no. (%)	513/553 (92.8)	552/585 (94.4)
Duration — min	62.9±28.9	42.0±19.8
Primary culprit vessel — no. (%)		
Circumflex artery	100 (18.0)	103 (17.5)
Left anterior descending artery	233 (41.9)	218 (37.1)
Right coronary artery	223 (40.1)	266 (45.3)
Culprit-vessel stents		
No. per patient	1.4±0.7	1.4±0.7
Mean diameter — mm	3.3±2.0	3.2±1.0
Mean length — mm	24.4±9.7	23.7±9.3
Nonculprit-lesion assessment		
No. of nonculprit lesions per patient	1.4±0.6	1.5±0.8
Residual SYNTAX score after culprit-lesion PCI†	6.9±4.3	7.1±4.7
Patients with iFR assessment — no. (%)	541 (97.3)	65 (11.1)
Patients with iFR value of ≤0.89 — no./total no. (%)‡	243/541 (44.9)	32/65 (49.2)
Patients with cardiac stress MRI assessment — no. (%)	0	476 (81.1)
Patients with positive cardiac MRI — no./total no. (%)	0	96/476 (20.2)
Positive lesions on iFR or MRI — no./total no. (%)	290/767 (37.8)	164/808 (20.3)
Patients with positive lesions on iFR or MRI — no. (%)	243 (43.7)	128 (21.8)
Nonculprit-lesion PCI		
Positive lesions treated with PCI — no./total no. (%)	281/290 (96.9)	132/164 (80.5)
Patients with positive lesions treated with PCI — no. (%)	237 (42.6)	110 (18.7)
Total no. of lesion stents per patient	0.7±1.0	0.4±0.8
Total length of lesion stents	33.5±18.1	36.1±20.9
All PCI		
Median time to nonculprit-lesion PCI (IQR) — days	0	40.0 (28.0–58.0)
Total duration of culprit- and nonculprit-lesion PCI among all patients — min	65.5±31.0	53.5±33.7
Total duration of culprit- and nonculprit-lesion PCI among patients who underwent nonculprit-lesion PCI — min	75.4±33.3	90.0±43.7
Total no. of culprit- and nonculprit-lesion stents per patient — no.	2.1±1.4	1.8±1.1
Total stent length — mm§	48.7±29.7	42.1±27.7

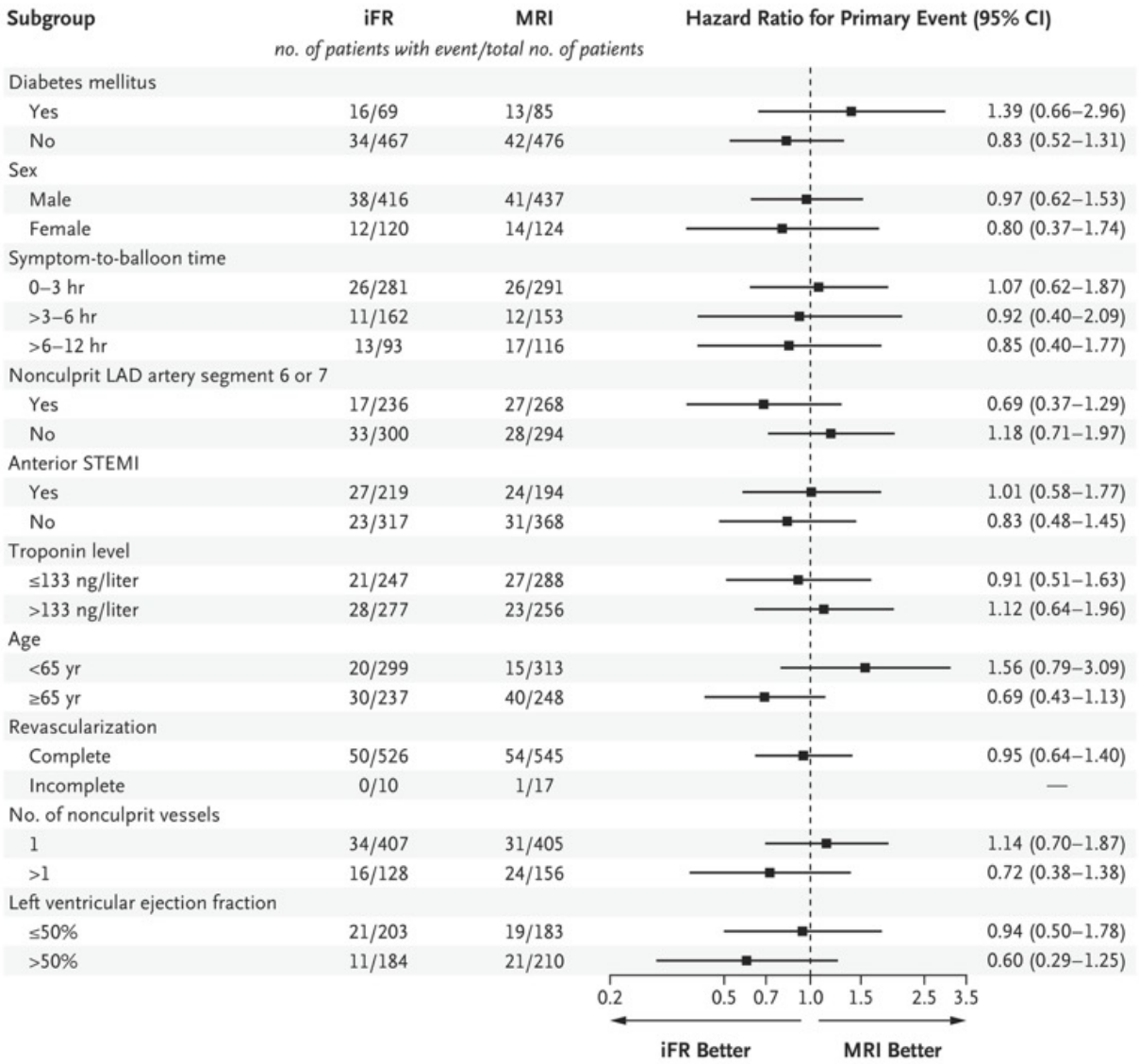
Primary and Secondary End Points.

End Point	iFR (N=556)	MRI (N=587)	Hazard Ratio (95% CI)
	no./total no. (%)		
Primary end point			
Composite of death from any cause, recurrent MI, or hospitalization for heart failure at 3 yr	50/536 (9.3)	55/562 (9.8)	0.95 (0.65–1.40)†
Death from any cause at 3 yr	22/536 (4.1)	22/562 (3.9)	1.04 (0.58–1.88)
Recurrent MI at 3 yr	29/536 (5.4)	31/562 (5.5)	0.99 (0.59–1.64)
Hospitalization for heart failure at 3 yr	3/536 (0.6)	13/562 (2.3)	0.24 (0.07–0.84)
Secondary end points			
Composite of death from any cause, recurrent MI, or hospitalization for heart failure at 6 mo	22/547 (4.0)	25/572 (4.4)	0.92 (0.52–1.63)
Death from any cause at 6 mo	7/547 (1.3)	11/572 (1.9)	0.66 (0.26–1.71)
Recurrent MI at 6 mo	14/547 (2.6)	10/572 (1.7)	1.47 (0.65–3.31)
Hospitalization for heart failure at 6 mo	2/547 (0.4)	9/572 (1.6)	0.23 (0.05–1.07)
Composite of death from any cause, recurrent MI, or hospitalization for heart failure at 12 mo	27/544 (5.0)	30/568 (5.3)	0.94 (0.56–1.58)
Death from any cause at 12 mo	8/544 (1.5)	12/568 (2.1)	0.69 (0.28–1.70)
Recurrent MI at 12 mo	18/544 (3.3)	13/568 (2.3)	1.45 (0.71–2.96)
Hospitalization for heart failure at 12 mo	2/544 (0.4)	10/568 (1.8)	0.21 (0.05–0.95)
Cardiac death at 3 yr	10/528 (1.9)	11/550 (2.0)	0.95 (0.40–2.23)
Target-lesion failure at 3 yr‡	54/531 (10.2)	58/554 (10.5)	0.98 (0.68–1.42)
Stroke or transient ischemic attack at 3 yr§	7/520 (1.3)	20/542 (3.7)	0.36 (0.15–0.86)
Stroke at 3 yr	5/520 (1.0)	12/542 (2.2)	
Transient ischemic attack at 3 yr	2/519 (0.4)	8/540 (1.5)	
Major bleeding at 3 yr	10/521 (1.9)	6/540 (1.1)	1.73 (0.63–4.76)
Unstable angina at 3 yr	17/520 (3.3)	21/541 (3.9)	0.84 (0.44–1.59)
Target-lesion revascularization at 3 yr	39/524 (7.4)	40/544 (7.4)	1.02 (0.66–1.59)
Any unplanned revascularization at 3 yr	45/524 (8.6)	46/545 (8.4)	1.03 (0.68–1.55)
Unplanned coronary angiography at 3 yr	64/525 (12.2)	78/548 (14.2)	0.85 (0.61–1.18)
Total stent thrombosis at 3 yr	9/522 (1.7)	3/540 (0.6)	3.12 (0.84–11.51)
Culprit-lesion stent thrombosis at 3 yr	8/521 (1.5)	2/540 (0.4)	4.16 (0.88–19.58)
Nonculprit-lesion stent thrombosis at 3 yr	1/520 (0.2)	1/540 (0.2)	1.04 (0.07–16.62)



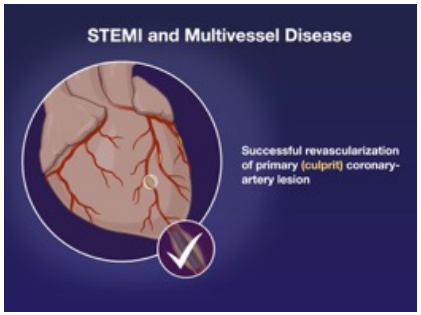
Kaplan–Meier Plot of Event-free Survival.

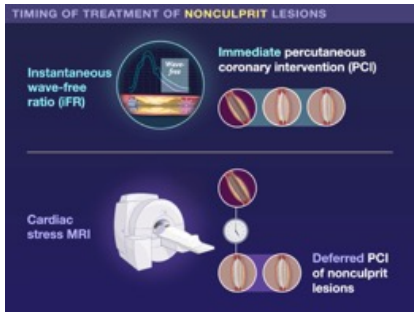
Shown is a Kaplan–Meier curve for freedom from a primary-end-point event, which was defined as a composite of death from any cause, recurrent myocardial infarction, or hospitalization for heart failure at 3 years. The inset shows the same data on an expanded y axis. Patients in the iFR group underwent immediate percutaneous coronary intervention (PCI) guided by instantaneous wave-free ratio (iFR), and patients in the MRI group underwent deferred PCI guided by cardiac stress magnetic resonance imaging (MRI).

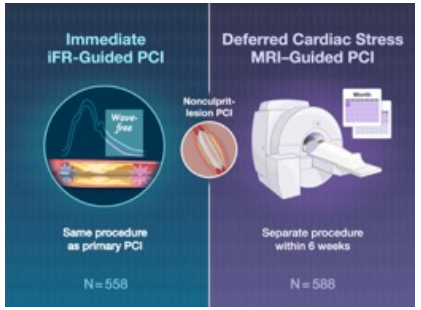


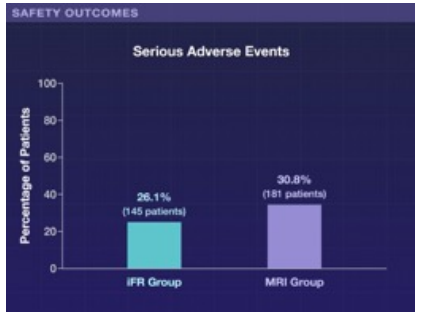
Primary Events in Prespecified Subgroups.

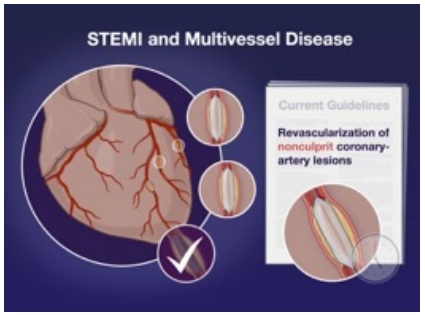
Shown is a forest plot of the number of patients with a primary-end-point event at 3 years in prespecified subgroups. The hazard ratio among patients with incomplete revascularization was not calculable owing to zero primary-end-point events in this subgroup, which resulted in a single hazard ratio for revascularization. In the iFR group, data for diabetes mellitus, sex, symptom-to-balloon time, nonculprit left anterior descending (LAD) artery, anterior ST-segment elevation myocardial infarction (STEMI), age, and revascularization were missing for 20 patients; data for the number of nonculprit vessels were missing for 21 patients; data for troponin level were missing for 32 patients; and data for left ventricular ejection fraction were missing for 169 patients. In the MRI group, data for nonculprit LAD artery, anterior STEMI, and revascularization were missing for 25 patients; data for diabetes mellitus, sex, age, and the number of nonculprit vessels were missing for 26 patients; data for symptom-to-balloon time were missing for 27 patients; data for troponin level were missing for 43 patients; and data for left ventricular ejection fraction were missing for 194 patients. The widths of the confidence intervals have not been adjusted for multiplicity and may not be used in place of hypothesis testing.

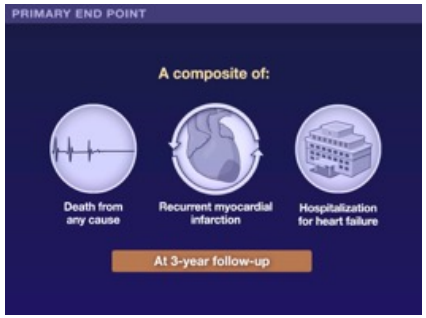


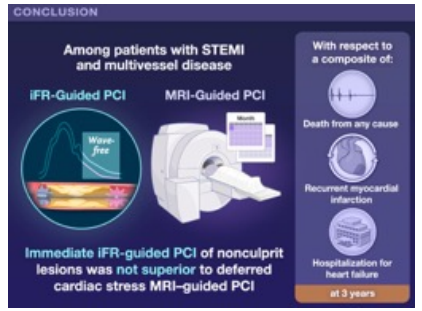


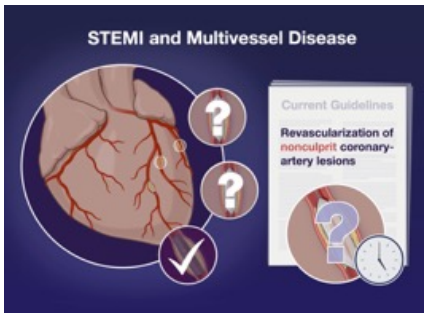


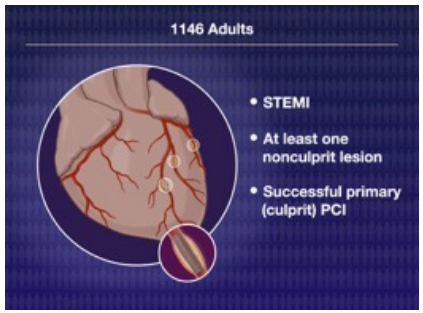


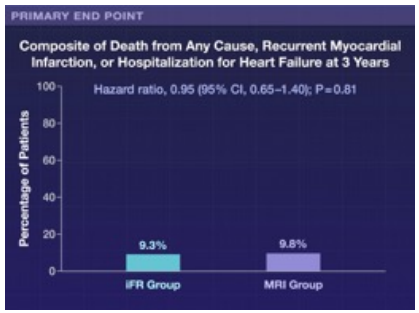






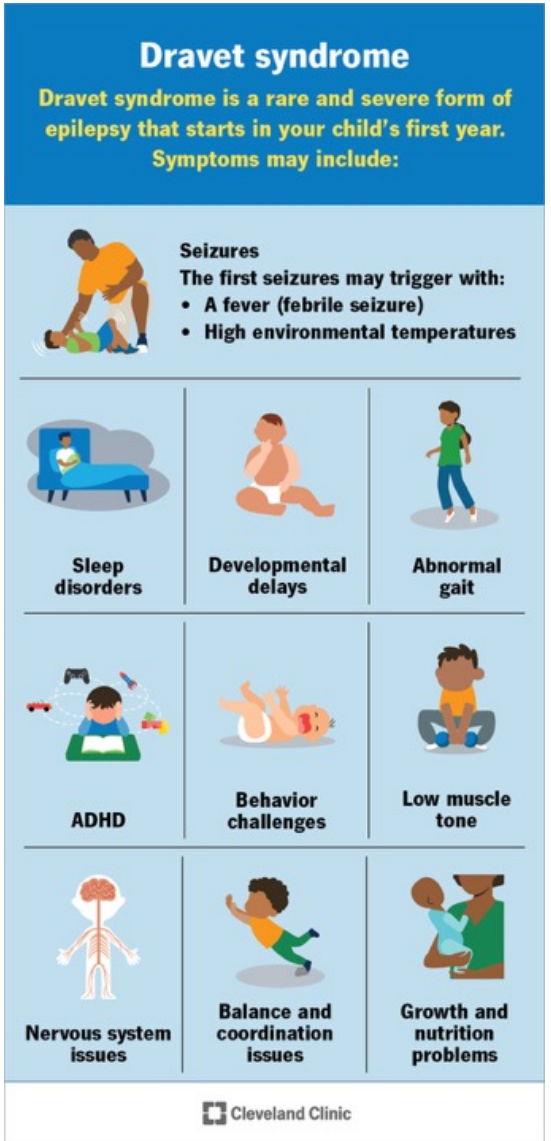






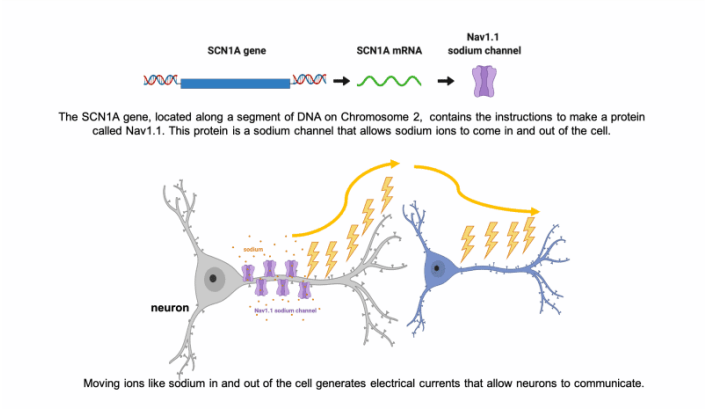
What about costs?

Das Dravet-Syndrom bzw. das Akronym SMEI bezeichnet eine frühkindliche Enzephalopathie, die der Gruppe der infantilen Epilepsie-Syndrome zuzuordnen ist. Ursache der epileptischen Anfälle sind neuronale Spontanentladungen in Folge pathologisch verändertem Schaltverhalten ("Gating") zentralnervöser spannungsabhängiger Natriumkanäle (NaV). Die Dysfunktion der Ionenkanäle beruht auf einer Spontanmutation des SCN1A-Gens, das für die alpha-Untereinheit der Kanäle kodiert (Kanalopathie).
Die Erstmanifestation des Dravet-Syndroms erfolgt innerhalb des ersten Lebensjahres. Erstsymptome sind fiebrige, fokale, in der Regel unilateral ausgeprägte, motorische Krampfanfälle. Sie treten zu Beginn etwa fünf Mal pro Jahr auf, können aber sekundär generalisieren und in einen Grand-mal-Anfall degenerieren. Als auslösende Stimuli gelten eine Erhöhung der Körpertemperatur in Folge fiebriger Infekte, Anstrengung und warme Bäder.
Dravet-Syndrom wird als autosomal-dominant vererbt, entsteht jedoch in den allermeisten Fällen (ca. 80-90 %) als Neumutation (de novo). Das bedeutet, die Mutation im SCN1A-Gen tritt spontan auf und ist nicht von den Eltern vererbt worden.



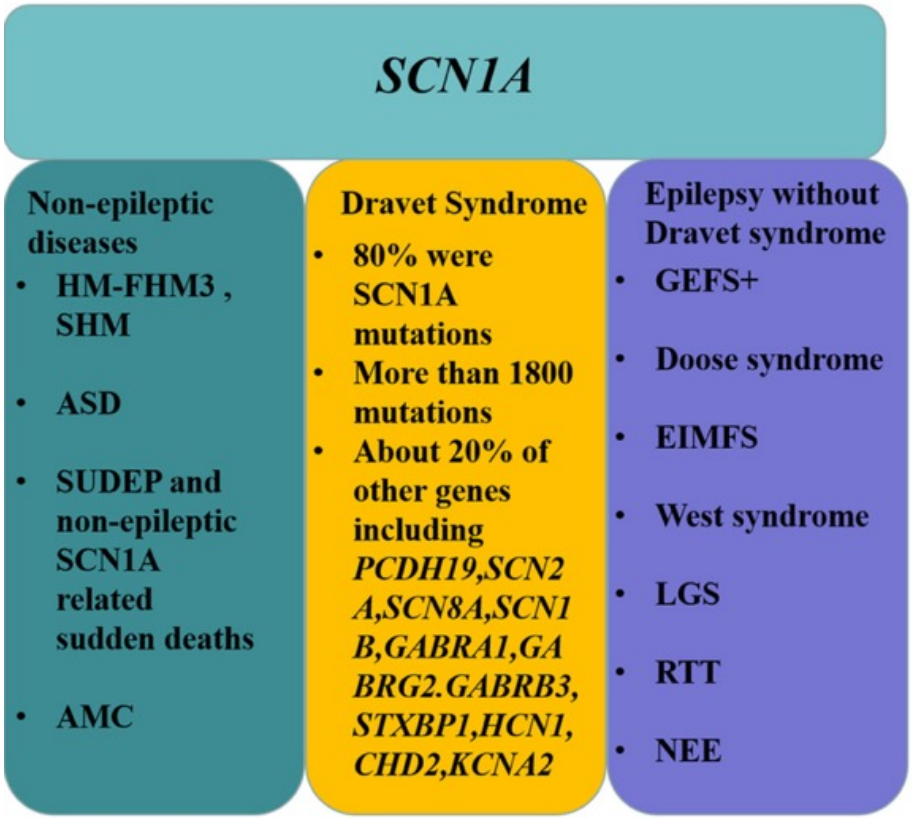
Das Dravet Syndrom

Nav1.1 (kodiert durch das *SCN1A*-Gen) ist ein spannungsabhängiger Natriumkanal, der primär in inhibitorischen GABAergen Interneuronen des zentralen Nervensystems vorkommt.



Dravet syndrome (DS) is fundamentally caused by a diminished function of the *SCN1A* gene, typically described as a "loss-of-function" mutation or haploinsufficiency.

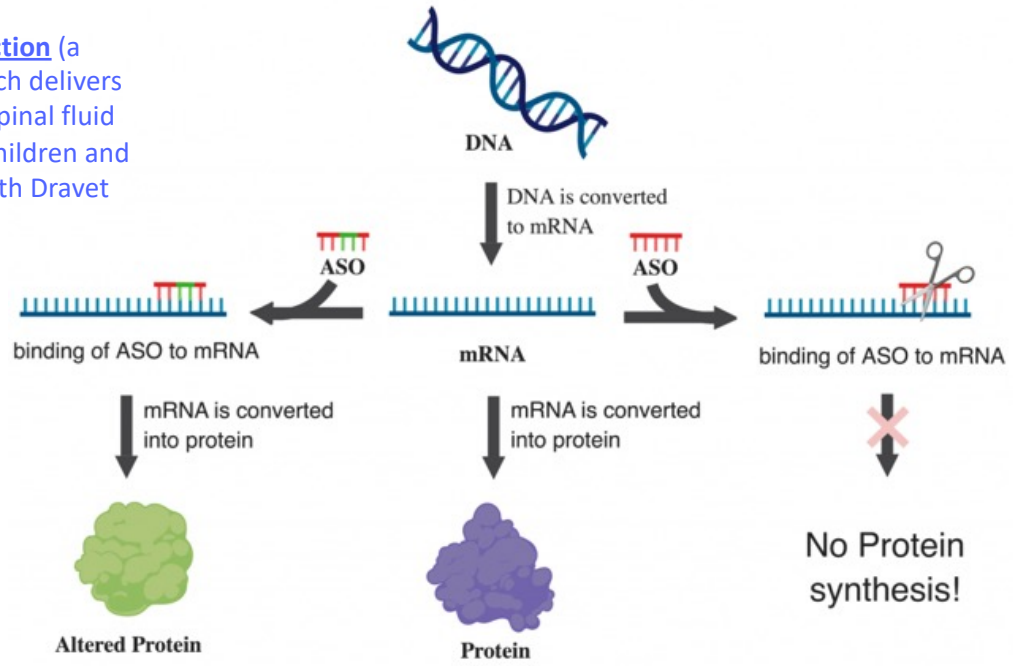
Cannabidiol (CBD), insbesondere das Medikament Epidyolex, ist seit 2019/2021 als Zusatztherapie für das Dravet-Syndrom bei Kindern ab 2 Jahren zugelassen, da es Krampfanfälle signifikant reduzieren kann. Studien zeigen, dass es die Anfallshäufigkeit bei der schweren, meist genetisch bedingten Epilepsieform senken kann, oft in Kombination mit Clobazam.



Genetische Ursach:
Poison Exons (, Gift-Exons“) sind nicht-kodierende RNA-Sequenzen, die durch Spleißfehler in das *SCN1A*-Gen eingebaut werden. Sie führen zum Abbau des Transkripts (Nonsense-mediated decay) und reduzieren so das funktionelle Protein, was das Dravet-Syndrom verursacht. Antisense-Oligonukleotide (ASOs) können diese fehlerhafte Einbindung korrigieren.

Zorevunersen (früher **STK-001**) ist ein experimentelles Medikament zur Behandlung des **Dravet-Syndroms**, einer schweren Form der genetisch bedingten Epilepsie bei Kindern.
Wichtige Informationen im Überblick
•**Wirkmechanismus**: Es handelt sich um ein **Antisense-Oligonukleotid (ASO)**. Es zielt darauf ab, die Produktion des NaV1.1-Proteins aus der nicht mutierten Kopie des SCN1A-Gens zu erhöhen, um den Proteinmangel im Gehirn auszugleichen.

Zorevunersen (STK-001) is administered via **intrathecal injection** (a lumbar puncture/spinal tap), which delivers the medication directly into the spinal fluid to reach the brain. It is used for children and adolescents (ages 2 and older) with Dravet syndrome.



This antisense knocks down a toxic mRNA, namely from a „poison“ exon.

Zorevunersen in Children and Adolescents with Dravet Syndrome

Dravet syndrome is a severe developmental and epileptic encephalopathy caused primarily by *SCN1A* haploinsufficiency. Risks of sudden unexpected death in epilepsy and cognitive deficits are higher among patients with this syndrome than in the general population with epilepsy. The effects of zorevunersen, an antisense oligonucleotide designed to up-regulate $Na_V1.1$ sodium channels, in patients with Dravet syndrome are not known.

We enrolled patients 2 to 18 years of age with Dravet syndrome who were receiving standard antiseizure medications in two phase 1–2a, open-label, multicenter studies (MONARCH and ADMIRAL). Patients were included in either a single-ascending-dose cohort, in which zorevunersen (10 to 70 mg) was administered on day 1 only, or a multiple-ascending-dose cohort, in which zorevunersen (20 to 70 mg) was administered two or three times in a 3-month period. Patients eligible for rollover to the two open-label extension studies (SWALLOWTAIL and LONGWING) continued to receive zorevunersen (≤45 mg) every 4 months. The safety and pharmacokinetics of zorevunersen were assessed in the primary analysis; clinical effects were also evaluated.

Conclusions

The safety profile and initial clinical improvement support the continued development of zorevunersen as a potential disease-modifying treatment for Dravet syndrome.

Dravet syndrome is a severe developmental and epileptic encephalopathy caused primarily by variants in one copy of the voltage-gated sodium channel type 1 alpha subunit gene (*SCN1A*), which result in *SCN1A* haploinsufficiency and reduced expression of $Na_V1.1$ sodium channels. These channels are highly expressed in inhibitory interneurons associated with γ-aminobutyric acid (GABA) and in some excitatory interneurons associated with glutamate in the brain. Reductions in $Na_V1.1$ disrupt the excitatory–inhibitory balance, leading to general hyperexcitability and seizures.

The clinical phenotype of Dravet syndrome includes a spectrum of symptoms that emerge early and evolve. Most patients have cognitive deficits, communication and behavioral impairments, motor dysfunction, growth delays, and autistic traits. Difficulties with feeding, poor appetite, and weight loss are also common. These impairments reduce quality of life for patients and caregivers. In addition, the risk of sudden unexpected death in epilepsy is higher among patients with Dravet syndrome than in the general population of patients with epilepsy.

Zorevunersen (formerly STK-001), an antisense oligonucleotide, was designed to target the channelopathy that underlies Dravet syndrome. In eukaryotes, precursor messenger RNA (mRNA) matures into mRNA through splicing, the process by which introns are removed and exons are joined together. Nonproductive (poison) exons contain a premature termination codon, which, if included in mRNA, results in its degradation. Zorevunersen binds to precursor mRNA of *SCN1A* to prevent the inclusion of nonproductive exons, thereby increasing productive mRNA synthesis and $Na_V1.1$ protein expression. Restoring $Na_V1.1$ to physiologic levels in the brain could improve overall function, including cognition and behavior, in patients with Dravet syndrome. Here, we present results from the phase 1–2a MONARCH and ADMIRAL studies, which investigated the effects of zorevunersen in patients with Dravet syndrome, including safety, pharmacokinetics, and effects on seizure frequency, overall clinical status, quality of life, and adaptive behavior. We also present interim results (data cutoff, May 30, 2025) from the ongoing SWALLOWTAIL and LONGWING open-label extension studies.

More on poison exons comes later

Characteristics of the Patients in the MONARCH–ADMIRAL Studies and in the SWALLOWTAIL–LONGWING Studies at Baseline.

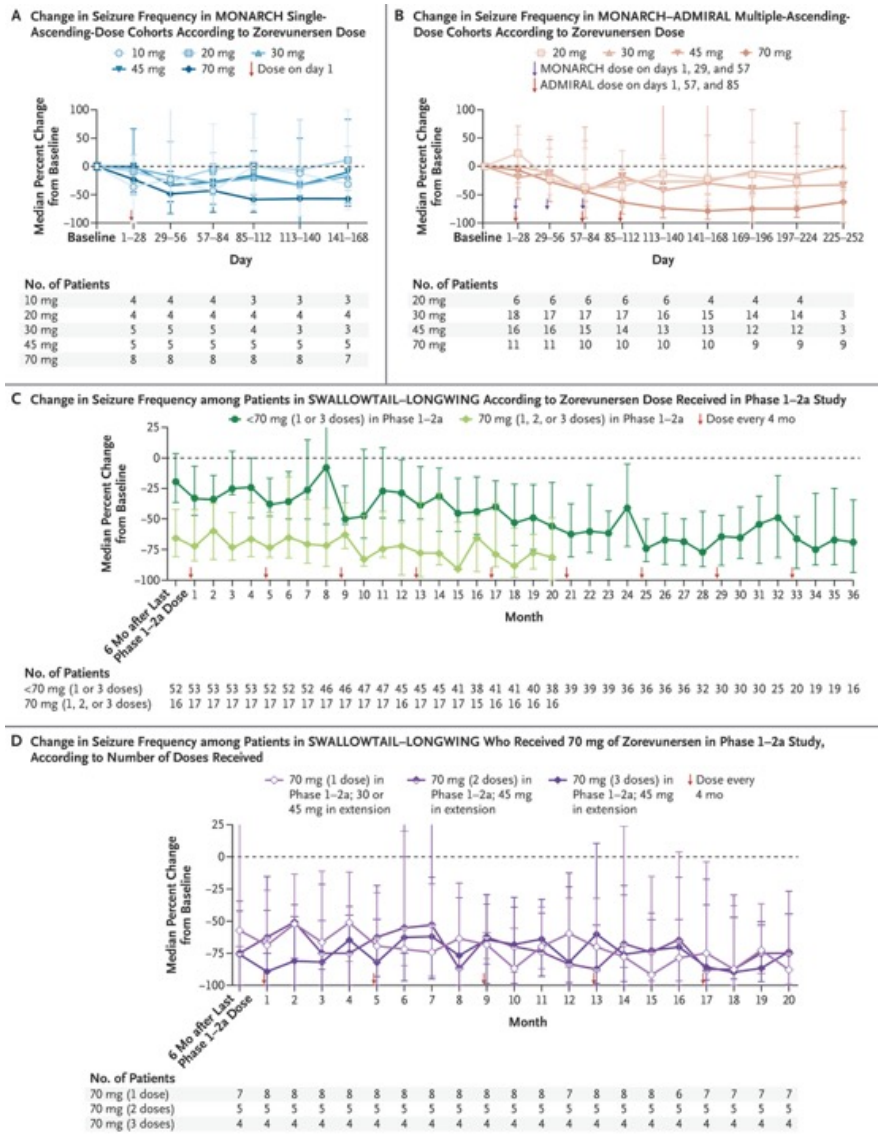
Characteristic	MONARCH–ADMIRAL (N=81)	SWALLOWTAIL–LONGWING (N=75)
Age at screening — yr		
Mean	9.9±5.1	10.4±5.0
Median (range)	10.0 (2–18)	11.0 (2–19)
Age group — no. (%)		
2–12 yr	46 (57)	42 (56)
≥13 yr	35 (43)	33 (44)
Sex — no. (%)		
Male	41 (51)	38 (51)
Female	40 (49)	37 (49)
Race — no. (%)†		
Asian	5 (6)	5 (7)
Black	5 (6)	5 (7)
White	71 (88)	66 (88)
Prefer not to answer	4 (5)	3 (4)
Ethnic group — no. (%)†		
Hispanic or Latino	10 (12)	10 (13)
Not Hispanic or Latino	70 (86)	64 (85)
Prefer not to answer	1 (1)	1 (1)
SCN1A variant type — no. (%)		
Missense	37 (46)	32 (43)
Nonsense	44 (54)	43 (57)
Antiseizure medications used concomitantly at baseline — no. (%)‡		
≥3	66 (81)	NA
≥4	41 (51)	NA
Concomitant use of fenfluramine at baseline — no. (%)	40 (49)	40 (53)
Median no. of convulsive seizures in 28-day observation period (range)§	17.0 (4.0–2335.4)	NA

Summary of Adverse Events in the MONARCH–ADMIRAL Studies and in the SWALLOWTAIL–LONGWING Studies.

Event	MONARCH–ADMIRAL (N=81)	SWALLOWTAIL–LONGWING (N=75)
	number of patients (percent)	
Any adverse event	78 (96)	75 (100)
Treatment-related adverse event	24 (30)	40 (53)
Adverse event related to CSF collection or study-drug administration	43 (53)	45 (60)
Grade ≥3 adverse event		
Any	13 (16)	12 (16)
Related to treatment	1 (1)	0
Serious adverse event		
Any	18 (22)	22 (29)
Related to treatment	1 (1)	0
Potential dose-limiting toxic effect†	1 (1)	0
Adverse event that led to treatment discontinuation	0	1 (1)
Adverse event that led to study withdrawal	0	1 (1)
Adverse event that led to death†	1 (1)	2 (3)

Exploratory end points included additional measures of seizure frequency and the change from baseline in adaptive behavior, as measured with the Vineland Adaptive Behavior Scales, Third Edition (Vineland-3), in the ADMIRAL study and the SWALLOWTAIL–LONGWING studies. Vineland-3 raw scores range from 0 to 116, with higher scores indicating better adaptive behavior and with the upper limit varying according to subdomain.

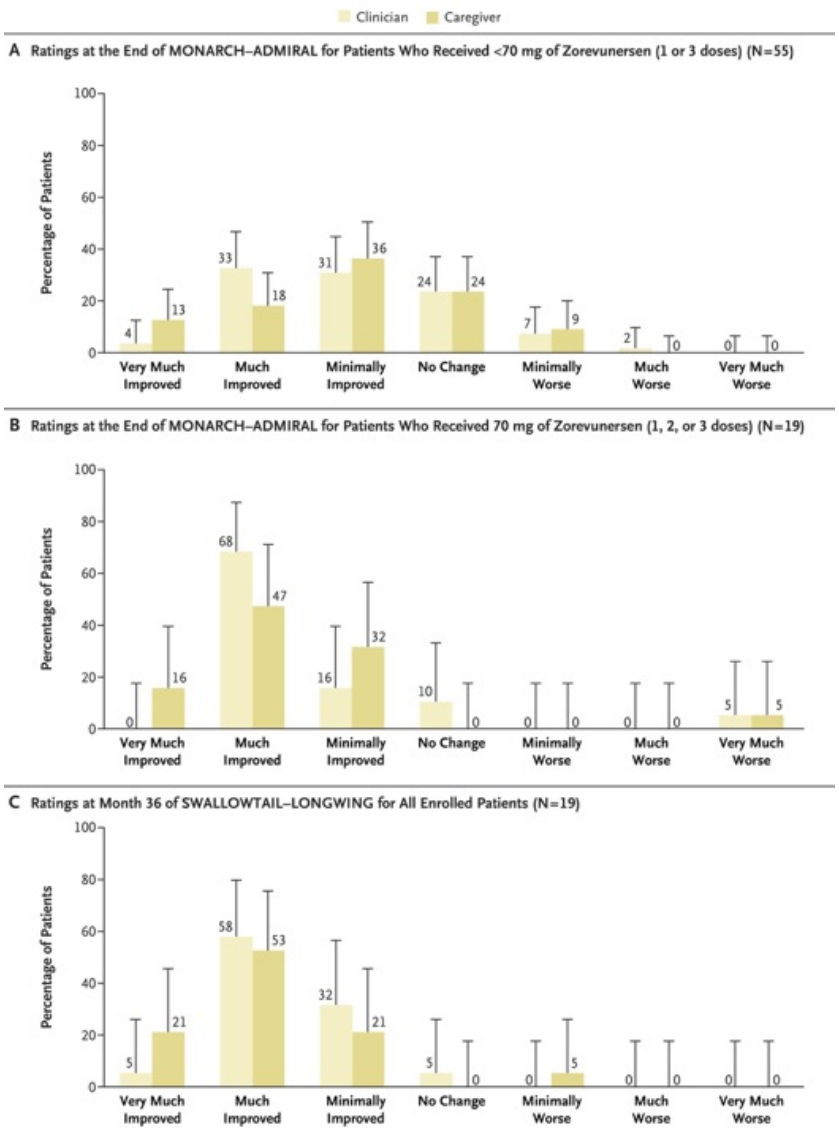
Seizures get a bit less



Change in the Frequency of Convulsive Seizures in the MONARCH–ADMIRAL Studies and in the SWALLOWTAIL–LONGWING Studies.

Panels A and B show the median percent change from baseline in the frequency of convulsive seizures through at least 6 months after the last dose of zorevunersen in the single-ascending-dose cohorts of the MONARCH study and in the multiple-ascending-dose cohorts of the MONARCH–ADMIRAL studies, respectively. In the MONARCH multiple-ascending-dose cohorts, zorevunersen (20, 30, or 45 mg) was administered on days 1, 29, and 57. In the ADMIRAL multiple-ascending-dose cohorts, zorevunersen (30, 45, or 70 mg) was administered on days 1, 57, and 85 or on days 1 and 57 with the reduced schedule. Panel C shows the median percent change from baseline (of the phase 1–2a studies) in the frequency of convulsive seizures among patients in the SWALLOWTAIL–LONGWING studies who had received zorevunersen at a dose level of less than 70 mg (one or three doses) in the phase 1–2a studies and those who had received zorevunersen at a dose level of 70 mg (one, two, or three doses) in the phase 1–2a studies. Panel D shows the median percent change from baseline in the frequency of convulsive seizures among patients in the SWALLOWTAIL–LONGWING studies who had received 70 mg of zorevunersen in the phase 1–2a studies, according to the number of doses received in the phase 1–2a studies. At 6 months after the last dose was administered in the phase 1–2a studies, data are shown only for patients who were enrolled in the extension studies. No exclusions were made for modification to antiseizure medications in the extension studies. Convulsive seizures included the following types: hemiclonic, focal with motor signs, focal-to-bilateral tonic–clonic, generalized tonic–clonic, tonic, tonic–atonic (drop attacks), and clonic. Seizure frequencies were calculated in 1-month (28-day) intervals. The data cutoff for the phase 1–2a studies was December 12, 2023 (after the end of the studies); the data cutoff for the extension studies was May 30, 2025. I bars indicate 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used to infer treatment effects.

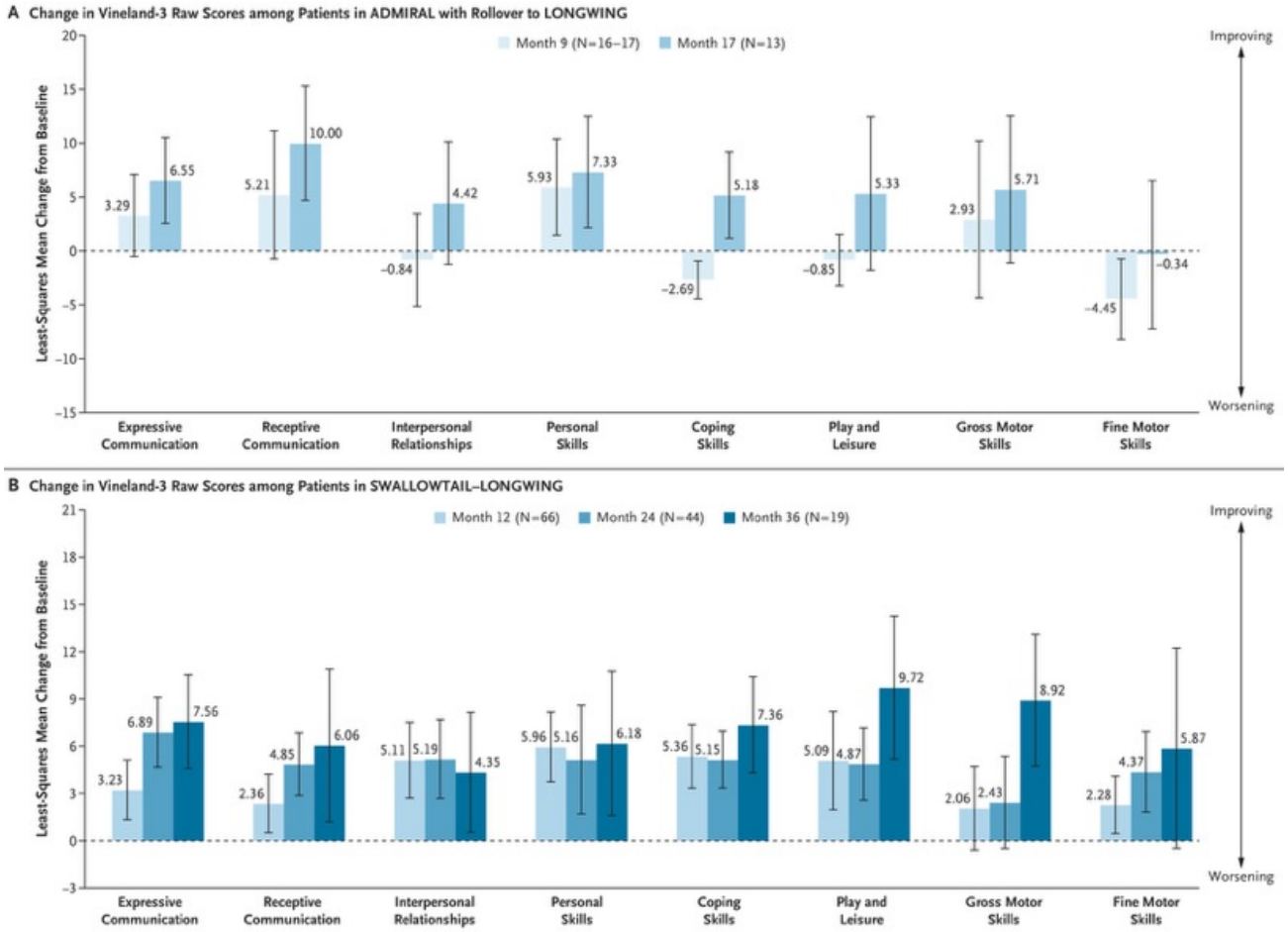
Symptoms get a bit better



Change in Overall Clinical Status in the MONARCH–ADMIRAL Studies and in the SWALLOWTAIL–LONGWING Studies.

Panels A and B show the change from baseline in overall clinical status, as measured with the Clinical and Caregiver Global Impression of Change assessments, at the end of the MONARCH–ADMIRAL studies (6 months after the last dose of zorevunersen) among patients who received zorevunersen at a dose level of less than 70 mg (one or three doses) and those who received zorevunersen at a dose level of 70 mg (one, two, or three doses), respectively. Panel C shows the change from baseline (of the extension studies) in overall clinical status at month 36 of the SWALLOWTAIL–LONGWING studies among all enrolled patients. The data cutoff for the phase 1–2a studies was December 12, 2023 (after the end of the studies); the data cutoff for the extension studies was May 30, 2025. I bars indicate 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used to infer treatment effects. Comparison of dose cohorts was performed in a post hoc analysis.

Adaptive behavior a bit better



Change in Adaptive Behavior in the ADMIRAL Study with Rollover to the LONGWING Study and in the SWALLOWTAIL–LONGWING Studies.

Panels A and B show the change from baseline in adaptive behavior, as measured with the Vineland Adaptive Behavior Scales, Third Edition (Vineland-3), among patients in all dose cohorts of the ADMIRAL study with rollover to the LONGWING study and among patients in the SWALLOWTAIL–LONGWING studies, respectively. Vineland-3 raw scores range from 0 to 116, with higher scores indicating better adaptive behavior and with the upper limit varying according to subdomain. The least-squares mean change from baseline in Vineland-3 raw scores was estimated over time with adjustment for baseline prognostic covariates. Mixed models for repeated measures were used to analyze data from the ADMIRAL study (17 or 18 total patients, depending on the subdomain, at baseline) and through week 96 of the LONGWING study (which corresponds to week 132 after baseline of the ADMIRAL study), as well as to analyze available data from the extension studies (74 total patients at baseline of the extension studies). The analyses focused on seven subdomains without minimum age criteria and one subdomain with a minimum age criterion of 2 years. With regard to the remaining three subdomains (Written, Domestic, and Community), baseline scores were at or below the age-equivalent lower limit in 9 of 17 patients (53%), 15 of 17 patients (88%), and 13 of 17 patients (76%), respectively, in the ADMIRAL study and in 26 of 71 patients (37%), 49 of 71 patients (69%), and 48 of 71 patients (68%), respectively, in the extension studies. The data cutoff for the phase 1–2a studies was December 12, 2023 (after the end of the studies); the data cutoff for the extension studies was May 30, 2025. I bars indicate 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used to infer treatment effects.

Discussion

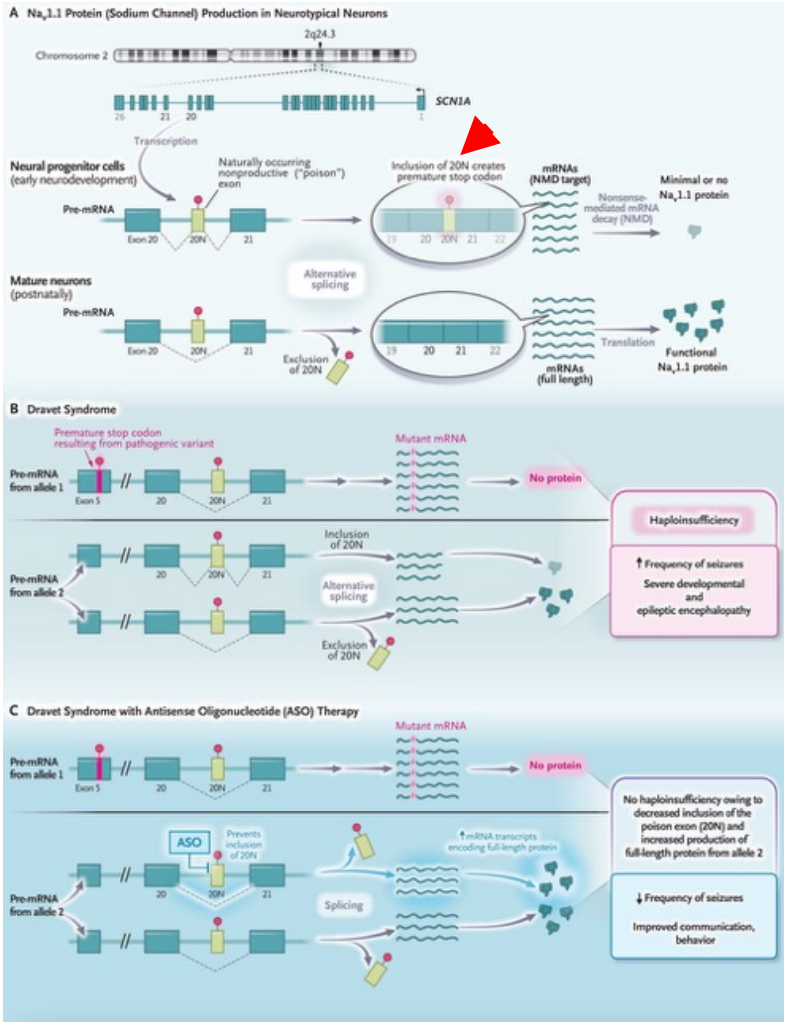
The results reported here support the continued development of zorevunersen as a potential disease-modifying treatment for Dravet syndrome. Most treatment-related adverse events were mild or moderate, with the most common across both the MONARCH–ADMIRAL studies and the SWALLOWTAIL–LONGWING studies being elevated CSF protein levels as observed on routine laboratory screening. Similar elevations in the CSF protein level have been reported with other intrathecal antisense oligonucleotides that have been approved by the Food and Drug Administration. Elevations in the CSF protein level have been reported with repeated doses of nusinersen; the CSF protein level may be a therapeutic marker. No patients had adverse events of hydrocephalus or increased intracranial pressure. One patient had CSF pleocytosis. Ongoing safety monitoring includes neurologic examinations and CSF laboratory testing.

Toward a Disease-Modifying Therapy for Dravet Syndrome

What Are Poison Exons?

Poison exons, also referred to as nonsense-mediated mRNA decay (NMD) or nonproductive exons, are naturally occurring, alternatively spliced exons present in roughly a third of genes in the genome. When spliced into a messenger RNA (mRNA) transcript, poison exons introduce a premature stop codon, leading to NMD of the resulting transcript and no subsequent protein production. *SCN1A* contains a poison exon (called 20N) between exons 20 and 21. In mice and humans, 20N is preferentially included early in neurodevelopment when $Na_V1.1$ is not needed; the 20N exon is increasingly skipped with advancing gestational age. Postnatally, a small fraction of *SCN1A* transcripts include the poison exon. The regulation of inclusion (or exclusion) of 20N (through alternative splicing) is thought to modulate $Na_V1.1$ protein levels across stages of development; disruption of this regulation can cause disease. For example, variants in *SCN1A* that lead to increased incorporation of the 20N exon are associated with Dravet syndrome and related phenotypes. Conversely, preventing the inclusion of a poison exon can increase the production of full-length protein by diminishing the pool of nonfunctional "poisoned" *SCN1A* mRNAs and increasing the pool of full-length *SCN1A* mRNAs. The latter approach was used by Laux et al.

Zorevunersen is a splice-switching antisense oligonucleotide that prevents the inclusion of exon 20N, thereby increasing levels of full-length *SCN1A* mRNA and $Na_V1.1$ protein.



We blitz exon20

Targeting a "Poison" (Nonproductive) Exon to Treat Dravet Syndrome.

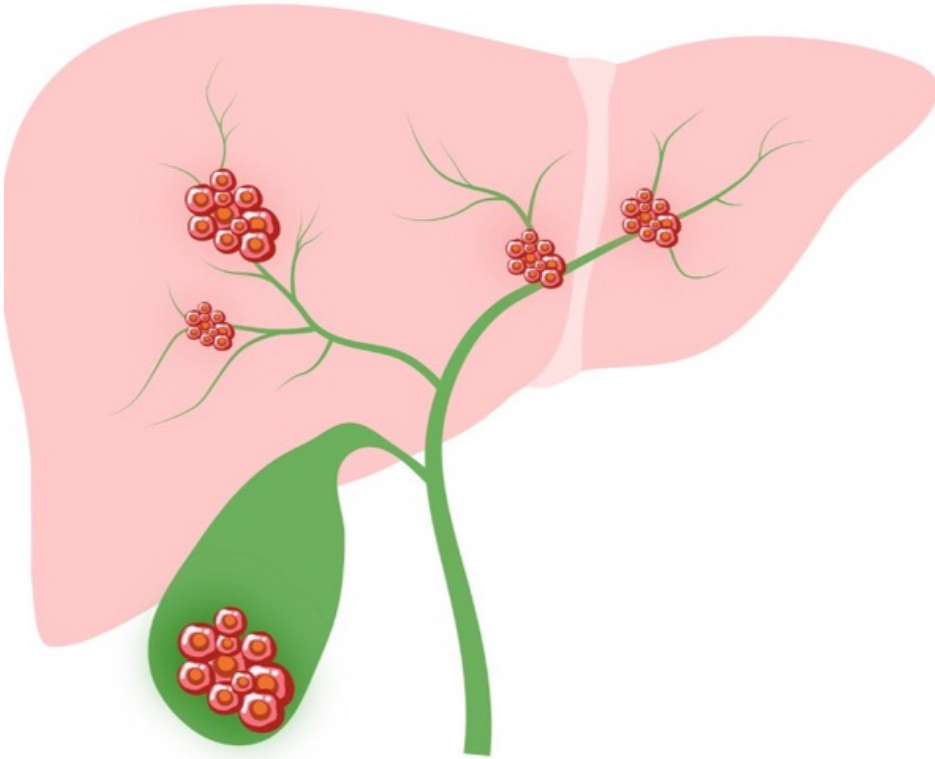
SCN1A contains a poison exon (called 20N) between protein-coding exons 20 and 21. When the poison exon is skipped, as is typically the case with advancing gestational age, the resulting transcript is translated to a full-length, functional $Na_V1.1$ protein (Panel A). Because the poison exon contains a stop codon, its inclusion (which occurs through alternative splicing) results in nonsense-mediated mRNA decay (NMD) and diminished levels of functional $Na_V1.1$. Dravet syndrome (Panel B) occurs when one allele of *SCN1A* has a pathogenic variant that leads to a nonfunctional or absent protein (allele 1); the full-length mRNA transcript produced from the wild-type allele (allele 2) is not sufficient to prevent disease. Zorevunersen (Panel C), an antisense oligonucleotide targeted to the poison exon, blocks the inclusion of 20N during alternative splicing, leading to an increase in the number of transcripts encoding full-length, functional $Na_V1.1$ protein from the wild-type allele (allele 2). Although zorevunersen also prevents inclusion of the poison exon in RNA transcribed from allele 1, the resulting transcript contains the pathogenic stop codon, so no functional protein is produced. The results reported by Laux et al.[1] support a reduction in the frequency of seizures among persons with Dravet syndrome who received zorevunersen.

Das **Cholangiokarzinom (CCA)**, auch als Gallengangskrebs bezeichnet, ist ein bösartiger Tumor, der von der Schleimhaut der Gallengänge ausgeht. Es handelt sich um eine seltene Erkrankung, die jedoch die zweithäufigste primäre Lebertumorart darstellt.

Einteilung

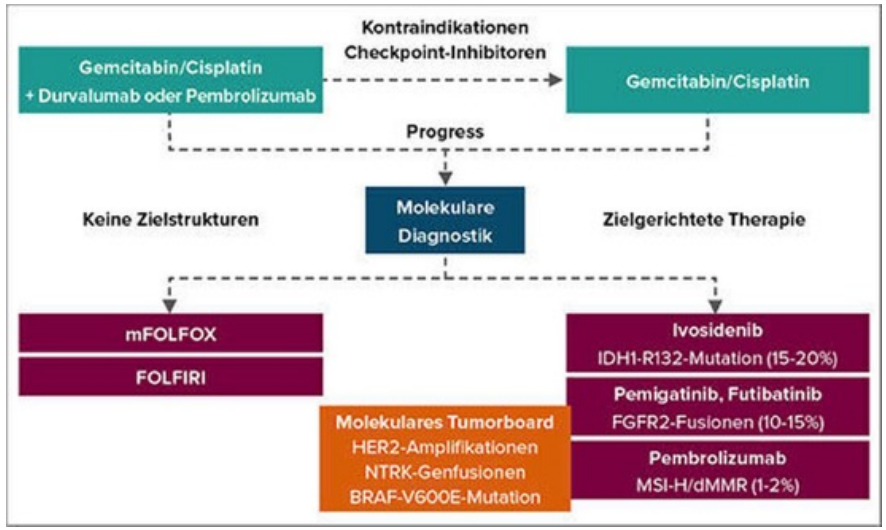
Je nach Lage des Tumors wird zwischen drei Haupttypen unterschieden:

- **Intrahepatisch:** Der Tumor liegt innerhalb der Leber in den kleinen Gallengängen.
- **Perihilär (Klatskin-Tumor):** Der Tumor befindet sich an der Gabelung, an der die rechten und linken Gallengänge aus der Leber austreten.
- **Extrahepatisch (distal):** Der Tumor liegt in den Gallengängen außerhalb der Leber in Richtung des Dünndarms.

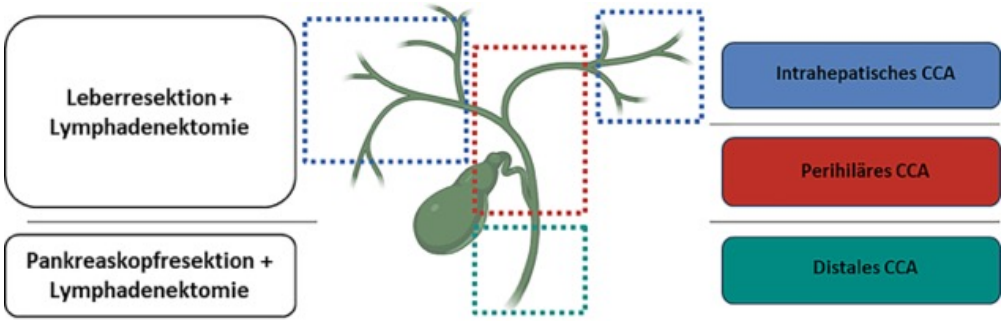


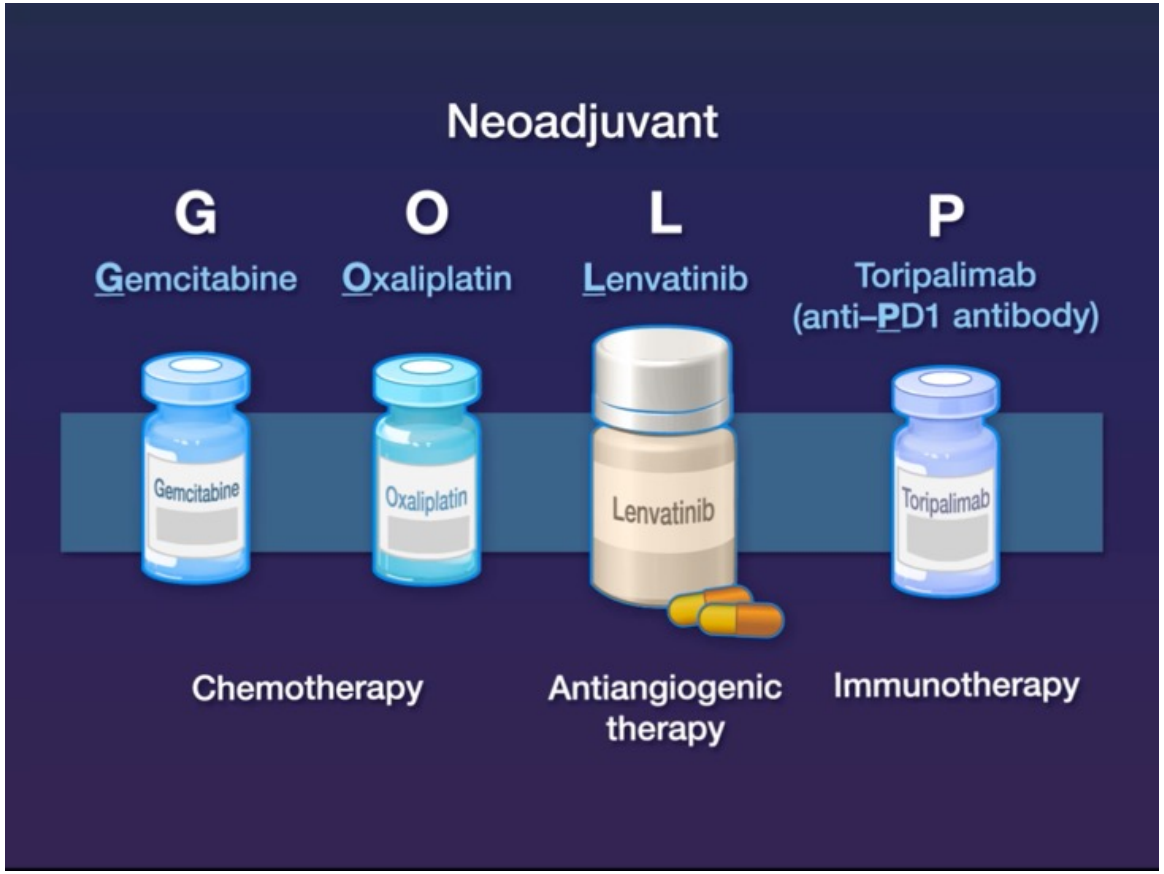
Therapie des Gallengangskarzinoms

Chemotherapie



Operationen

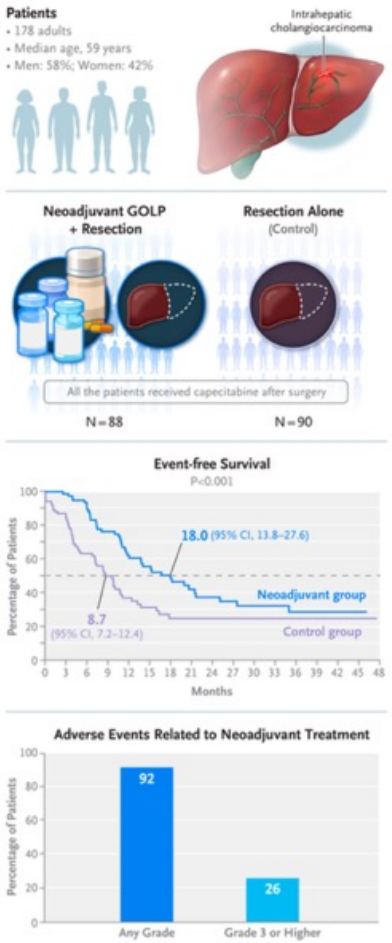




Die neoadjuvante Therapie ist eine Behandlungsform in der Onkologie, die vor einem geplanten operativen Eingriff (oder einer Strahlentherapie) erfolgt. Ziel ist es, den Tumor zu verkleinern, die Operabilität zu verbessern (Downstaging), Mikrometastasen zu behandeln und die Prognose zu optimieren.

Neoadjuvant GOLP in Resectable High-Risk Intrahepatic Cholangiocarcinoma

No neoadjuvant treatment has been considered to be standard therapy for patients with resectable intrahepatic cholangiocarcinoma with high-risk factors for recurrence. The GOLP regimen (gemcitabine–oxaliplatin, lenvatinib, and an anti–programmed death 1 antibody) has shown promising efficacy with a manageable safety profile in advanced intrahepatic cholangiocarcinoma and biliary tract cancer. In a phase 2–3 trial, we randomly assigned, in a 1:1 ratio, patients with resectable high-risk intrahepatic cholangiocarcinoma to the neoadjuvant group (intravenous gemcitabine–oxaliplatin plus toripalimab every 3 weeks for three cycles and oral lenvatinib once daily for 9 weeks, followed by curative resection) or the control group (curative resection and no neoadjuvant treatment). All patients received adjuvant capecitabine for eight cycles after surgery. The primary end point was event-free survival. Secondary end points included overall survival and safety.



Intrahepatic cholangiocarcinoma is the second most common primary hepatic cancer, and the prognosis is dismal. More than 50% of patients with intrahepatic cholangiocarcinoma have postoperative recurrence, and overall survival at 5 years is only 30% after curative resection. A particularly vulnerable subgroup is characterized by high-risk factors for postoperative recurrence, such as large tumor size, multifocal disease, vascular invasion, hepatic portal lymph-node metastasis, and an elevated serum CA 19-9 level, which are associated with very early recurrence and shortened overall survival. Although neoadjuvant therapy is considered to be a promising strategy for the treatment of high-risk intrahepatic cholangiocarcinoma, existing evidence has been limited to small observational cohorts and exploratory single-group trials such as NEO-GAP and NEO-ERA-01. Because evidence from randomized, controlled trials has been limited, no neoadjuvant regimens have been endorsed by current guidelines.
Given the encouraging findings of the GOLP regimen, we assessed its efficacy as a neoadjuvant strategy in the treatment of patients with high-risk intrahepatic cholangiocarcinoma. Here, we report the results of a prespecified interim analysis of a phase 2–3 randomized trial designed to investigate this neoadjuvant approach.

Eligible patients were between 18 and 70 years of age, with an Eastern Cooperative Oncology Group performance-status score of 0 (on a scale from 0 to 5, with higher scores indicating greater disability) and preserved liver function (defined as Child–Pugh class A according to a three-category evaluation, with class A indicating normal function, class B reduced function, and class C severe dysfunction). Patients had to have resectable intrahepatic cholangiocarcinoma with high-risk factors for recurrence, including at least one of the following: a tumor diameter greater than 5 cm, vascular invasion, multiple intrahepatic tumors, hepatic portal lymph-node metastasis, or an elevated CA 19-9 level. Detailed eligibility criteria regarding resectability, vascular invasion, and elevated CA 19-9 level are provided in the Supplementary Methods section. Full eligibility criteria are specified in the protocol.

Procedures

Eligible patients were randomly assigned in a 1:1 ratio to the neoadjuvant group or the control group. Randomization was centralized, with stratification according to tumor diameter (>5 cm vs. ≤5 cm), multiple tumors (yes vs. no), and hepatic portal lymph-node metastasis (yes vs. no).

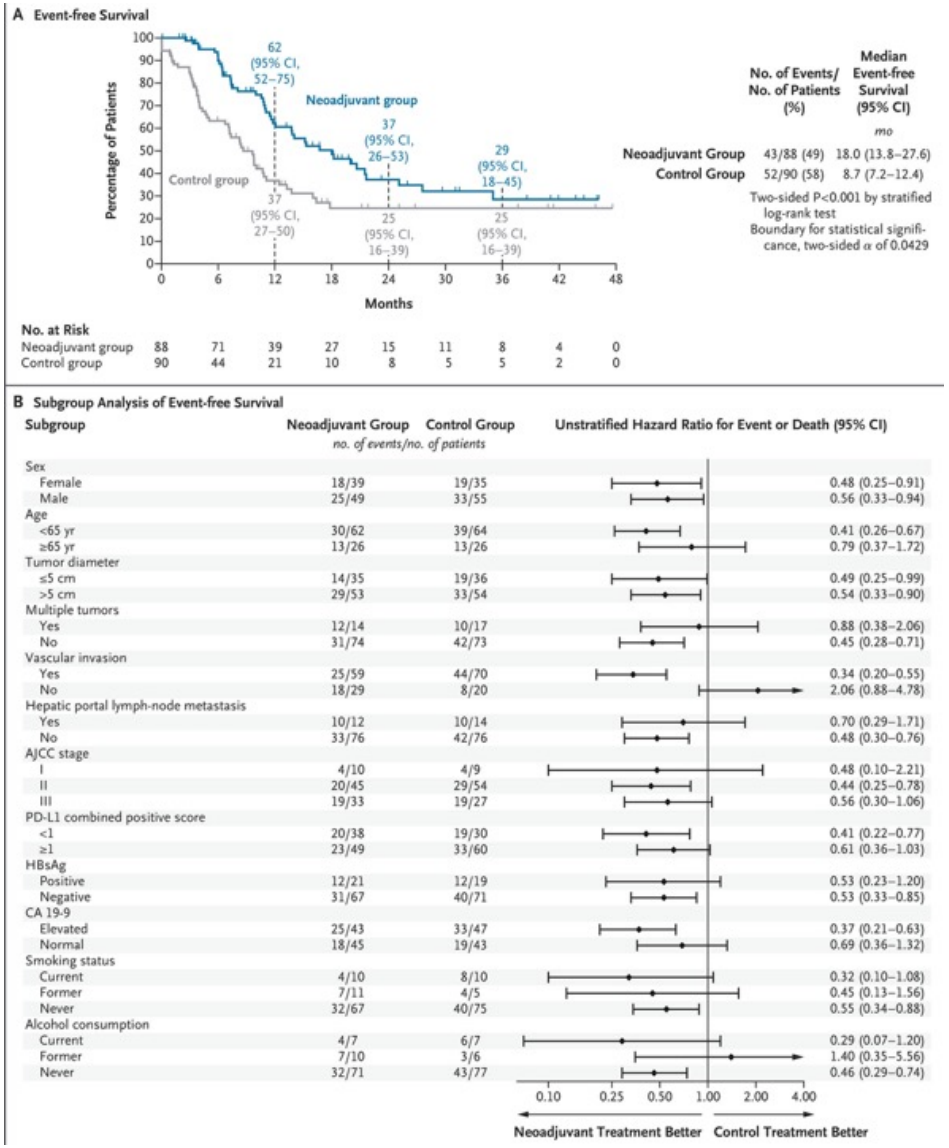
End Points and Assessments

The primary end point was event-free survival, defined as the time from randomization to the first occurrence of any of the following: any progression that precluded radical resection, postoperative recurrence or metastasis, development of a second primary cancer, or death from any cause.

Characteristic	Neoadjuvant Group (N=88)	Control Group (N=90)	Total (N=178)
Age			
Median (IQR) — yr	59 (52.5–65)	60 (55–65)	59 (54–65)
≥65 yr — no. (%)	26 (30)	26 (29)	52 (29)
Male sex — no. (%)	49 (56)	55 (61)	104 (58)
ECOG performance-status score of 0 — no. (%)†	88 (100)	90 (100)	178 (100)
Smoking history — no. (%)			
Current	10 (11)	10 (11)	20 (11)
Former	11 (12)	5 (6)	16 (9)
Never	67 (76)	75 (83)	142 (80)
Alcohol consumption — no. (%)			
Current	7 (8)	7 (8)	14 (8)
Former	10 (11)	6 (7)	16 (9)
Never	71 (81)	77 (86)	148 (83)
Child–Pugh class A — no. (%)‡	88 (100)	90 (100)	178 (100)
Tumor characteristics — no. (%)			
Diameter >5 cm	53 (60)	54 (60)	107 (60)
Multiple tumors	14 (16)	17 (19)	31 (17)
Vascular invasion	59 (67)	70 (78)	129 (72)
Hepatic portal lymph-node metastasis	12 (14)	14 (16)	26 (15)
AJCC stage — no. (%)§			
IA	1 (1)	1 (1)	2 (1)
IB	9 (10)	8 (9)	17 (10)
II	45 (51)	54 (60)	99 (56)
IIIA	21 (24)	12 (13)	33 (19)
IIIB	12 (14)	15 (17)	27 (15)
Median serum CA 19-9 level (IQR) — U/ml	33.1 (16.4–271.8)	40.5 (11.4–387.5)	37.9 (11.9–315.0)
Elevated serum CA 19-9 level — no. (%)¶	43 (49)	47 (52)	90 (51)
PD-L1 combined positive score — no. (%)‖			
<1	38 (43)	30 (33)	68 (38)
≥1	49 (56)	60 (67)	109 (61)
Missing data	1 (1)	0	1 (1)
HBsAg-positive — no. (%)	21 (24)	19 (21)	40 (22)
HCV antibody–positive — no. (%)	4 (5)	1 (1)	5 (3)
Histologic type — no. (%)			
Intrahepatic cholangiocarcinoma	87 (99)	86 (96)	173 (97)
Other**	1 (1)	4 (4)	5 (3)

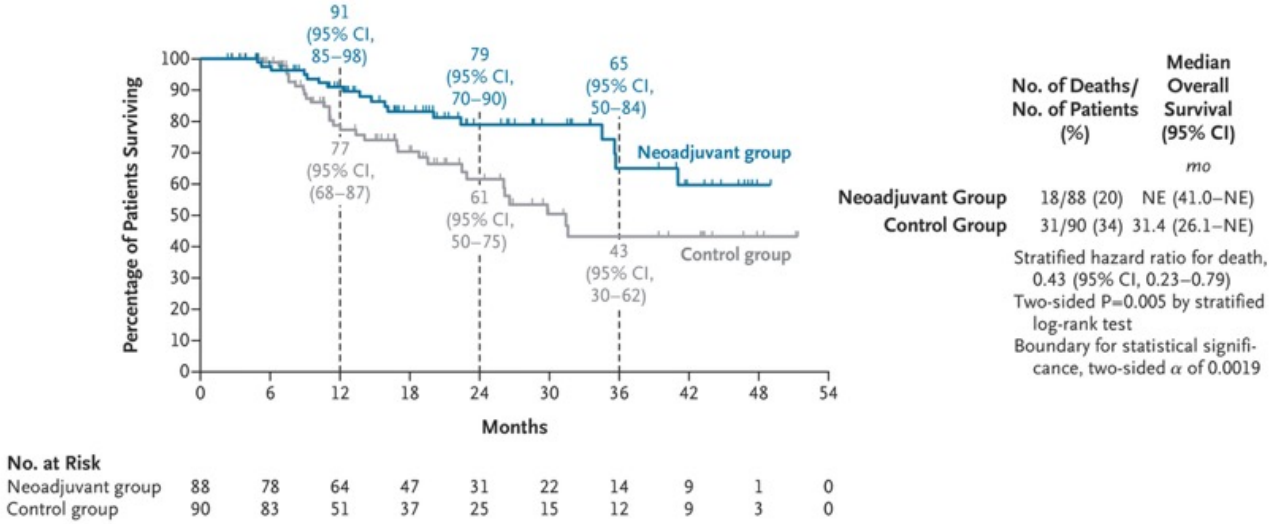
Adverse Events

Event	Neoadjuvant Group		Control Group	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Overall				
No. of patients	87	87	89	89
Any adverse event — no. (%)	84 (97)	35 (40)	62 (70)	7 (8)
Any treatment-related adverse event — no. (%)	83 (95)	30 (34)	52 (58)	4 (4)
Neoadjuvant phase†				
No. of patients	87	87	—	—
Any adverse event — no. (%)	80 (92)	24 (28)	—	—
Any treatment-related adverse event — no. (%)	80 (92)	23 (26)	—	—
Neutrophil count decreased	58 (67)	15 (17)		
White-cell count decreased	56 (64)	6 (7)		
Aspartate aminotransferase increased	53 (61)	0		
Alanine aminotransferase increased	47 (54)	0		
Platelet count decreased	37 (43)	3 (3)		
Vomiting	16 (18)	0		
Fatigue	16 (18)	0		
Hypertension	16 (18)	2 (2)		
Nausea	12 (14)	0		
Decreased appetite	10 (11)	0		
Blood bilirubin increased	10 (11)	0		
Rash	9 (10)	0		
Hypothyroidism	8 (9)	0		
Hyperthyroidism	7 (8)	0		
Pyrexia	7 (8)	0		
Constipation	5 (6)	0		
Adjuvant phase‡				
No. of patients	75	75	72	72
Any adverse event — no. (%)	63 (84)	11 (15)	55 (76)	6 (8)
Any treatment-related adverse event — no. (%)	59 (79)	8 (11)	52 (72)	4 (6)
Blood bilirubin increased	35 (47)	2 (3)	29 (40)	1 (1)
Neutrophil count decreased	21 (28)	4 (5)	17 (24)	1 (1)
Platelet count decreased	19 (25)	0	12 (17)	1 (1)
White-cell count decreased	11 (15)	0	6 (8)	0
Aspartate aminotransferase increased	10 (13)	0	8 (11)	0
Alanine aminotransferase increased	7 (9)	0	12 (17)	0
Drug eruption	5 (7)	0	6 (8)	0
Pigmentation disorder	5 (7)	1 (1)	3 (4)	0
Palmar–plantar erythrodysesthesia syndrome	4 (5)	0	9 (12)	0
Pain in arm or leg	3 (4)	0	4 (6)	1 (1)
Anemia	1 (1)	0	4 (6)	0



Interim Analysis of Event-free Survival (Intention-to-Treat Population).

Shown are the results in the intention-to-treat population, which included all 178 patients who had undergone randomization as of the data-cutoff date (April 30, 2025). Panel A shows Kaplan–Meier estimates of event-free survival, defined as the time from randomization to the first occurrence of disease progression that precluded curative resection, postoperative recurrence or metastasis, development of a second primary tumor, or death from any cause, whichever occurred first. Because the proportional-hazards assumption was violated for the primary analysis of event-free survival, the hazard ratio was not reported, in order to avoid potential misinterpretation. Tick marks indicate censored data. Panel B shows the hazard ratios for event or death in prespecified subgroups in the intention-to-treat population. The randomization stratification factors were not applied to the subgroup analysis, so unstratified data are reported. The programmed death ligand 1 (PD-L1) combined positive score was defined as the number of PD-L1–positive cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells and multiplied by 100. The widths of the confidence intervals for subgroups have not been adjusted for multiplicity and should not be used in place of hypothesis testing. Arrows indicate that the confidence interval extends outside the graphed area. AJCC denotes American Joint Committee on Cancer, and HBsAg hepatitis B virus surface antigen.



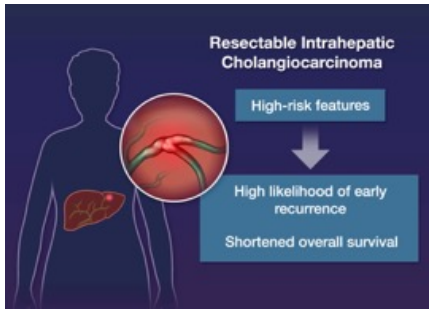
	No. of Deaths/ No. of Patients (%)	Median Overall Survival (95% CI)
		mo
Neoadjuvant Group	18/88 (20)	NE (41.0–NE)
Control Group	31/90 (34)	31.4 (26.1–NE)

Stratified hazard ratio for death, 0.43 (95% CI, 0.23–0.79)
Two-sided P=0.005 by stratified log-rank test
Boundary for statistical significance, two-sided α of 0.0019

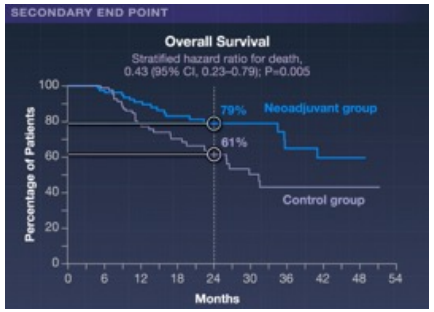
Interim Analysis of Overall Survival (Intention-to-Treat Population).

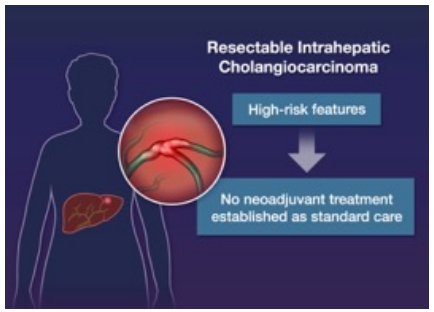
Shown are the results in the intention-to-treat population, which included all 178 patients who had undergone randomization as of the data-cutoff date (April 30, 2025). Shown are Kaplan–Meier estimates of overall survival, defined as the time from randomization to death from any cause. The hazard ratio and confidence intervals were estimated by a stratified Cox proportional-hazards model with the use of the stratification factors at randomization and with the treatment group as a covariate. Tick marks indicate censored data. NE denotes could not be estimated.

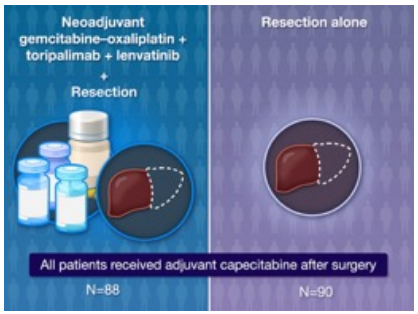
The most frequent such events were a decreased neutrophil count (in 17% of the patients) and a decreased white-cell count (in 7%). Across all treatment phases, immune-related adverse events occurred in 36% of the patients in the neoadjuvant group, with the most common events including rash (in 10% of the patients), hypothyroidism (in 10%), and hyperthyroidism (in 8%).

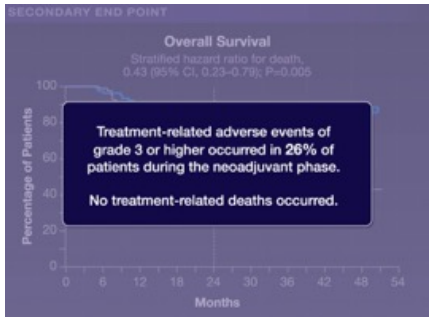

Resectable Intrahepatic Cholangiocarcinoma
High-risk features
High likelihood of early recurrence
Shortened overall survival

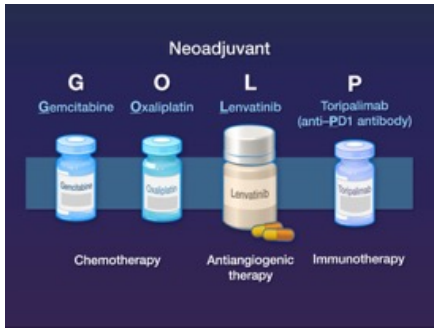

ZSAB-neoGOLP Trial
• Phase 2–3
• Randomized
• Open-label
178 Patients with resectable high-risk intrahepatic cholangiocarcinoma


SECONDARY END POINT
Overall Survival
Stratified hazard ratio for death, 0.43 (95% CI, 0.23–0.79); P=0.005
79%
Neoadjuvant group
61%
Control group
Percentage of Patients
Months


Resectable Intrahepatic Cholangiocarcinoma
High-risk features
No neoadjuvant treatment established as standard care


Neoadjuvant gemcitabine–oxaliplatin + toripalimab + lenvatinib
+
Resection
Resection alone
All patients received adjuvant capecitabine after surgery
N=88
N=90


SECONDARY END POINT
Overall Survival
Stratified hazard ratio for death, 0.43 (95% CI, 0.23–0.79); P=0.005
Treatment-related adverse events of grade 3 or higher occurred in 26% of patients during the neoadjuvant phase.
No treatment-related deaths occurred.
Percentage of Patients
Months


Neoadjuvant
G
Gemcitabine
O
Oxaliplatin
L
Lenvatinib
P
Toripalimab (anti–PD1 antibody)
Chemotherapy
Antiangiogenic therapy
Immunotherapy


PRIMARY END POINT
Event-free Survival
P<0.001
18.0 mo
8.7 mo
Neoadjuvant group
Control group
Percentage of Patients
Months


Neoadjuvant GOLP
Significantly longer event-free survival

Effects of Radiotherapy in Normal Tissue

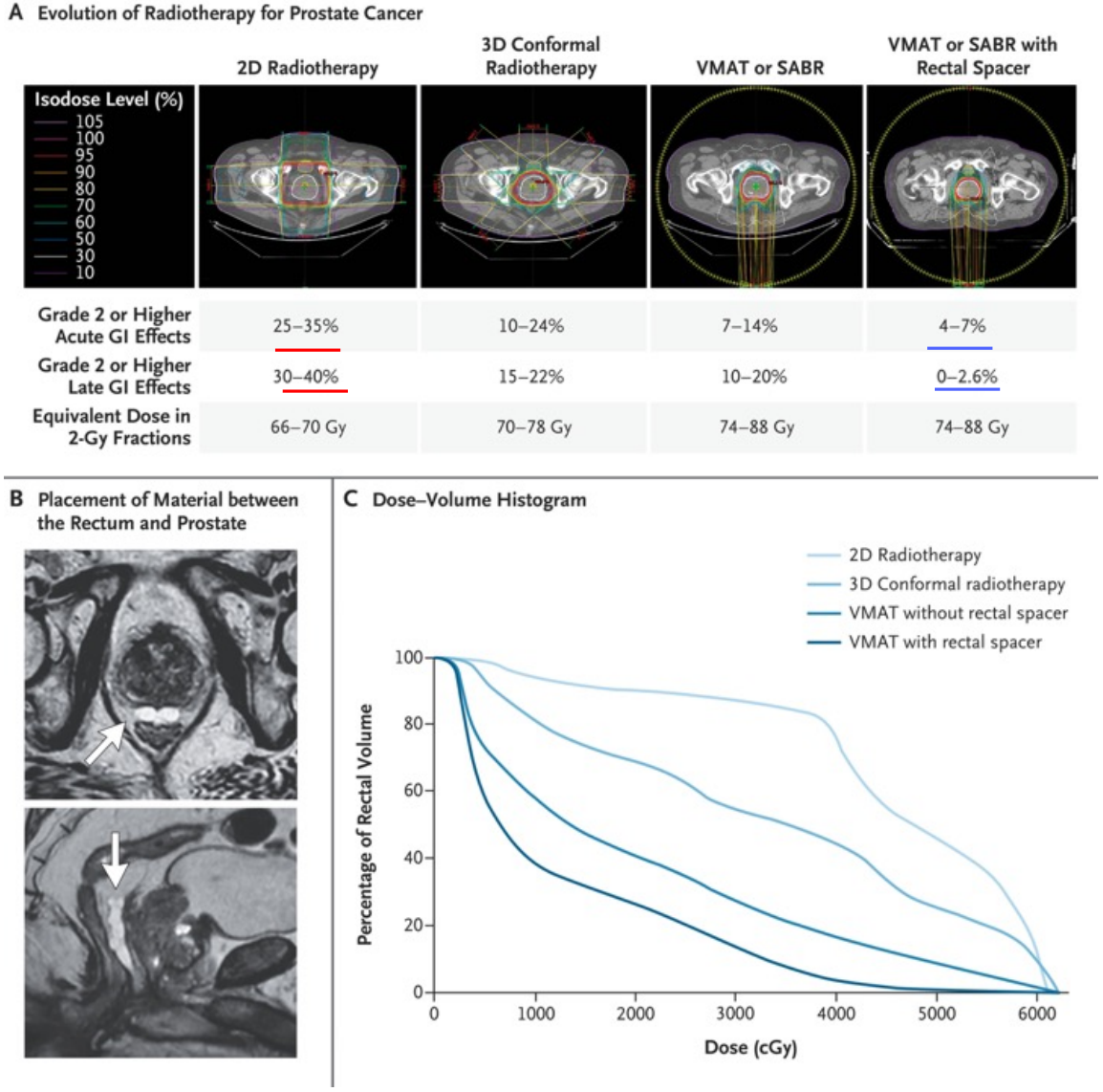
Summary

Radiotherapy is a key foundation of oncologic treatment that is used across the spectrum of cancer indications. Advances in imaging, treatment planning, and dose delivery have led to increasingly conformal and even ablative treatments, which have resulted in improved tumor control with no increase in the risk of side effects (or with a decrease in risk) as compared with previous treatments. These advances have facilitated the combined use of radiotherapy with efficacious systemic therapies, including targeted treatments and immunotherapies. Radiation-induced changes in normal tissue occur as a result of stem-cell senescence, inflammation, vascular changes, fibroblast activation, and loss of parenchymal cells. Research into the biologic underpinnings of radiation-induced changes in normal tissue, biomarkers of side effects of various irradiation regimens, and new treatment methods offers great promise for further increasing the efficacy of radiotherapy and improving the side-effect profile through personalized approaches.

KEY POINTS

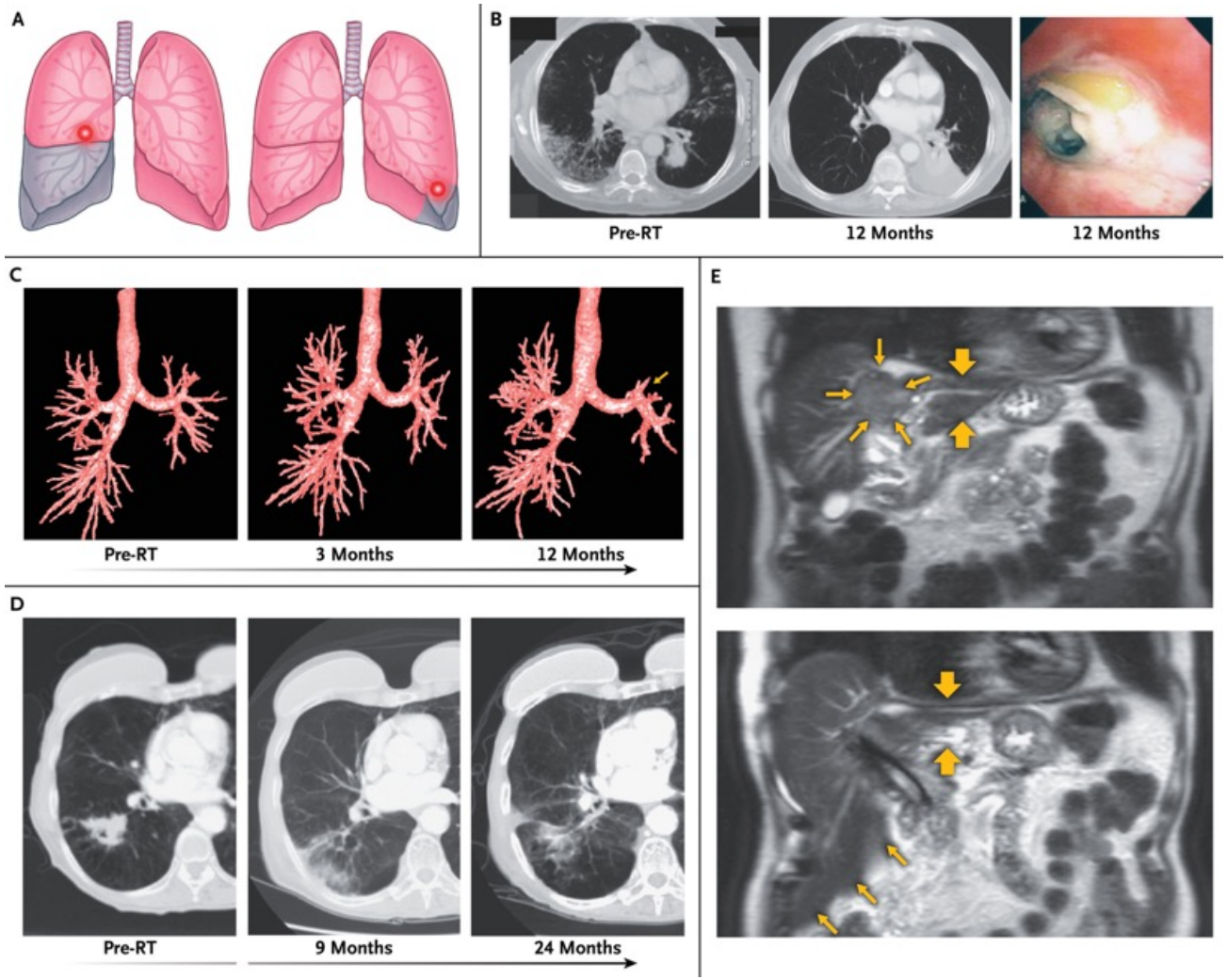
Effects of Radiotherapy in Normal Tissue

- Radiotherapy is a key component of oncologic care for a variety of cancers.
- Innovations in imaging and in delivery of radiation have improved the accuracy and precision of radiation treatments, which has led to marked reductions in the incidence and severity of effects in normal tissues.
- The expected side effects from radiation treatments depend on the dose delivered, the volume of tissue treated, concurrent treatments (e.g., surgery and systemic therapy), and coexisting conditions.
- Our understanding of biologic processes in normal tissue after radiation exposure has deepened in recent years, and several candidate agents have been developed for the prevention, mitigation, and treatment of side effects of irradiation.
- Management of radiation toxicity benefits from multidisciplinary collaboration.

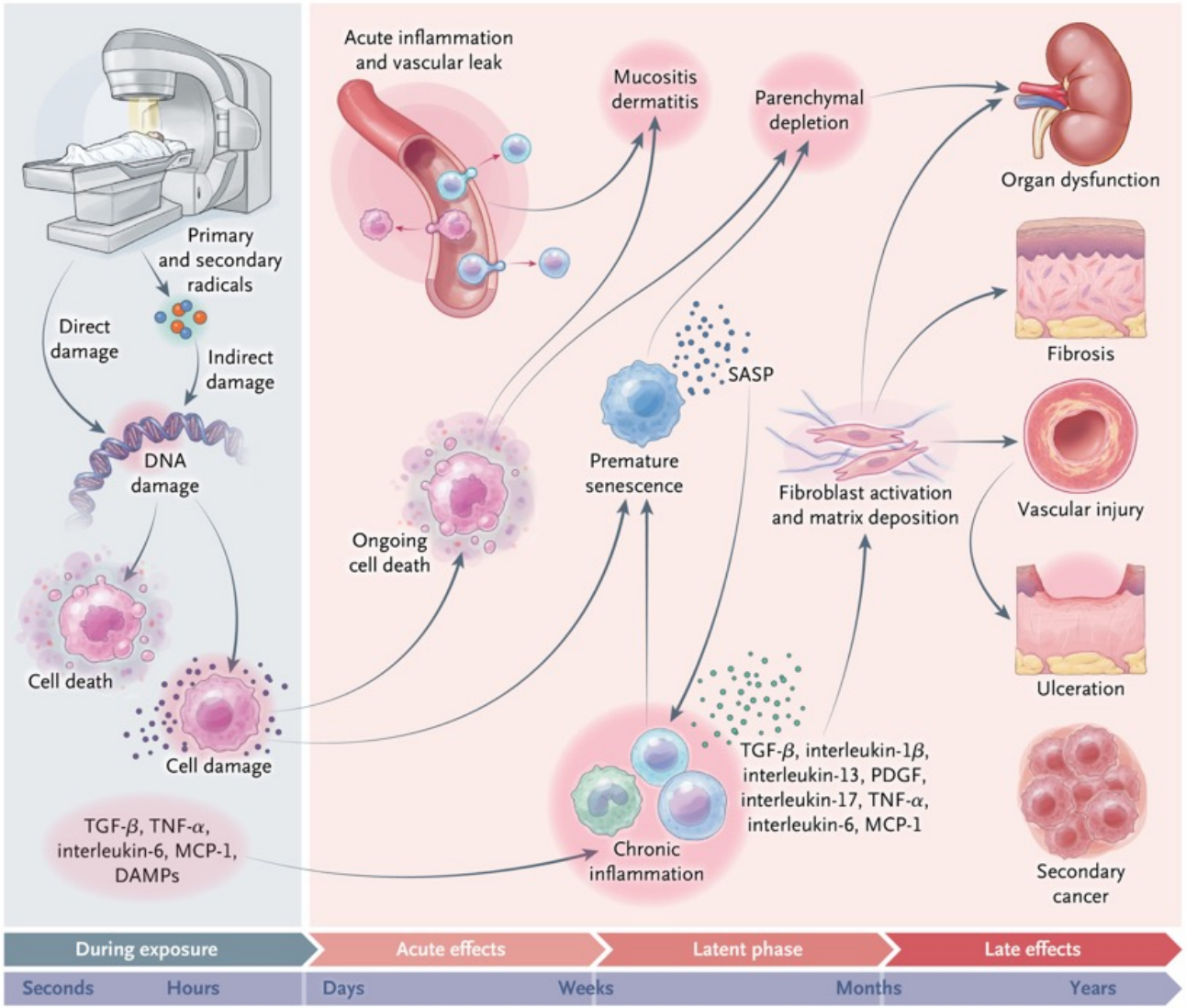


Evolution of Radiotherapy for Prostate Cancer and Gastrointestinal Effects.

Panel A shows the evolution of radiotherapy for prostate cancer from two-dimensional (2D) radiotherapy to three-dimensional (3D) conformal radiotherapy to intensity-modulated radiotherapy with the use of volumetric-modulated arc therapy (VMAT) or stereotactic ablative radiotherapy (SABR). Representative axial images for treatment planning are shown (the thick white lines indicate the prostate). Both intensity-modulated radiotherapy and SABR are commonly used treatments in contemporary radiation oncology. The expected incidence of grade 2 or higher acute or late adverse effects involving the gastrointestinal (GI) system — typically, proctitis or rectal bleeding — is based on data from multi-institutional and cooperative-group trials.[11-17] Grade 3 rectal adverse effects are rare (incidence, <1%) with contemporary prostate radiation treatments. Placement of material that creates space between the rectum and prostate has further facilitated a reduction in the radiation dose to the rectum when the prostate and seminal vesicles are the intended radiation target. Representative axial and sagittal images from magnetic resonance imaging after spacer placement are shown in Panel B (arrows indicate spacers). The dose–volume histogram in Panel C shows the percentage of the rectum exposed to each dose for the four treatment plans in Panel A, assuming that the intended dose to the target area is equal in the four plans.

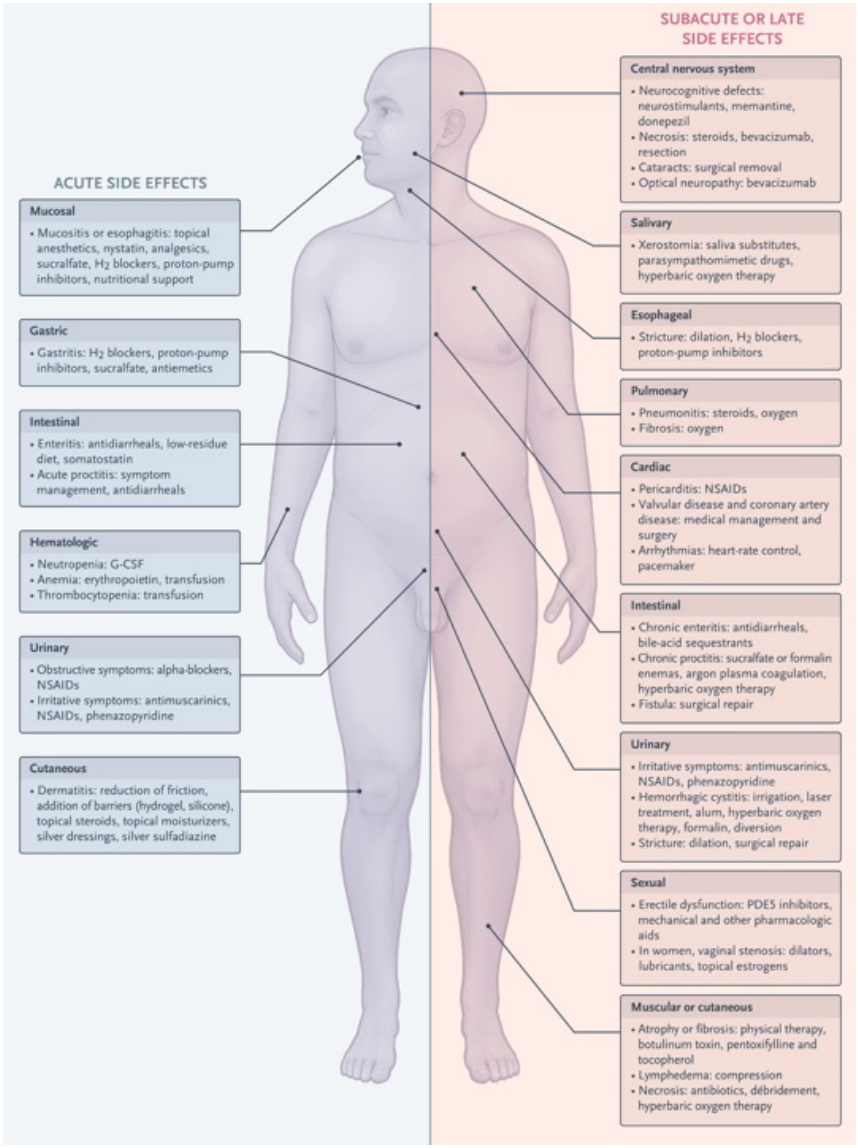


As shown in Panel A, the lung is composed of branching airways and alveoli. The airways are arranged in series (left-hand image), such that when an ablative dose is delivered to a portion of the airway (red and white sphere), the airway is obstructed and distal airways and alveoli collapse (gray area). When more-peripheral portions of the lung are targeted (right-hand image), only the terminal airways and associated alveoli, which are arranged in parallel, are damaged (gray area). In Panel B, a pretreatment computed tomographic (CT) image shows a central non–small-cell lung cancer posterior to the left hilum (left-hand image; identifying information is masked), with an unrelated right-lower-lobe infiltrate. A CT image obtained 12 months after delivery of 50 Gy in 5 fractions shows complete collapse of the superior segment of the left lower lobe, with a focal pleural effusion (middle image). A bronchoscopic view of the superior-segment airway shows intense mucositis with obstructive debris (right-hand image). Panel C shows virtual bronchoscopic reconstruction in a patient with locally advanced non–small-cell lung cancer that was treated with 60 Gy in 30 fractions. A post-treatment decline in pulmonary function was attributed to radiation. Pretreatment virtual bronchoscopic reconstruction of airways showed a baseline paucity of viable airways on the left side. Imaging at 3 months after radiotherapy showed mild worsening of airway patency in the left lung, which was followed by substantial worsening at 12 months (arrow). Panel D shows serial CT images from a patient with stage IB non–small-cell lung cancer treated with 54 Gy of radiation delivered to the superior segment of the right upper lobe in 3 fractions. Pretreatment imaging showed a large, lobulated lung tumor. Images obtained 9 and 24 months after radiotherapy showed a complete response of the treated tumor, with wedgelike atelectasis. Panel E shows tissue repair after radiation injury. The coronal view (top) shows a large colorectal liver metastasis (thin yellow arrows), with an intact left lobe (wide yellow arrows). The metastasis was treated with 60 Gy delivered in 5 fractions. An image obtained after treatment (bottom) shows a complete response of the treated tumor, with radiation-related amputation of the entire left lobe of the liver, which resulted from injury of the serially functioning ducts and blood vessels (wide yellow arrows). Hypertrophy of the remaining right lobe of the liver (hyperplasia) is evident (thin yellow arrows). Collectively, these findings represent an injury-and-repair response to the ablative radiotherapy used to eliminate the central tumor. Pre-RT denotes preradiotherapy.



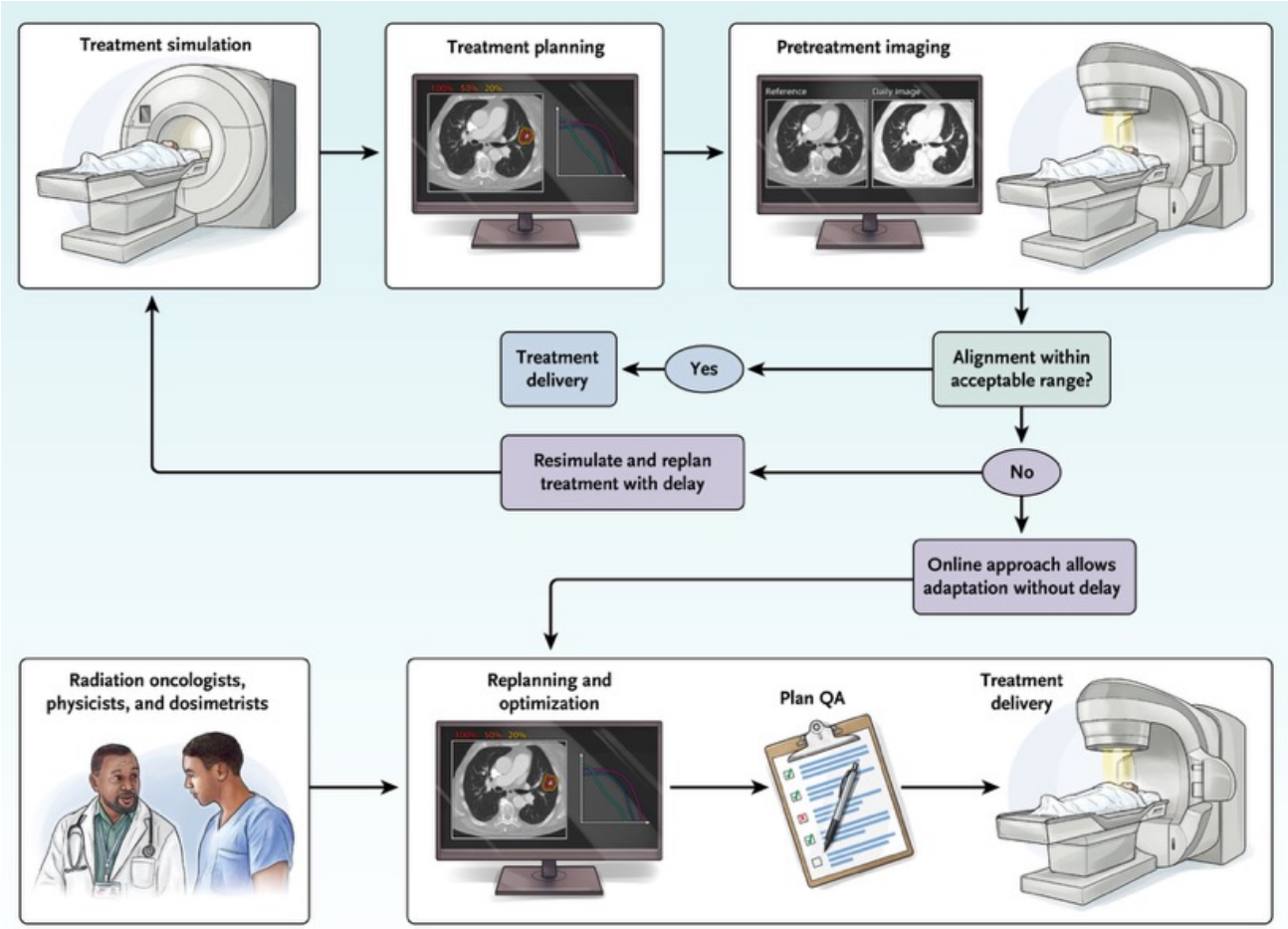
Radiobiologic Processes in Normal Tissue.

Immediately after the exposure of tissue to radiation, numerous events are initiated, including direct damage of cellular components and indirect damage through primary and secondary radicals. Cell death and cell injury initiate the release of numerous cytokines, chemokines, and immunomodulatory molecules, a process that causes acute inflammation and effects in normal tissue. Cells that are damaged by radiation may repair the damage, die, or undergo premature senescence and contribute to chronic inflammation through elaboration of the senescence-associated secretory phenotype (SASP). Collectively, these processes lead to loss of organ function, fibrosis, and other late effects of radiation. DAMPs denotes damage-associated molecular patterns, MCP-1 monocyte chemoattractant protein 1, PDGF platelet-derived growth factor, TGF-β transforming growth factor β, and TNF-α tumor necrosis factor α.



Representative Acute, Subacute, and Late Effects of Radiotherapy and Their Management.

Treatment options are based on published guidelines, clinical practice, and published summaries.[46-48] Alum denotes potassium aluminum sulfate, G-CSF granulocyte colony-stimulating factor, H_2 blocker histamine H_2–receptor antagonist, NSAIDs nonsteroidal antiinflammatory drugs, and PDE5 phosphodiesterase type 5.



Online and Offline Approaches to Adaptive Radiotherapy.

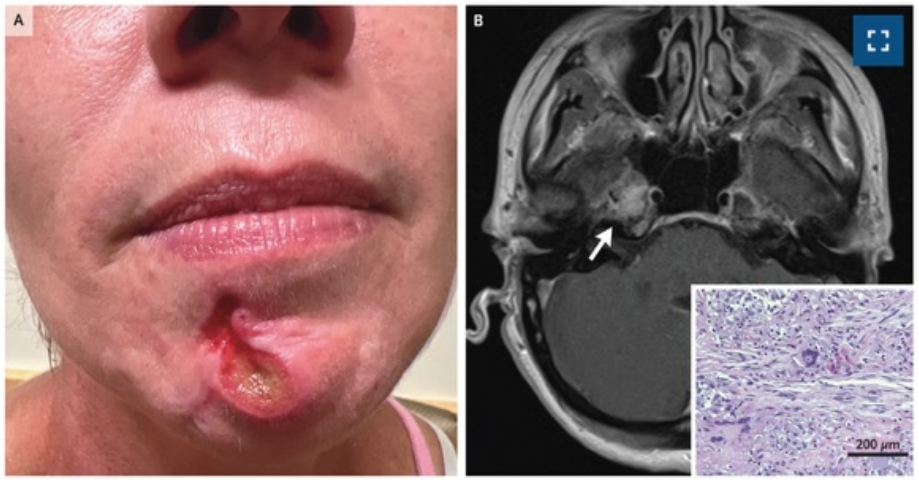
In both online and offline approaches, the patient undergoes a simulation and treatment planning. On the day of treatment delivery, a pretreatment image is obtained and compared with a reference (planning) image. If the alignment is within an acceptable range, the treatment is delivered. If the alignment is outside the acceptable range or if marked anatomical changes are noted, the treatment must be replanned. With online adaptive approaches, replanning and quality assurance (QA) occur while the patient remains on the treatment table, and the new treatment is delivered without delay. Online adaptive approaches are resource-intensive and require real-time availability of radiation oncologists, physicists, and dosimetrists. Offline approaches allow for the care team to prepare a new plan without real-time availability, but a delay or break in the treatment may occur.

Conclusions

The field of radiotherapy continues to incorporate new technology and personalized approaches to improve oncologic outcomes while reducing the risk of side effects. With modern innovations that reduce the exposure of uninvolved tissues to radiation, the advent of treatment approaches that prioritize highly conformal ablative dosing only to grossly visible disease, and the availability of treatments for side effects of irradiation, radiation oncologists and collaborating physicians have begun to revisit what is defined as an “acceptable risk” of side effects from radiation, with the emerging concept that allowing otherwise preventable injury or repairable injury to occur may permit more effective treatment and a more favorable overall side-effect profile. Yet radiation oncologists continue to prioritize avoidance of side effects altogether, a strategy that allows radiotherapy to retain its reputation as an effective and safe treatment for a broad scope of malignant conditions.

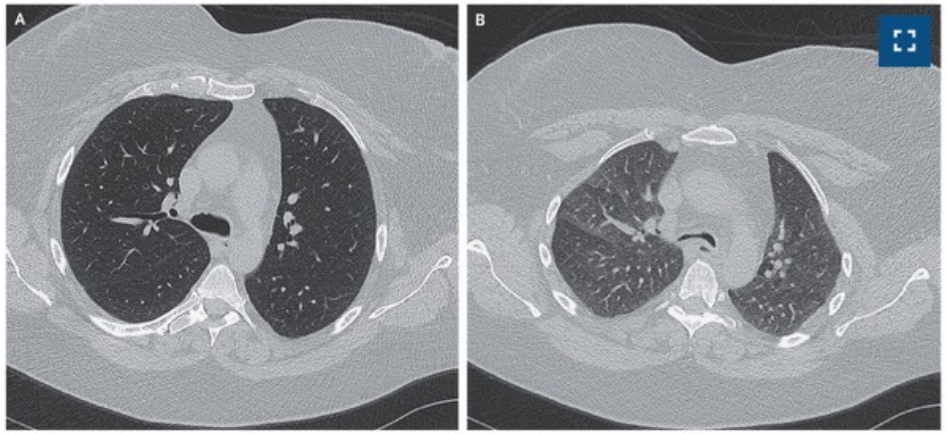
conformal ablative dosing = angepasste zerstörende Hochpräzisebestrahlung

Trigeminal Trophic Syndrome



A 47-year-old woman presented to the dermatology clinic with a 1-year history of a crawling sensation on her chin that caused her to scratch the area. Physical examination was notable for an irregular ulcer on the right side of her chin (Panel A). The right corneal reflex was decreased, and pinprick and temperature sensation around the mouth, lip, and chin on the right side was reduced. A punch biopsy of the skin ulcer was consistent with chronic trauma. With occlusive dressings, the ulcer healed, but it later recurred after being left uncovered. Subsequent magnetic resonance imaging of the head showed an enhancing lesion of the trigeminal nerve that partially filled Meckel's cave (Panel B, arrow; T1-weighted image). A diagnosis of trigeminal trophic syndrome was made. Trigeminal trophic syndrome is a rare complication of trigeminal nerve injury that results in dysesthesia and self-induced skin ulceration in the associated trigeminal dermatome. Possible causes include iatrogenic nerve injury, stroke, or a brain mass. In this case, neurosarcoidosis was found to be the cause on the basis of histopathological examination of the resected brain lesion, which showed noncaseating granulomas (Panel B, inset; hematoxylin and eosin stain). Four months after surgery, the patient's dysesthesia had abated, and the ulceration had healed with some scarring.

Expiratory Central Airway Collapse



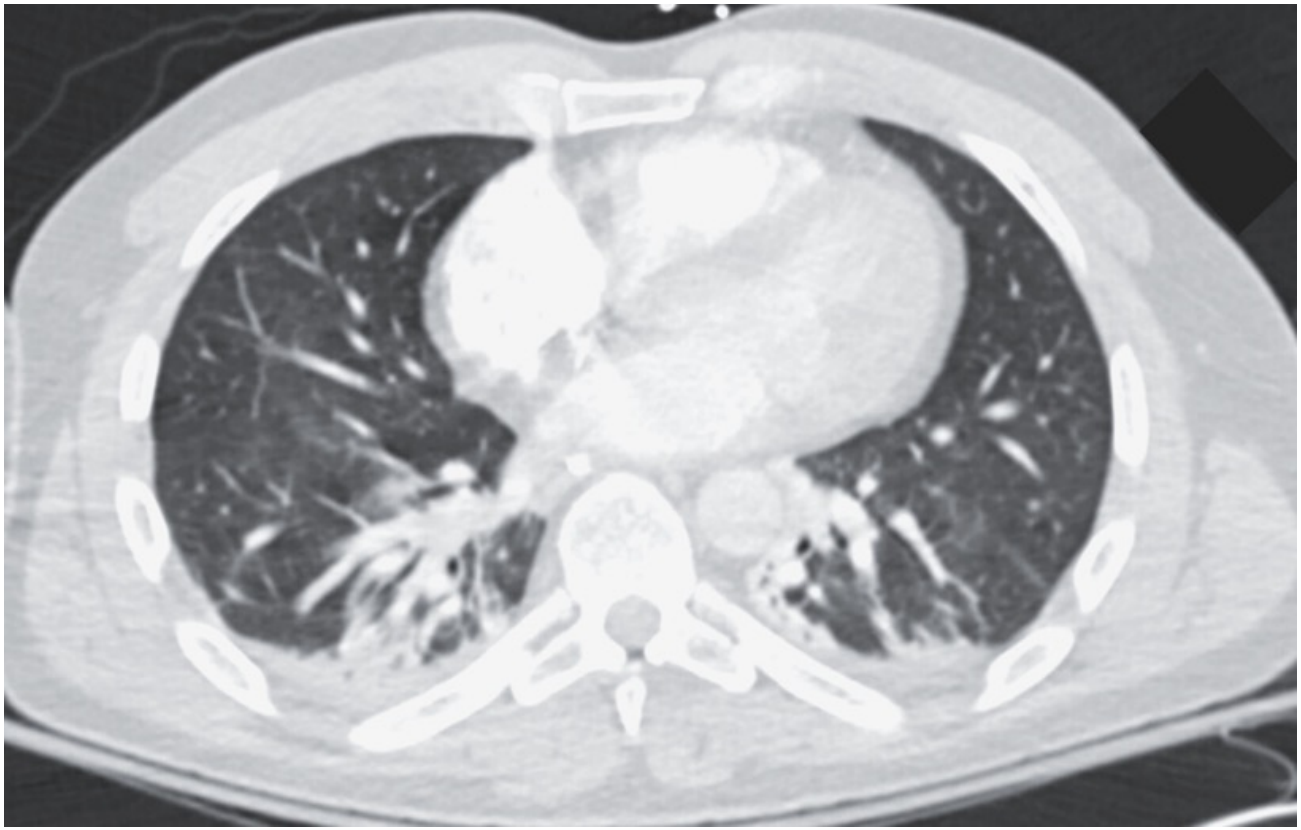
A 50-year-old woman with asthma, obstructive sleep apnea, and obesity presented to the pulmonary clinic with a 1-month history of worsening shortness of breath and dry cough despite maximal treatment for asthma. On physical examination, expiratory stridor and reduced breath sounds throughout the chest were noted. Dynamic computed tomography of the chest — a study of the airway during different phases of respiration — showed anterior bowing of the posterior wall of the intrathoracic trachea and mainstem bronchi on expiration, with more than 70% collapse as compared with inspiration (Panel A, inspiration; Panel B, expiration). A diagnosis of expiratory central airway collapse — a condition characterized by pathologic collapse of the central airways during expiration, resulting in dynamic outflow obstruction — was made. Expiratory central airway collapse is associated with common conditions such as asthma, obesity, and chronic obstructive pulmonary disease. Thus, it is important to consider this diagnosis in patients with persistent respiratory symptoms despite treatment of known coexisting illnesses. After a 1-week hospital stay for pulmonary clearance and initiation of nocturnal continuous positive airway pressure, the patient's symptoms abated. She was referred to a multidisciplinary program for complex airway management. She underwent robotic-assisted mesh tracheobronchoplasty, after which her condition improved substantially.

The Eyes Have It

A 47-year-old man was transported to the emergency department (ED) by emergency medical services (EMS) after being found dyspneic in his car. He reported a history of drinking 4 to 6 alcoholic beverages per day and stated that he had been drinking alcohol for 6 hours before presentation. During the previous 2 hours, he had had a sensation of tongue swelling, along with difficulty breathing. He reported no headache, sore throat, odynophagia, nausea, vomiting, rash, itching, or swelling of the face or limbs. He stated that he had a penicillin allergy. He reported no recent use of medications, consumption of new foods, or insect bites. He had had multiple ED visits for alcohol intoxication over the course of the previous 2 years (with the most recent visit occurring 10 days before presentation); he also had a history of chronic thrombocytopenia and of episodes of delirium tremens. He reported that he was taking no medications on a long-term basis. Other social history was limited owing to his acute condition, but previous documentation from a social worker indicated that he was unemployed and living with his mother locally in the southeastern United States.

On arrival at the ED, the patient had a blood pressure of 139/102 mm Hg, a pulse of 104 beats per minute, a respiratory rate of 22 breaths per minute, and an oxygen saturation of 91% while he was breathing ambient air. He was afebrile but diaphoretic, and he was awake and alert although intermittently inattentive. He had slurred, muffled speech but could speak full sentences without stridor or cough. No facial edema or tongue swelling was present. The lungs were clear on auscultation, and the abdomen was soft and nontender. En route to the ED, he had received treatment with epinephrine, diphenhydramine, and glucocorticoids, but his symptoms did not abate.

On arrival at the ED, the patient had vital-sign measurements that were similar to those recorded on EMS assessment. The oral temperature was 37.3°C. The neck was supple, without palpable abnormalities. His extraocular movements were abnormal; he could not direct either eye in any direction. No other neurologic deficits were reported. The white-cell count was 3800 per cubic millimeter, with 86% neutrophils, 5.5% lymphocytes, 6.7% monocytes, and no eosinophils. The hemoglobin level was 15.8 g per deciliter, and the platelet count was 58,000 per cubic millimeter. The results of a basic metabolic panel were normal. The total bilirubin level was 1.6 mg per deciliter (27 µmol per liter; normal value, <1.2 mg per deciliter [<21 µmol per liter]), the aspartate aminotransferase level 297 IU per liter (normal value, <34), the alanine aminotransferase level 168 IU per liter (normal value, <49), the alkaline phosphatase level 61 IU per liter (normal value, <116), and the international normalized ratio 0.93. The blood ethanol level was 209 mg per deciliter (normal value, <10). Urine toxicology tests were negative for amphetamines, cocaine, barbiturates, benzodiazepines, cannabinoids, and narcotics. The serum lactate level was 1.5 mmol per liter (14 mg per deciliter; normal value, <1.8 mmol per liter [<16 mg per deciliter]).



CT Angiogram of the Chest.

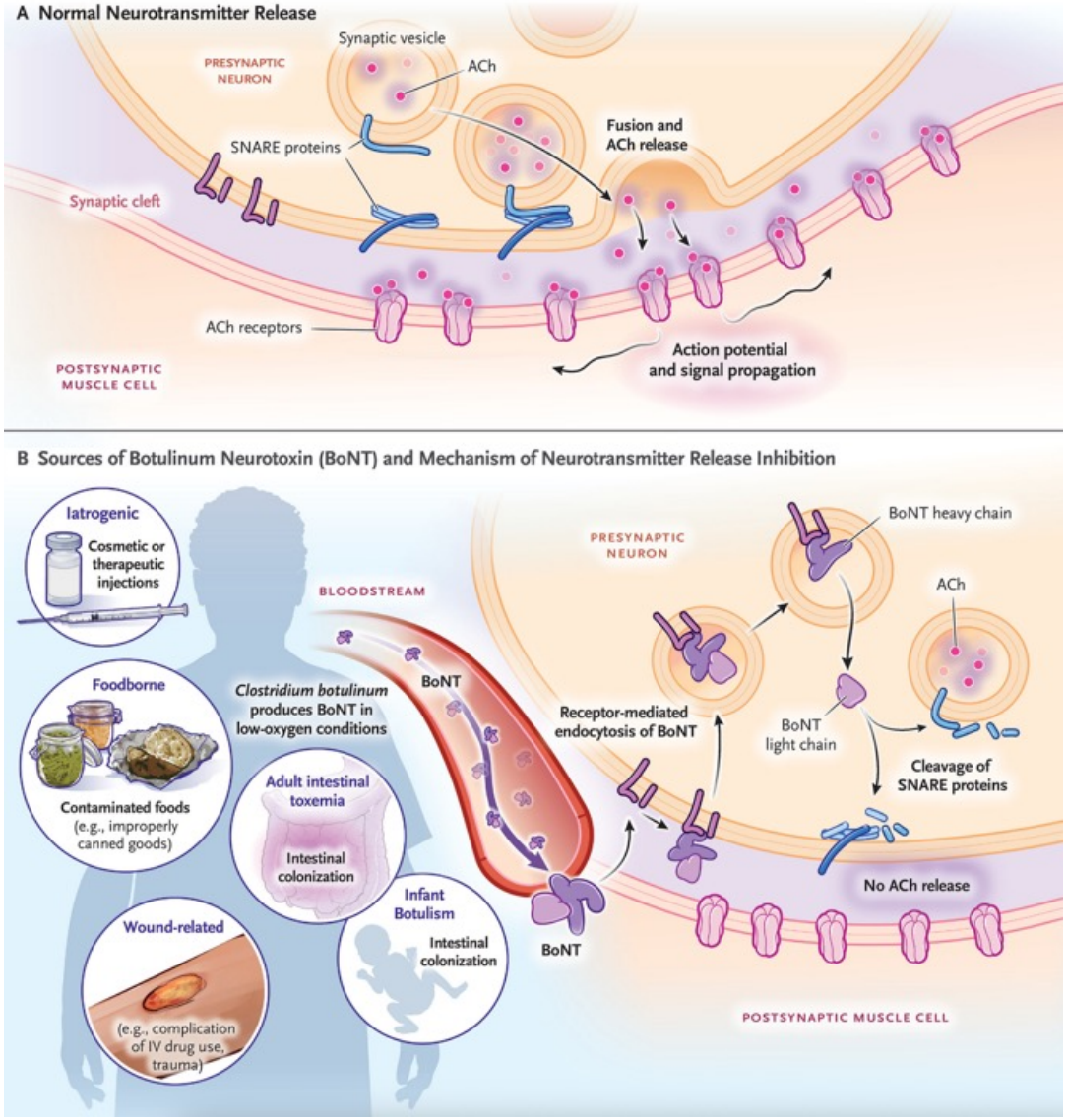
An initial CT angiogram of the chest shows bibasilar atelectasis. Note that the dark box in the upper right corner obscures equipment associated with the ventilator.

In the intensive care unit (ICU), the patient received treatment with thiamine and folate, given the concern about Wernicke's encephalopathy, and was monitored for alcohol withdrawal, given his history of delirium tremens. The neurology service was consulted, and a comprehensive neurologic examination that was performed without sedation showed that he could open his eyes on command and could nod or shake his head appropriately to answer questions. The pupils were reactive and equal, but he could not move his eyes vertically or laterally; his eyes also did not move with passive head rotation. The corneal reflexes were intact, as was the cough reflex. Intermittent tremulous movements were noted in both forearms. Motor strength was at least 3/5 in all four limbs. Sensation to light touch was intact. Reflexes were 2+ in the biceps, brachioradialis, and triceps of both arms; the patellae; and the ankles. The Babinski reflex and Hoffmann's sign were absent. An examination of the cerebellum was not performed.

The next day, while the patient was not under sedation, he no longer opened his eyes on command or withdrew in response to noxious stimuli. An electroencephalogram showed continuous low-amplitude alpha activity. Later that evening, a fever with a temperature of up to 39.7°C developed, along with tachycardia (heart rate, 130 beats per minute), leukocytosis (white-cell count, 14,000 per cubic millimeter), and worsening hypoxemia (fraction of inspired oxygen, 0.70). Repeat chest radiography revealed consolidation in both lower lobes. The C-reactive protein level was 16 mg per liter (normal value, <10), and the lactate level was 2.6 mmol per liter (23 mg per deciliter). The patient received treatment with ceftriaxone, but hypotension subsequently developed (blood pressure, 86/60 mm Hg). Given concern about possible ceftriaxone-mediated anaphylaxis, intramuscular epinephrine, methylprednisolone (at a dose of 125 mg), and vasopressors were administered.

The next morning (hospital day 3), a neurologic examination revealed new loss of pupillary and corneal reflexes, as well as new loss of cough and gag reflexes. He did not withdraw in response to noxious stimuli, but spontaneous toe movement was observed. Motor reflexes were now absent throughout; no pathologic reflexes were noted. Repeat CT of the head showed no new findings. A lumbar puncture was performed. Analysis of the cerebrospinal fluid (CSF) showed 1 nucleated cell per microliter, 0 erythrocytes per microliter, a protein level of 53 mg per deciliter (normal range, 20 to 59), and a glucose level of 140 mg per deciliter (7.8 mmol per liter; normal range, 48 to 79 mg per deciliter [2.7 to 4.4 mmol per liter]). The serum glucose level, which had been measured in the morning after the patient had received his dose of methylprednisolone, was 278 mg per deciliter (15.4 mmol per liter). A CSF treponemal antibody test and a rapid plasma reagin test were both negative.

Botulism was now the leading diagnosis. The patient's mother, who first arrived at the hospital on the morning of hospital day 3, stated that the patient often ate perishable foods that had been left at room temperature for several days. The state health department and the Centers for Disease Control and Prevention (CDC) were contacted to request botulism antitoxin, and stool and serum samples were obtained and sent to the CDC for botulinum neurotoxin testing. The patient received the antitoxin 90 hours after presentation in the ED. Electromyography and nerve-conduction studies that were performed in the medical ICU 48 hours after administration of the antitoxin showed the absence of motor-unit action potentials throughout his body, but sensory-nerve action potentials were found to be intact. Repetitive nerve stimulation showed neither a decremental response to slow rates of stimulation nor a substantive incremental response to high rates of stimulation. Given the concern that the acute motor axonal neuropathy (AMAN) subtype of the Guillain–Barré syndrome, which involves motor axons only, remained a possible alternative explanation for the patient's presentation, empirical treatment with intravenous immune globulin (at a dose of 2 g per kilogram of body weight) was also administered. However, no neurologic improvement was noted.



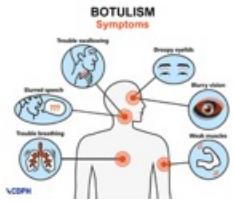
Botulinum Neurotoxin Mechanism of Action at the Neuromuscular Junction.

The normal mechanism of acetylcholine (ACh) release at the neuromuscular junction (Panel A) involves soluble *N*-ethylmaleimide–sensitive factor attachment protein receptor (SNARE)–mediated fusion of ACh-containing synaptic vesicles with the cellular membrane, resulting in ACh release. In cases of botulism (Panel B), botulinum neurotoxin (BoNT) — either preformed (foodborne or iatrogenic botulism) or locally produced (wound botulism, infant botulism [infant intestinal colonization], or intestinal colonization in adults) — reaches the neuromuscular junction, where it binds to receptors on the surface of nerve terminals and is internalized through endocytosis followed by release of the BoNT light chain. Release of the BoNT light chain causes cleavage of the SNARE proteins and irreversible inhibition of ACh vesicle fusion and ACh release, which leads to the development of flaccid paralysis. IV denotes intravenous.

The patient remained dependent on mechanical ventilation and underwent tracheostomy. Once his condition was medically stable, he was discharged to a long-term acute care facility. One month after diagnosis, a neurologic examination showed 0/5 strength in both arms and hands, except for 1/5 strength in finger flexion and extension. Strength was 1/5 in flexion and extension of both hips and both knees and 3/5 in dorsiflexion and plantar flexion of both feet. After 3 months of rehabilitation after the administration of the antitoxin, the patient still had not regained voluntary function beyond movement of his feet.

Commentary

This patient with alcohol use disorder presented with dyspnea, a globus sensation, and ophthalmoplegia. After initial suspicion for anaphylaxis or angioedema, Wernicke's encephalopathy was suspected. The subsequent development of descending paralysis led to the diagnosis of botulism. His botulism was probably foodborne, given his history of consuming perishable foods left at room temperature for several days. Unfortunately, his history of alcohol use disorder delayed his diagnosis, and the antitoxin was administered only after diaphragmatic paralysis had developed.

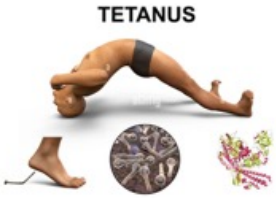


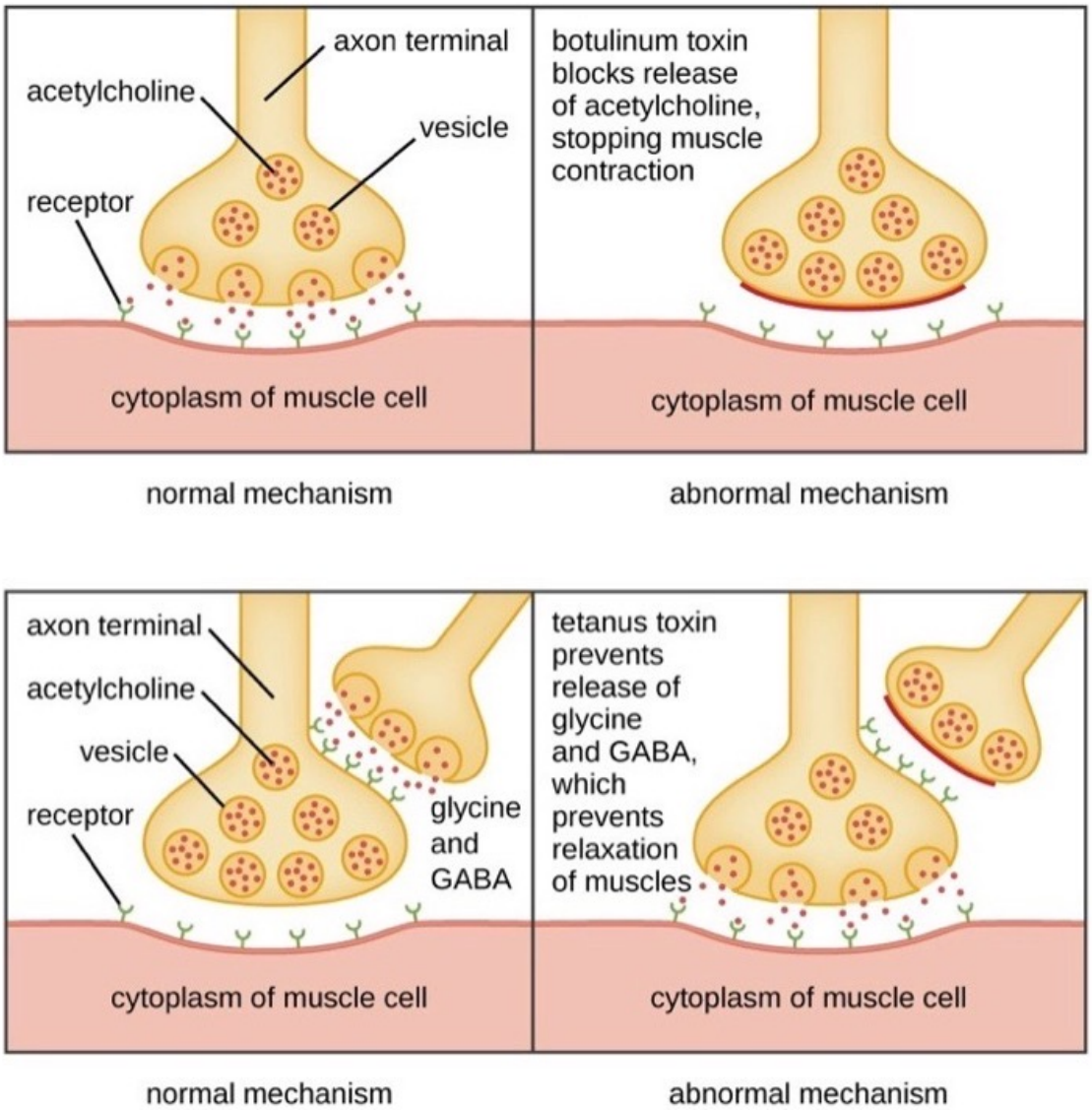
Botulism and tetanus

Clostridium botulinum

Clostridium tetani

Both block vesicular transport by interfering with snare proteins





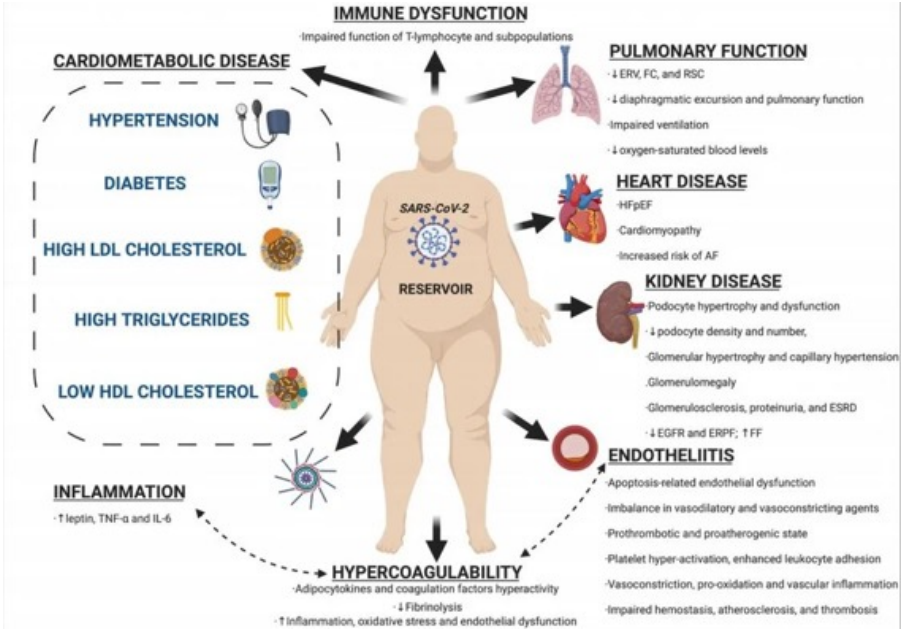
Botulism:
Flacid paralysis from cranial nerves on down

Tetanus:
Spastic paralysis
Risus sardonicus
on down

THE LANCET

Common Types of Infections Linked to Obesity
The increased risk spans a wide range of bacterial, viral, and fungal pathogens:

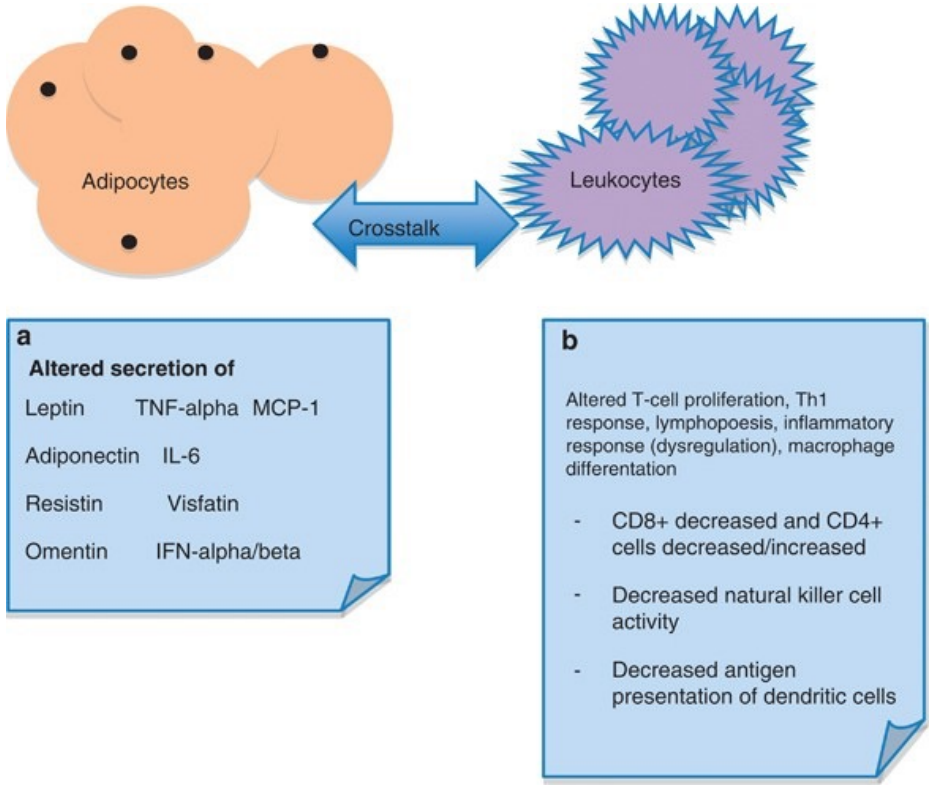
- **Respiratory Infections**: Higher rates of severe **COVID-19**, **influenza (H1N1)**, and **pneumonia**. Obesity-related mechanical issues, such as reduced lung volume and airway restriction, further complicate recovery.
- **Skin and Soft Tissue Infections**: The strongest association is with skin-related issues like **cellulitis**, **erysipelas**, and **fungal infections** (e.g., Candidiasis). Excess skin folds and impaired wound healing create environments where pathogens thrive.
- **Urinary Tract Infections (UTIs)**: Increased risk of both initial and recurrent UTIs, as well as more severe cases like **pyelonephritis**.
- **Surgical and Nosocomial Infections**: Higher risk of **surgical site infections (SSIs)** and hospital-acquired conditions due to prolonged hospitalization and technical difficulties in medical care.



Mechanisms of Increased Risk

•**Chronic Low-Grade Inflammation**: Adipose tissue is an active endocrine organ that secretes proinflammatory cytokines (e.g., TNF-α, IL-6), leading to a persistent inflammatory state that "exhausts" or misdirects the immune response.
•**Leptin Resistance**: Obesity is characterized by high levels of leptin (hyperleptinemia). While leptin normally supports immune function, chronic excess leads to **leptin resistance**, which blunts the body's ability to mount a focused immune defense.
•**Impaired Vaccine Efficacy**: Individuals with obesity often show a **reduced response to vaccinations** for the flu, Hepatitis B, and tetanus, making them more vulnerable despite being immunized.
•**Anatomical and Physiological Factors**: Fat deposition in the neck and abdomen can obstruct airways, while reduced tissue oxygenation in adipose layers slows down the healing of wounds and infections

Chronic inflammation



Adult obesity and risk of severe infections: a multicohort study with global burden estimates

Summary

Background Adult obesity has been linked to specific infections, but evidence across the full spectrum of infectious diseases remains scarce. In this multicohort study with impact modelling, we examined the association between this preventable risk factor and the incidence, hospitalisations, and mortality of 925 bacterial, viral, parasitic, and fungal infectious diseases, and estimated their global and regional attributable impact.

Methods We used pooled data from two Finnish cohort studies and repeated analyses in an independent population from the UK Biobank. BMI was assessed at baseline (1998–2002 in the Finnish studies; 2006–10 in UK Biobank), and participants were categorised as having healthy weight (18·5–24·9 kg/m²), overweight (25·0–29·9 kg/m²) or obesity, classified as class I (30·0–34·9 kg/m²), class II (35·0–39·9 kg/m²), or class III (≥40·0 kg/m²). Participants were followed up through national hospitalisation and mortality registries for hospital admissions and deaths due to infectious diseases. Using hazard ratios derived from the Finnish cohorts and UK Biobank, along with obesity prevalence estimates from the Global Burden of Diseases, Injuries, and Risk Factors Study database, we estimated the proportion of fatal infections attributable to obesity globally, regionally, and by country for the years 2018 (before), 2021 (during), and 2023 (after the COVID-19 pandemic).

As of early 2026, the population of Finland is approximately **5.66 million**. The population has experienced recent growth driven by migration, with a total of roughly 5.61 million residents recorded at the end of 2024 and 5.62 million in 2025. Finland is one of the most sparsely populated countries in the EU.

Findings The analysis included 67 766 adults (mean age 42·1 [SD 10·8] years; 49 516 [73·1%] females, 18 250 [26·9%] males) from the Finnish cohorts and 479 498 adults (mean age 57·0 [SD 8·1] years; 261 084 [54·4%] females, 218 414 [45·6%] males) from UK Biobank. Participants had no recent history of infection-related hospitalisations at baseline. During follow-up, there were 8230 incident infection cases in the Finnish cohorts and 81 945 in UK Biobank. Compared with individuals of healthy weight, those with class III obesity had a three-times higher risk of infection-related hospital admissions (Finnish cohorts 2·75 [95% CI 2·24–3·37], UK Biobank 3·07 [2·95–3·19]), death (Finnish cohorts 3·06 [1·25–7·49], UK Biobank 3·54 [3·15–3·98]), or either outcome (Finnish cohorts 2·69 [2·19–3·30], UK Biobank 3·07 [2·95–3·19]). The corresponding pooled hazard ratio for either fatal or non-fatal severe infection among individuals with any obesity (classes I–III) was 1·7 (1·7–1·8). This association was consistent across different indicators of obesity (BMI, waist circumference, and waist-to-height ratio), demographic and clinical subgroups, and a wide range of infections (non-fatal and fatal, acute and chronic, bacterial and viral [including subtypes], and parasitic and fungal). Applying these risk estimates to global burden of disease data, the population attributable fractions of infection-related deaths due to obesity were estimated at 8·6% (6·6–11·1) in 2018, 15·0% (12·8–17·4) in 2021, and 10·8% (8·6–13·6) in 2023.

Interpretation Adult obesity is a risk factor for infection-related hospitalisations and mortality across diverse pathogen types, populations, and baseline clinical profiles, with evidence suggesting that approximately one in ten infection-related deaths worldwide might be attributable to obesity.

	Finnish cohorts (n=67766)	UK Biobank (n=479498)
Sex		
Female	49516 (73·1%)	261084 (54·4%)
Male	18250 (26·9%)	218414 (45·6%)
Missing	0	0
Age, years	42·1 (10·8)	57·0 (8·1)
Ethnicity		
White	..	452104 (94·3%)
Asian	..	9167 (1·9%)
Black	..	7483 (1·6%)
Other	..	8514 (1·8%)
Missing	..	2230 (0·5%)
BMI category		
Healthy weight	39156 (57·8%)	157917 (32·9%)
Overweight	21216 (31·3%)	205319 (42·8%)
Obesity, class I	5779 (8·5%)	83797 (17·5%)
Obesity, class II	1272 (1·9%)	23567 (4·9%)
Obesity, class III	343 (0·5%)	8898 (1·9%)
Missing	0	0
Socioeconomic status*		
Intermediate or high	36201 (80·9%)	361439 (75·4%)
Low	8064 (18·0%)	117480 (24·5%)
Missing	478 (1·1%)	579 (0·1%)
Education		
Intermediate or high	55230 (81·5%)	390390 (81·4%)
Low	12292 (18·1%)	79986 (16·7%)
Missing	244 (0·4%)	9122 (1·9%)
Current smoking		
No	50464 (74·5%)	427772 (89·2%)
Yes	13273 (19·6%)	49358 (10·3%)
Missing	4029 (5·9%)	2368 (0·5%)
Low physical activity		
No	53290 (78·6%)	236471 (49·3%)
Yes	13188 (19·5%)	207163 (43·2%)
Missing	1288 (1·9%)	35864 (7·5%)
Heavy alcohol consumption		
No	57260 (84·5%)	296862 (61·9%)
Yes	9382 (13·8%)	179712 (37·5%)
Missing	1124 (1·7%)	2924 (0·6%)
Use of glucocorticoids		
No	62899 (92·8%)	460666 (96·1%)
Yes	4867 (7·2%)	18832 (3·9%)
Missing	0	0
Hypertension		
No	60351 (89·1%)	210558 (43·9%)
Yes	7415 (10·9%)	256280 (53·4%)
Missing	0	12660 (2·6%)
Metabolic syndrome		
No	..	293749 (61·3%)
Yes	..	147543 (30·8%)
Missing	..	38206 (8·0%)
Depression		
No	48019 (70·9%)	335067 (69·9%)
Yes	19712 (29·1%)	126056 (26·3%)
Missing	35 (0·1%)	18375 (3·8%)
Chronic physical disease		
No	63746 (94·1%)	427470 (89·1%)
Yes	4020 (5·9%)	52028 (10·9%)
Missing	0	0
Diabetes		
No	66273 (97·8%)	455125 (94·9%)
Yes	1493 (2·2%)	24373 (5·1%)
Missing	0	0
Cardiometabolic disease		
No	65891 (97·2%)	449423 (93·7%)
Yes	1875 (2·8%)	30075 (6·3%)
Missing	0	0
Respiratory disease		
No	66106 (97·6%)	465053 (97·0%)
Yes	1660 (2·5%)	14445 (3·0%)
Missing	0	0
Cancer		
No	67163 (99·1%)	468224 (97·6%)
Yes	603 (0·9%)	11274 (2·4%)
Missing	0	0

Data shown are n (%) or mean (SD). *These data were not available in the Health and Social Support study.

Table: **Baseline characteristics of the participants by cohort**

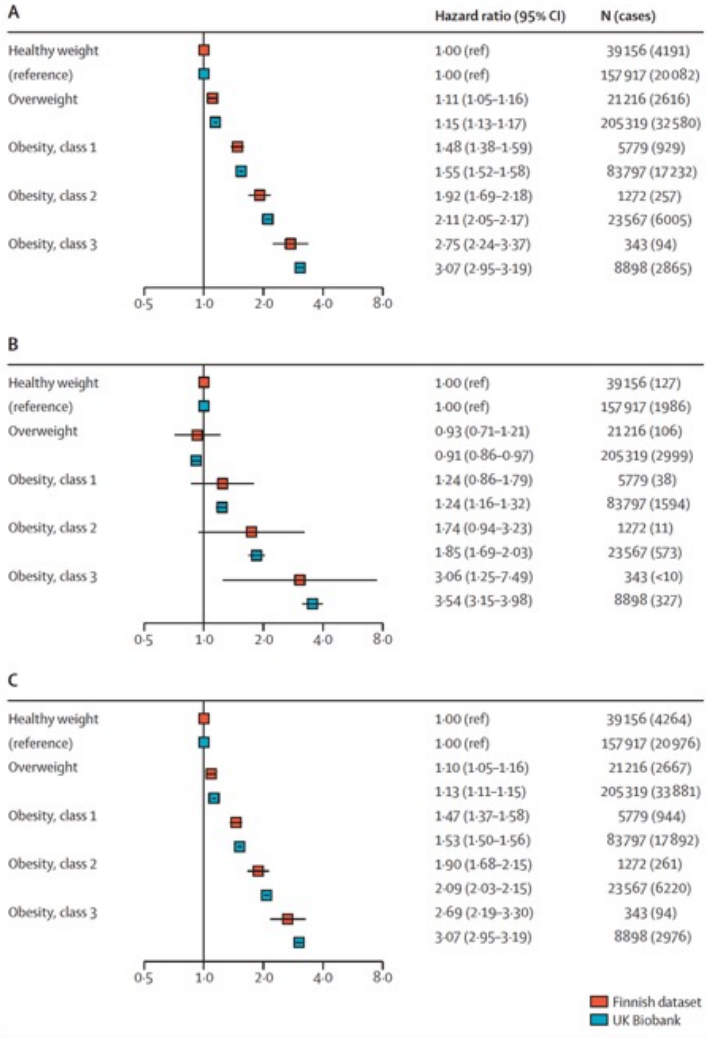


Figure 1: **Association between BMI category and risk of severe infectious disease, including non-fatal hospital-treated infections (A), fatal infections (B), and any infections (C) in the Finnish cohorts and UK Biobank**

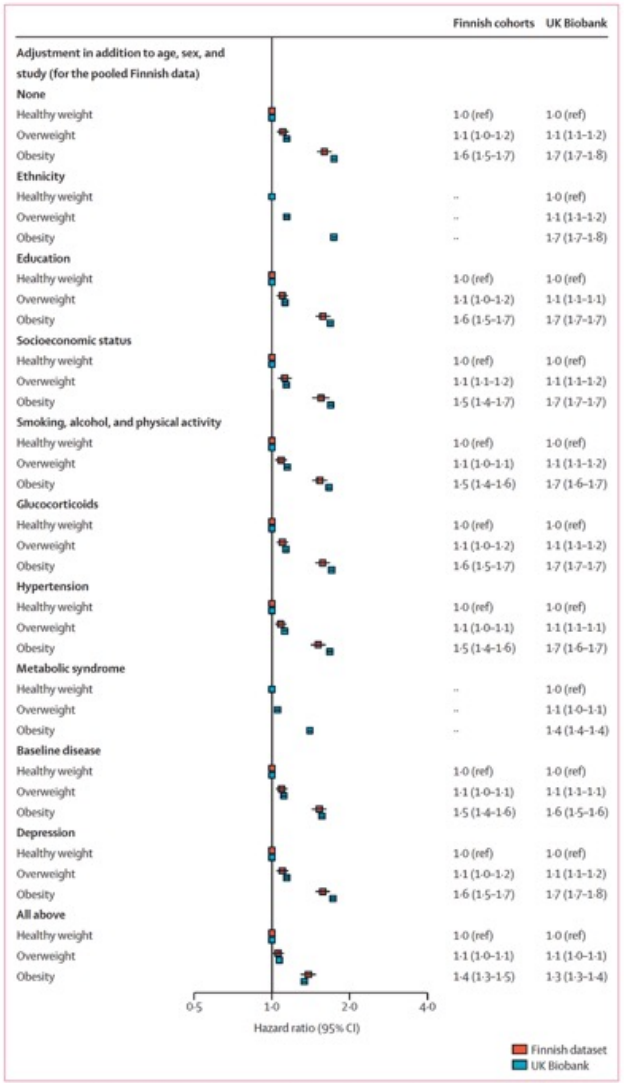
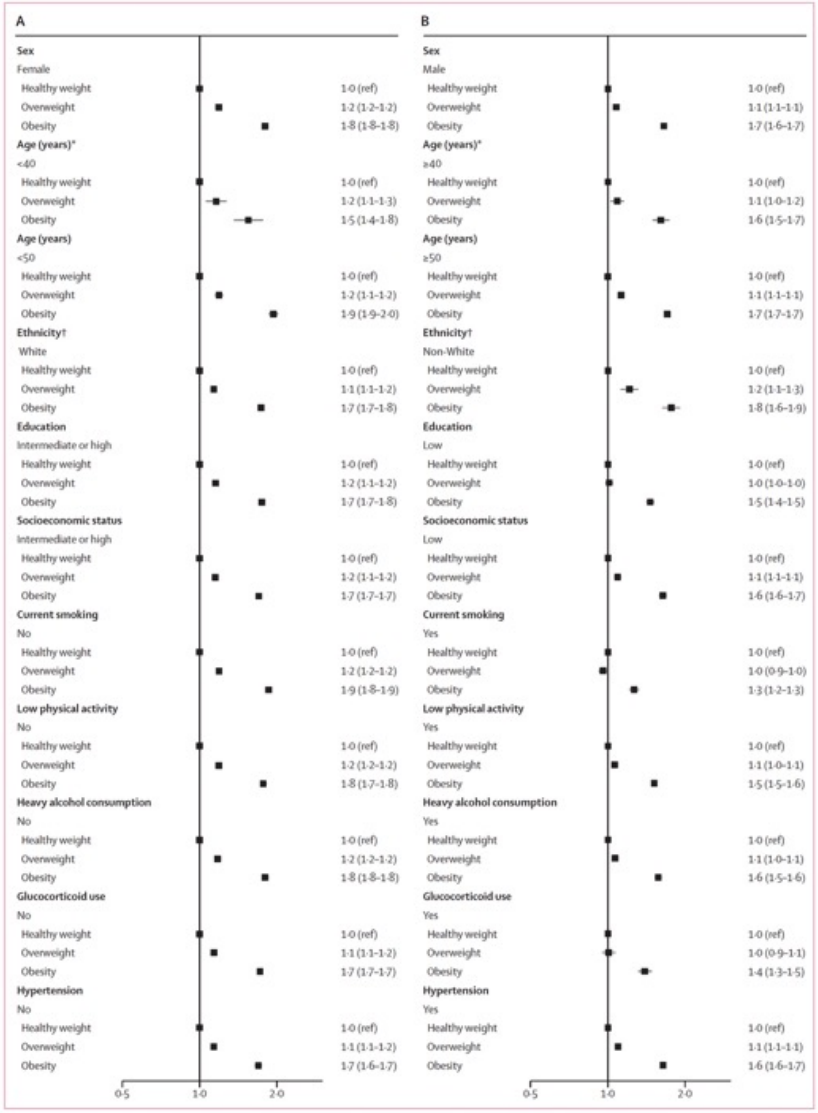


Figure 2: Association between BMI category and risk of severe infectious disease after multivariable adjustments in the Finnish cohorts and UK Biobank



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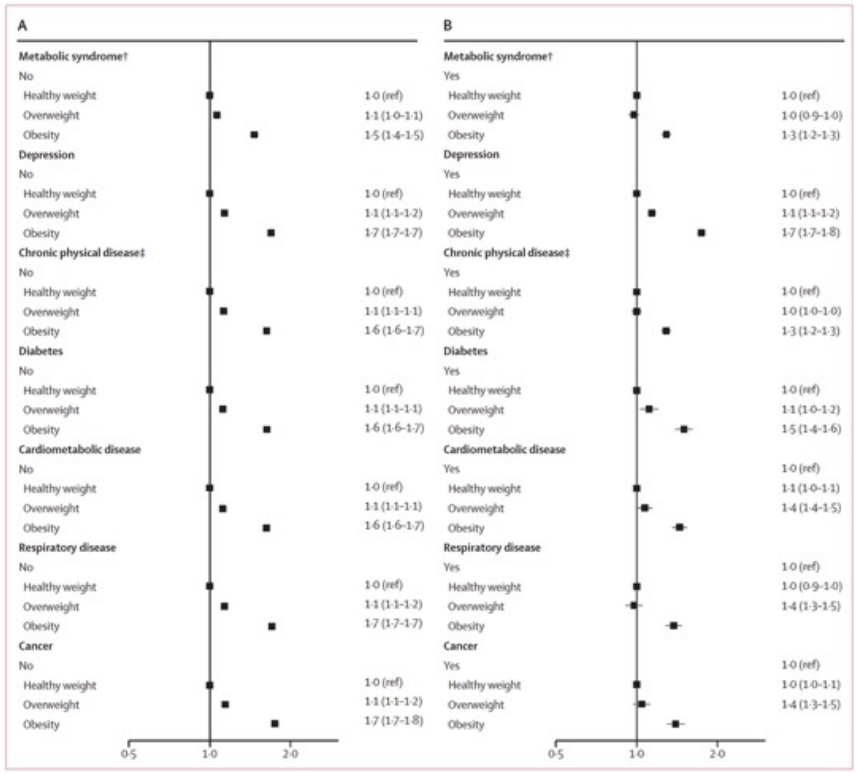


Figure 3: **Association between BMI category and risk of severe infections in subgroups, including subgroups with lower infection risk (A) and those with higher infection risk (B)**
*Only Finnish cohorts. †Only UK Biobank. ‡Diabetes, coronary heart disease, stroke, asthma, chronic obstructive pulmonary disease, or cancer.

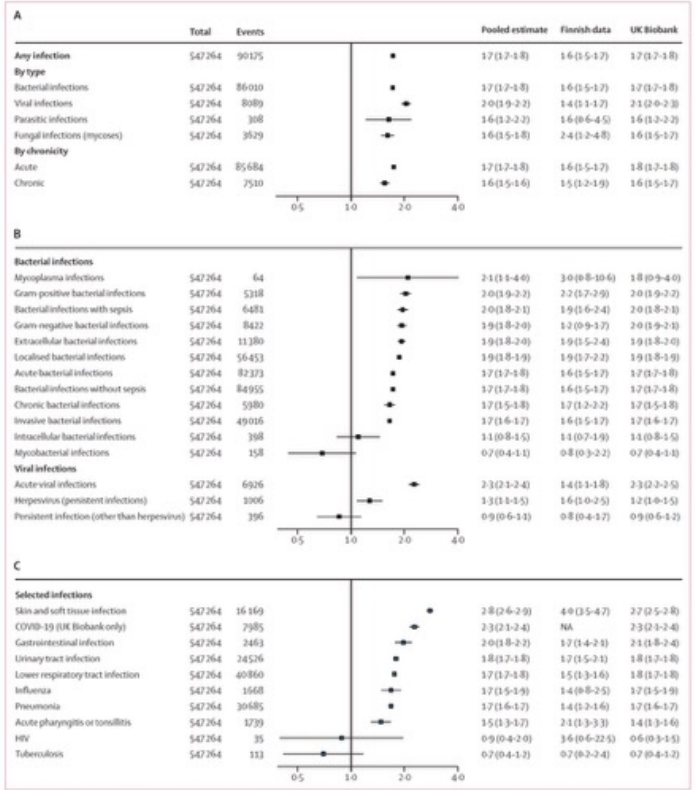


Figure 4: **Associations between obesity and severe infection risk by type and chronicity (A), by bacterial and viral subtypes (B), and for specific infections (C)**
Analyses for each infection type were performed separately. Participant numbers might exceed the total because individuals with multiple infection types contributed to more than one analysis. NA=not applicable.

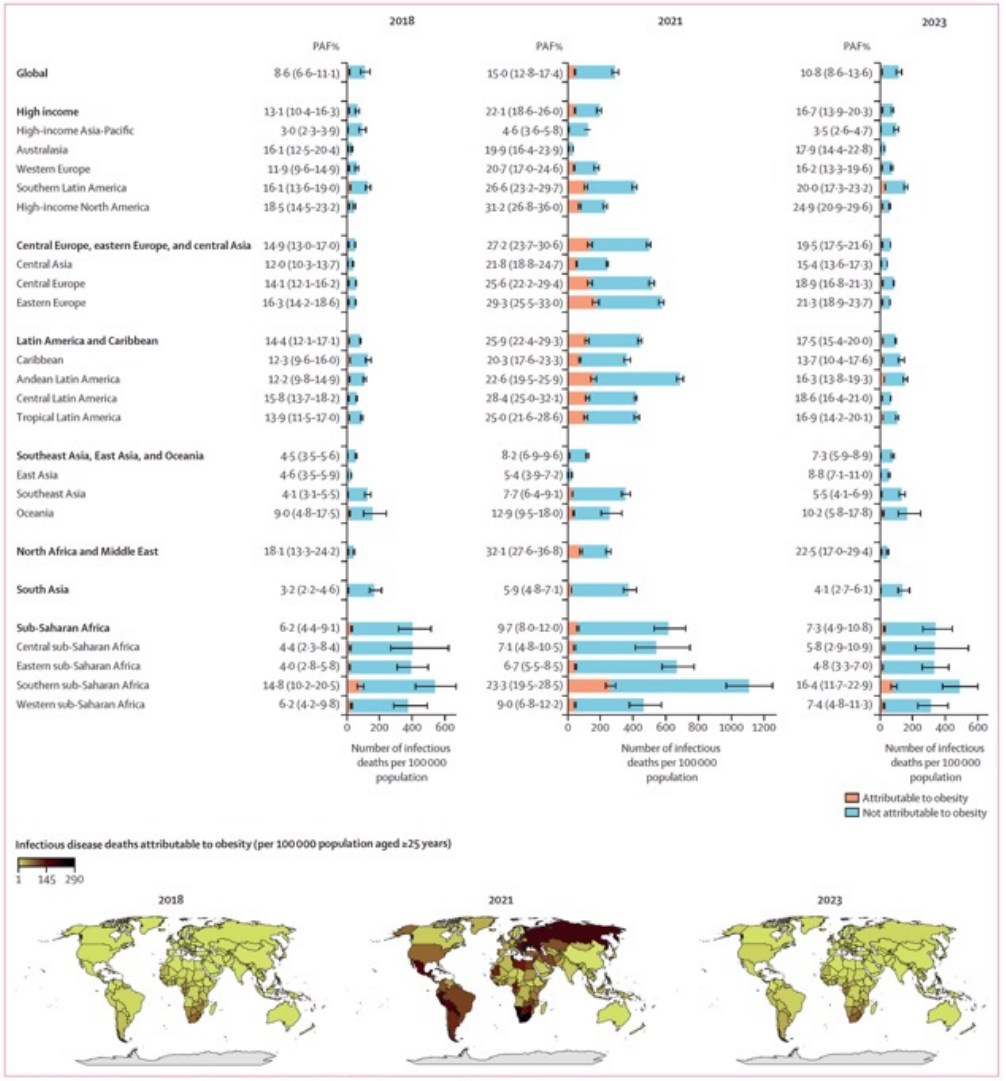


Figure 5: **Contribution of obesity to infectious disease burden globally, by region (A) and by country (B)**
PAF=population attributable fraction.

Research in context

Evidence before this study

Obesity might worsen the clinical course of infections by impairing immune and metabolic functions and altering life circumstances. However, few studies have examined the association between obesity and the full spectrum of severe infectious diseases. We searched PubMed for studies examining the association between obesity and infections, including original research, meta-analyses, and systematic reviews, without language or date restrictions, from database inception to Nov 19, 2025. The search terms were (BMI OR obesity OR obese) AND (infection OR infectious), and reference lists of relevant publications were also screened. Evidence suggests that obesity is associated with an increased risk of several infections, including those affecting the respiratory tract and skin. Obesity has also been linked to more severe courses of infectious diseases such as COVID-19 and is recognised as a risk factor for surgical site infections and hospital-acquired infections. Conversely, infections with specific pathogens, such as adenovirus 36 and *Helicobacter pylori*, have been proposed as potential risk factors for obesity, although the direction of these associations remains uncertain and might be bidirectional. Few meta-analyses or large-scale studies using individual-level data have systematically examined the association between adulthood obesity and the risk of hospitalisation or death from a broad range of infectious diseases, or estimated the global or regional proportion of infection-related deaths attributable to obesity.

Added value of this study

This multicohort analysis of more than 540 000 participants, combining data from the Finnish Public Sector study, the Finnish Health and Social Support study, and the UK Biobank, examined the prospective association between adult obesity and the risk of severe infections across multiple infection categories. The study encompassed 925 distinct diagnostic codes for hospitalisations and deaths due to infections, classified by chronicity (acute *vs* chronic) and pathogen type (bacterial, viral, parasitic, or fungal). Bacterial infections were further subdivided by site (invasive or localised), presence or absence of sepsis, cellular tropism (extracellular or intracellular), and pathogen type (Gram-positive, Gram-negative, mycobacterial, or mycoplasma). Viral infections were grouped as acute, herpesvirus (persistent) infections, or other persistent viral infections. With few exceptions (eg, HIV and tuberculosis), there was consistent evidence of a dose–response relationship between obesity classes I–III and higher risk of severe infections compared with healthy weight. The association between obesity and infection risk was observed across subgroups defined by sociodemographic and lifestyle factors, baseline health status, and infection category. When applied to Global Burden of Diseases, Injuries, and Risk Factors Study data, the findings suggest that the proportion of infection-related deaths attributable to adult obesity was 8·6% (95% CI 6·6–11·1) before the COVID-19 pandemic, 15·0% (12·8–17·4) during the pandemic, and 10·8% (8·6–13·6) after the pandemic.

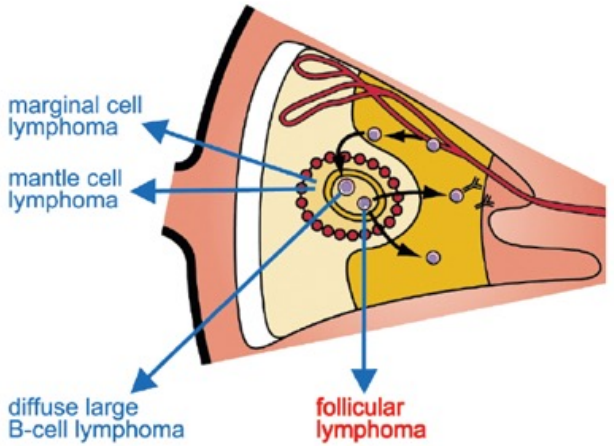
Implications of all the available evidence

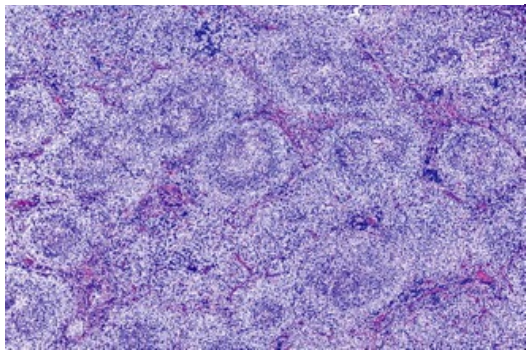
A large body of research has linked obesity to an increased risk of non-communicable diseases. Our findings suggest that adult obesity is also associated with a higher risk of hospitalisation and death from a broad spectrum of severe infections. This risk follows a clear dose–response pattern across obesity classes 1–3 and is estimated to account for approximately one in ten infection-related deaths worldwide. Given the rising global prevalence of obesity, its contribution to the burden of severe infections is likely to increase further in the coming decades.

THE LANCET

Das Marginalzonen-Lymphom (MZL) ist eine seltene, meist langsam wachsende (indolente) Form des **B-Zell-Non-Hodgkin-Lymphoms**. Es macht etwa 5–17 % aller Non-Hodgkin-Lymphome aus und betrifft vorwiegend ältere Erwachsene.

Man unterscheidet drei Hauptsubtypen basierend auf dem Ursprungsort:
1. Extranodales Marginalzonen-Lymphom (MALT-Lymphom)
Dies ist mit ca. 70 % die häufigste Form. Es entsteht außerhalb der Lymphknoten in Schleimhäuten (Mucosa-Associated Lymphoid Tissue).
- **Häufigster Ort:** Der Magen (**gastrales MALT-Lymphom**), oft ausgelöst durch eine chronische Infektion mit dem Bakterium *Helicobacter pylori*.
- **Weitere Orte:** Lunge, Speicheldrüsen, Augenhöhle, Schilddrüse oder Haut.
- **Besonderheit:** Da es oft durch chronische Entzündungen oder Infektionen entsteht, kann die Behandlung der Ursache (z. B. Antibiotika gegen *H. pylori*) das Lymphom manchmal heilen.



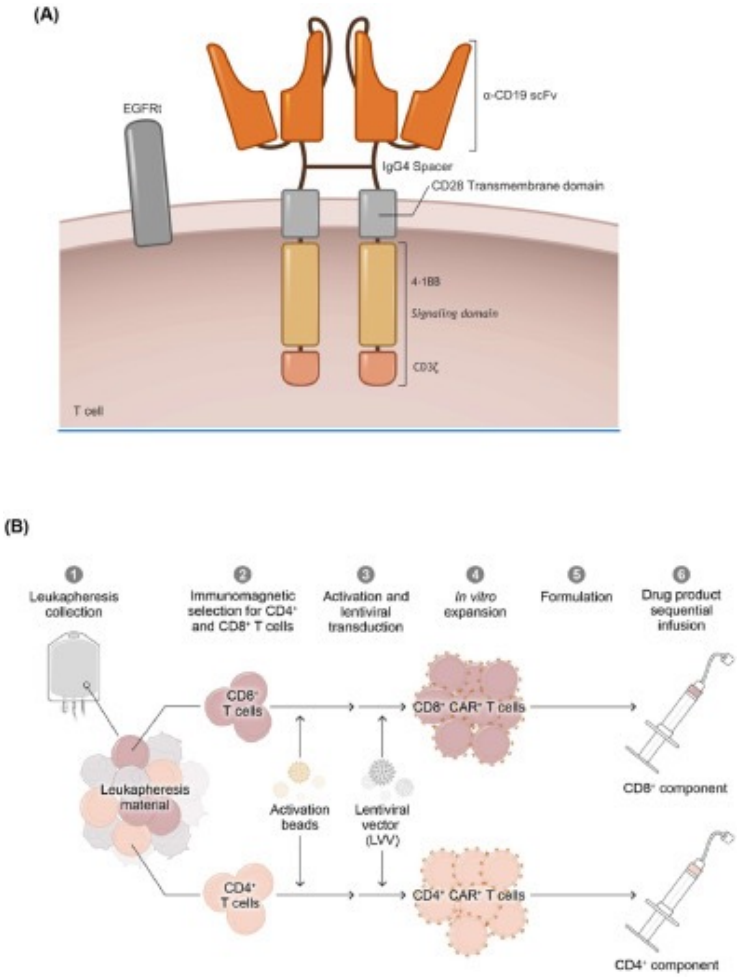


Bestimmte wegweisende Mutationen kommen vor

CAR T-cell therapy for marginal-zone lymphoma

Lisocabtagen-Maraleucel (Handelsname: **Breyanzi**) ist eine personalisierte Immuntherapie zur Behandlung bestimmter Formen von Blutkrebs. Es gehört zur Gruppe der **CAR-T-Zell-Therapien** (Chimeric Antigen Receptor T-cell therapy), bei der körpereigene Immunzellen des Patienten genetisch so verändert werden, dass sie Krebszellen erkennen und vernichten können.
Wichtigste Merkmale

- **Wirkmechanismus**: T-Zellen des Patienten werden entnommen und im Labor mit einem künstlichen Rezeptor (CAR) ausgestattet, der gezielt das **CD19-Protein** auf der Oberfläche von B-Zell-Lymphomzellen bindet und deren Zerstörung einleitet.
- **Indikationen**: In der EU und den USA ist es primär für Erwachsene mit verschiedenen Formen des **B-Zell-Lymphoms** zugelassen, wenn die Erkrankung nach mindestens zwei vorangegangenen Therapien zurückgekehrt ist (rezidiviert) oder nicht auf diese angesprochen hat (refraktär).
    - Dazu gehören unter anderem das Diffus großzellige B-Zell-Lymphom (DLBCL), das primär mediastinale großzellige B-Zell-Lymphom (PMBCL) und das follikuläre Lymphom (FL).
- **Anwendung**: Die Behandlung erfolgt als **einmalige intravenöse Infusion** in spezialisierten Behandlungszentren.



Lisocabtagene maraleucel in patients with relapsed or refractory marginal zone lymphoma (TRANSCEND FL): primary analysis results from the global, multicohort, single-arm, phase 2 study

Summary

Background Effective treatments with deep and durable responses for relapsed or refractory marginal zone lymphoma (MZL) are lacking. The objective of the primary analysis from the MZL cohort of TRANSCEND FL was to evaluate the efficacy and safety of the CD19-directed chimeric antigen receptor (CAR) T-cell therapy lisocabtagene maraleucel.

Methods In this phase 2, single-arm, multicohort study, patients from 30 sites in the USA, Canada, Europe, and Japan with relapsed or refractory MZL who had at least two previous lines of systemic therapy were eligible to receive lisocabtagene maraleucel (100×10^6 CAR^+ T cells). Bridging therapy was allowed. The primary endpoint was overall response rate per independent review committee by CT by use of Lugano 2014 criteria (null hypothesis ≤50%). This study is registered with ClinicalTrials.gov, NCT04245839, and is ongoing.

Findings Of 77 leukapheresed patients recruited between November 11, 2020, and August 24, 2023, 67 received lisocabtagene maraleucel and 66 were efficacy evaluable. MZL subtypes included nodal (n=32 [48%]), splenic (n=18 [27%]), and extranodal–mucosa-associated lymphoid tissue (n=17 [25%]). Median (IQR) previous lines of systemic therapy was 3 (2–4). Median on-study follow-up was 24·1 months. The primary endpoint was met, with an overall response rate of 95% (n=63; 95% CI, 87·3–99·1; one-sided p<0·0001). All patients experienced a treatment-related adverse event. Grade 3 cytokine release syndrome or neurological events occurred in three (4%) patients each (no grade 4–5 events). 11 (16%) patients had grade ≥3 infections: six (9%) patients during the 90-day treatment-emergent period and seven (10%) during the post-treatment-emergent period.

Interpretation In patients with relapsed or refractory MZL, lisocabtagene maraleucel showed high rates of durable responses. The safety profile was manageable, with no new safety signals. These results support lisocabtagene maraleucel as a new treatment option for patients with relapsed or refractory MZL.

Introduction

Marginal zone lymphoma (MZL) is an indolent B-cell malignancy that accounts for 7% of mature non-Hodgkin lymphomas.[1–4] MZL is characterised by slow growth, and it does not always require immediate therapy. A proportion of patients will eventually require treatment, which typically includes a CD20 monoclonal antibody as first-line therapy. Although patients with MZL generally respond to initial treatment, repeated relapses are common.[2] Patients with progression of disease up to 24 months (POD24) after diagnosis or initial treatment have inferior outcomes, with higher risk of disease transformation and shorter survival.[2,5–7] Although some systemic therapies, including lenalidomide plus rituximab (R2) and Bruton tyrosine kinase inhibitors (eg, zanubrutinib), can be used to treat MZL from first relapse,[8,9] patients with relapsed or refractory MZL in their third line or later of therapy represent a high-risk subset of patients for whom more effective therapies with deep and durable responses are needed.[2]

Promising outcomes have been observed with axicabtagene ciloleucel chimeric antigen receptor (CAR) T-cell therapy in patients with relapsed or refractory MZL (n=31) in the third line or later setting.[10] Nevertheless, this therapy is not approved for the treatment of relapsed or refractory MZL, is associated with considerable toxicity, and its efficacy in splenic MZL was not evaluated in the ZUMA-5 study.

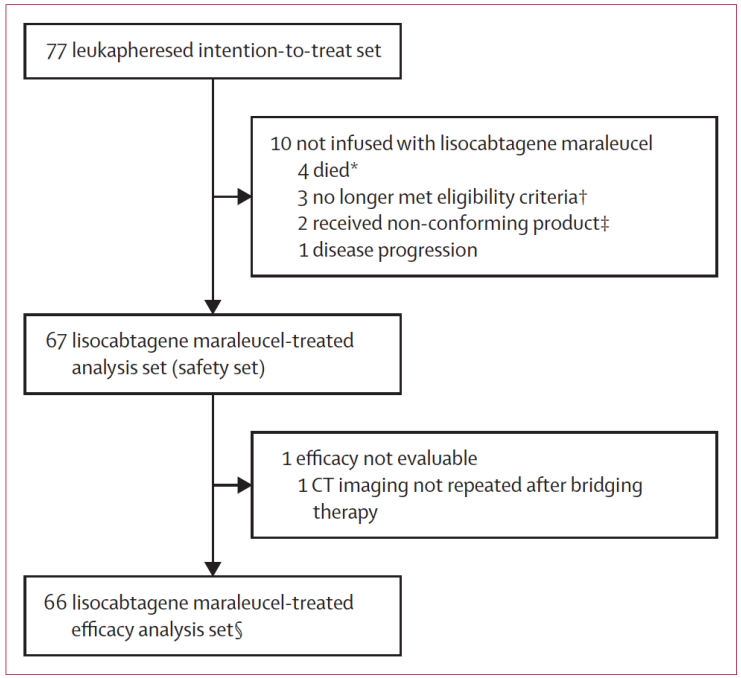


Figure 1: **CONSORT diagram**

*Including three deaths due to disease progression and one to suicide; for these four patients, death was the reason for study discontinuation. †Including one patient who did not have marginal zone lymphoma histologically confirmed within 6 months of screening, one patient with a substantial medical condition, and one patient with worsening Eastern Cooperative Oncology Group performance status. ‡Non-conforming product was defined as any product wherein one of the CD8 or CD4 cell components did not meet one of the requirements to be considered lisocabtagene maraleucel, but could be considered appropriate for infusion. §Patients who received lisocabtagene maraleucel and had positive disease present before lisocabtagene maraleucel infusion per independent review committee. Patients without baseline assessment repeated after anticancer therapy for disease control and before lisocabtagene maraleucel infusion were excluded.

	Lisocabtagene maraleucel–treated analysis set (n=67)*
Age, years	62 (57–71)
<65 years	37 (55%)
≥65 years	30 (45%)
≥70 years	20 (30%)
≥75 years	10 (15%)
Sex	
Male	39 (58%)
Female	28 (42%)
Race	
White	38 (57%)
Asian	4 (6%)
Black or African American	1 (1%)
Not collected or unknown†	24 (36%)
Ethnicity	
Hispanic or Latinx	1 (1%)
Not Hispanic or Latinx	45 (67%)
Not reported	21 (31%)
MZL subtype	
Nodal	32 (48%)
Splenic	18 (27%)
Extranodal–mucosa-associated lymphoid tissue	17 (25%)
Eastern Cooperative Oncology Group performance status at screening	
0	37 (55%)
1	30 (45%)
Ann Arbor stage at screening	
Stage I	3 (4%)
Stage II	7 (10%)
Stage III	8 (12%)
Stage IV	49 (73%)
mGELF criteria‡	41 (61%)
Bulky disease at screening§	15 (22%)
Follicular Lymphoma International Prognostic Index at screening	
Low risk (0–1)	11 (16%)
Intermediate risk (2)	13 (19%)
High risk (3–5)	41 (61%)
Not available	2 (3%)
MZL-IPI¶	
Low risk (0)	0
Intermediate risk (1–2)	14 (21%)
High risk (3–5)	53 (79%)

(Table 1 continues in next column)

	Lisocabtagene maraleucel–treated analysis set (n=67)*
(Continued from previous column)	
Mucosa-Associated Lymphoid Tissue International Prognostic Index for patients with extranodal–mucosa-associated lymphoid tissue MZL (n=17)	
Low risk (0)	1 (6%)
Intermediate risk (1)	11 (65%)
High risk (2–3)	5 (29%)
Lactate dehydrogenase > upper limit of normal before lymphodepleting chemotherapy	32 (48%)
Bone marrow involvement at screening	28 (42%)
≥20% lymphoma cells in bone marrow	20 (30%)
CNS involvement at screening	1 (1%)
Splenomegaly at screening	21 (31%)
Previous splenectomy	6 (9%)
Previous lines of systemic therapy‖	3 (2–4)
Previous haematopoietic stem cell transplantation	11 (16%); all ASCT
Received previous rituximab and lenalidomide	15 (22%)
Received previous bendamustine	52 (78%)
Received previous Bruton tyrosine kinase inhibitor	26 (39%)
Refractory to last systemic therapy**	26 (39%)
Relapsed after last systemic therapy**	41 (61%)
Progression of disease ≤24 months from initiation of first-line chemoimmunotherapy	24 (36%)
Received bridging therapy	30 (45%)
Time from initial MZL diagnosis to first progression, years	2 (1–5)
Time from initial MZL diagnosis to infusion, years	7 (4–10)

Data are n (%) or median IQR. mGELF=modified Groupe d'Etude des Lymphomes Folliculaires. ASCT=autologous stem cell transplantation. MZL=marginal zone lymphoma. MZL-IPI=Marginal Zone Lymphoma International Prognostic Index. *Percentages may not add up to 100% due to rounding. †Due to some European country regulations. ‡Met the following criteria at study screening: presence of B symptoms, cytopenias (leukocyte count $<1 \times 10^9$/L or platelet count $<100 \times 10^9$/L), bulky disease (single mass >7 cm or at least three masses >3 cm), or splenomegaly.[14] §On the basis of mGELF criteria, bulky disease was defined as any mass greater than 7 cm, or at least three masses (each >3 cm), per investigator's assessment. ¶For MZL-IPI, disseminated MZL was not assessed in this study and, therefore, patients were assigned a point for MZL subtype only if they had nodal MZL; the proportion of patients with high-risk MZL-IPI might be under-reported in this study. ‖Including chemotherapy, immunotherapy, and radioimmunotherapy. **Refractory disease was defined as a best response of stable disease or progressive disease after previous therapy. Relapsed disease was defined as relapse after initial complete response or partial response to previous therapy.

Table 1: **Demographics and baseline characteristics (lisocabtagene maraleucel–treated analysis set; n=67)**

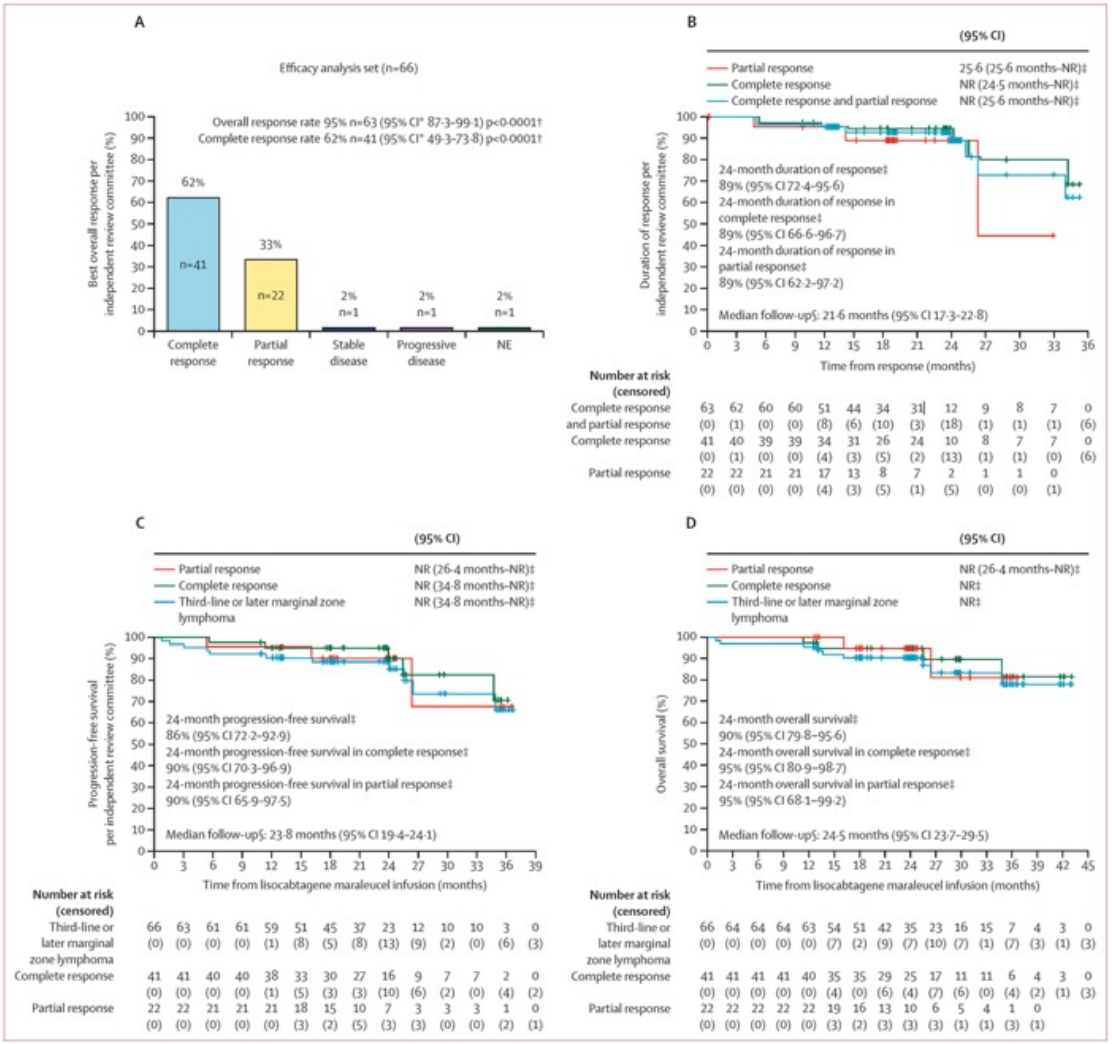


***Figure 2*: Efficacy outcomes per independent review committee assessment by CT by use of Lugano 2014 criteria[18] (efficacy analysis set; n=66)**

(A) Response rates. (B) Duration of response. (C) Progression-free survival. (D) Overall survival. NE=not evaluable. NR=not reached. *Two-sided 95% CI based on exact Clopper–Pearson method. †One-sided p value based on the exact binomial test (H_0 of overall response rate ≤50%; H_0 of complete response rate ≤5%). ‡Based on Kaplan–Meier estimates. §Based on the reverse Kaplan–Meier method.

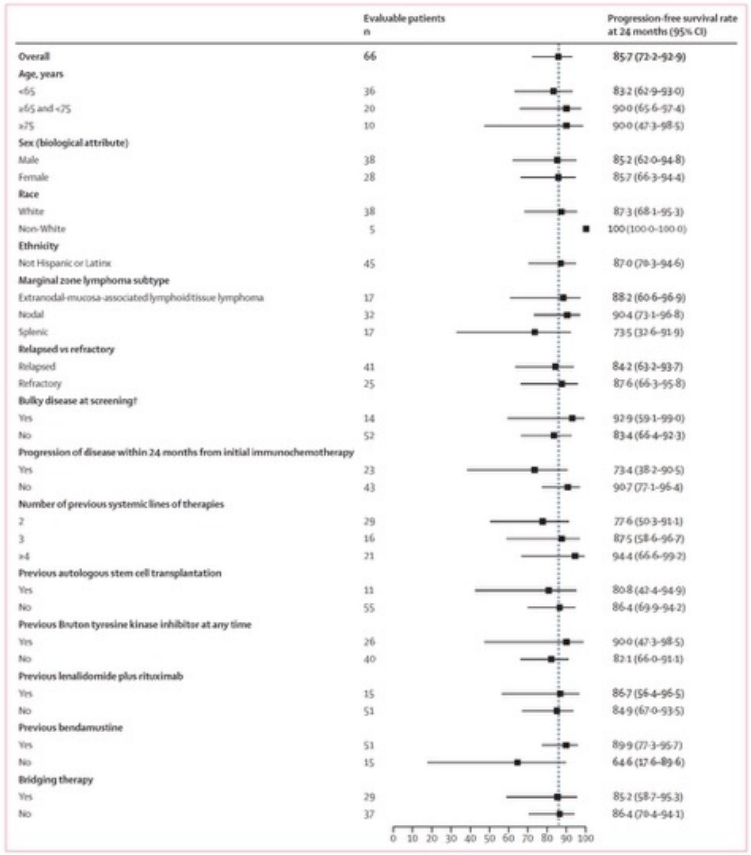


Figure 3: **Forest plots of subgroup analysis: 24-month rates of progression-free survival per independent review committee based on CT assessment (efficacy analysis set; n=66)***

mGELF=modified Groupe d'Etude des Lymphomes Folliculaires. *95% CIs (represented as bars) were based on Kaplan-Meier estimates in the efficacy-evaluable population. Analyses were done in subgroups with at least five patients. †Based on mGELF criteria, bulky disease was defined as any mass greater than 7 cm, or at least three masses (each >3 cm) per investigator's assessment.

	Any grade	Grade ≥3
Any	67 (100%)	59 (88%)
Most common (≥10% in any grade)		
Cytokine release syndrome	51 (76%)	3 (4%)
Neutropenia	50 (75%)	48 (72%)
Thrombocytopenia	26 (39%)	14 (21%)
Anaemia	21 (31%)	12 (18%)
Diarrhoea	19 (28%)	1 (1%)
Hypokalaemia	16 (24%)	2 (3%)
Fatigue	15 (22%)	1 (1%)
Leukopenia	15 (22%)	13 (19%)
Headache	14 (21%)	1 (1%)
Tremor	13 (19%)	0
Nausea	12 (18%)	1 (1%)
Increased aspartate aminotransferase	9 (13%)	2 (3%)
Dizziness	8 (12%)	0
Hypophosphataemia	8 (12%)	3 (4%)
Lymphopenia	8 (12%)	7 (10%)
Increased alanine aminotransferase	7 (10%)	4 (6%)
Decreased appetite	7 (10%)	2 (3%)
Pyrexia	7 (10%)	0
Hypotension	7 (10%)	0

Data are n (%). TEAE=treatment-emergent adverse event. *TEAE was defined as any adverse event that occurred from initiation of lisocabtagene maraleucel infusion and up to 90 days after infusion. Any adverse event that occurred after the initiation of another anticancer treatment was not considered a TEAE.

Table 2: **Most common TEAEs* (≥10%; lisocabtagene maraleucel–treated analysis set; n=67)**

	Lisocabtagene maraleucel-treated analysis set (n=67)
CRS*	
Any grade	51 (76%)
Grade 1	31 (46%)
Grade 2	17 (25%)
Grade 3	3 (4%)
Grade 4/5	0
Time to first onset of CRS, days	4 (2–7)
Time to resolution of first CRS, days	4 (3–8)
Treatment for CRS	
Tocilizumab only	20 (30%)
Corticosteroids only	2 (3%)
Both tocilizumab and corticosteroids	17 (25%)
Tocilizumab or corticosteroids, or both	39 (58%)
Neurological events†	
Any grade	22 (33%)
Grade 1	10 (15%)
Grade 2	9 (13%)
Grade 3	3 (4%)
Grade 4/5	0
Time to first onset of neurological event, days	8·5 (5–13)
Time to resolution of first neurological event, days	8 (3–17)
Treatment for neurological events	
Corticosteroids only	14 (21%)
Tocilizumab alone or in combination with corticosteroids	0
Grade ≥3 cytopenia at day 29 visit‡	28 (42%)
Recovered to grade ≤2 by day 90§	21/28 (75%)
Recovered to grade ≤2 by day 365§	27/28 (96%)
Grade ≥3 cytopenia at day 90 visit‡	16 (24%)
Recovered to grade ≤2 by day 180§	7/16 (44%)
Recovered to grade ≤2 by day 365§	16/16 (100%)
Second primary malignancy¶	8 (12%)
Grade ≥3 infection‖	11 (16%)
During the 90-day treatment-emergent period**	6 (9%)
During the post-treatment-emergent period††	7 (10%)
Macrophage activation syndrome-haemophagocytic lymphohistiocytosis (all grade 3 and all resolved)	3 (4%)
Tumour lysis syndrome	1 (1%)
Infusion-related reaction	0

Data are n (%), n/N (%), or median (IQR). CRS=cytokine release syndrome. *Graded according to the Lee 2014 criteria.* †Defined as investigator-identified neurological adverse events related to lisocabtagene maraleucel and graded per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. ‡Grade 3 or higher laboratory results based on local laboratory assessments of decreased haemoglobin, neutrophil, or platelet count at the day 29 (±2 days) or day 90 (±14 days) visit. §Recovery data are presented for patients with grade 3 or higher cytopenia at day 29 or day 90. ¶Including four patients with non-melanoma skin cancer, two patients with acute myeloid leukaemia, one patient with T-cell lymphoma, and one patient with myelodysplastic syndromes. ‖Some patients might have grade 3 or higher infections in both treatment-emergent and post-treatment-emergent periods. **Five patients had grade 3 infections: pneumonia, COVID-19 infection, sepsis, sinusitis, and staphylococcal sepsis (n=1 each); all grade 3 infections resolved. One patient had grade 5 neutropenic sepsis (mentioned in manuscript as grade 5 treatment-emergent adverse event). ††Seven patients had nine events of grade 3 or higher infection: COVID-19 (n=4; including pneumonia [n=1]) and other pneumonia (n=5). All events resolved.

Table 3: **Adverse events of special interest (lisocabtagene maraleucel–treated analysis set; n=67)**

Research in context

Evidence before this study

We searched PubMed for clinical studies published from March 20, 2005, to March 20, 2025, using the terms "chimeric antigen receptor" and "marginal zone lymphoma". Our search identified two manuscripts reporting clinical study results of chimeric antigen receptor (CAR) T-cell therapy in marginal zone lymphoma (MZL). Both manuscripts were based on ZUMA-5, a single-arm, multicentre, phase 2 study of axicabtagene ciloleucel in patients with relapsed or refractory indolent non-Hodgkin lymphoma, representing results from the primary analysis and the 3-year follow-up. Although axicabtagene ciloleucel showed high response rates and durable responses in patients with relapsed or refractory MZL, the number of patients with relapsed or refractory MZL was low (n=31 at 3-year follow-up) and only included patients with nodal or extranodal MZL. Furthermore, axicabtagene ciloleucel was associated with substantial toxicities; grade 3 or higher cytokine release syndrome in two (8%) patients, grade 3 or higher neurological events in nine (38%) patients, and grade 3 or higher infections occurred in seven (29%) patients. Findings from ZUMA-5 remain to be validated in larger studies.

Added value of this study

TRANSCEND FL is a multicentre, clinical study, which evaluated CD19-directed CAR T-cell therapy in the largest number of patients with relapsed or refractory MZL to date. The study included patients with all three subtypes of MZL (nodal, extranodal–mucosa-associated lymphoid tissue, and splenic). In TRANSCEND FL, lisocabtagene maraleucel showed deep and durable responses with high survival rates at 24 months in patients with relapsed or refractory MZL. The clinical benefit of lisocabtagene maraleucel was observed in a broad population of patients, showing high response rates across all subgroups. The safety profile was manageable, and no new safety signals were identified beyond those observed in lisocabtagene maraleucel studies in other B-cell malignancies. These data support a one-time infusion of lisocabtagene maraleucel as an effective treatment option for patients with relapsed or refractory MZL after at least two previous lines of systemic therapy, a population with poor outcomes for which effective and tolerable treatments are needed.

Implications of all the available evidence

TRANSCEND FL represents the most recent and extensive effort to explore CAR T-cell therapy in the largest cohort of patients with relapsed or refractory MZL to date, building on the initial observations from ZUMA-5. These results show that the CAR T-cell therapy lisocabtagene maraleucel can provide meaningful clinical benefit, driving advances in the treatment of relapsed or refractory MZL.

THE LANCET

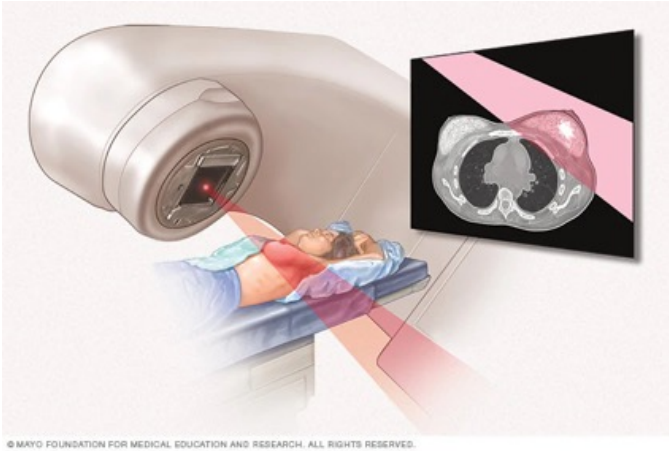
Can radiation treatments be reduced?

Radiotherapy (Strahlentherapie) is a standard local treatment for breast cancer that uses high-energy X-rays to destroy cancer cells and reduce the risk of recurrence.

When It's Used

Radiation therapy is most often used as **adjuvant therapy** after surgery:

- **After Breast-Conserving Surgery (Lumpectomy):** To kill any remaining microscopic cancer cells in the breast tissue.
- **After Mastectomy:** In cases of high risk, such as large tumors (>5 cm) or when cancer has spread to the lymph nodes.
- **For Advanced Cancer:** To shrink tumors or relieve pain caused by metastases in bones or the brain.



5-year results of hypofractionated locoregional radiotherapy in early breast cancer HypoG-01 (UNICANCER): a French multicentre, randomised, non-inferiority, phase 3, open-label, controlled trial

Summary

Background Hypofractionated radiotherapy is standard for whole-breast radiotherapy, but 50 Gy in 25 fractions (5-week radiotherapy) is still standard in many countries when nodal radiotherapy is needed for morbidity concerns. The UNICANCER HypoG-01 trial aimed to assess morbidity and efficacy of hypofractionated locoregional radiotherapy delivering 40 Gy in 15 fractions (3-week radiotherapy) versus 5-week radiotherapy.

Methods This non-inferiority, open-label, multicentre, randomised phase 3 trial, conducted in 29 centres in France, included female patients 18 years and older, with invasive breast carcinoma requiring nodal irradiation after complete microscopic resection of the primary tumour. Patients were randomly allocated in a 1:1 ratio to either 3-week radiotherapy (experimental group) or 5-week radiotherapy (control group) to the regional nodes and thoracic wall or breast. The primary endpoint was ipsilateral arm lymphoedema, defined as a 10% or greater increase in arm circumference at 15 cm proximal, 10 cm distal, or both, to the ipsilateral olecranon relative to baseline and contralateral arm, with a non-inferiority margin on the hazard ratio (HR) of 1·545. This trial was registered at ClinicalTrials.gov (NCT03127995) and is closed to recruitment.

Findings Between Sept 26, 2016, and March 27, 2020, 1265 patients were enrolled, and 1221 were included in per-protocol analysis (median follow-up 4·8 years [IQR 4·01–5·02]), 614 assigned to 3-week radiotherapy and 607 to 5-week radiotherapy. The median age was 58 years (IQR 49–68). Arm lymphoedema occurred in 275 (25%) patients (143 with 3-week radiotherapy and 132 with 5-week radiotherapy). 3-week radiotherapy was non-inferior to 5-week radiotherapy regarding arm lymphoedema risk (HR 1·02 [95% CI 0·79–1·31] $p_{non\text{-}inferiority}<0·001$), with a 3-year cumulative incidence of 23·4% (95% CI 19·7–27·6) and 22·2% (95% CI 19·5–26·3), respectively. Safety profiles were similar between groups; grade 3 or worse adverse events frequencies were 8% and 13%, respectively. Following French regulation, data on race and ethnicity were not collected.

Interpretation 3-week radiotherapy (40 Gy in 15 fractions) was found to be non-inferior to 5-week radiotherapy (50 Gy in 25 fractions) for arm lymphoedema risk and was comparably safe regarding other late normal tissue effects for patients prescribed locoregional radiotherapy for early-breast cancer.

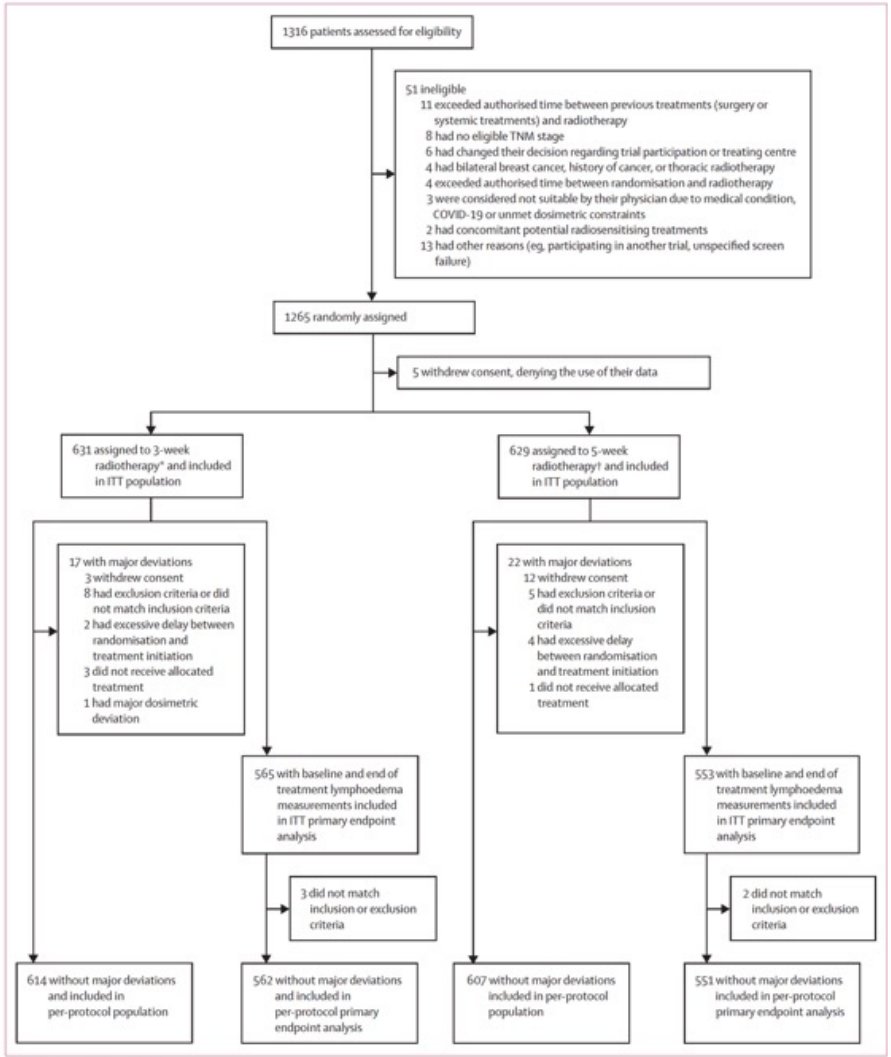


Figure 1: **HypoG-01 trial profile**
ITT=intention-to-treat. *3-week radiotherapy (experimental group) comprised moderately hypofractionated radiation therapy (40 Gy in 15 fractions every 3 weeks, with or without a tumour bed boost). †5-week radiotherapy (standard group) comprised 50 Gy in 25 fractions every 5 weeks, with or without a tumour bed boost.

	Experimental group (N=614)*	Standard group (N=607)†
Age, years		
Mean (SD)	58·5 (13·1)	58·2 (12·8)
Median (IQR)	58 (49–68)	58 (48–68)
Range	23–91	29–87
Breast size‡		
Small	69 (11%)	82 (14%)
Medium	241 (39%)	230 (38%)
Large	257 (41%)	236 (39%)
Unknown	47 (8%)	59 (10%)
Laterality		
Left	309 (50%)	324 (53%)
Right	305 (49%)	283 (47%)
Tumour size, mm		
Patients with tumour size available	607 (97%)	600 (99%)
Mean tumour size, mm (SD)	26·2 (18·1)	26·1 (18·6)
Histology		
Ductal	491 (79%)	493 (81%)
Lobular	87 (14%)	78 (13%)
Other	35 (6%)	32 (5%)
Unknown	1 (<1%)	4 (1%)
Grade		
I	63 (10%)	57 (9%)
II	319 (51%)	351 (58%)
III	223 (36%)	191 (31%)
Unknown	9 (1%)	8 (1%)
Breast cancer subtype		
HER2+	114 (18%)	125 (21%)
HER2– with ER+ or PR+	426 (68%)	420 (69%)
HER2– and ER– and PR–	69 (11%)	61 (10%)
Unknown	5 (1%)	1 (<1%)
T stage		
0	19 (3%)	17 (3%)
1	205 (33%)	202 (33%)
2	293 (48%)	285 (47%)
3	80 (13%)	83 (14%)
4	5 (1%)	4 (1%)
Unknown	12 (2%)	16 (3%)
N stage		
0	255 (42%)	236 (39%)
1	292 (48%)	297 (49%)
2	40 (7%)	41 (7%)
3	15 (2%)	16 (3%)
Unknown	12 (2%)	17 (3%)
Breast surgery		
Mastectomy	276 (45%)	274 (45%)
Breast conservation	338 (55%)	333 (55%)

(Table 1 continues in next column)

(Continued from previous column)

	Experimental group (N=614)*	Standard group (N=607)†
Axillary exploration		
Axillary clearance only	310 (50%)	326 (54%)
Axillary clearance and sentinel node or nodes biopsy	195 (32%)	173 (29%)
Sentinel node or nodes biopsy only	109 (18%)	108 (18%)
Radiotherapy technique		
IMRT	324 (53%)	314 (52%)
RT3D	290 (47%)	293 (48%)
Tumour-bed boost		
Total	293 (48%)	303 (50%)
Integrated (SIB)	97 (16%)	95 (16%)
Sequential	196 (32%)	208 (34%)
Irradiated nodal levels§¶		
CTVn_L1–2§	0	0
CTVn_L3–4	88 (14%)	72 (12%)
CTVn_L1–4§	16 (3%)	21 (3%)
CTVn_L3–4_IMN	133 (22%)	115 (19%)
CTVn_L1–4_IMN§	98 (16%)	99 (16%)
CTVn_L2–4_IMN	8 (1%)	12 (2%)
CTVn_L2–4_IMN§	131 (21%)	137 (23%)
Systemic treatment		
Preoperative chemotherapy	130 (21%)	155 (26%)
Adjuvant Chemotherapy	389 (63%)	386 (64%)
Trastuzumab	106 (17%)	116 (19%)
Preoperative endocrine therapy	13 (2%)	7 (1%)
Adjuvant endocrine therapy	496 (81%)	498 (82%)

Data are n (%) unless otherwise stated. The number of patients may vary for some characteristics due to missing data, because they are applicable only to a subset of patients, or because they are not mutually exclusive (eg, some patients had a combination of several systemic treatments). Level 1=lower region of axilla (L1). Level 2=upper region of axilla (L2). Level 3=infraclavicular region (L3). Level 4=supraclavicular region (L4). CTV=clinical target volume. CTVn_L=CTV of corresponding nodal level¶. ER=oestrogen receptor. ESTRO=European Society for Radiotherapy and Oncology. PR=progesterone receptor. HER2=Human epidermal growth factor receptor 2. IMN=internal mammary nodal level. IMRT=intensity modulated radiation therapy. RT3D=conformal 3D radiation therapy. SIB=simultaneous integrated tumour-bed boost. *Experimental group was moderately hypofractionated radiation therapy (40 Gy in 15 fractions every 3 weeks, with or without a tumour bed boost). †Standard group was 5-week radiotherapy (50 Gy in 25 fractions every 5 weeks, with or without a tumour bed boost). ‡Breast size was categorised based on bra size as declared by the patient at baseline using chest circumference in cm and the depth of the bra cup (A–G). Small was a chest circumference <80 cm, <80 cm cup A or B, 85 cm cup A or B, or 90 cm with cup A. Medium was chest circumference 80 cm or 85 cm cup size C, 90 cm cup size B or C, or 95 cm cup sizes A–C. Large was counted as any chest circumference >95 cm or cup sizes of ≥D. Unknown refers either to not recorded at baseline or not measurable as a category. §Irradiated nodal levels including Rotter interpectoral levels. ¶CTV delineation was based on ESTRO consensus guidelines.

Table 1: **Baseline demographic, clinical, and treatment characteristics of the per protocol population**

	3-week radiotherapy n/N	5-week radiotherapy n/N	HR (95% CI) 3-week *vs* 5-week radiotherapy	3-week radiotherapy, 5-year rate (95% CI)	5-week radiotherapy, 5-year rate (95% CI)
Arm lymphoedema	143/562	132/551	1·02 (0·79–1·31)	33·1% (28·5–37·8)	32·6% (27·8–37·8)
Range of motion impairment	205/609	199/604	0·97 (0·79–1·19)	39·2% (34·9–43·7)	39·5% (35·1–44·1)
Locoregional relapse-free survival	43/614	58/607	0·62 (0·38–1·01)	92·7% (90·1–94·6)	89·6% (86·6–92·0)
Invasive-disease-free survival.	71/614	89/607	0·60 (0·32–1·14)	87·8% (84·8–90·3)	83·6% (80·1–86·6)
Distant disease-free survival	52/614	70/607	0·54 (0·31–0·96)	91·2% (88·5–93·3)	86·9% (83·7–89·6)
Breast cancer-specific survival	24/614	35/607	0·53 (0·30–0·94)	95·9% (93·8–97·3)	93·9% (91·4–95·7)
Overall survival	36/614	51/607	0·59 (0·37–0·93)	94·0% (91·6–95·7)	90·8% (87·9–93·1)

Data are n=number of events and N=number of participants. HR=hazard ratio.

Table 2: **Time-to-event outcomes in the per protocol population**

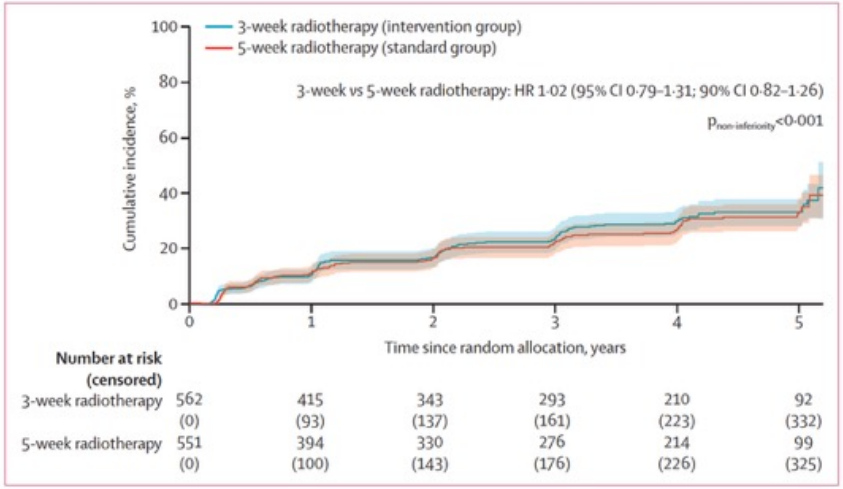


Figure 2: **Cumulative incidence of ipsilateral arm lymphoedema by fractionation schedule in the per-protocol population**

3-week radiotherapy (experimental group) comprised moderately hypofractionated radiation therapy (40 Gy in 15 fractions every 3 weeks, with or without a tumour bed boost). 5-week radiotherapy (standard group) comprised 50 Gy in 25 fractions every 5 weeks, with or without a tumour bed boost. HR=hazard ratio.

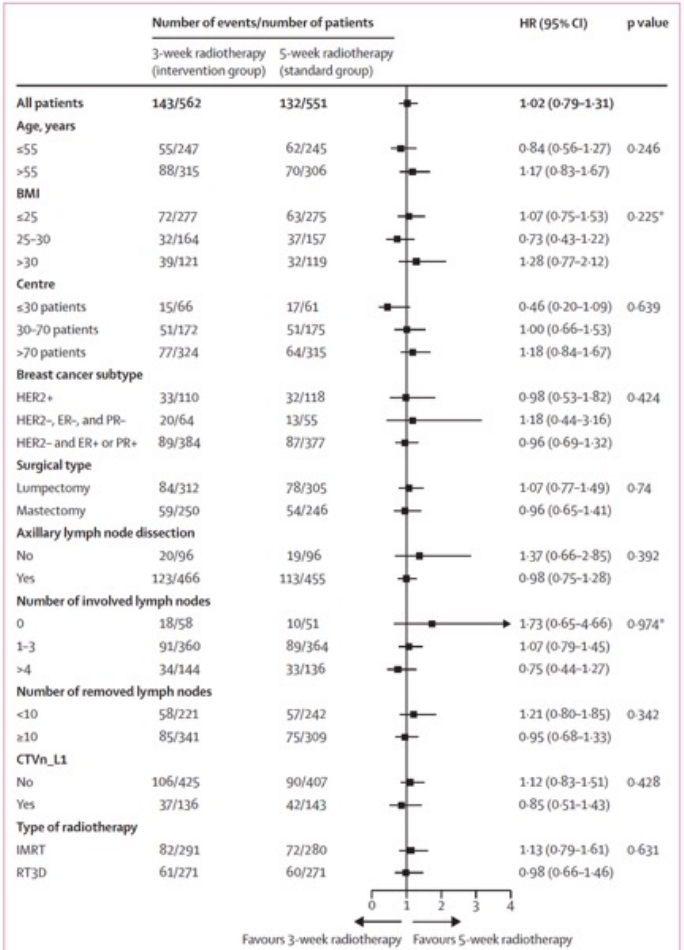


Figure 3: **Hazard ratios for risk of arm lymphoedema by predefined factors in the per-protocol population**

Forest plot of subgroup analysis for the primary endpoint of arm lymphoedema. p-values correspond to tests for interaction, or for trend. Asterisks designate tests for trends. 3-week radiotherapy (experimental group) comprised moderately hypofractionated radiation therapy (40 Gy in 15 fractions every 3 weeks, with or without a tumour bed boost). 5-week radiotherapy (standard group) comprised 50 Gy in 25 fractions every 5 weeks, with or without a tumour bed boost. CTVn_L1=Clinical target volume of the nodal level 1. IMRT=intensity modulated radiation therapy. RT3D=conformal 3D radiation therapy. HER2=human epidermal growth factor receptor 2. ER=oestrogen receptor. PR=progesterone receptor.

Research in context

Evidence before this study

Approximately one-third of breast cancer patients are diagnosed with regional-stage disease and require regional nodal irradiation as part of their treatment to reduce the risk of recurrence and improve survival. Hypofractionated radiotherapy has been shown to be non-inferior to the historical 50 Gy in 25 fractions over 5 weeks for whole breast irradiation with level 1A evidence, introducing a major shift in modern breast cancer management when no regional irradiation was needed. The UK START trials established that 40 Gy in 15 fractions is non-inferior to 50 Gy in 25 fractions for efficacy outcomes and is associated with lower rates of late normal tissue effects. We searched PubMed on Oct 2, 2025, using the search terms "breast cancer", "regional nodal irradiation", "hypofractionation", and "randomised clinical trials" and combinations thereof. We searched for original research articles and reviews published in English between Jan 1, 1980, and April 22, 2020. We found the primary endpoint report of three randomised studies (one phase 2, two phase 3) testing adjuvant locoregional hypofractionated radiotherapy against 5-week regimens, ranging in sample size from 50 to 820 patients. All offered consistent support for hypofractionation but only the smallest one included irradiation of the internal mammary chain and a small proportion of patients were irradiated on the lower axilla. Previously, the Early Breast Cancer Trialists' Collaborative Group meta-analysis has shown that regional irradiation improves survival in women receiving effective local and systemic therapies. As none of the included trials used hypofractionation, the morbidity and risk/benefit of hypofractionated regional irradiation remained to be evaluated.

Added value of this study

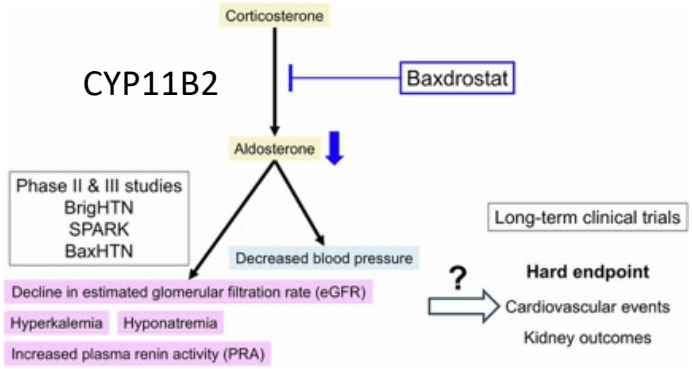
The UNICANCER HypoG-01 trial, alongside the Danish Breast Cancer Group Skagen trial 1, are the first phase III randomised controlled trials to publish 5-year outcome data specifically comparing locoregional radiotherapy over 3 weeks with 40 Gy in 15 fractions versus 5 weeks with 50 Gy in 25 fractions. HypoG-01 shows non-inferiority of the shorter regimen in terms of ipsilateral arm lymphoedema with a reassuring safety profile. Additionally, HypoG-01 trial provides contemporary evidence confirming the safety of moderately hypofractionated radiotherapy for comprehensive regional nodal volumes, including the internal mammary nodes (IMN) on survival endpoints: locoregional relapse-free survival, distant disease-free survival, breast cancer specific-survival, and overall survival. While 40 Gy in 15 fractions has been the standard of care for nodal irradiation in the UK since NICE guidance in 2009, based on the 5-year results of the START B trial, IMN irradiation was not carried out in the trial. Hypofractionation adoption for IMN irradiation became widespread in the UK following the 2016 consensus of the UK Royal College of Radiologists. HypoG-01 provides robust, prospective data from a phase 3 trial specifically designed to assess the lymphoedema risk of this modern treatment approach, confirming its safety and supporting its use as a global standard of care.

Implications of all the available evidence

HypoG-01 provides evidence that moderately hypofractionated, 3-week, locoregional radiotherapy is a safe alternative to historical 5-week radiotherapy for patients with high-risk early breast cancer requiring nodal irradiation. Survival outcomes in HypoG-01 are encouraging and should be integrated with evidence from efficacy-focused trials. Our findings contribute to a growing body of evidence supporting a shift in clinical practice towards a 3-week radiotherapy standard of care, offering substantial benefits to both patients and health-care systems, increasing treatment sustainability without compromising oncological outcomes.

THE LANCET

Baxdrostat ist ein neuartiger, hochselektiver Aldosteron-Synthase-Inhibitor, der in klinischen Studien (insb. Phase 2 BrigHTN, Phase 3 BaxHTN) eine signifikante, dosisabhängige Senkung des systolischen und diastolischen Blutdrucks bei therapieresistenter Hypertonie zeigte. Durch die gezielte Hemmung der Aldosteronproduktion, ohne die Cortisolsynthese zu beeinflussen, bietet es eine vielversprechende Behandlungsoption mit gutem Sicherheitsprofil.



- **Wirkmechanismus:** Es hemmt selektiv das Enzym CYP11B2 (Aldosteron-Synthase), welches für die Produktion von Aldosteron in der Nebenniere verantwortlich ist.
- **Anwendungsgebiete:** Primär untersucht bei therapieresistenter oder unkontrollierter Hypertonie (Blutdruck >130/80 mmHg trotz Multi-Drug-Therapie).
- **Studienergebnisse:** In der Phase-3-Studie BaxHTN reduzierte 1 mg bzw. 2 mg Baxdrostat den systolischen Blutdruck signifikant (Placebo-adjustiert um ca. 8,7–9,8 mmHg).
- **Sicherheit:** Bisher zeigten sich überwiegend milde Nebenwirkungen. Relevante Kaliumanstiege (>5.4 mmol/l) traten selten auf.

Effect of baxdrostat on ambulatory blood pressure in patients with resistant hypertension (Bax24): a phase 3, randomised, double-blind, placebo-controlled trial

Summary

Background Aldosterone dysregulation is an important contributor in the pathogenesis of hard-to-control hypertension. We aimed to assess the effect of baxdrostat, a selective aldosterone synthase inhibitor, on ambulatory blood pressure in patients with resistant hypertension.

Methods The Bax24 international, phase 3, randomised, double-blind, placebo-controlled trial recruited adults (aged ≥18 years) with seated systolic blood pressure (SBP) ≥140 mm Hg and <170 mm Hg, despite receiving three or more antihypertensive medications, including a diuretic, from 79 clinical sites (primary, secondary, and tertiary centres, in addition to research centres) in 22 countries. Following a 2-week placebo run-in period, patients with 24 h ambulatory SBP ≥130 mm Hg were randomly assigned (1:1) to receive 2 mg baxdrostat or placebo orally once daily for 12 weeks, in addition to background therapy (stratified by baseline ambulatory SBP <140 mm Hg or ≥140 mm Hg). Investigators, patients, and trial staff were masked to treatment assignment. The primary endpoint was change in 24 h ambulatory SBP from baseline to week 12, assessed by analysis of covariance in patients administered at least one dose of study medication with valid ambulatory SBP measurement at baseline and week 12. Missing or invalid ambulatory SBP measurements were not imputed. The safety analysis included all patients who received at least one dose of study medication. This trial is registered with ClinicalTrials.gov, NCT06168409, and is complete.

Findings Between March 1, 2024, and April 16, 2025, 854 patients were screened, 636 were excluded (437 before the placebo run-in and 199 during the placebo run-in) and 217 were randomly assigned to and received baxdrostat (n=108) or placebo (n=109). 140 patients (65%) were male, 77 (35%) patients were female, and 170 patients (78%) were White. The median age was 60·0 years (IQR 51·0–68·0). At 12 weeks, the change from baseline in the least-squares mean 24 h ambulatory SBP was –16·6 mm Hg (95% CI –18·8 to –14·3) in the baxdrostat group (n=89) and –2·6 mm Hg (–4·7 to –0·4) in the placebo group (n=95); the estimated placebo-corrected difference was –14·0 mm Hg (–17·2 to –10·8; p<0·0001). Adverse events occurred in 56 (52%) of 108 patients in the baxdrostat group and 40 (37%) of 109 patients in the placebo group. A confirmed potassium level of more than 6 mmol/L occurred in three (3%) of the 108 baxdrostat recipients and in none of the placebo recipients.

Interpretation Baxdrostat significantly reduced 24 h ambulatory SBP versus placebo in patients with resistant hypertension, providing further evidence of the potential of aldosterone synthase inhibition for treatment of hard-to-control hypertension.

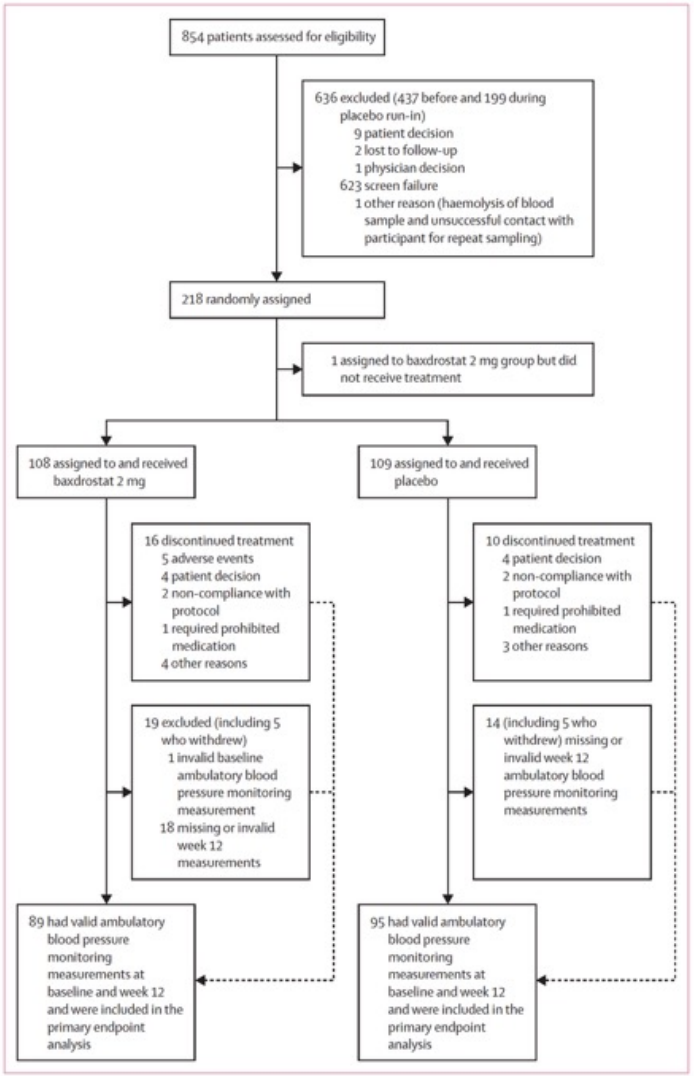


Figure 1: **Trial profile**
Patients who discontinued from the study also accounted for some of the excluded patients.

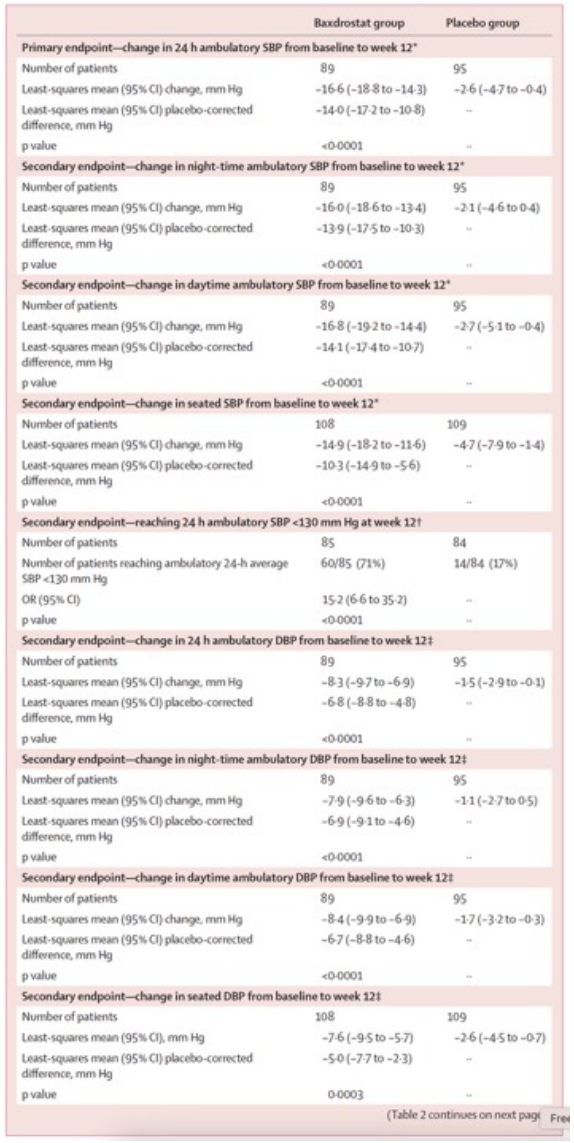
	Baxdrostat group (n=108)	Placebo group (n=109)
Age, years	60·0 (52·0–67·0)	61·0 (51·0–69·0)
Sex		
Male	70 (65%)	70 (64%)
Female	38 (35%)	39 (36%)
Race*		
White	86 (80%)	84 (77%)
Black	4 (4%)	6 (6%)
Asian	16 (15%)	19 (17%)
Multiple or other	2 (2%)	0
Ethnicity*		
Hispanic or Latino	25 (23%)	21 (19%)
Not Hispanic or Latino	82 (76%)	84 (77%)
BMI (kg/m²)	32·4 (28·4–36·1)	31·6 (27·9–35·8)
≥30	70 (65%)	66 (61%)
Ambulatory systolic blood pressure (mm Hg)†		
24 h average	140·5 (8·4)	141·8 (11·8)
Night-time average	133·6 (11·0)	135·4 (14·1)
Daytime average	144·0 (8·7)	145·0 (11·8)
Ambulatory diastolic blood pressure (mm Hg)†		
24 h average	79·7 (9·2)	80·0 (9·3)
Night-time average	74·0 (9·4)	74·7 (10·1)
Daytime average	82·6 (9·8)	82·8 (9·5)
Seated blood pressure (mm Hg)		
Systolic	146·9 (12·0)	148·3 (14·5)
Diastolic	85·4 (11·6)	85·7 (9·2)
Dipping status‡		
Dipping	34 (31%)	34 (31%)
Non-dipping	73 (68%)	75 (69%)
Missing	1 (1%)	0
eGFR (mL/min per 1·73 m²)§	86·3 (18·1)	84·8 (19·5)
<60 mL/min per 1·73 m²	11 (10%)	14 (13%)
Medical history		
Type 2 diabetes	35 (32%)	39 (36%)
Dyslipidaemia	27 (25%)	39 (36%)
Myocardial infarction	7 (6%)	1 (1%)
Coronary revascularisation	7 (6%)	3 (3%)
Stroke	6 (6%)	6 (6%)
Sleep apnoea	6 (6%)	15 (14%)
Heart failure¶	5 (5%)	9 (8%)
Hypokalaemia	3 (3%)	3 (3%)
Peripheral arterial disease	3 (3%)	4 (4%)
Transient ischaemic attack	1 (1%)	1 (1%)
Primary aldosteronism	0	1 (1%)

(Table 1 continues in next column)

	Baxdrostat group (n=108)	Placebo group (n=109)
(Continued from previous column)		
Serum potassium (mmol/L)	4·14 (0·42)	4·10 (0·43)
Serum sodium (mmol/L)	140·2 (2·6)	139·9 (2·6)
Serum aldosterone (ng/dL)‖	7·6 (5·2–13·2)	9·0 (5·3–12·6)
Plasma renin activity (ng/mL per h)**	1·2 (0·7–3·5)	0·9 (0·4–2·5)
Time since hypertension diagnosis, years	10·0 (4·0–18·5)	11·0 (7·0–21·0)
Background antihypertensive medications		
Mean number of medications (range)	3·7 (3–6)	3·8 (3–6)
3	56 (52%)	46 (42%)
4	37 (34%)	41 (38%)
5 or more	15 (14%)	22 (20%)
Background classes of antihypertensive medications		
Diuretic	108 (100%)	109 (100%)
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker	100 (93%)	104 (95%)
Calcium channel blocker	96 (89%)	95 (87%)
Beta blocker	49 (45%)	56 (51%)
Other††	35 (32%)	44 (40%)

Data are n (%), mean (SD), or median (IQR). Baseline characteristics are shown for all the patients who underwent randomisation and received at least one dose of baxdrostat or placebo. Percentages may not total 100 because of rounding. eGFR=estimated glomerular filtration rate. *Race and ethnic group were reported by the patients; "multiple" and "other" race was recorded for one patient each receiving baxdrostat. †Data for 107 patients receiving baxdrostat and 109 patients receiving placebo with valid ambulatory blood pressure monitoring measurements at baseline. ‡Patients with at least a 10% reduction in night-time systolic blood pressure compared with daytime systolic blood pressure are characterised as dippers. §eGFR was calculated according to the Chronic Kidney Disease Epidemiology Collaboration equation as described by Inker and colleagues.[14] ¶Heart failure was documented according to the clinical record only and was not independently evaluated or defined further (eg, as heart failure with preserved ejection fraction or heart failure with reduced ejection fraction). ‖Data for 106 patients receiving baxdrostat and 103 patients receiving placebo with measurements of serum aldosterone at baseline. **Data for 70 patients receiving baxdrostat and 73 patients receiving placebo with measurements of plasma renin activity at baseline. ††Other antihypertensive medications included hydralazine (baxdrostat: six [6%]; placebo: six [6%]), alpha-1 blockers (baxdrostat: 18 [17%]; placebo: 24 [22%]), and centrally acting drugs (baxdrostat: 15 [14%]; placebo: 19 [17%]).

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



	Baxdrostat group	Placebo group
Primary endpoint—change in 24 h ambulatory SBP from baseline to week 12*		
Number of patients	89	95
Least-squares mean (95% CI) change, mm Hg	−16·6 (−18·8 to −14·3)	−2·6 (−4·7 to −0·4)
Least-squares mean (95% CI) placebo-corrected difference, mm Hg	−14·0 (−17·2 to −10·8)	..
p value	<0·0001	..
Secondary endpoint—change in night-time ambulatory SBP from baseline to week 12*		
Number of patients	89	95
Least-squares mean (95% CI) change, mm Hg	−16·0 (−18·6 to −13·4)	−2·1 (−4·6 to 0·4)
Least-squares mean (95% CI) placebo-corrected difference, mm Hg	−13·9 (−17·5 to −10·3)	..
p value	<0·0001	..
Secondary endpoint—change in daytime ambulatory SBP from baseline to week 12*		
Number of patients	89	95
Least-squares mean (95% CI) change, mm Hg	−16·8 (−19·2 to −14·4)	−2·7 (−5·1 to −0·4)
Least-squares mean (95% CI) placebo-corrected difference, mm Hg	−14·1 (−17·4 to −10·7)	..
p value	<0·0001	..
Secondary endpoint—change in seated SBP from baseline to week 12*		
Number of patients	108	109
Least-squares mean (95% CI) change, mm Hg	−14·9 (−18·2 to −11·6)	−4·7 (−7·9 to −1·4)
Least-squares mean (95% CI) placebo-corrected difference, mm Hg	−10·3 (−14·9 to −5·6)	..
p value	<0·0001	..
Secondary endpoint—reaching 24 h ambulatory SBP <130 mm Hg at week 12†		
Number of patients	85	84
Number of patients reaching ambulatory 24-h average SBP <130 mm Hg	60/85 (71%)	14/84 (17%)
OR (95% CI)	15·2 (6·6 to 35·2)	..
p value	<0·0001	..
Secondary endpoint—change in 24 h ambulatory DBP from baseline to week 12‡		
Number of patients	89	95
Least-squares mean (95% CI) change, mm Hg	−8·3 (−9·7 to −6·9)	−1·5 (−2·9 to −0·1)
Least-squares mean (95% CI) placebo-corrected difference, mm Hg	−6·8 (−8·8 to −4·8)	..
p value	<0·0001	..
Secondary endpoint—change in night-time ambulatory DBP from baseline to week 12‡		
Number of patients	89	95
Least-squares mean (95% CI) change, mm Hg	−7·9 (−9·6 to −6·3)	−1·1 (−2·7 to 0·5)
Least-squares mean (95% CI) placebo-corrected difference, mm Hg	−6·9 (−9·1 to −4·6)	..
p value	<0·0001	..
Secondary endpoint—change in daytime ambulatory DBP from baseline to week 12‡		
Number of patients	89	95
Least-squares mean (95% CI) change, mm Hg	−8·4 (−9·9 to −6·9)	−1·7 (−3·2 to −0·3)
Least-squares mean (95% CI) placebo-corrected difference, mm Hg	−6·7 (−8·8 to −4·6)	..
p value	<0·0001	..
Secondary endpoint—change in seated DBP from baseline to week 12‡		
Number of patients	108	109
Least-squares mean (95% CI), mm Hg	−7·6 (−9·5 to −5·7)	−2·6 (−4·5 to −0·7)
Least-squares mean (95% CI) placebo-corrected difference, mm Hg	−5·0 (−7·7 to −2·3)	..
p value	0·0003	..

(Table 2 continues on next page)

	Baxdrostat group	Placebo group
(Continued from previous page)		
Secondary endpoint—reaching a nocturnal SBP dipping of ≥10% at week 12§		
Number of patients	89	95
Number of patients reaching a nocturnal SBP dipping of ≥10%	36/89 (40%)	28/95 (29%)
OR (95% CI)	1·6 (0·9 to 3·0)	..
p value	0·15	..

For analyses of ambulatory blood pressure endpoints, in the baxdrostat group, one patient was excluded due to an invalid baseline ambulatory blood pressure monitoring measurement and 18 patients were excluded due to missing or invalid week 12 ambulatory blood pressure monitoring measurements; in the placebo group, 14 patients were excluded due to missing or invalid week 12 ambulatory blood pressure monitoring measurements. Missing data were imputed for seated blood pressure endpoints only. DBP=diastolic blood pressure. OR=odds ratio. SBP=systolic blood pressure. *Endpoint analysed using an ANCOVA model with treatment as a factor; the covariate was baseline 24 h ambulatory SBP, night-time ambulatory SBP, daytime ambulatory SBP, or seated SBP, as appropriate for the endpoint. †Endpoint analysed using a logistic regression model with treatment as a factor and baseline 24 h ambulatory SBP as a covariate; only patients with baseline 24 h ambulatory SBP of 130 mm Hg or higher were included in the analysis. ‡Endpoint analysed using an ANCOVA model with treatment as a factor; the covariate was baseline 24 h ambulatory DBP, night-time ambulatory DBP, daytime ambulatory DBP, or seated DBP, as appropriate for the endpoint. §Endpoint analysed using a logistic regression model with treatment as a factor and baseline dipping status as a covariate.

***Table 2*: Primary and secondary endpoints in hierarchical order in the modified intention-to-treat population**

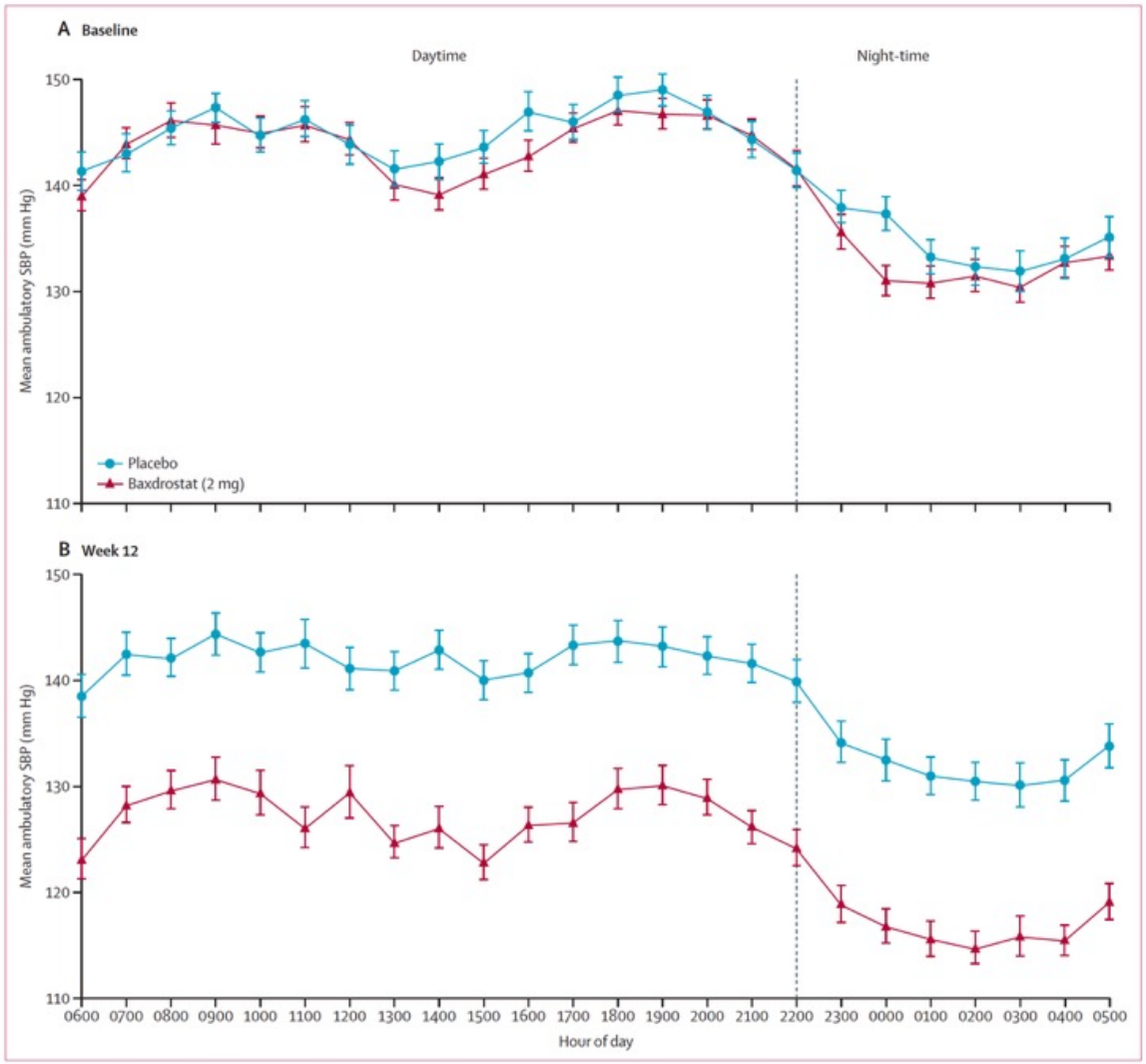


Figure 2: **Hourly mean ambulatory systolic blood pressure profile over 24 h at baseline (A) and week 12 (B)**
Error bars represent SE. The daytime period was 0600 h to 2159 h; the night-time period was 2200 h to 0559 h. SBP=systolic blood pressure.

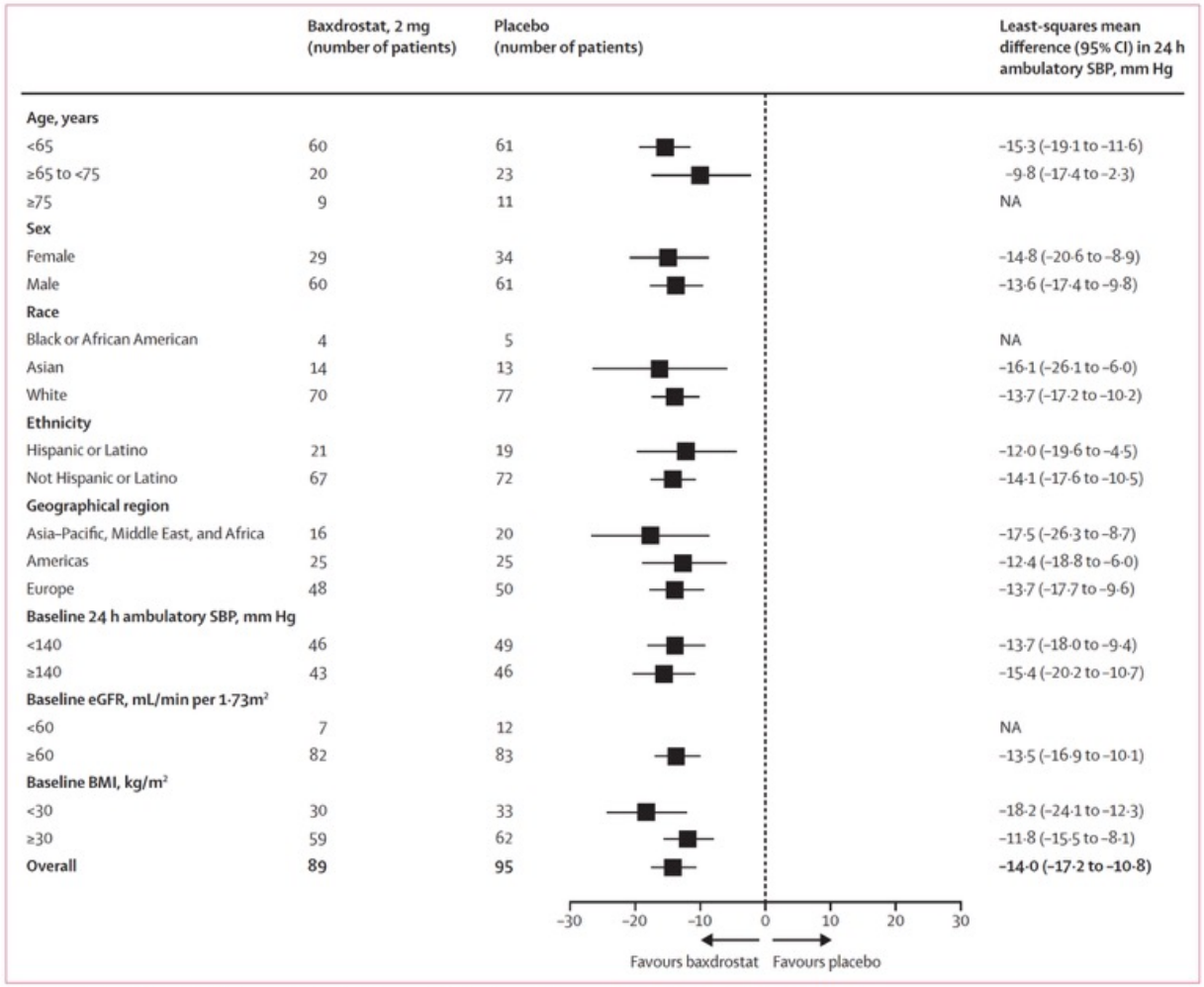


Figure 3: **Change from baseline in 24 h ambulatory systolic blood pressure at week 12 by prespecified subgroup**
The forest plot shows least-squares mean difference versus placebo for change from baseline in 24 h ambulatory SBP at week 12 with baxdrostat 2 mg, by subgroup. The squares denote the point estimates. Treatment difference was not analysed for subgroups with fewer than ten patients within treatment groups. Interaction p values for all the subgroup analyses were more than 0·05. eGFR=estimated glomerular filtration rate. NA=not applicable. SBP=systolic blood pressure.

	Baxdrostat group (n=108)	Placebo group (n=109)
Any serious adverse event*	1 (1%)	1 (1%)
Death	0	0
Any adverse event	56 (52%)	40 (37%)
Moderate or severe	15 (14%)	8 (7%)
Severe	2 (2%)	1 (1%)
Adverse event leading to discontinuation†		
Any	5 (5%)	0
Hyperkalaemia leading to discontinuation	2 (2%)	0
Adverse event of special interest‡		
Hyperkalaemia	7 (6%)	1 (1%)
Hyponatraemia	1 (1%)	1 (1%)
Hypotension	1 (1%)	0
Serum potassium concentration, mmol/L§		
>5·5	13/107 (12%)	3 (3%)
>6·0	5 (5%)	0
>6·5	1 (1%)	0
More than 30% decrease in estimated glomerular filtration rate at any time from baseline to 14 weeks§	26 (24%)	5 (5%)

Data are n (%) or n/N (%). Adverse events were collected throughout the trial (ie, up to 14 weeks and including the 2-week treatment withdrawal period). *No serious adverse event was deemed by the investigators to be related to baxdrostat. †Other adverse events leading to discontinuation in the baxdrostat group were hyponatraemia (1 [1%]), arthralgia (1 [1%]), and serum potassium increase (1 [1%]). ‡Low sodium concentration, low blood pressure, and elevated potassium concentration were reported as adverse events of special interest if they required clinical intervention. §Complete clinical chemistry treatment-emergent abnormalities by predefined criteria are reported in the appendix (p 52).

Table 3: **Adverse events in the safety population**

Research in context

Evidence before this study

We searched PubMed for papers published between Jan 1, 2010, and Oct 15, 2025, using the search terms "aldosterone synthase inhibitors", "hypertension", "placebo", "randomised controlled trials", "meta-analysis", "systematic review", and various combinations of these words with no language restrictions. We aimed to identify systematic reviews and meta-analyses of blood pressure-lowering efficacy of aldosterone synthase inhibitors that specifically included those with selectivity for aldosterone synthase (cytochrome P450 11B2, mitochondrial; CYP11B2) versus cortisol synthase (cytochrome P450 11B1, mitochondrial; CYP11B1). We identified seven meta-analyses, two of which only included trials with the aldosterone synthase inhibitor lorundrostat. Four others included trials conducted in settings other than hypertension or involved the non-selective aldosterone synthase inhibitor osilodrostat, which was later developed for Cushing's disease. A 2025 meta-analysis, including four placebo-controlled trials of selective aldosterone synthase inhibitors (baxdrostat and lorundrostat) in patients with uncontrolled or resistant hypertension (1838 patients), reported a mean reduction in office systolic blood pressure (SBP) of −8·21 mm Hg (95% CI −10·64 to −5·78) and in diastolic blood pressure of −3·64 mm Hg (−5·65 to −1·63) compared with placebo. None of the meta-analyses reported 24 h ambulatory blood pressure reductions because only a single trial has previously reported changes in 24 h ambulatory blood pressure with lorundrostat, but did not report night-time blood pressure changes, a parameter most closely associated with all-cause and cardiovascular mortality risk. This trial (Advance-HTN), which included 285 patients with either uncontrolled or resistant hypertension, reported a placebo-adjusted change in 24 h ambulatory SBP at 12 weeks of −7·9 mm Hg (97·5% CI −13·3 to −2·6) with lorundrostat 50 mg daily and of −6·5 mm Hg (−11·8 to −1·2) in those up-titrated to lorundrostat 100 mg daily.

Added value of this study

The Bax24 trial was designed to assess the 24 h ambulatory blood pressure-lowering effect of baxdrostat in patients with true resistant hypertension despite treatment with three or more antihypertensive medications, including a diuretic, confirmed by ambulatory blood pressure monitoring. Baxdrostat 2 mg daily added to background antihypertensive therapy was associated with the largest placebo-corrected reductions in 24 h ambulatory SBP ever reported in patients with resistant hypertension, as well as very substantial reductions in night-time SBP, which might provide additional benefits in reducing cardiovascular events. Furthermore, the magnitude of the placebo-corrected office SBP reduction with baxdrostat was consistent with the results of the meta-analysis of selective aldosterone synthase inhibitors.

Implications of all the available evidence

Existing data show that selective aldosterone inhibitors significantly reduce office blood pressure in patients with resistant as well as uncontrolled hypertension and are generally well tolerated. Aldosterone synthase inhibitors might raise serum potassium concentrations and be associated with a functional decrease in estimated glomerular filtration rate due to improved blood pressure control. However, data on 24 h blood pressure lowering are scarce, and no data on night-time blood pressure have been reported. The Bax24 study provides the most comprehensive data to date on the effect of selective aldosterone synthase inhibition with baxdrostat on 24 h and night-time blood pressure.

Is CYP11B2 inhibition better than spironolactone?

Was cortisol production reduced?

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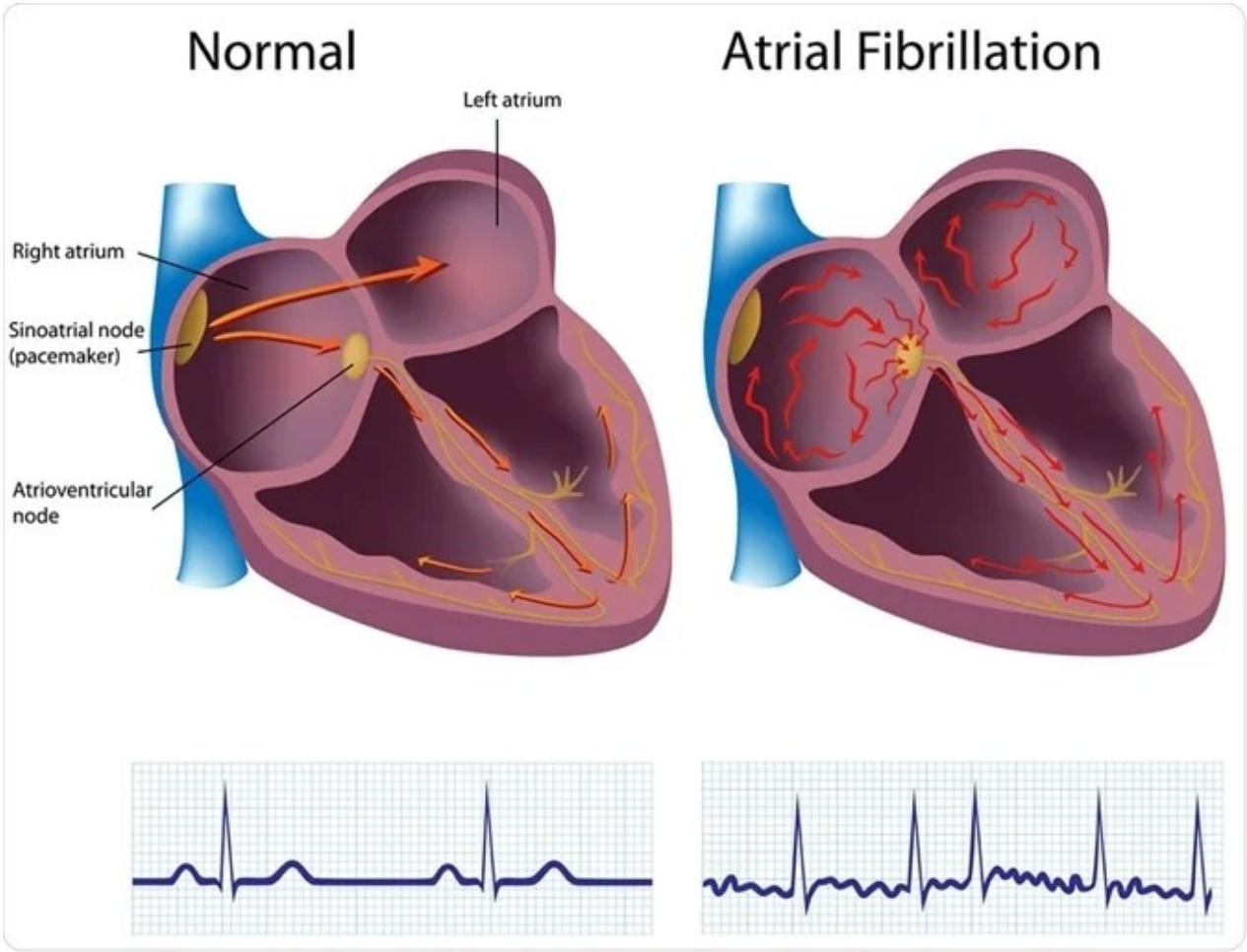
Normal
Atrial Fibrillation
Left atrium
Right atrium
Sinoatrial node
(pacemaker)
Atrioventricular
node

Atrial fibrillation

Atrial fibrillation affects approximately 37·6 million people worldwide, with the prevalence predicted to double over the next 35 years. The ubiquitous use of wearable devices and other technologies with inbuilt diagnostic algorithms allows greater detection of atrial fibrillation among the general public than previously. Atrial fibrillation increases the risk of stroke and thromboembolism, heart failure, and death, and is associated with reductions in quality of life. Patients with atrial fibrillation frequently have comorbidities, and the accumulation of risk factors, including lifestyle factors associated with poorer health outcomes, and increasing age, often adds to the complexity of managing such patients. All major clinical guidelines advocate that stroke prevention, symptom relief, identification of risk factors, and optimisation of risk factor management, incorporated into an integrated care approach, with multidisciplinary input as required, are essential elements of atrial fibrillation management. Avoidance of stroke with oral anticoagulation remains the default for most patients with atrial fibrillation and, more recently, catheter ablation has been reconsidered as an initial treatment option for symptom relief. The dynamic nature of risk factors requires early identification and appropriate management of new and existing risk factors to optimise atrial fibrillation care. Patient-centred care and better health literacy can empower patients to take a more active role in their atrial fibrillation management.

These management frameworks are similar

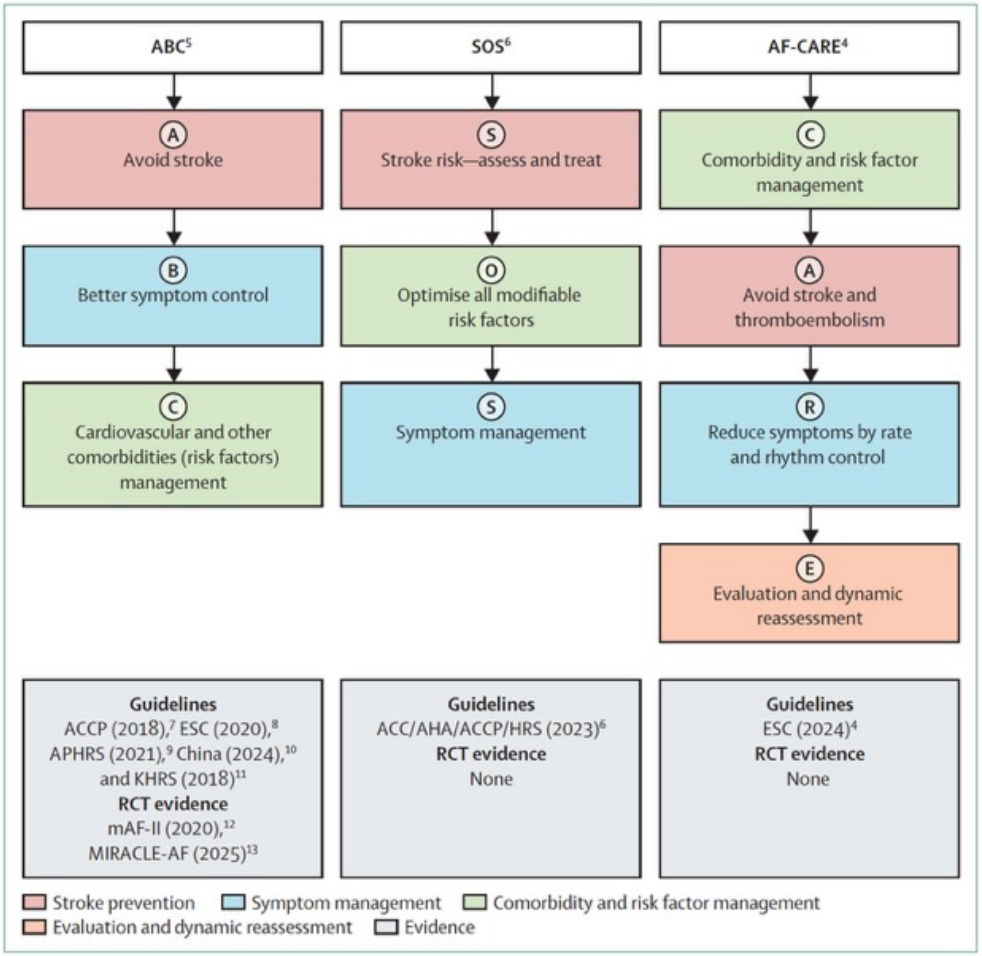

Figure 1: **Atrial fibrillation management frameworks**
ABC=Atrial Fibrillation Better Care pathway. ACC=American College of Cardiology. ACCP=American College of Chest Physicians. AHA=American Heart Association. APHRS=Asia Pacific Heart Rhythm Society. ESC=European Society of Cardiology. HRS=Heart Rhythm Society. KHRS=Korean Heart Rhythm Society. RCT=randomised controlled trial. SOS=stroke risk, optimise risk factor management, and symptom management.

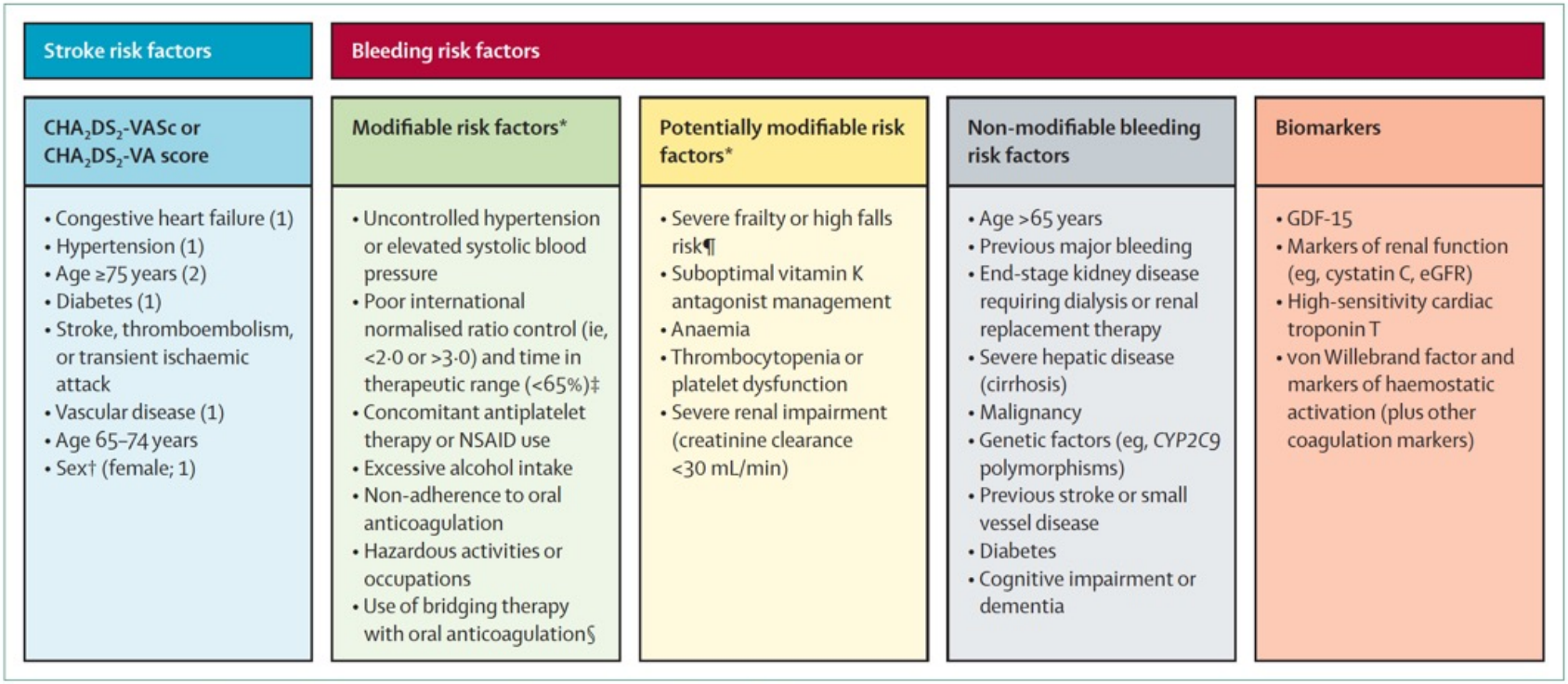

Figure 2: **Stroke and bleeding risk factors assessment for patients with atrial fibrillation**
Adapted from Lip et al,[7] by permission of the authors. Numbers in parentheses indicate the point weights assigned to each component of the score. NSAIDs=non-steroidal anti-inflammatory drugs. *Increased international normalised ratio monitoring, dedicated oral anticoagulation clinics, self-monitoring or self-management, educational or behavioural interventions. †Sex is not included as a category in the CHA_2DS_2-VA score. ‡For patients receiving vitamin K antagonist treatment. §Dose based on patient's age, bodyweight, and serum creatinine concentration. ¶Walking aids and appropriate footwear, home review to remove trip hazards, and neurological assessment where appropriate.

GDF15 (Growth Differentiation Factor 15) ist ein körpereigenes Protein, das als zentraler Botenstoff für zellulären Stress und als wichtiger Regulator des Stoffwechsels fungiert.

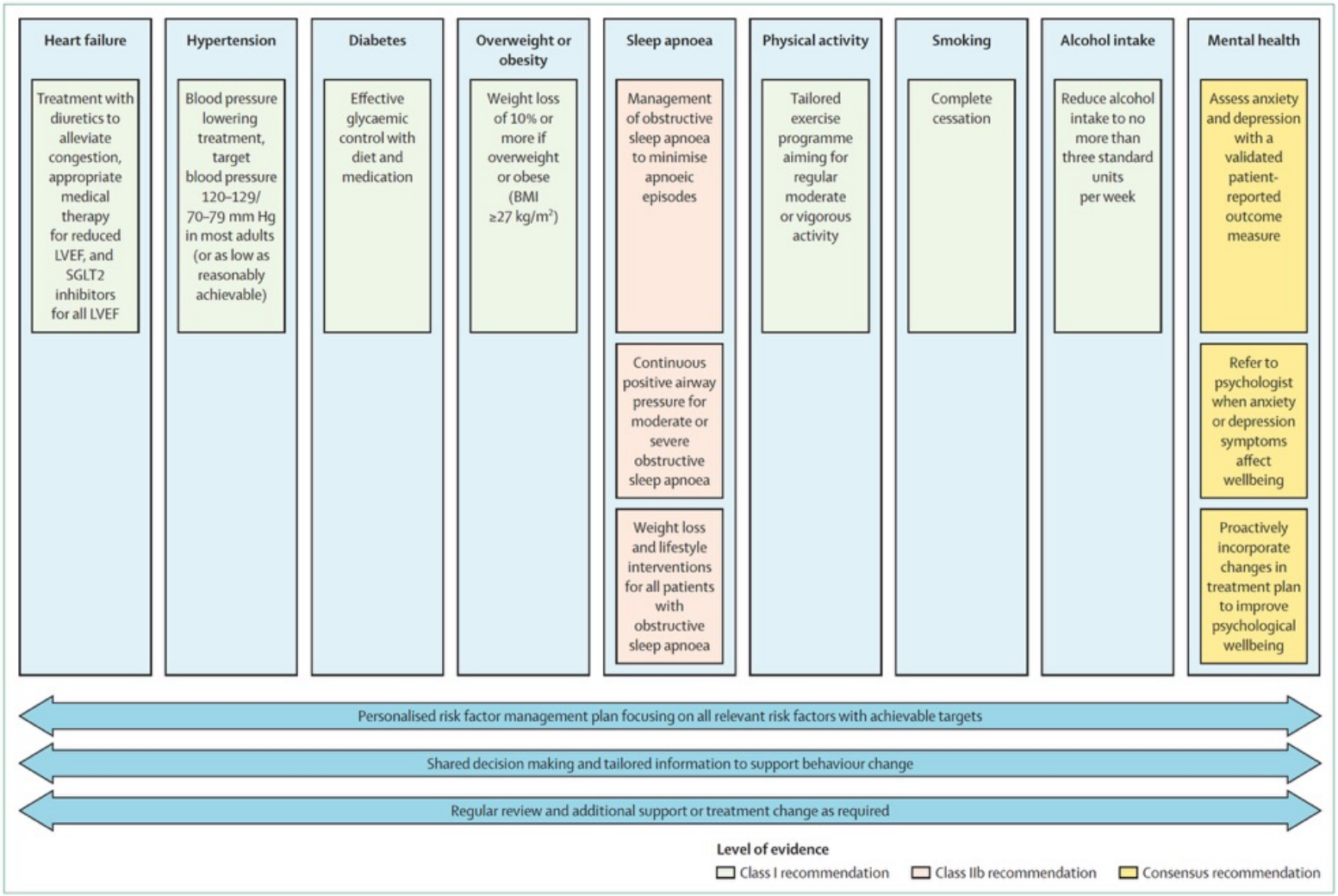

Figure 3: **Comorbidity and risk factor management for patients with atrial fibrillation**
Adapted from Van Gelder et al.[4] Levels of evidence as defined by European guidelines.[4] LVEF=left ventricular ejection fraction. SGLT2=sodium–glucose co-transporter-2.

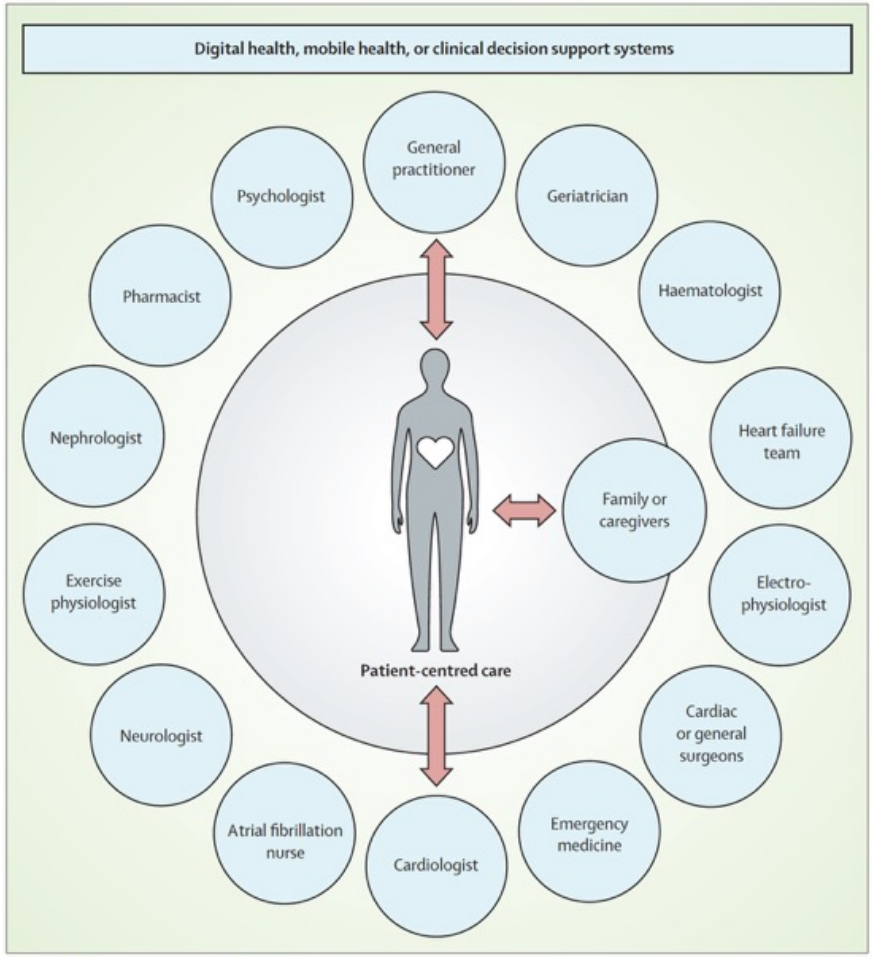

Figure 4: **Integrated atrial fibrillation management team**
The composition of the atrial fibrillation management team is dependent on many factors (eg, clinical status of patient, their comorbidities, cultural and country specific factors, or organisation of the health-care system). For example, for patients requiring catheter ablation, involvement of an electrophysiologist is required. For patients where atrial fibrillation is detected after stroke, a stroke physician, neurologist, or geriatrician might be involved in their care. Most patients with atrial fibrillation are managed by their general practitioner or cardiologist.

Concluding remarks

Global guidelines for the management of atrial fibrillation recommend an integrated approach to provide comprehensive, patient-centred care, tailored to the needs and preferences of patients, aligned with the latest evidence, provided by a multidisciplinary team, and supported by digital and mobile health and wearable devices. Crucial components of atrial fibrillation care are avoidance of stroke with oral anticoagulation, identification and optimal management of comorbidities and lifestyle risk factors, and reduction or alleviation of symptoms. For stroke prevention, the default should be oral anticoagulation, preferably a direct oral anticoagulant, unless the patient is at low risk of stroke based on the CHA_2DS_2-VA or CHA_2DS_2-VASc score (no oral anticoagulation required), has a mechanical heart valve or moderate-to-severe mitral stenosis (vitamin K antagonist recommended), or creatinine clearance of less than 30 min/L. Rhythm control can improve symptoms, quality of life, and reduce health-care use, particularly when pursued with catheter ablation. Regular patient review is warranted as risk factors and treatment effectiveness can change over time, requiring alterations to the treatment plan. For patients with atrial high-rate episodes or subclinical atrial fibrillation, personalised and shared decision making on the risk–benefit of oral anticoagulation according to the patient's profile is needed, combined with monitoring to detect progression to clinical atrial fibrillation or atrial high-rate episodes or subclinical atrial fibrillation of long duration.

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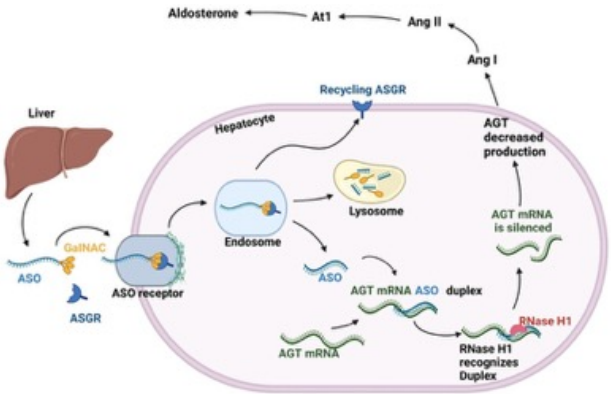
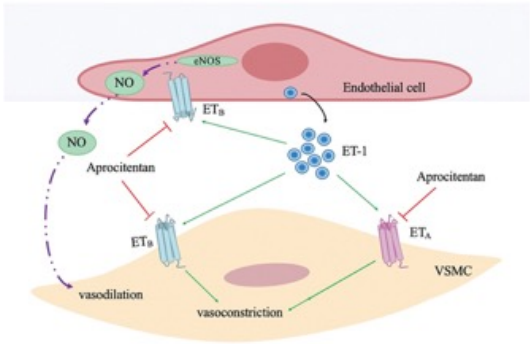
„Newer“ blood pressure-lowering drugs

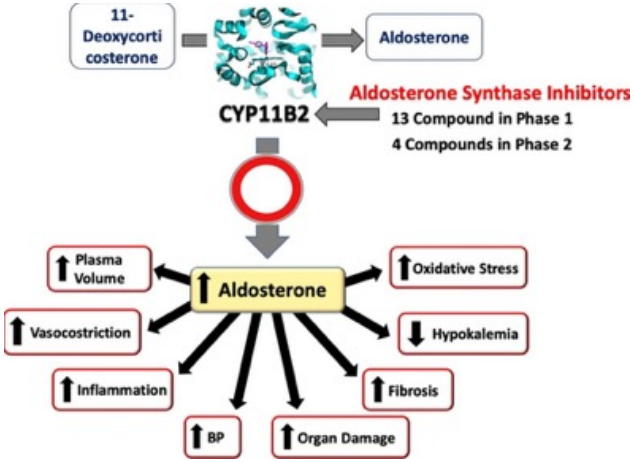
siRNA against Angiotensinogen



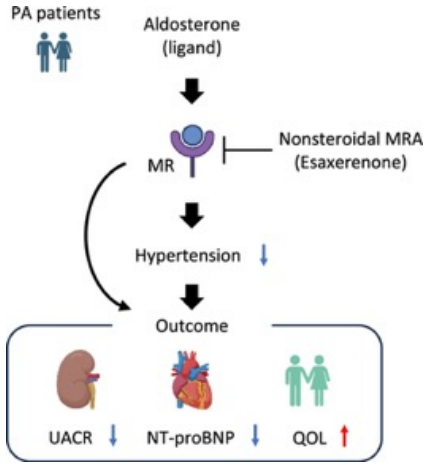
ETA and ETB Receptor Blocker



Aldosterone Synthase Inhibitors



Nonsteroidal MR Antagonists



New drug therapies for hypertension

Despite the availability of effective antihypertensive therapies, global blood pressure control rates remain unacceptably low. Contributing factors, such as low treatment adherence, therapeutic inertia, and rising multimorbidity, underscore the need for innovative approaches to improve hypertension care. New antihypertensive drug therapies that act on physiological pathways beyond those targeted by conventional drug classes are emerging. These therapies include small interfering RNA agents that inhibit angiotensinogen synthesis as a novel approach to inhibit the renin–angiotensin system, and new strategies to more selectively modulate aldosterone, such as aldosterone synthase inhibitors and non-steroidal mineralocorticoid receptor antagonists. There is also growing interest in therapies to enhance the action of the natriuretic peptide system. Although these innovations present valuable therapeutic opportunities, their benefits must be carefully balanced against considerations of safety, cost, clinical outcomes, and equitable access—all of which are crucial to reducing the residual burden of cardiovascular and chronic kidney disease.

Is this statement really true? What about ARBs, ACE inhibitors, Aliskiren, and Spironolactone?
Endothelin pathway has been known for 40 years (1988).

Zilbesiran knocks down angiotensinogen

	KARDIA-1 (phase 2, dose-ranging),[18] n=394	KARDIA-2 (phase 2, add-on therapy),[19] n=663	KARDIA-3 (phase 2, add-on therapy),[20] n=663
Patient population	Patients with mild-to-moderate hypertension either untreated or receiving a stable regimen of up to two antihypertensive medications; daytime ambulatory systolic blood pressure of 135–160 mm Hg following washout of background antihypertensive medications	Patients with uncontrolled hypertension despite receiving one or two antihypertensive medications; 24 h ambulatory systolic blood pressure of 130–160 mm Hg following washout of background antihypertensive medications and a 4-week run-in open-label treatment with indapamide 2·5 mg/day, amlodipine 5 mg/day, or olmesartan 20–40 mg/day*	Patients with established cardiovascular disease, high cardiovascular risk or eGFR ≥30 to <60 mL/min per 1·73 m² and uncontrolled hypertension on two to four antihypertensive medications (including a calcium channel blocker or a diuretic); 24 h ambulatory systolic blood pressure of 140–170 mm Hg; cohort A eGFR ≥45 mL/min per 1·73 m²; and cohort B eGFR 30 mL/min per 1·73 m² to <45 mL/min per 1·73 m² (ongoing)
Intervention	Zilebesiran (subcutaneous injection) 150 mg every 6 months, 300 mg every 6 months or every 3 months, or 600 mg every 6 months, *vs* placebo	Zilebesiran (subcutaneous injection) 600 mg *vs* placebo as a single dose	Cohort A: zilebesiran (subcutaneous injection) 300 mg or 600 mg *vs* placebo as a single dose; cohort B: zilebesiran (subcutaneous injection) 150 mg, 300 mg or 600 mg *vs* placebo, as a single dose (ongoing)
Trial duration	6 months	6 months	6 months
Primary endpoint	Change in 24 h ambulatory systolic blood pressure at month 3: −7·3 mm Hg with 150 mg, −10·0 mm Hg† with 300 mg, −8·9 mm Hg with 600 mg, and 6·8 mm Hg with placebo; difference *vs* placebo: −14·1 mm Hg (−19·2 to −9·0) with 150 mg, −16·7 mm Hg (−21·2 to −12·3)† with 300 mg, and −15·7 mm Hg (−20·8 to −10·6) with 600 mg	Change in 24 h ambulatory systolic blood pressure at month 3: −15·7 mm Hg with indapamide, −10·5 mm Hg with amlodipine, −7·7 mm Hg with olmesartan, and −3·7 mm Hg, −0·7 mm Hg, and −3·2 mm Hg with placebo, respectively; difference *vs* placebo: −12·1 mm Hg (−16·5 to −7·6) with indapamide, −9·7 mm Hg (−12·9 to −6·6) with amlodipine, and −4·5 mm Hg (−8·2 to −0·8) with olmesartan	Change in office systolic blood pressure at month 3†: −12·3 mm Hg with 300 mg, −10·6 mm Hg with 600 mg, and −7·3 mm Hg with placebo; difference *vs* placebo‡: −5·0 mm Hg (−9·9 to −0·2) with 300 mg and −3·9 mm Hg (−8·2 to 1·0) with 600 mg
Additional endpoints	Change in office systolic blood pressure at month 3 (difference *vs* placebo): −9·6 mm Hg (−13·8 to −5·3) with 150 mg, −12·0 mm Hg (−15·7 to −8·3)† with 300 mg, and −9·1 mm Hg (−13·4 to −4·8) with 600 mg; change in 24 h ambulatory systolic blood pressure at 6 months (difference *vs* placebo): −11·1 mm Hg (−15·8 to −6·4) with 150 mg, −14·5 mm Hg (−19·1 to −9·9)† with 300 mg, and −14·2 mm Hg (−18·9 to −9·5) with 600 mg; responder rate at month 6§: 30·8% with 150 mg, 50·7% every 6 months and 38·7% every 3 months with 300 mg, 47·4% with 600 mg, and 6·7% with placebo; add-on use of at least one antihypertensive medication through 6 months: 32·1% with 150 mg, 20·5% every 6 months and 26·7% every 3 months with 300 mg, 27·6% with 600 mg, and 52·0% with placebo; angiotensinogen reduction: >90% (300 mg or 600 mg by month 6)	Change in office systolic blood pressure at month 3 (difference *vs* placebo): −18·5 mm Hg (−22·8 to −14·2) with indapamide, −10·2 mm Hg (−13·4 to −6·9) with amlodipine, and −6·7 mm Hg (−10·2 to −3·3) with olmesartan; time-adjusted change in 24 h ambulatory systolic blood pressure through 6 months (difference *vs* placebo): −11·0 mm Hg (−14·7 to −7·3) with indapamide, −7·9 mm Hg (−10·6 to −5·3) with amlodipine, and −1·8 mm Hg (−4·6 to 1·0) with olmesartan; responder rate at month 6§: 64·2% with indapamide *vs* 14·0% with placebo, 39·8% with amlodipine *vs* 13·7% with placebo, and 26·0% with olmesartan *vs* 17·2% with placebo; rescue antihypertensive medications at month 6: 15·5% with indapamide *vs* 41·7% with placebo, 25·2% with amlodipine *vs* 48·7% with placebo, 42·5% with olmesartan *vs* 54·0% with placebo; angiotensinogen reduction: >95% (all groups)	Change in 24 h ambulatory systolic blood pressure at month 3‡ (difference *vs* placebo): −3·6 mm Hg (−7·7 to 0·4) with 300 mg and −2·6 mm Hg (−6·7 to 1·6) with 600 mg; change in 24 h ambulatory systolic blood pressure at month 6‡ (difference *vs* placebo): −5·5 mm Hg (−9·4 to −1·5) with 300 mg and −7·4 mm Hg (−11·3 to −3·4) with 600 mg; responder rate at month 6: not reported; rescue antihypertensive medications at month 6: not reported; angiotensinogen reduction: not reported
Key safety observations	Hyperkalaemia: 6·3% in all zilebesiran groups *vs* 2·7% with placebo; acute kidney failure: 1·0% in all zilebesiran groups *vs* 0% with placebo; eGFR change at month 6: −1·5% with 150 mg, −2·9% every 6 months and −2·7% every 3 months with 300 mg, −3·0% with 600 mg, and −2·4% with placebo; hypotension: 4·0% in all zilebesiran groups *vs* 0% with placebo; injection-site reactions: 6·3% in all zilebesiran groups *vs* 1·0% with placebo	Hyperkalaemia >5·5 mmol/L: 6·1% in all zilebesiran groups *vs* 1·2% with placebo (indapamide: 3·2%; amlodipine: 6·8%; and olmesartan: 6·7%); ≥30% decrease in eGFR: 8·5% in all zilebesiran groups *vs* 3·0% with placebo (indapamide: 12·7%; amlodipine: 8·5%; and olmesartan: 6·8%); eGFR change at month 6: not reported; hypotension: 4·3% in all zilebesiran groups *vs* 2·1% with placebo (indapamide: 0%; amlodipine: 5·9%; and olmesartan: 4·7%); injection-site reactions: 3·0% in all zilebesiran groups *vs* 0·3% with placebo (indapamide: 6·3%; amlodipine: 1·7%; and olmesartan: 2·7%)	Hyperkalaemia >5·5 mmol/L‡: 4·4% with 300 mg, 8·8% with 600 mg; and 4·5% with placebo; eGFR decrease ≥30% and <60 mL/min per 1·73 m²‡: 5·5% with 300 mg, 8·8% with 600 mg, and 1·1% with placebo; eGFR change at month 6: not reported; hypotension‡: 3·3% with 300 mg; 4·4% with 600 mg; 3·4% with placebo; injection-site reactions: not reported

Changes in blood pressure are expressed as means, and differences *vs* placebo are expressed as mean (95% CI), unless otherwise stated. eGFR=estimated glomerular filtration rate. *Patients with eGFR <45 mL/min per 1·73 m² or urine albumin–creatinine ratio >300 mg/g were preferentially assigned to olmesartan; the olmesartan dose was 20 mg for patients with eGFR ≤60 mL/min per 1·73 m² in countries other than the USA. †Every 6 months or every 3 months dosing combined. ‡Cohort A only. §Defined as reaching a 24 h ambulatory systolic blood pressure <130 mm Hg, a ≥20 mm Hg reduction from baseline, or both, without rescue medication.

Table 1: **Blood pressure-lowering effects, angiotensinogen suppression, and key safety issues with zilebesiran in three phase 2 trials conducted in patients with hypertension**

	Potential indications	Potential risks
RNA-based therapies targeting angiotensinogen Anti-AGT	Patients with elevated cardiovascular and renal risk; patients with very low adherence to treatment; patients with ACE inhibitor-related or ARB-related adverse events; patients with renin–angiotensin system-dependent target organ damage such as left ventricular hypertrophy, endothelium dysfunction, or early kidney damage (eg, microalbuminuria); Black patients; and patients with oestrogen-induced hypertension	Risk of adverse events shared with all other renin–angiotensin system blockers: excessive hypotension and renal failure when blood pressure and renal function are renin-dependent* or when combined with conventional oral renin–angiotensin system blockers (dual renin–angiotensin system blockade), hyperkalaemia, ionic disturbances in patients with chronic kidney disease or when combined with other medications, haematocrit decrease, or anaemia in patients with chronic kidney disease, and other unexpected adverse events; contraindicated during pregnancy; specific adverse event risks: permanent and continuous renin–angiotensin system blockade and need for rapid reversal of the effect
Aldosterone-targeted therapies (aldosterone synthase inhibitors and non-steroidal MRAs) Anti CYP11B2	Patients with difficult-to-control hypertension including uncontrolled or resistant hypertension; patients with aldosterone dysregulation; patients with primary aldosteronism; patients with heart failure and low or preserved ejection fraction†; and patients with diabetes, obesity, or chronic kidney disease and albuminuria†	Risk of adverse events shared between aldosterone synthase inhibitors and non-steroidal MRAs: hyperkalaemia (especially in patients with chronic kidney disease, diabetes, or when combined with other medications); hyponatraemia, hypotension, and reduced eGFR; contraindicated during pregnancy; specific adverse events risk with aldosterone synthase inhibitors: hypocortisolism or hypercortisolism, and other unexpected adverse events
Endothelin 1 receptor antagonists (aprocitentan‡)	Patients with resistant hypertension who are either intolerant of MRAs or for whom MRAs are contraindicated	Fluid retention, peripheral oedema, or both (caution is warranted in individuals with a history of heart failure); contraindicated during pregnancy
Sacubitril–valsartan§ Sacubitril ist ein Neprilysin-Inhibitor, welcher den Abbau der im Körper produzierten natriuretischen Peptide hemmt.	Patients with resistant hypertension not responding to a conventional ARB included in a triple antihypertensive therapy including a diuretic; and patients with hypertension and heart failure with low ejection fraction	Risk of adverse events shared with all other renin–angiotensin system blockers: excessive hypotension and renal failure when blood pressure and renal function are renin-dependent*, hyperkalaemia, ionic disturbances in patients with chronic kidney disease or when combined with other medications, haematocrit decrease or anaemia in patients with chronic kidney disease, pregnancy, and with other unexpected adverse events; specific adverse events risks: angioedema (more in Black patients) especially if combined with ACE inhibitors or dipeptidyl peptidase IV inhibitors

eGFR=estimated glomerular filtration rate. ACE=angiotensin converting enzyme. ARB=angiotensin receptor blocker. MRAs=mineralocorticoid receptor antagonists. *For example: elderly patients, salt depletion, hypovolaemia, heat wave, use of cyclo-oxygenase enzyme inhibitors, presence of renal artery stenosis, anaesthetic induction, urgent surgery, haemorrhage, septic shock, or myocardial infarction. †Alone or in combination with a SGLT2 inhibitor. ‡Aprocitentan is approved for the treatment of hypertension inadequately controlled by at least three antihypertensive medications in the USA, Europe, and the UK. §Sacubitril–valsartan is approved for the treatment of hypertension only in Japan, China, and Russia.

Table 2: **Potential indications and risks of new drug therapies for hypertension**

Anti CYP11B2 trials

	BrigHTN[55] (phase 2), n=275	HALO trial[56] (phase 2), n=249	BaxHTN[60] (phase 3), n=794	Target-HTN[57] (phase 2), n=200	Advance-HTN[58] (phase 2), n=285	Launch-HTN[59] (phase 3), n=1083
Patient population	Resistant hypertension despite at least three antihypertensive medications including a diuretic; office blood pressure ≥130/80 mm Hg after 2-week run-in period on placebo plus background antihypertensive medications	Uncontrolled hypertension while taking an ACE inhibitor or ARB, or an ACE inhibitor or ARB plus a thiazide diuretic, or an ACE inhibitor or ARB plus a calcium channel blocker; office systolic blood pressure ≥140 mm Hg after 2–4-week run-in period on placebo plus background antihypertensive medications	Uncontrolled hypertension despite two antihypertensive medications or resistant hypertension despite at least three antihypertensive medications, including a diuretic in both cases; office systolic blood pressure ≥135 mm Hg after 2-week run-in period on placebo plus background antihypertensive medications	Uncontrolled hypertension despite at least two antihypertensive medications at maximum tolerated doses; office systolic blood pressure ≥130 mm Hg after 2-week run-in period on placebo plus background antihypertensive medications	Uncontrolled or resistant hypertension despite two to five antihypertensive medications; 24 h ambulatory systolic blood pressure 130–180 mm Hg or 24 h ambulatory diastolic blood pressure >80 mm Hg after 3-week run-in period on placebo plus standardised antihypertensive medications (ie, olmesartan plus a thiazide diuretic with or without amlodipine)	Uncontrolled or resistant hypertension despite two to five antihypertensive medications; office systolic blood pressure 135–180 mm Hg and diastolic blood pressure 65–110 mm Hg or diastolic blood pressure 90–110 mm Hg after 2-week run-in period on placebo plus background antihypertensive medications
Intervention	Baxdrostat: 0·5 mg daily, 1 mg daily, or 2 mg daily *vs* placebo	Baxdrostat: 0·5 mg daily, 1 mg daily, or 2 mg daily *vs* placebo	Baxdrostat: 1 mg daily or 2 mg daily *vs* placebo	Lorundrostat: 12·5 mg daily, 12·5 mg twice daily, 25 mg twice daily, 50 mg daily, or 100 mg daily *vs* placebo	Lorundrostat: 50 mg daily for 12 weeks, or 50 mg daily for 4 weeks with titration to 100 mg daily for 8 weeks (lorundrostat with dose adjustment) *vs* placebo	Lorundrostat: 50 mg daily for 12 weeks, or 50 mg daily for 6 weeks with titration to 100 mg daily for 6 weeks (lorundrostat with dose adjustment) *vs* placebo
Trial duration (primary)	12 weeks	8 weeks	12 weeks	8 weeks	12 weeks	6 weeks
Primary endpoint	Change in office systolic blood pressure: −12·1 mm Hg with baxdrostat 0·5 mg, −17·5 mm Hg with baxdrostat 1 mg, −20·3 mm Hg with baxdrostat 2 mg, and −9·4 mm Hg with placebo; difference *vs* placebo: −3·0 mm Hg (−8·6 to 2·7)* with baxdrostat 0·5 mg, −8·1 mm Hg (−13·5 to −2·8) with baxdrostat 1 mg, and −11·0 mm Hg (−16·4 to −5·5) with baxdrostat 2 mg	Change in office systolic blood pressure: −17·0 mm Hg with baxdrostat 0·5 mg; −16·0 mm Hg with baxdrostat 1 mg, −19·8 mm Hg with baxdrostat 2 mg, and −16·6 mm Hg with placebo; difference *vs* placebo (mean [SE])†: −0·5 mm Hg (±2·21) with baxdrostat 0·5 mg, 0·6 mm Hg (±2·20) with baxdrostat 1 mg, and −3·2 mm Hg (±2·23) with baxdrostat 2 mg	Change in office systolic blood pressure: −14·5 mm Hg with baxdrostat 1 mg, −15·7 mm Hg with baxdrostat 2 mg, and −5·8 mm Hg with placebo; difference *vs* placebo: −8·7 mm Hg (− 11·5 to −5·8) with baxdrostat 1 mg, and −9·8 mm Hg (− 12·6 to −7·0) with baxdrostat 2 mg	Change in office systolic blood pressure: −5·6 mm Hg with lorundrostat 12·5 mg, −11·3 mm Hg with lorundrostat 12·5 mg twice daily, −11·1 mm Hg with lorundrostat 25 mg twice daily, −13·7 mm Hg with lorundrostat 50 mg, −11·9 mm Hg with lorundrostat 100 mg, −4·1 mm Hg with placebo; difference *vs* placebo (mean [90% CI]): −1·5 mm Hg (−8·3 to 5·3) with lorundrostat 12·5 mg, −7·2 mm Hg (−14·0 to −0·4) with lorundrostat 12·5 mg twice daily, −7·0 mm Hg (−13·1 to −0·8) with lorundrostat 25 mg twice daily, −9·6 mm Hg (−15·8 to −3·4) with lorundrostat 50 mg, and−7·8 mm Hg (−14·1 to −1·5) with lorundrostat 100 mg	Change in 24 h ambulatory systolic blood pressure: −15·4 mm Hg with lorundrostat 50 mg, −13·9 mm Hg with lorundrostat with dose adjustment, and −7·9 mm Hg with placebo; difference *vs* placebo (mean [97·5% CI]): −7·9 mm Hg (−13·3 to −2·6) with lorundrostat 50 mg, and −6·5 mm Hg (−11·8 to −1·2) with lorundrostat with dose adjustment	Change in office systolic blood pressure: −16·9 mm Hg with lorundrostat 50 mg, and −7·9 mm Hg with placebo; difference *vs* placebo: −9·1 mm Hg (−13·3 to −4·9) with lorundrostat 50 mg
Additional endpoints	Blood pressure responder rate: not reported; change in the urinary aldosterone–creatinine ratio: −187 ng/g with baxdrostat 0·5 mg, −180 ng/g with baxdrostat 1 mg, −273 ng/g with baxdrostat 2 mg, and 6 ng/g with placebo	Blood pressure responder rate (systolic blood pressure <130 mm Hg): 57·1% with baxdrostat 0·5 mg, 53·2% with baxdrostat 1 mg, 71·7% with baxdrostat 2 mg, and 56·3% with placebo; change in serum aldosterone: −40·3% with baxdrostat 0·5 mg, −41·3% with baxdrostat 1 mg, −39·8% with baxdrostat 2 mg, and −10·7% with placebo	Blood pressure responder rate (systolic blood pressure <130 mm Hg): 39·4% with baxdrostat 1 mg, 40·0% with baxdrostat 2 mg, and 18·7% with placebo; change in serum aldosterone: −59·9% with baxdrostat 1 mg, −65·4% with baxdrostat 2 mg, no change with placebo	Blood pressure responder rate (systolic blood pressure <130/80 mm Hg): 26·1% with lorundrostat 12·5 mg, 31·8% with lorundrostat 12·5 mg twice daily, 43·3% with lorundrostat 25 mg twice daily, 42·9% with lorundrostat 50 mg, 30·0% with lorundrostat 100 mg, and 23·3% with placebo; change in serum aldosterone at week 4: −14·9% with lorundrostat 12·5 mg, −36·1% with lorundrostat 12·5 mg twice daily, −51·6% with lorundrostat 25 mg twice daily, −41·2% with lorundrostat 50 mg, −43·8% with lorundrostat 100 mg, and 2·2% with placebo	Blood pressure responder rate at week 4 (24 h ambulatory systolic blood pressure <125 mm Hg): 41·0% with lorundrostat (pooled), and 18·0% with placebo; change in serum aldosterone: −47·7% with lorundrostat 50 mg, −55·7% with lorundrostat with dose adjustment, and 22·5% with placebo	Blood pressure responder rate (systolic blood pressure <130 mm Hg): 44·1% with lorundrostat 50 mg, and 24·1% with placebo; change in serum aldosterone: not reported

(Table 3 continues on next page)

Anti CYP11B2 trials

	BrigHTN[55] (phase 2), n=275	HALO trial[56] (phase 2), n=249	BaxHTN[46] (phase 3), n=794	Target-HTN[57] (phase 2), n=200	Advance-HTN[58] (phase 2), n=285	Launch-HTN[59](phase 3), n=1083
(Continued from previous page)						
Key safety observations	Hyperkalaemia ≥6 mmol/L, n (%): 0 with baxdrostat 0·5 mg, 2 (3·0%) with baxdrostat 1 mg, 1 (2·0%) with baxdrostat 2 mg, and 0 with placebo; hyperkalaemia 5·5–5·9 mmol/L, n (%): 1 (1·0%) with baxdrostat 0·5 mg, 2 (3·0%) with baxdrostat 1 mg, 1 (2·0%) with baxdrostat 2 mg, and 0 with placebo; hyponatraemia that required clinical intervention, n (%): 0 with baxdrostat 0·5 mg, 2 (3·0%) with baxdrostat 1 mg, 1 (2·0%) with baxdrostat 2 mg, and 0 with placebo; adrenal insufficiency: none; change in serum potassium, mmol/L: 0·19 with baxdrostat 0·5 mg, 0·36 with baxdrostat 1 mg, 0·29 with baxdrostat 2 mg, and −0·08 with placebo; change in eGFR, mL/min per 1·73 m^2: −2·6 with baxdrostat 0·5 mg, −7·9 with baxdrostat 1 mg, −10·7 with baxdrostat 2 mg, and 0·1 with placebo	Hyperkalaemia, n (%): 0 with baxdrostat 0·5 mg, 1 (1·6%) with baxdrostat 1 mg, 3 (5·0%) with baxdrostat 2 mg, and 1 (1·6%) with placebo; hyponatraemia, n (%): 0 with baxdrostat 0·5 mg, 0 with baxdrostat 1 mg, 1 (1·7%) with baxdrostat 2 mg, and 0 with placebo; hyponatraemia <135 mmol/L, n (%): not reported; adrenal insufficiency: not reported; change in serum potassium, mmol/L: not reported; change in eGFR, mL/min per 1·73 m^2: not reported	Hyperkalaemia ≥6 mmol/L, n (%): 6 (2·3%) with baxdrostat 1 mg, 8 (3·0%) with baxdrostat 2 mg, and 1 (0·4%) with placebo; hyperkalaemia 5·5–5·9 mmol/L, n (%): 16 (6·1%) with baxdrostat 1 mg, 29 (11·1%) with baxdrostat 2 mg, and 1 (0·4%) with placebo; hyponatraemia <135 mmol/L, n (%); 49 (19·1%) with baxdrostat 1 mg, 59 (22·8%) with baxdrostat 2 mg, and 18 (7·0%) with placebo; ≥30% decrease in eGFR: 12·6% with baxdrostat 1 mg, 15·6% with baxdrostat 2 mg, and 1·5% with placebo; adrenal insufficiency: none; change in serum potassium, mmol/L‡: approximately 0·30 with baxdrostat 1 mg, approximately 0·40 with baxdrostat 2 mg, and approximately 0 with placebo (estimated from the figure); change in eGFR, mL/min per 1·73 m^2: −7·0 with baxdrostat 1 mg, −6·9 with baxdrostat 2 mg, and −0·1 with placebo	Hyperkalaemia ≥6 mmol/L, n (%): 1 (4·0%) with lorundrostat 12·5 mg, 1 (5·0%) with lorundrostat 12·5 mg twice daily, 1 (3·0%) with lorundrostat 25 mg twice daily, 1 (4·0%) with lorundrostat 50 mg, 1 (3·0%) with lorundrostat 100 mg, and 0 with placebo; hyperkalaemia 5·5–5·9 mmol/L, n (%): 3 (13·0%) with lorundrostat 12·5 mg, 2 (9·0%) with lorundrostat 12·5 mg twice daily, 2 (7·0%) with lorundrostat 25 mg twice daily, 1 (4·0%) with lorundrostat 50 mg, 5 (16·0%) with lorundrostat 100 mg, and 0 with placebo; hyponatraemia, <135 mmol/L, n (%): not reported; adrenal insufficiency: none; change in serum potassium, mmol/L: 0·31 with lorundrostat 12·5 mg, 0·32 with lorundrostat 12·5 mg twice daily, 0·34 with lorundrostat 25 mg twice daily, 0·25 with lorundrostat 50 mg, 0·29 with lorundrostat 100 mg, and 0·03 with placebo; change in eGFR, mL/min per 1·73 m^2: −3·7 with lorundrostat 12·5 mg, −6·7 with lorundrostat 12·5 mg twice daily, −5·6 with lorundrostat 25 mg twice daily, −4·6 with lorundrostat 50 mg, −7·8 with lorundrostat 100 mg, and 0·9 with placebo	Hyperkalaemia ≥6 mmol/L, n (%): 5 (5·0%) with lorundrostat 50 mg, 7 (7·0%) with lorundrostat with dose adjustment, and 0 with placebo; hyperkalaemia 5·5–5·9 mmol/L, n (%): 6 (6·0%) with lorundrostat 50 mg, 10 (11·0%) with lorundrostat with dose adjustment, and 3 (3·0%) with placebo; hyponatraemia <135 mmol/L, n (%): 8 (9·0%) with lorundrostat 50 mg, 10 (11·0%) with lorundrostat with dose adjustment, and 6 (6·0%) with placebo; ≥25% decrease in eGFR or eGFR <30 mL/min per 1·73 m^2: 3 (3·0%) with lorundrostat 50 mg, 7 (7·0%) with lorundrostat with dose adjustment, and 3 (3·0%) with placebo; adrenal insufficiency: none; change in serum potassium, mmol/L: 0·59 with lorundrostat 50 mg, 0·57 with lorundrostat with dose adjustment, and 0·10 with placebo; change in eGFR, mL/min per 1·73 m^2: −8·0 with lorundrostat 50 mg, −11·8 with lorundrostat with dose adjustment, and −2·8 with placebo	Hyperkalaemia ≥6 mmol/L, n (%): 6 (1·1%) with lorundrostat 50 mg, 4 (1·5%) with lorundrostat with dose adjustment, and 2 (0·7%) with placebo; hyperkalaemia 5·5–5·9 mmol/L, n (%): 38 (7·1%) with lorundrostat 50 mg, 29 (10·7%) with lorundrostat with dose adjustment, and 3 (1·1%) with placebo; hyponatraemia <135 mmol/L, n (%): 37 (6·9%) with lorundrostat 50 mg, 28 (10·4%) with lorundrostat with dose adjustment, and 9 (3·3%) with placebo; glucocorticoid deficiency: 0 with lorundrostat 50 mg, 0 with lorundrostat with dose adjustment, and 3 (1·1%) with placebo; change in serum potassium, mmol/L‡: approximately 0·43 with lorundrostat 50 mg, and approximately 0·10 with placebo; change in eGFR, %: −9·3% with lorundrostat (pooled), and 0·4% with placebo

Changes in blood pressure, serum potassium, and eGFR are expressed as means, and differences vs placebo are expressed as mean (95% CI), unless otherwise stated. Key safety observations are those reported using laboratory safety measurements done at central laboratories. ACE=angiotensin converting enzyme. ARB=angiotensin receptor blocker. eGFR=estimated glomerular filtration rate. *Reported in the per-protocol population only. †All the differences vs placebo are not significant. ‡Mean value estimated from graphs showing serum potassium values from baseline to end of study period.

Table 3: **Summary of key findings from phase 2 and 3 trials of aldosterone synthase inhibition in hypertension**

Anti ETA and ETB receptors (aprocitentan)

	PRECISION study[85] (phase 3), n=730	Dose-response study[84] (phase 2), n=490
Patient population	Patients with resistant hypertension despite three or more antihypertensive medications; unattended seated systolic blood pressure of ≥140 mm Hg despite at least 4 weeks of treatment with a triple combination in a single pill continued throughout the trial*	Patients with grade 1 to 2 hypertension; unattended seated diastolic blood pressure of ≥90 mm Hg to <110 mm Hg after 4–6 weeks placebo run-in period
Intervention	Aprocitentan 12·5 mg and 25 mg once daily *vs* placebo	Aprocitentan 5 mg, 10 mg, 25 mg, or 50 mg once daily *vs* placebo and *vs* active comparator (lisinopril 20 mg once daily)
Trial duration	48 weeks including 4-week double-blind phase, 32-week single-blind active treatment phase, and 12-week randomised withdrawal phase	8 weeks
Primary endpoint	Unattended office systolic blood pressure decrease at 4 weeks: −15·3 mm Hg with aprocitentan 12·5 mg, −15·2 mm Hg with aprocitentan 25 mg, and −11·5 mm Hg with placebo; difference *vs* placebo: −3·8 mm Hg (97·5% CI −6·8 to −0·8) with aprocitentan 12·5 mg, and −3·7 mm Hg (97·5% CI −6·2 to −2·1) with aprocitentan 25 mg	Unattended office diastolic blood pressure decrease at 8 weeks: −6·3 mm Hg with aprocitentan 5 mg, −9·9 mm Hg with aprocitentan 10 mg, −12·0 mm Hg with aprocitentan 25 mg, −10·0 mm Hg with aprocitentan 50 mg, −8·4 mm Hg with lisinopril 20 mg, and −4·9 mm Hg with placebo; difference *vs* placebo: −1·31 mm Hg (−5·10 to 2·49) with aprocitentan 5 mg, −4·93 mm Hg (−8·68 to −1·17) with aprocitentan 10 mg, −6·99 mm Hg (−10·80 to −3·19) with aprocitentan 25 mg, −4·95 mm Hg (−8·75 to −1·15) with aprocitentan 50 mg, and −3·81 mm Hg (−7·26 to −0·37) with lisinopril 20 mg
Additional endpoints†	Change in 24 h ambulatory systolic blood pressure at 4 weeks (difference *vs* placebo): −4·2 mm Hg (−6·2 to −2·1) with aprocitentan 12·5 mg, and −5·9 mm Hg (−7·9 to −3·8) with aprocitentan 25 mg; changes in office systolic blood pressure after 4 weeks in the placebo-controlled randomised withdrawal phase: 5·8 mm Hg (3·7 to 7·9) for placebo *vs* aprocitentan 25 mg	Unattended office systolic blood pressure decrease at 8 weeks: −10·3 mm Hg with aprocitentan 5 mg, −15·0 mm Hg with aprocitentan 10 mg, −18·5 mm Hg with aprocitentan 25 mg, −15·1 mm Hg with aprocitentan 50 mg, −12·8 mm Hg with lisinopril 20 mg, and −7·7 mm Hg with placebo; difference *vs* placebo: −2·45 mm Hg (−8·44 to 3·54) with aprocitentan 5 mg, −7·05 mm Hg (−12·98 to −1·12) with aprocitentan 10 mg, −9·90 mm Hg (−15·92 to −3·88) with aprocitentan 25 mg, −7·58 mm Hg (−13·58 to −1·59) with aprocitentan 50 mg, and −4·84 mm Hg (−10·49 to 0·82) with lisinopril 20 mg; change in 24 h ambulatory systolic blood pressure at 8 weeks‡ (difference *vs* placebo): 0·87 mm Hg (−3·58 to 5·32) with aprocitentan 5 mg, −3·99 mm Hg (−8·49 to 0·52) with aprocitentan 10 mg, −4·83 mm Hg (−9·33 to −0·33) with aprocitentan 25 mg, −3·67 mm Hg (−8·08 to 0·73) with aprocitentan 50 mg, and −3·43 mm Hg (−8·30 to 1·44) with lisinopril 20 mg
Key safety observations	Peripheral oedema: 9% of patients who received aprocitentan 12·5 mg and 18% in those who received aprocitentan 25 mg *vs* 2% in those who received placebo; hospitalisation for heart failure: ten patients who received aprocitentan and one who received placebo; eGFR changes at week 4: approximately −1·0 mL/min per 1·73 m^2 with aprocitentan 12·5 mg, approximately −2·0–3·0 mL/min per 1·73 m^2 with aprocitentan 25 mg, and approximately −0·5 mL/min per 1·73 m^2 with placebo; no hepatotoxicity	Mild-to-moderate peripheral oedema in four patients (mainly at higher doses); dose-related decreases in haemoglobin, and increase in estimated plasma volume; eGFR changes: not reported; no significant weight changes; no hepatotoxicity

Changes in blood pressure and eGFR are expressed as means, and differences *vs* placebo are expressed as mean (95% CI), unless otherwise stated. eGFR=estimated glomerular filtration rate. *The triple combination in a single pill included hydrochlorothiazide, valsartan, and amlodipine. †Responder rates and use of rescue antihypertensive medications have not been reported. ‡In a subset of 281 patients.

Table 4: **Blood pressure-lowering effects and key safety issues with aprocitentan in phase 2 and 3 trials in hypertension**

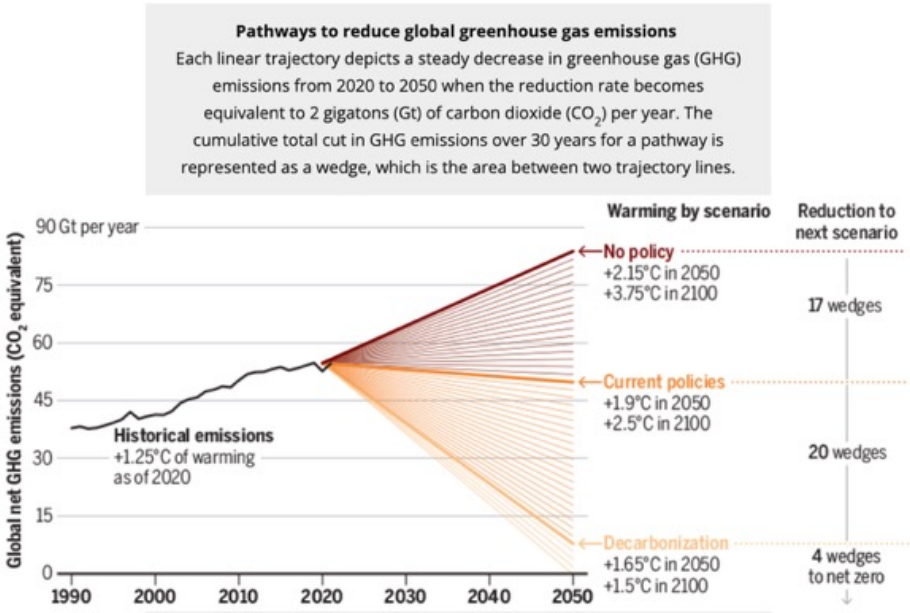
Conclusions

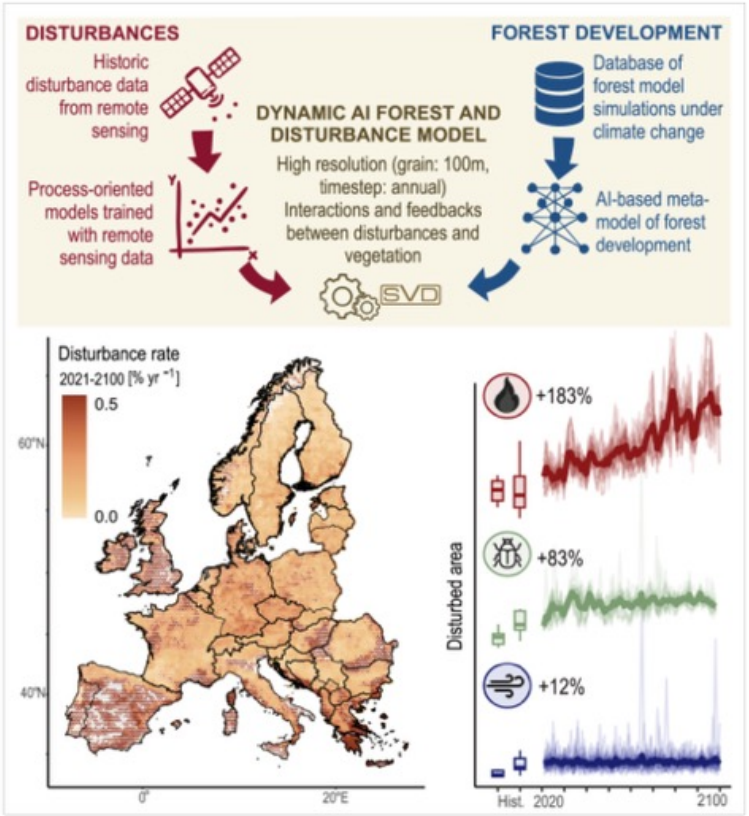
There has been renewed interest in the development of new antihypertensive medications; however, how these treatments will be integrated with established, low-cost generic antihypertensive drugs remains uncertain. Moreover, combining these novel agents into single-pill combination products would also be challenging given regulatory requirements for outcomes-based trials and the poor uptake of existing single-pill products, despite their increasing endorsement in clinical guidelines worldwide. Furthermore, in low-income and middle-income countries, where the availability, accessibility, and affordability of care and therapies remain constrained, demonstration of cost-effectiveness will be essential to establish the feasibility and the potential global effect of these new therapeutic approaches. Thus, it could be argued that the focus should be on developing more effective systems of care to enhance adherence to existing low-cost treatments. However, this approach has proved challenging, and despite multiple iterations of guidelines and various models of care, overall global blood pressure control rates have not improved substantially. Moreover, recent advances in other medical fields challenge the assumption that we already have all of the treatments we need. The advent of SGLT2 inhibitors and GLP-1 receptor agonists has transformed the management of patients with high cardiovascular risk, chronic kidney disease, diabetes, obesity, and heart failure—conditions once considered adequately treated with existing therapies. These developments highlight the potential for innovative antihypertensive drugs to improve standards of care and address residual disease risk, even in a therapeutic landscape dominated by inexpensive generic drugs.

Thirty-six solutions to stabilize Earth's climate

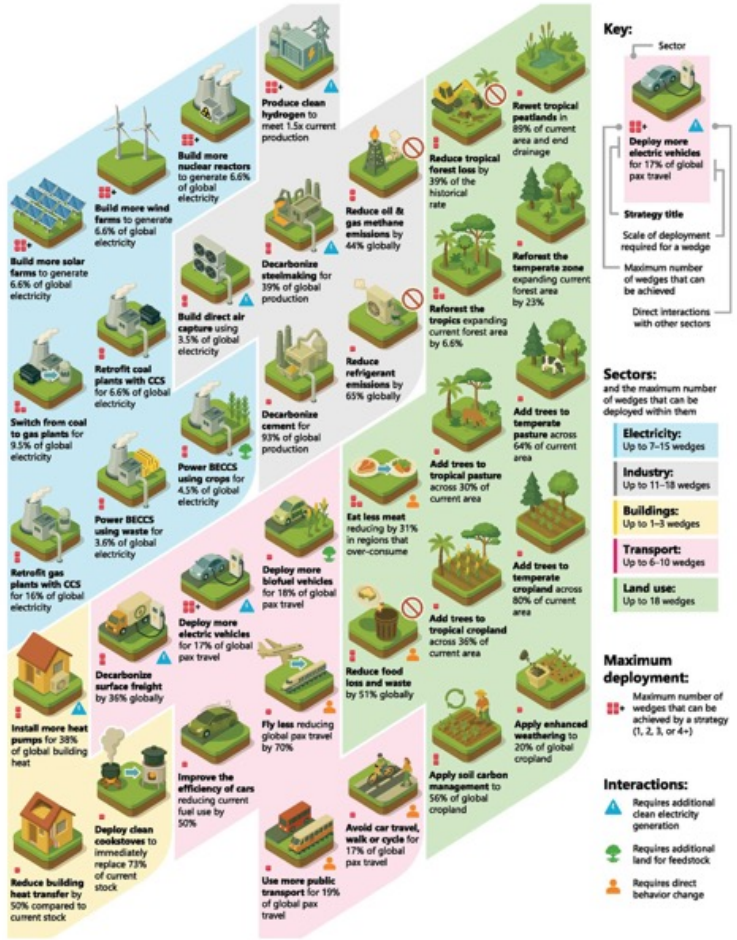
About two decades ago, an idea was proposed to visualize the amount of carbon dioxide (CO_2) emission that must be mitigated over the next 50 years to plateau its atmospheric abundance. Put forward was a stabilization triangle divided into seven equal wedges, each representing the amount of carbon emissions that can be reduced by existing technologies. However, a decade later, when the 2015 Paris Agreement was adopted, climate goals shifted from fixing carbon emissions at a constant level to achieving a balance between the amount of anthropogenic greenhouse gas put into and removed from the atmosphere (net zero). Technologies have also advanced, and mitigation approaches now span many sectors. On page 1009 of this issue, Johnson and Staffell report an updated framework of modernized wedges that maps out 36 decarbonization strategies. This construct allows diverse approaches for different stakeholders to pursue in order to reduce greenhouse gas emission.

Johnson and Staffell present a modernized framework in which each wedge represents a linear trajectory to avoid greenhouse gas emission that is comparable to 2 Gt of CO_2 per year by 2050 (a cumulative reduction of 30 Gt of CO_2 equivalent over 30 years per wedge) (see the figure). The authors compiled 36 strategies across different sectors, such as energy, transport, industry, buildings, and land use, where each approach can potentially achieve a minimum of one wedge. Present climate policies account for ~17 wedges, although 20 additional wedges are required to limit global mean surface tempera ture to 1.5°C above the preindustrial level (a target of the Paris Agreement). The 36 strategies in the new framework can be combined to achieve this goal.





Simulation framework. Shown is a simulation framework combining process-oriented disturbance models trained with remote sensing data and local process-model simulations in a deep learning–based dynamic forest and disturbance model (top). This framework was used to simulate future forest disturbance regimes in Europe at 100-meter spatial resolution (bottom left) and annual time step (bottom right). Our results show that disturbances in Europe's forests will increase throughout the 21st century (shown here for a scenario of unabated warming).



The 36 mitigation strategies that have the potential to achieve at least one wedge of mitigation and the scale of deployment required for each. Each strategy is depicted by an icon with a sentence that quantifies the scale of deployment needed to achieve 2 $GtCO_2e$ of mitigation in 2050, expressed relative to the global scale in 2050 unless otherwise stated. Strategies are grouped by sector, which is indicated by colored backgrounds. The key on the right explains other elements of the figure. Indicative upper bounds for how many wedges can be achieved collectively within each sector were calculated by translating sectoral emissions in 2050 from four baseline scenarios into wedges, with the exception of land use, which was derived from (27). Upper bounds for individual strategies are derived from a meta-review of mitigation potentials (see materials and methods). Strategies within industry cannot collectively mitigate all of the sector's emissions because emissions savings from avoided fuel extraction and production are accounted for in end-use sectors and many smaller actions are also needed (see main text). pax, passenger.

Meet Fancy, 37, the world's oldest horse — and her lifelong caretaker

Paige Blumer always loved horses. She started taking riding lessons when she was 5, after launching a campaign to convince her parents to sign her up.

"She had this very motherly energy, which is weird to say about a horse," Blumer said. "I just always felt like she was going to take care of me."

The two even had the same birthday, April 1, though Blumer was 8 and the horse — whom she called "Fancy" — was 12.

Blumer and Fancy grew up together, winning many equestrian competitions as a pair and maintaining a steadfast connection for 25 years. Now Fancy's longevity is being recognized: Guinness World Records just named Fancy, 37, the World's Oldest Horse.

"Fancy" wird im Deutschen je nach Kontext meist als Schick-edelelegant, kunstvoll oder ausgefallen übersetzt.

Blumer and Fancy. According to Guinness World Records, Fancy is the world's oldest living horse. (Courtesy of Paige Blumer)

"It's kind of cool because it's the year of the horse," Blumer said. "And she's coming up on her 38th birthday."

Blumer will be 34 that day.

Blumer was shocked in June 2000 when her parents bought her the horse. Blumer quickly renamed her "Fancy," because, as she told her parents, "she was too fancy to be called anything else."

"Paige and Fancy were meant to be," Cox said.

“A horse’s useful life is not just for being ridden,” Blumer said. “They have so much more purpose and so much more worth and so many things we can learn from them. I enjoy my weekends going out and just bathing her and being in her presence. It’s very peaceful. It’s so enjoyable to still have her in our life and we’re just very grateful.”