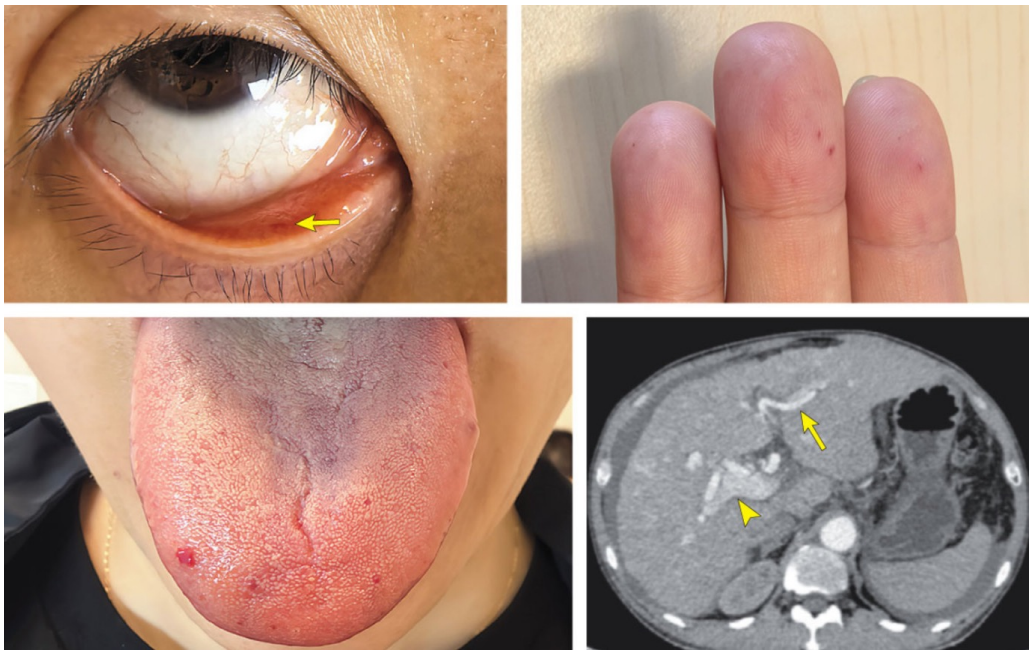
https://www.mdc-berlin.de/de/veroeffentlichungstypen/clinical-journal-club



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 56-year-old woman was evaluated for abnormal liver imaging results. She reported 2 months of fatigue and decades of intermittent epistaxis that had recently increased in frequency. Laboratory testing showed a hemoglobin level of 8.9 g per deciliter (reference range, 11.0 to 15.0) with normal liver function tests. Contrast-enhanced abdominal computed tomography is shown. Which of the following is seen in the abdominal imaging?

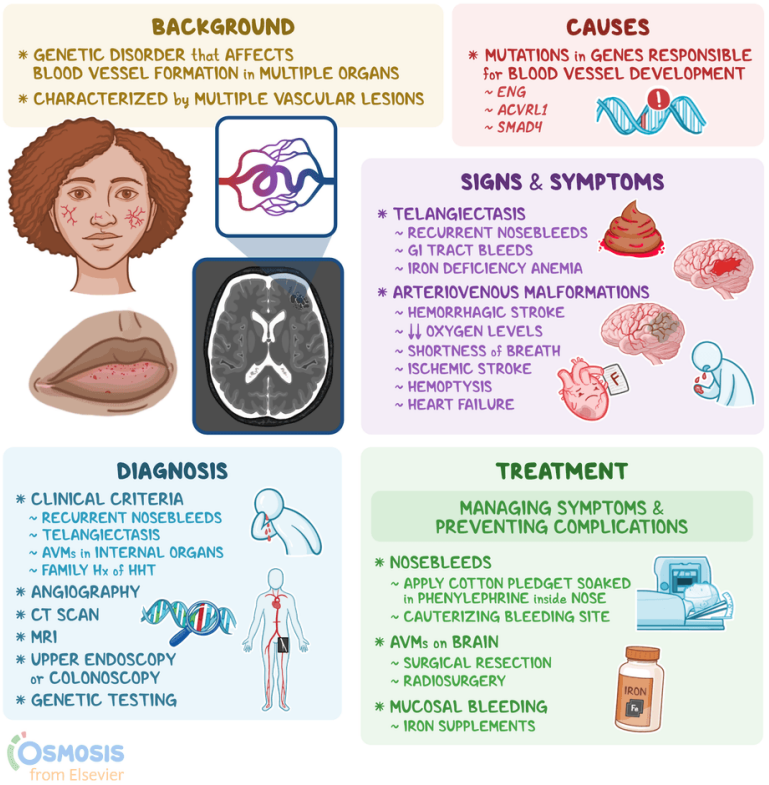
- Arterioportal shunting
- Cirrhosis
- Hepatic artery aneurysm
- Hepatic hemangioma
- Hepatic vein thrombosis

The CT showed an enlarged, tortuous hepatic artery with early opacification of the portal vein and hepatic veins during the arterial phase – findings suggestive of intrahepatic arterioportal and arteriovenous shunting. The patient met criteria for hereditary hemorrhagic telangiectasia on the basis of the findings of mucocutaneous telangiectasia at characteristic sites (conjunctiva, tongue, fingers), hepatic vascular malformations, and recurrent epistaxis. The diagnosis was confirmed with genetic testing.

Hereditary hemorrhagic telangiectasia (HHT), auch bekannt als Morbus Osler (oder Osler-Weber-Rendu-Syndrom), ist eine seltene, autosomal-dominant vererbte Gefäßerkrankung. Sie führt zu einer fehlerhaften Angiogenese (Gefäßneubildung), bei der sich Kapillargebiete nicht richtig ausbilden. Dadurch fließen arterielle Gefäße direkt in venöse Gefäße über. Diese fragilen Verbindungen neigen zu chronischen Blutungen und Fehlfunktionen.

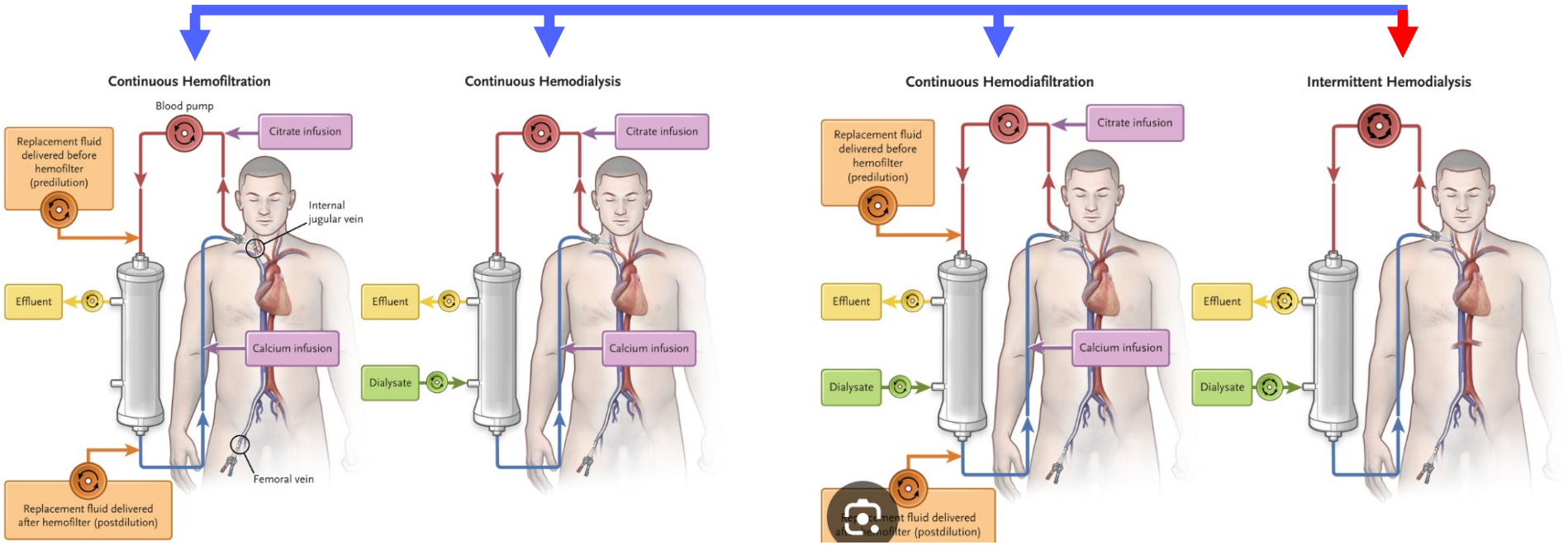
Leitsymptome und Manifestationen

- **Rezidivierendes Nasenbluten (Epistaxis):** Tritt bei ca. 90–95 % der Betroffenen auf, beginnt oft in der Kindheit und verstärkt sich im Laufe des Lebens.
- **Mukokutane Teleangiektasien:** Kleine, stecknadelkopfgroße rote bis violette Gefßerweiterungen an sichtbaren Stellen wie den Lippen, der Zunge, der Mundschleimhaut, dem Gesicht und den Fingerspitzen.
- **Gastrointestinale Blutungen:** Teleangiektasien im Magen-Darm-Trakt können chronische, teils unbemerkt bleibende Blutungsverluste verursachen, die zu einer ausgeprägten Eisenmangelanämie führen



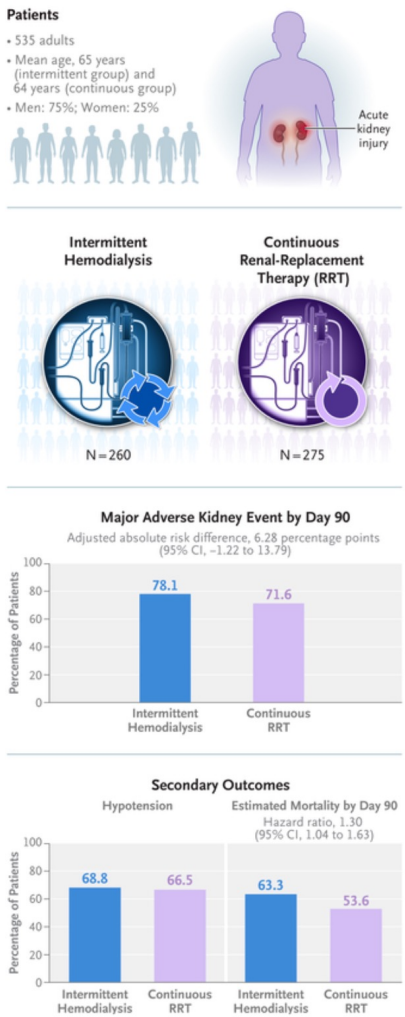
Two hit, somatic loss of heterozygosity

Any difference here?!?



Intermittent or Continuous Renal-Replacement Therapy in Acute Kidney Injury

The preferred method of renal-replacement therapy for acute kidney injury in critically ill patients remains uncertain.
In this multicenter, open-label, noninferiority trial, we randomly assigned critically ill adults with acute kidney injury who had indications for renal-replacement therapy to undergo intermittent hemodialysis or continuous renal-replacement therapy as the initial treatment. The primary outcome was a major adverse kidney event — defined as death, dependence on renal-replacement therapy, or a serum creatinine concentration more than 25% above the baseline value — by day 90.



Acute kidney injury is associated with an increase in short-term mortality, prolonged hospital stays, and long-term sequelae, including chronic kidney disease. Renal-replacement therapy is the cornerstone of management of acute kidney injury, but the question of which method is most appropriate is still debated. Intermittent hemodialysis and continuous renal-replacement therapy are the two principal methods used. Intermittent hemodialysis is generally delivered in 3- to 6-hour sessions, whereas continuous renal-replacement therapy is delivered continuously as dialysis, hemofiltration, or hemodiafiltration.

To provide contemporary evidence, we conducted the ICRAKI (Intermittent Hemodialysis versus Continuous Renal-Replacement Therapy for Severe Acute Kidney Injury) trial to compare intermittent hemodialysis with continuous renal-replacement therapy as the initial treatment method in critically ill patients with acute kidney injury and guideline-recommended indications for renal-replacement therapy. We hypothesized that intermittent hemodialysis as the initial renal-replacement therapy would be noninferior to continuous renal-replacement therapy with respect to major adverse kidney events by day 90.

Trial Patients

We enrolled adult patients (≥18 years of age) hospitalized in an ICU with acute kidney injury who had indications for renal-replacement therapy and were receiving, or had received, invasive mechanical ventilation, catecholamine infusion, or both for the same episode. To be included, patients had to have at least one recognized criterion for initiation of renal-replacement therapy. The numerical definitions provided for urgent metabolic indications were intended as general guidance rather than mandatory thresholds. Eligibility criteria, including the indications for renal-replacement therapy, were verified against source data during monitoring by the AP-HP. The main exclusion criteria were conditions that favored one method of renal-replacement therapy over the other (for example, brain injury or other causes of increased intracranial pressure and drug overdose or other conditions involving a dialyzable toxin).

Interventions

In the intermittent group, renal-replacement therapy was provided exclusively with diffusion-based techniques. In the continuous group, continuous venovenous hemodialysis (with diffusion-based techniques), hemofiltration (with convection-based techniques), or hemodiafiltration (with diffusion-based and convection-based techniques) was used at the discretion of the treating physician.

Outcomes

The primary outcome was a major adverse kidney event by day 90, defined as death from any cause, dependence on renal-replacement therapy, or a serum creatinine concentration at day 90 that was more than 25% above the baseline value.

1970‘s criteria:

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	AKIKI[1] (NEJM 2016)	STARRT-AKI[2] (NEJM 2020)	IDEAL-ICU[3] (NEJM 2018)	RENAL[4] (NEJM 2009)	VA/NIH [5](NEJM 2008)	HEMODIAF[6] (Lancet 2006)
Hyperkalemia criteria	serum potassium > 6 mmol/l or > 5.5 mmol/l despite medical treatment	serum potassium ≥ 6.0 mmol/l [1]	serum potassium >6.5 mmol/l [1]	serum potassium > 6.5 mmol/l [1]	No definition	No definition
Acidosis criteria	pH < 7.15 in a context of pure metabolic acidosis or in a context of mixed acidosis with $PaCO_2$ > 50 mmHg	pH ≤ 7.20 or a serum bicarbonate level ≤ 12 mmol/l [1]	metabolic acidosis with pH <7.15 [1]	acidemia with pH <7.2 [1,2]	No definition	No definition
Severe pulmonary edema criteria	acute overload pulmonary edema responsible for severe hypoxemia requiring oxygen flow rate > 5 L/min to maintain an SpO_2 > 95% or requiring an FiO_2 > 50% in patients on mechanical ventilation and despite diuretic therapy	evidence of severe respiratory failure based on a P/F ratio < 200 and clinical perception of volume overload	extravascular fluid overload that was refractory to diuretics, with pulmonary edema	presence of clinically significant organ edema (e.g., pulmonary edema)	No definition	No definition

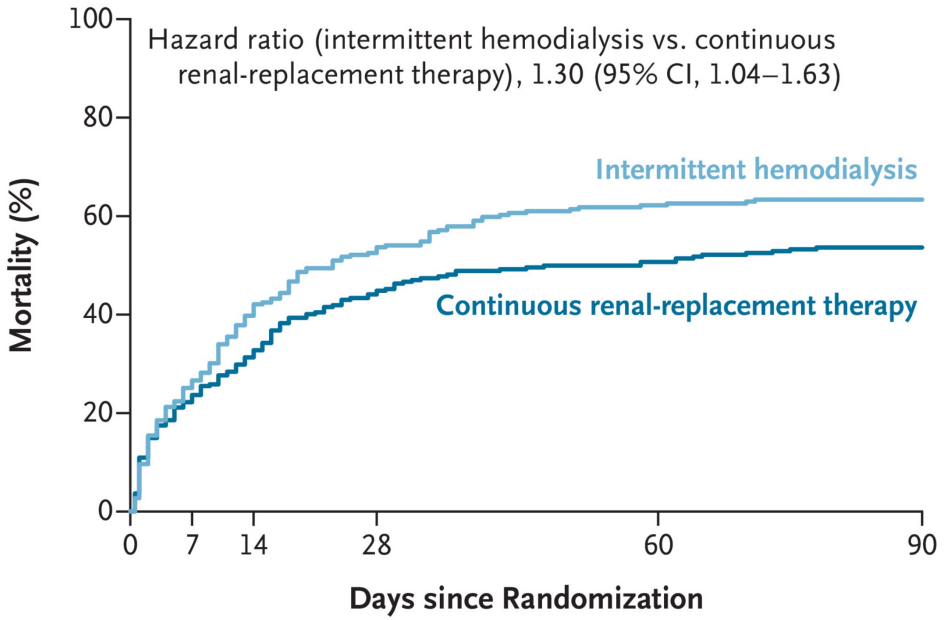
[1] does not indicate whether this value is observed before or after any medical treatment
[2] does not indicate whether such pH value is due to pure metabolic or mixed acidosis

Characteristic	Intermittent Hemodialysis (N = 260)	Continuous Renal-Replacement Therapy (N = 275)
Age — yr	65.2±11.5	64.1±11.7
Female sex — no. (%)	66 (25.4)	66 (24.0)
Body-mass index†	28.9±7.8	28.4±7.4
Median serum creatinine level before ICU admission (IQR) — mg/dl‡	1.0 (0.8–1.1)	1.0 (0.8–1.2)
Main reason for ICU admission — no./total no. (%)		
Medical	197/260 (75.8)	225/274 (82.1)
Surgical, emergency	47/260 (18.1)	26/274 (9.5)
Surgical, scheduled	16/260 (6.2)	23/274 (8.4)
Coexisting condition — no./total no. (%)§		
Chronic kidney disease	57/260 (21.9)	42/273 (15.4)
Hypertension	133/260 (51.2)	135/274 (49.3)
Diabetes mellitus	68/260 (26.2)	80/275 (29.1)
Congestive heart failure	28/259 (10.8)	34/273 (12.5)
Ischemic heart disease	25/260 (9.6)	32/274 (11.7)
Median time from admission to randomization (IQR) — days	3.0 (1.0–5.0)	3.0 (1.0–5.0)
Sepsis status — no./total no. (%)¶		
Sepsis	45/259 (17.4)	46/275 (16.7)
Septic shock	121/259 (46.7)	117/275 (42.5)
Acute respiratory distress syndrome — no./total no. (%)‖	114/257 (44.4)	136/272 (50.0)
SAPS III**	51.7±13.9	51.3±14.7
SOFA score††	12.2±3.0	12.0±3.4
Invasive mechanical ventilation — no. (%)		
At ICU admission	193 (74.2)	193 (70.2)
On the day of randomization	219 (84.2)	230 (83.6)
Catecholamine support at ICU admission — no. (%)	222 (85.4)	214 (77.8)
Norepinephrine	221 (85)	212 (77.1)
Epinephrine	7 (2.7)	3 (1.1)
Catecholamine support on the day of randomization — no. (%)	206 (79.2)	215 (78.2)
Norepinephrine	199 (76.5)	212 (77.1)
Epinephrine	7 (2.7)	3 (1.1)
Catecholamine dose of >0.5 μg/kg/min on the day of randomization — no. (%)‡‡	84 (32.3)	82 (29.8)
Median catecholamine dose on the day of randomization (IQR) — μg/kg/min‡‡		
Norepinephrine	0.4 (0.2–1.4)	0.4 (0.2–1.2)
Epinephrine	0.2 (0.1–1.4)	0.2 (0.2–0.3)
Cumulative fluid balance		
≥6 liters — no. (%)	92 (35.4)	102 (37.1)
Median (IQR) — ml	4089 (2000–8158)	4518 (1597–8000)
Indication for initiation of renal-replacement therapy — no. (%)§§		
Refractory severe hyperkalemia	82 (31.5)	77 (28.0)
Refractory severe metabolic acidosis	93 (35.8)	107 (38.9)
Refractory severe pulmonary edema	38 (14.6)	29 (10.5)
KDIGO stage 3 AKI with serum urea level of >40 mmol/liter	98 (37.7)	103 (37.5)
KDIGO stage 3 AKI with oliguria for >3 days	107 (41.2)	108 (39.3)
Biologic characteristics at ICU admission		
Median serum creatinine level (IQR) — mg/dl	2.0 (1.2–3.6)	2.2 (1.4–3.6)
Median blood urea nitrogen level (IQR) — mg/dl	42.3 (24.4–78.0)	45.4 (28.0–72.0)
Median serum potassium level (IQR) — mmol/liter	4.5 (3.8–5.4)	4.4 (3.8–5.1)
Median serum bicarbonate level (IQR) — mmol/liter	18.4 (14.9–22.5)	19.2 (15.2–22.8)
Median pH (IQR)	7.3 (7.2–7.4)	7.3 (7.2–7.4)
Biologic characteristics on the day of randomization¶¶		
Median serum creatinine level (IQR) — mg/dl	4.4 (3.3–5.7)	4.4 (3.3–6.0)
Median blood urea nitrogen level (IQR) — mg/dl	69.2 (45.6–108.6)	78.4 (53.2–109.8)
Median serum potassium level (IQR) — mmol/liter	4.9 (4.1–5.5)	4.8 (4.2–5.5)
Median serum bicarbonate level (IQR) — mmol/liter	19.1 (16.0–22.0)	17.8 (14.5–21.0)
Median pH (IQR)	7.3 (7.2–7.4)	7.3 (7.2–7.3)

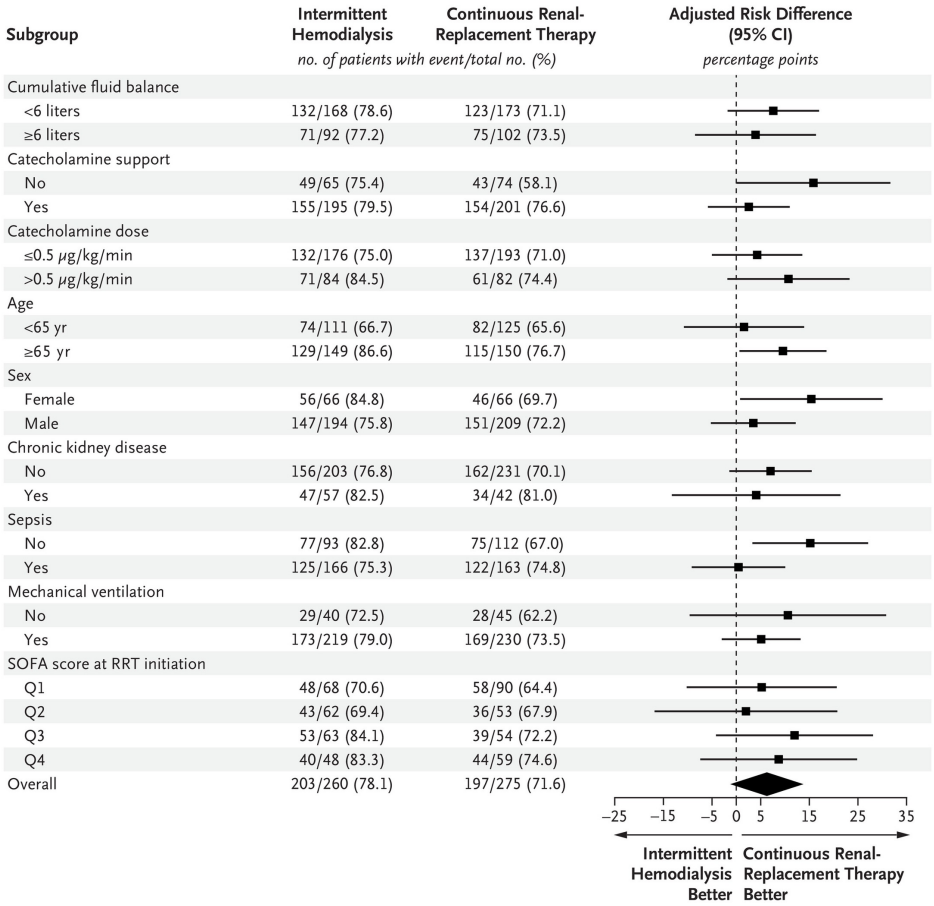
The assigned therapy was maintained for at least 4 consecutive days, unless kidney function recovered; after the fourth day, clinicians were free to switch to the other treatment method on the basis of usual clinical practice. The primary outcome was a composite of death, dependence on renal-replacement therapy, or a decline in kidney function from baseline (as indicated by a serum creatinine concentration more than 25% above the baseline value), assessed at day 90.

Primary and Secondary Outcomes.

Outcome	Intermittent Hemodialysis (N=260)	Continuous Renal-Replacement Therapy (N=275)	Adjusted Risk Difference (95% CI)	Effect Measure (95% CI)†
			percentage points	
Primary outcome				
Major adverse kidney event by day 90 — no. of patients/total no. (%)	203/260 (78.1)	197/275 (71.6)	6.28 (−1.22 to 13.79)	1.09 (0.98 to 1.20)
Secondary outcomes				
Kaplan–Meier estimate of mortality (95% CI) — %				1.30 (1.04 to 1.63)‡
By day 28	53.6 (47.2 to 59.3)	44.8 (38.6 to 50.4)	—	—
By day 60	62.2 (55.8 to 67.6)	50.7 (44.4 to 56.2)	—	—
By day 90	63.3 (57.0 to 68.8)	53.6 (47.3 to 59.2)	—	—
Dependence on RRT — no. of patients/total no. (%)				
At day 60	7/99 (7.1)	6/136 (4.4)	2.81 (−3.47 to 9.09)	1.62 (0.57 to 4.59)
At day 90	2/96 (2.1)	3/128 (2.3)	−0.17 (−4.48 to 4.13)	0.92 (0.17 to 5.11)
Serum creatinine concentration >25% above baseline value — no. of patients/total no. (%)				
At day 60	40/92 (43.5)	50/130 (38.5)	4.71 (−9.24 to 18.66)	1.12 (0.80 to 1.58)
At day 90	37/94 (39.4)	47/125 (37.6)	1.62 (−12.17 to 15.41)	1.04 (0.73 to 1.50)
Median length of stay in ICU (IQR) — days				
All patients	12 (4 to 20)	13 (6 to 22)	—	—
Patients who were alive at day 90	17 (8 to 31)	17 (11 to 28)	—	—
Patients who had died by day 90	9 (3 to 17)	8 (2 to 16)	—	—
Median length of stay in hospital (IQR) — days				
All patients	18 (6 to 43)	22 (7 to 58)	—	—
Patients who were alive at day 90	52 (27 to 90)	52 (27 to 90)	—	—
Patients who had died by day 90	10 (3 to 19)	10 (2 to 20)	—	—
Cumulative incidence of cessation of RRT (95% CI) — %				0.77 (0.61 to 0.97)§
At day 7	23.1 (18.0 to 28.2)	27.6 (22.4 to 32.9)	—	—
At day 14	29.6 (24.1 to 35.1)	39.3 (33.5 to 45.0)	—	—
At day 28	41.2 (35.2 to 47.1)	52.7 (46.9 to 58.6)	—	—
Median no. of days free from indicated intervention through day 28 (IQR)¶				
Catecholamine-free days	0 (0 to 24)	3 (0 to 23)	—	—
Ventilator-free days	0 (0 to 17)	0 (0 to 20)	—	—
Days free from RRT	0 (0 to 19)	1 (0 to 21)	—	—
Median eGFR at ICU discharge (IQR) — ml/min/1.73 m²	25.2 (13.1 to 52.5)	29.6 (15.5 to 51.1)	−2.18 (−11.0 to 6.62)	—
Complications potentially related to AKI or RRT — no. of patients/total no. (%)‖			—	—
Hypotension	179/260 (68.8)	183/275 (66.5)	—	—
Hemorrhage	61/260 (23.5)	59/275 (21.5)	—	—
Thrombocytopenia	107/259 (41.3)	107/274 (39.1)	—	—
Hypophosphatemia	24/256 (9.4)	15/271 (5.5)	—	—
Hypothermia	7/260 (2.7)	10/274 (3.6)	—	—
Cardiac rhythm disorders			—	—
Severe	14/260 (5.4)	10/275 (3.6)	—	—
Moderate	46/260 (17.7)	38/275 (13.8)	—	—
Air embolism	1/260 (0.4)	0	—	—
Bloodstream infection, catheter-related or with unknown origin	16/260 (6.2)	20/275 (7.3)	—	—



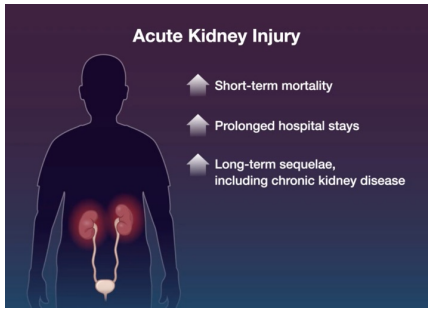
Kaplan–Meier Curves of the Probability of Death from Randomization to Day 90. Shown is the cumulative probability of death from randomization through day 90, as estimated with the Kaplan–Meier method. The risk of death was higher with intermittent hemodialysis than with continuous renal-replacement therapy (hazard ratio, 1.30; 95% confidence interval [CI], 1.04 to 1.63), as analyzed with a Cox proportional-hazards model adjusted for the stratification factors used for randomization (a cumulative fluid balance of ≥6 liters or <6 liters from admission to randomization and a catecholamine dose of >0.5 μg per kilogram of body weight per minute or ≤0.5 μg per kilogram per minute on the day of randomization).

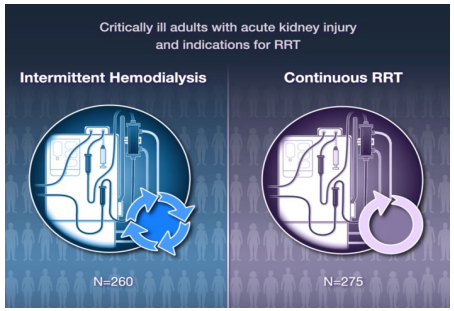


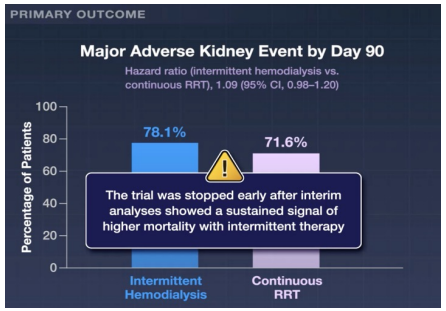
Subgroup Analyses of the Primary Outcome.

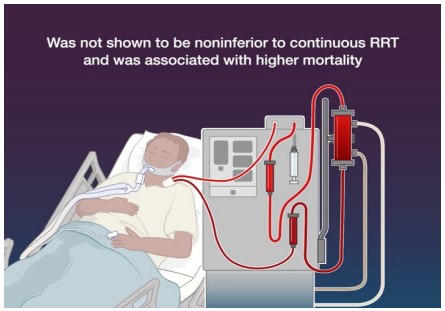
Shown are the adjusted absolute differences in the risk of a major adverse kidney event by day 90 (the primary outcome) with intermittent hemodialysis as compared with continuous renal-replacement therapy in each prespecified subgroup, with 95% confidence intervals. Differences were estimated with the Cochran–Mantel–Haenszel method with stratification according to the factors used for randomization (cumulative fluid balance and catecholamine dose), with multiple imputation for missing components of the composite outcome among surviving patients. Results were combined across imputations with the use of Rubin's rules. Quartiles of Sepsis-Related Organ Failure Assessment (SOFA) scores were defined at randomization, with quartile 1 (Q1) representing the lowest scores and quartile 4 (Q4) the highest (higher scores indicate more severe organ failure). Differences in risk of more than 0 indicate a higher incidence of major adverse kidney events by day 90 with intermittent hemodialysis than with continuous renal-replacement therapy. The widths of the confidence intervals were not adjusted for multiplicity and should not be used to infer definitive differences in treatment effects between the two groups. The squares indicate the point estimates of the adjusted absolute risk difference in each subgroup, the horizontal lines the 95% confidence intervals, and the diamond the point estimate and 95% confidence interval for the overall population. RRT denotes renal-replacement therapy.

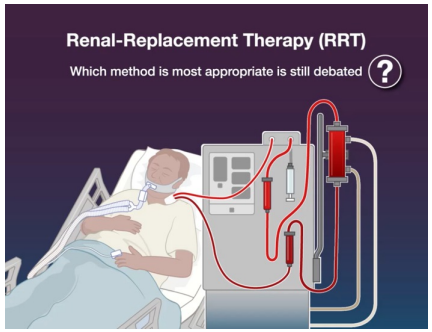
Death by day 90 occurred in 63.1% of the patients in the intermittent group, as compared with 53.5% of those in the continuous group; Kaplan-Meier mortality estimates at day 90 were 63.3% and 53.6%, respectively

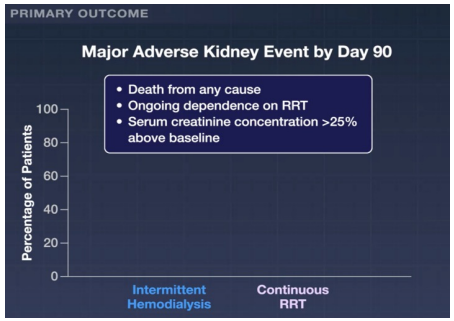


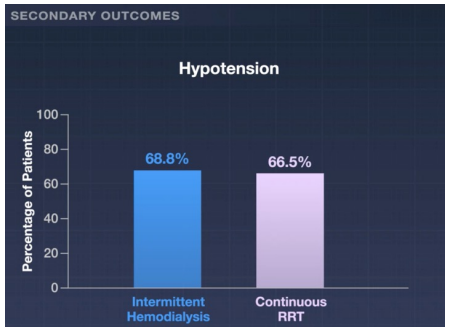


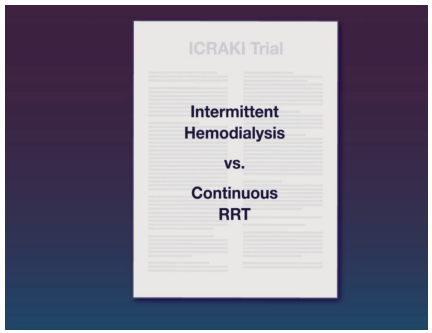


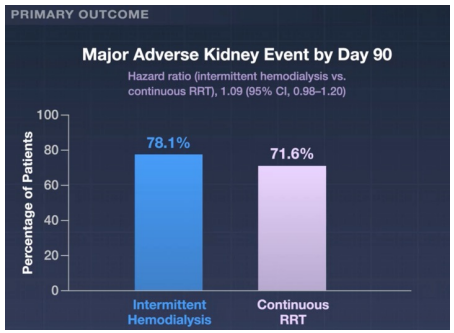


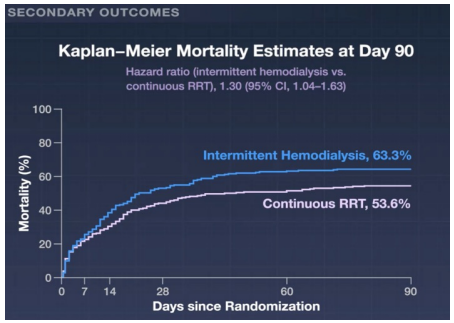












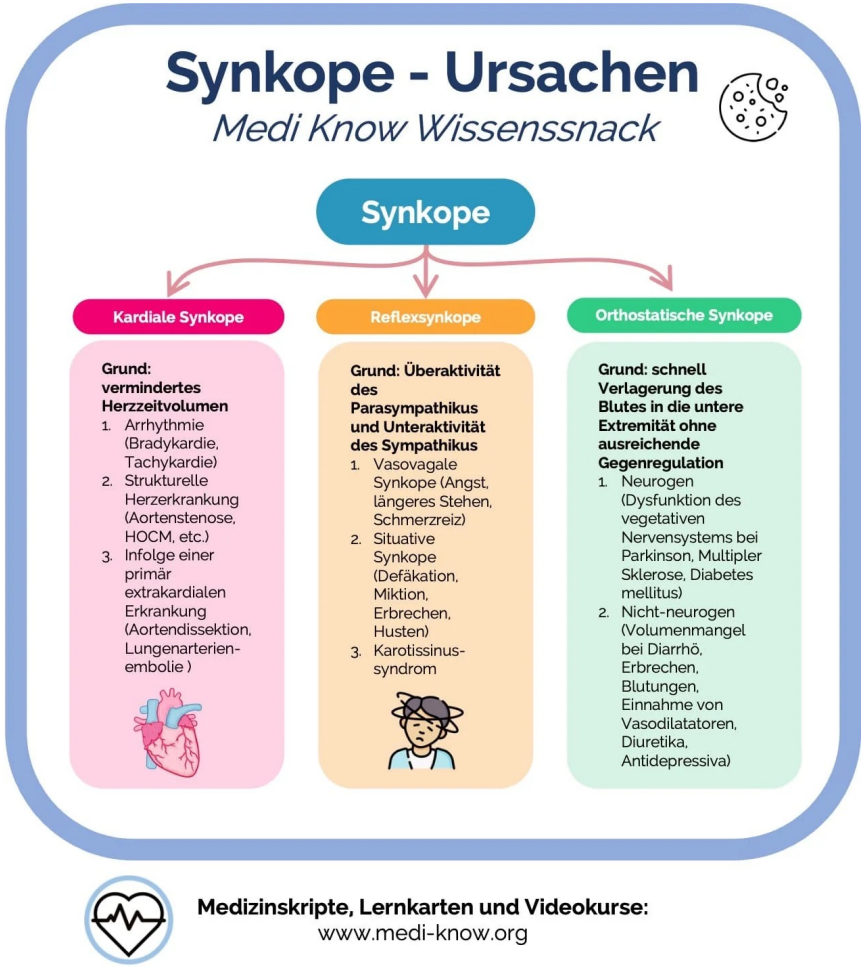
Because of early termination, the trial was underpowered, which limits the interpretation of the primary outcome.

Eine vasovagale Synkope ist eine harmlose, kurzzeitige Ohnmacht, die durch eine Fehlregulation des autonomen Nervensystems ausgelöst wird. Sie ist die mit Abstand häufigste Ursache für plötzlichen Bewusstseinsverlust und tritt besonders oft bei jüngeren Menschen auf.

Dabei führt eine Überstimulation des Nervus vagus (Kardioinhibition) bei gleichzeitiger Hemmung des sympathischen Nervensystems dazu, dass der **Blutdruck massiv abfällt und sich der Puls verlangsamt**. Dadurch versackt das Blut in den Beinen, das Gehirn wird kurzzeitig mit zu wenig Sauerstoff versorgt und man verliert das Bewusstsein.

Typische Auslöser

- **Langes, unbewegliches Stehen** (z. B. in der Schlange oder bei Hitze)
- **Starke Emotionen**, Angst, Schreck oder psychischer Stress
- **Anblick von Blut** oder medizinischen Nadeln
- **Schmerzen** oder plötzliche körperliche Überanstrengung
- **Körperliche Reflexe** wie starkes Pressen beim Toilettengang oder schnelles Aufstehen

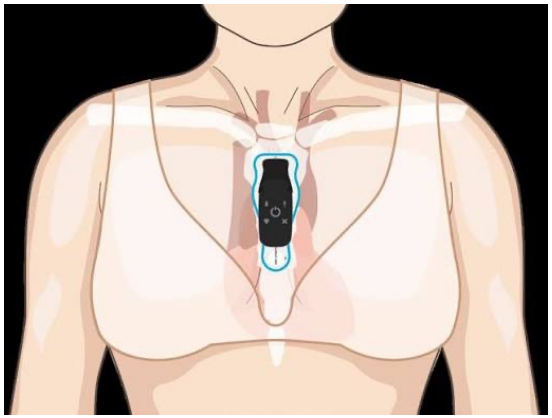


Der **BodyGuardian™ MINI** von Boston Scientific ist ein kleiner, wasserdichter und kabelloser Echtzeit-Herzmonitor für die ambulante Rhythmusüberwachung (Remote Cardiac Monitoring). Er wird auf der Brust getragen und zeichnet kontinuierlich jeden Herzschlag auf, um Herzrhythmusstörungen (wie Vorhofflimmern) bei Erwachsenen und Kindern zu erkennen.



Technische Kernkomponenten & Varianten

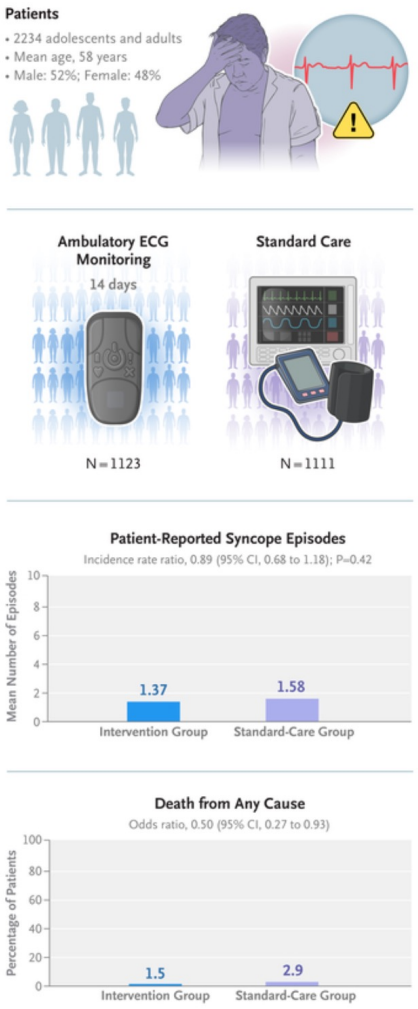
Das System ist hochgradig flexibel und kann je nach ärztlicher Verordnung als klassischer Langzeit-**Holter-Monitor**, als **Event-Rekorder (CEM)** oder für die mobile kardiale Telemetrie (**MCT**) eingesetzt werden. Es gibt zwei Hauptausführungen des Sensors.



Immediate Ambulatory Electrocardiographic Monitoring in Syncope

In patients with syncope who present to the emergency department for evaluation, diagnosing an underlying cardiac arrhythmia remains difficult.

We conducted an open-label, randomized, controlled trial at 45 hospitals in the United Kingdom to assess the effects of 14-day cardiac monitoring on diagnosis, treatment, and outcomes among patients with syncope. Adults with syncope that remained unexplained after an evaluation in the emergency department were assigned in a 1:1 ratio to undergo 14-day ambulatory electrocardiographic (ECG) monitoring (the intervention group) or to receive the standard care provided for patients with unexplained syncope at each participating site (the standard-care group). The primary outcome was the mean number of patient-reported episodes of syncope at 1 year.



Syncope is a clinical problem that is commonly evaluated in the emergency department; it accounts for approximately 650,000 visits to the emergency department in the United Kingdom and approximately 1.2 million such visits in the United States annually. The three principal types of syncope are neurocardiogenic syncope (also called vasovagal syncope), syncope due to postural hypotension, and cardiac syncope due to structural heart disease or arrhythmia.

In approximately 50% of the patients who present to the emergency department with syncope, no cause is identified after assessment. Although vasovagal and postural syncope are usually benign, clinically important pathologic conditions are identified in approximately 7% of patients with syncope within 1 month after an emergency department visit. The challenge is to differentiate benign syncope from potentially serious cardiac causes.

Evidence suggests that detection of an arrhythmia in a patient with unexplained syncope is most likely to occur when cardiac monitoring is initiated early, ideally at the index visit to the emergency department. To address the limitations of routine ECG monitoring, several ambulatory devices have been developed that provide continuous high-fidelity ECG recording during normal daily activities for up to 14 days, with patient-triggered symptom markers for subsequent analysis.

Patients

Patients 16 years of age or older who presented to the emergency department or acute medical unit with syncope that remained unexplained after an initial assessment were invited to participate in the trial. Syncope was defined as a transient loss of consciousness with the inability to maintain postural tone, followed by immediate complete spontaneous recovery without medical intervention. Patients who were subsequently admitted to the hospital after evaluation could still participate in the trial if the cause of syncope remained unexplained. Those not admitted to the hospital were contacted after discharge and offered the option to participate, with informed consent obtained either in writing or orally during a telephone call. Randomization occurred within 72 hours after presentation to the emergency department.

Interventions

Patients assigned to the intervention group were fitted with a 14-day ambulatory heart monitor (BodyGuardian Mini, Boston Scientific) as soon as possible after randomization. The device recorded cardiac rhythm continuously. The patients in the intervention group were instructed to press a button on the heart monitor after recovery from any syncopal event.

Outcomes

The primary outcome was the number of patient-reported episodes of syncope at 1 year. Secondary outcomes included clinically significant cardiac arrhythmia (serious or symptomatic), death from any cause, symptomatic syncope, the number of episodes of syncope identified in the medical records and the recurrence of syncope.

Characteristic	Intervention (N=1122)	Standard Care (N=1111)
Age — yr	58.3±19.8	58.3±19.7
Male sex — no. (%)	594 (52.9)	570 (51.3)
Race or ethnic group — no. (%)†		
White	1006 (89.7)	994 (89.5)
Asian or Asian British	60 (5.3)	53 (4.8)
Black or Black British	31 (2.8)	23 (2.1)
Mixed	4 (0.4)	13 (1.2)
Other	21 (1.9)	28 (2.5)
Medical history — no./total no. (%)		
Syncope		
Previous episode	522/1118 (46.7)	487/1111 (43.8)
>1 episode in the past year	278/1122 (24.8)	262/1111 (23.6)
Coronary artery disease	95/1119 (8.5)	88/1111 (7.9)
Myocardial infarction	59/1119 (5.3)	71/1111 (6.4)
Atrial fibrillation or flutter	97/1119 (8.7)	85/1111 (7.7)
Hypertension	349/1119 (31.2)	352/1111 (31.7)
Congestive heart failure	18/1119 (1.6)	29/1111 (2.6)
Valvular heart disease	36/1119 (3.2)	40/1111 (3.6)
Chronic lung disease	84/1119 (7.5)	101/1111 (9.1)
Chronic kidney disease	48/1119 (4.3)	60/1111 (5.4)
Symptoms occurring with syncope — no./total no. (%)		
Prodromal or preceding symptoms	446/1118 (39.9)	452/1111 (40.7)
Palpitation before syncope	110/1118 (9.8)	107/1111 (9.6)
Associated chest pain	124/1118 (11.1)	125/1111 (11.3)
Clinical characteristics on admission‡		
Systolic blood pressure — mm Hg	138.1±23.6	138.4±24.5
Respiratory rate — breaths/min	17.4±2.6	17.4±2.8
Pulse — beats/min	77.6±16.4	77.6±16.1
Postural drop in blood pressure		
No. of patients/total no. (%)	41/530 (7.7)	48/529 (9.1)
Change in systolic blood pressure — mm Hg	10.8±11.2	10.4±9.6

Hospitalization and Follow-up after the Index Visit to the Emergency Department.

Result of Visit	Intervention (N=1122)	Standard Care (N=1111)
Admitted to the hospital — no./total no. (%)	442/1118 (39.5)	436/1111 (39.2)
Reason for admission — no./total no. (%)†		
High-risk syncope	286/442 (64.7)	270/436 (61.9)
Coexisting condition	62/442 (14.0)	53/436 (12.2)
Investigation of syncope	393/442 (88.9)	373/436 (85.6)
Social reason‡	13/442 (2.9)	12/436 (2.8)
Other	37/442 (8.4)	45/436 (10.3)
Duration of index hospital stay — days§	3.3±4.7	3.6 ±4.6
Participated in outpatient follow-up — no./total no. (%)	658/1118 (58.9)	681/1110 (61.4)
Discharged alive — no./total no. (%)¶	1114/1118 (99.6)	1109/1111 (99.8)

Placement of an implantable cardioverter–defibrillator, ablation, and discontinuation of medications that were thought to be contributing to arrhythmia all occurred in a higher percentage of patients in the intervention group than in the standard-care group, but individually, these results did not reach significance. Taken together, the data suggest that the diagnostic findings did lead to important changes in clinical management.

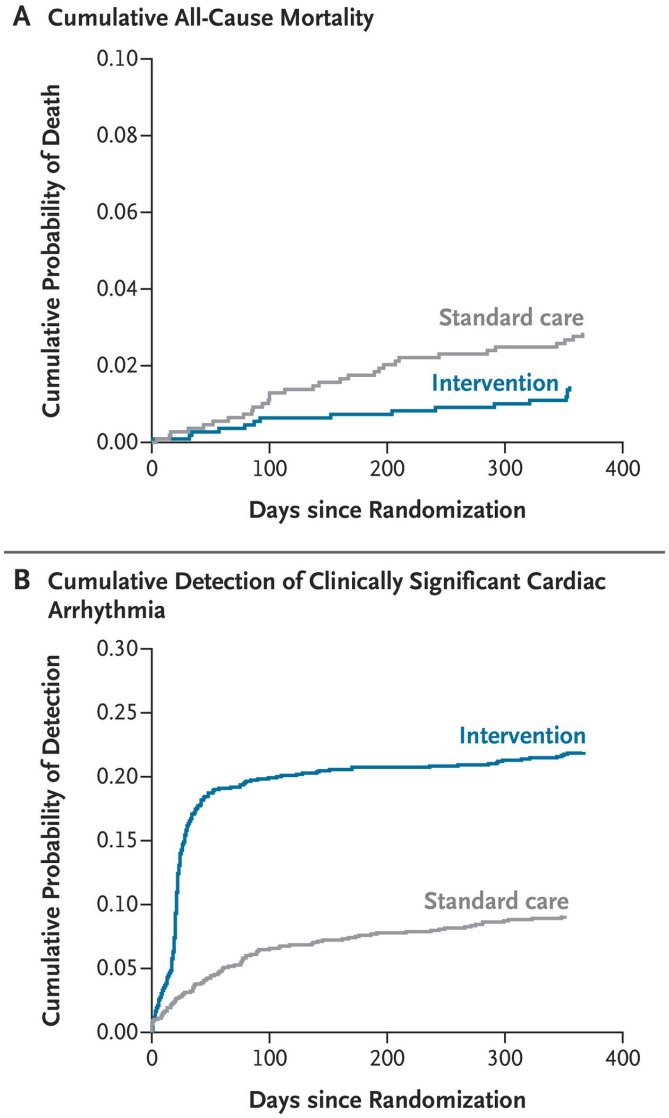
Primary and Secondary Outcomes.

Outcome	Intervention (N=1122)	Standard Care (N=1111)	Odds Ratio or Incidence Rate Ratio (95% CI)†
Primary outcome			
Patient-reported syncope episodes at 1 yr‡	1.37±5.10	1.58±8.56	0.89 (0.68 to 1.18)§
Secondary outcomes¶			
Syncope episodes identified in the medical records at 1 yr‖	0.22±0.64	0.25±0.82	0.90 (0.71 to 1.15)§
Syncope recurrence at 1 yr — no. of patients with recurrence/total no. of patients (%)	280/1004 (27.9)	276/966 (28.6)	0.97 (0.79 to 1.17)
Duration of index hospital stay — days**	1.3±3.4	1.4±3.4	0.91 (0.76 to 1.08)
Clinically significant cardiac arrhythmia at 1 yr — no. of patients/total no. (%)††	241/1095 (22.0)	98/1085 (9.0)	2.95 (2.28 to 3.81)
Death from any cause at 1 yr — no. of patients/total no. (%)	16/1095 (1.5)	31/1085 (2.9)	0.50 (0.27 to 0.93)
Symptomatic cardiac arrhythmia at 1 yr — no. of patients/total no. (%)	102/1095 (9.3)	64/1085 (5.9)	1.66 (1.20 to 2.31)
Time to detection of clinically significant cardiac arrhythmia (IQR) — days‡‡	22.0 (17.0–32.0)	54.5 (18.0–117.0)	0.35 (0.28 to 0.44)
Serious cardiac arrhythmia at 1 yr — no. of patients/total no. (%)§§			
Sustained VT	16/1095 (1.5)	6/1085 (0.6)	2.67 (1.04 to 6.86)
Nonsustained VT	109/1095 (10.0)	13/1085 (1.2)	9.50 (5.29 to 17.06)
Complete or third-degree heart block	11/1095 (1.0)	8/1085 (0.7)	1.36 (0.55 to 3.41)
Second-degree atrioventricular heart block, Mobitz type II	13/1095 (1.2)	7/1085 (0.6)	1.85 (0.73 to 4.65)
Pause of ≥6 sec	30/1095 (2.7)	13/1085 (1.2)	2.32 (1.20 to 4.48)
Sinus bradycardia	20/1095 (1.8)	10/1085 (0.9)	2.00 (0.93 to 4.29)
Bradycardia	19/1095 (1.7)	8/1085 (0.7)	2.37 (1.02 to 5.49)
Diagnostic tests and therapeutic interventions at 1 yr			
Initiation of antiarrhythmic medication — no. of patients/total no. (%)	117/1085 (10.8)	79/1078 (7.3)	1.47 (1.11 to 1.95)
Pacemaker implantation — no. of patients/total no. (%)	74/1085 (6.8)	50/1078 (4.6)	1.49 (1.04 to 2.13)
Ablation — no. of patients/total no. (%)	5/1085 (0.5)	4/1078 (0.4)	1.24 (0.33 to 4.64)
Implantable cardioverter–defibrillator placement — no. of patients/total no. (%)	7/1085 (0.6)	4/1078 (0.4)	1.74 (0.51 to 5.97)
Discontinuation of medical therapy thought to be causing arrhythmia — no. of patients/total no. (%)	29/1085 (2.7)	28/1078 (2.6)	1.03 (0.61 to 1.75)
Total number of short-term monitors¶¶	0.29±0.74	0.40±0.55	0.72 (0.63 to 0.84)§
Placement of implantable loop recorder — no. of patients/total no. (%)	81/1085 (7.5)	82/1078 (7.6)	0.96 (0.70 to 1.33)
Echocardiography — no. of patients/total no. (%)	431/1085 (39.7)	384/1078 (35.6)	1.21 (1.01 to 1.44)
Computed tomographic coronary angiography — no. of patients/total no. (%)	34/1085 (3.1)	39/1078 (3.6)	0.86 (0.54 to 1.38)
Diagnostic invasive coronary angiography — no. of patients/total no. (%)	13/1085 (1.2)	20/1078 (1.9)	0.64 (0.32 to 1.30)

Kaplan–Meier Curves for Death from Any Cause and Detection of Clinically Significant Cardiac Arrhythmias.

Panel A shows cumulative all-cause mortality in the intervention group and in the standard-care group. Panel B shows the cumulative probability of detection of a clinically significant cardiac arrhythmia in the two groups.

At 1 year, a clinically important arrhythmia was identified in 22% of the patients in the intervention group and in 9% of those in the standard-care group (odds ratio, 2.95; 95% CI, 2.28 to 3.81). This outcome, one of many secondary outcomes, appears to have been driven by the detection of ventricular tachycardia, both sustained and nonsustained, a finding that most clinicians would want to know about.



Für den BodyGuardian™ MINI von Boston Scientific gibt es keinen festen, öffentlich zugänglichen Endverbraucherpreis, da es sich um ein verschreibungspflichtiges medizinisches Gerät handelt. Die Kosten für die Nutzung und die anschließende Auswertung werden in der Regel direkt über die Krankenkassen oder Kliniken abgerechnet.

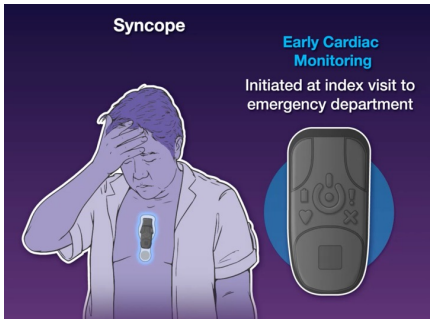
Für die Beschaffung im medizinischen Bereich oder auf dem Sekundärmarkt gelten folgende Orientierungswerte:

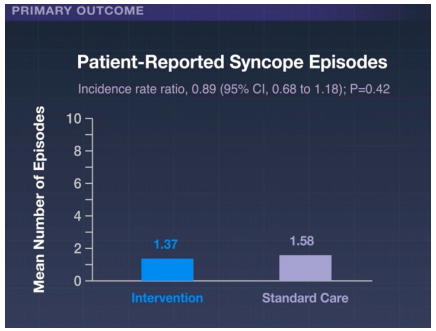
- **Gerätepreis (Gebraucht-/Medizintechnikmarkt):** Auf spezialisierten Plattformen für medizinische Geräte (wie DotMED) wird das System original für rund **244 USD** gelistet und gebraucht für etwa **144 USD** gehandelt.
- **Klinik- und Behördeneinkauf:** Krankenhäuser, Großabnehmer oder Behörden beziehen die Monitore über spezielle Beschaffungsprogramme (wie das Boston Scientific Ordering-Portal oder Rahmenverträge), bei denen individuelle Rabatte vereinbart werden.
- **Zubehör (Pflaster/Elektroden):** Die passenden Einweg-Adhäsivstreifen (Strip/Bridge) für den Patientenwechsel kosten im freien Online-Handel (z. B. Ebay) je nach Packungsgröße zwischen **10 USD und 60 USD**.

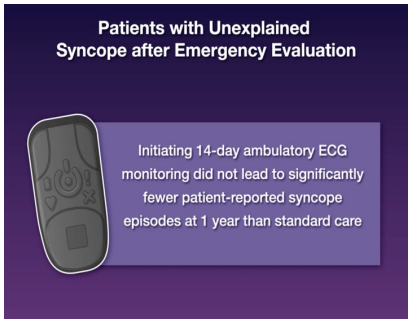


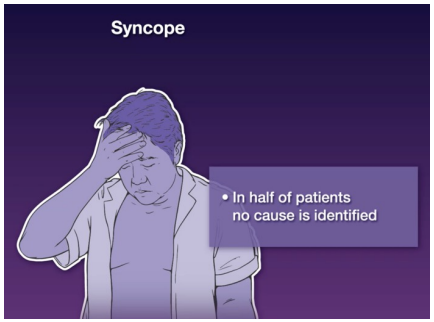


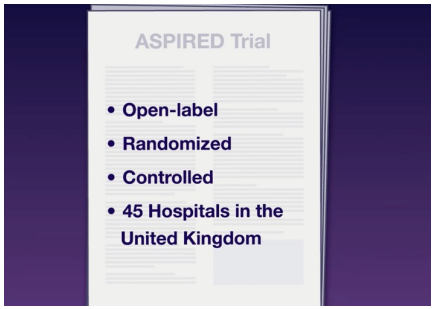


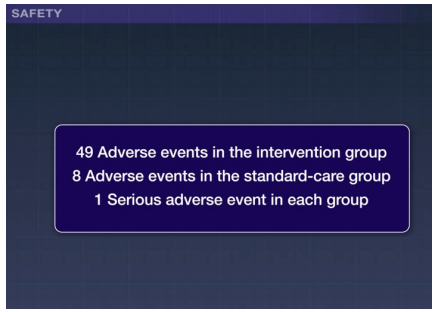


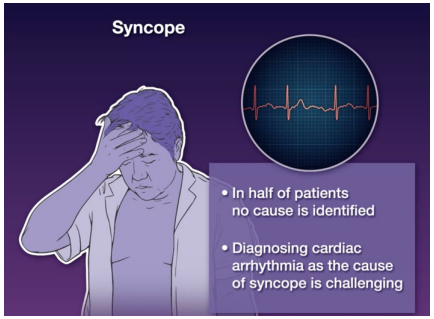


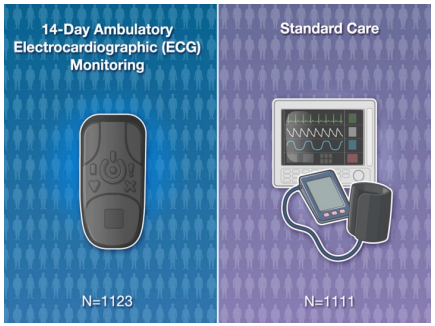


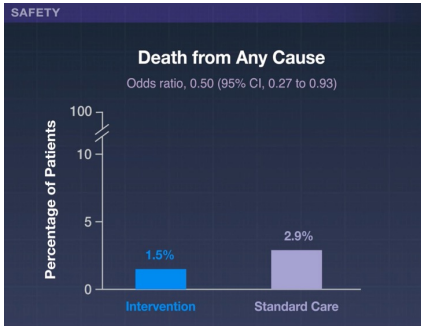












The most surprising finding may be the difference in 1-year mortality between the two groups: 1.5% in the intervention group and 2.9% in the standard-care group. Do monitors save lives? Probably not.

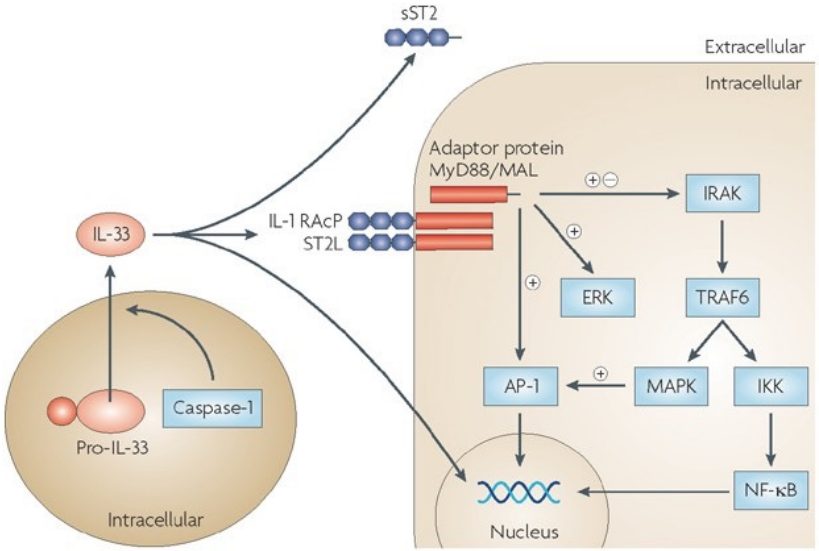
The ease of this device would encourage me to selectively order it.

Interleukin-33 (IL-33) ist ein multifunktionales Zytokin aus der IL-1-Superfamilie, das im menschlichen Körper durch das *IL33*-Gen auf Chromosom 9 kodiert wird. Es fungiert als sogenanntes **Alarmin** (Gefahrensignal), das das Immunsystem bei Gewebeschäden warnt, spielt aber auch eine direkte Rolle bei der Genregulation im Zellkern.

Duale Funktion & Wirkmechanismus
IL-33 besitzt eine charakteristische Doppelrolle im Organismus:

Intrazellulär (im Zellkern): In ruhenden Zellen (vor allem in Epithel-, Endothel- und fibroblastischen Stromazellen) ist IL-33 an das Chromatin gebunden und wirkt dort als Transkriptionsfaktor bzw. Repressor, der die Genaktivität reguliert.

Extrazellulär (als Alarmin): Wird eine Zelle durch Verletzung, Infektion oder Nekrose beschädigt, wird IL-33 freigesetzt. Es bindet extrazellulär an seinen spezifischen Rezeptorkomplex bestehend aus **ST2** (IL1RL1) und dem Corezeptor IL-1RAcP. Dies aktiviert Signalwege wie NF-κB und MAPK, die Entzündungsreaktionen einleiten.



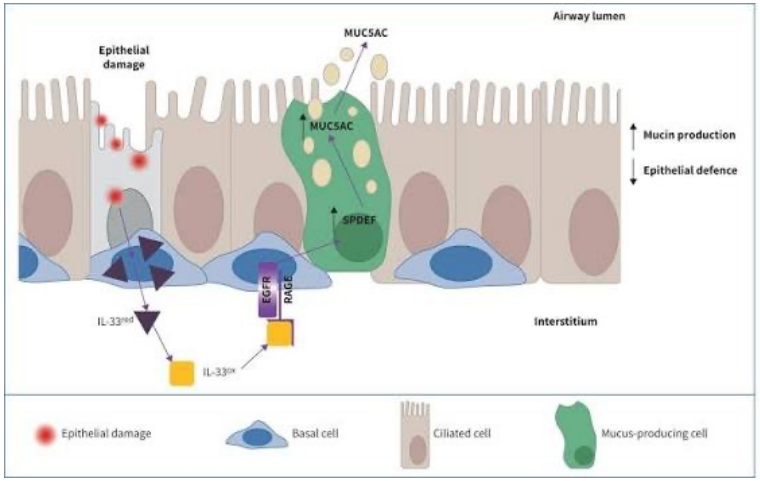
Nature Reviews | Drug Discovery

Der biologische Mechanismus: Die zwei Gesichter von IL-33

Wenn die Lungenoberfläche (Epithel) durch Zigarettenrauch, Feinstaub oder Infektionen geschädigt wird, wird IL-33 freigesetzt. Neueste wissenschaftliche Erkenntnisse zeigen, dass IL-33 in zwei verschiedenen Formen vorliegt, die die COPD auf unterschiedliche Weise verschlimmern:

- **Reduziertes IL-33:** Diese Form bindet an den ST2-Rezeptor und kurbelt die klassische Entzündungsreaktion (Typ-2-Inflammation) an. Dies aktiviert Immunzellen wie Eosinophile und Neutrophile, die das Lungengewebe chronisch schädigen.

- **Oxidiertes IL-33:** Durch den oxidativen Stress in der COPD-Lunge (z.B. durch anhaltendes Rauchen) verändert sich das Protein. Es wirkt über einen unbeschriebenen, ST2-unabhängigen Weg (RAGE/EGFR). Diese Form treibt die krankhafte Gewebeveränderung voran und führt zur Überproduktion von zähem Schleim sowie zur Bildung von gefährlichen Schleimpfropfen (*Mucus Plugs*).

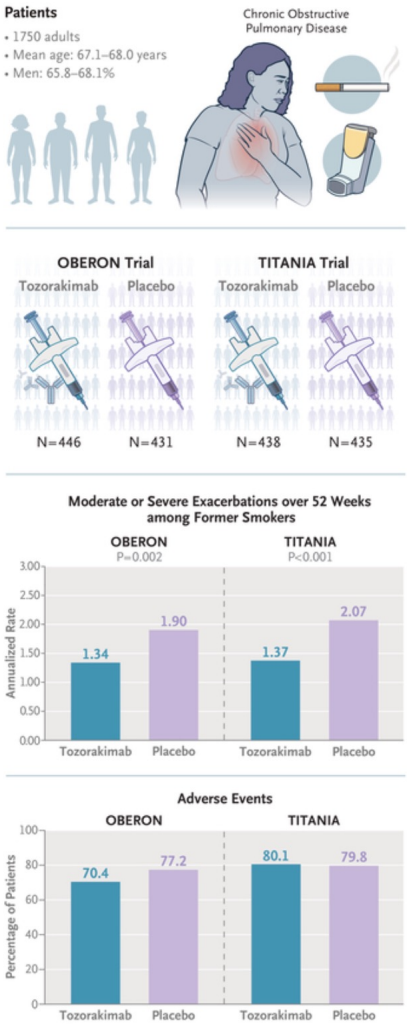


Epithelial damage, repair and remodelling are critical features of chronic airway diseases including chronic obstructive pulmonary disease (COPD). Interleukin (IL)-33 released from damaged airway epithelia causes inflammation via its receptor, serum stimulation-2 (ST2). Oxidation of IL-33 to a non-ST2-binding form (IL-33ox) is thought to limit its activity. We investigated whether IL-33ox has functional activities that are independent of ST2 in the airway epithelium.

Tozorakimab to Prevent COPD Exacerbations

Many patients with chronic obstructive pulmonary disease (COPD) have exacerbations despite receiving standard-of-care inhaled maintenance therapy. Dysregulated interleukin-33 signaling is implicated in the pathogenesis of COPD. Tozorakimab is a monoclonal antibody that inhibits the activity of interleukin-33.

In two replicate phase 3 trials (OBERON and TITANIA), we enrolled adults with COPD who were current or former smokers and had a history of exacerbations in the previous year despite receiving stable standard-of-care inhaled maintenance therapy. There were no eligibility criteria related to blood eosinophil count. Patients were randomly assigned to receive add-on subcutaneous tozorakimab (300 mg) or placebo every 4 weeks for 52 weeks. The primary end point was the annualized rate of moderate or severe exacerbations that occurred over a 52-week period among former smokers, and the first key secondary end point was the annualized rate of moderate or severe exacerbations in the overall population. Safety was also assessed.



Chronic obstructive pulmonary disease (COPD) is a leading cause of death worldwide, and the prevalence is projected to reach approximately 600 million by 2050. COPD exacerbations are clinically important events that are associated with accelerated decline in lung function, impaired health-related quality of life, and increased risks of further exacerbations, cardiopulmonary events, and death. Exacerbations impose a substantial health care burden, especially when they result in hospitalization or emergency department (ED) visits.

Tozorakimab is a high-affinity human anti–interleukin-33 monoclonal antibody that inhibits the activity of both the reduced form and the oxidized form of interleukin-33. LUNA was a phase 3 clinical trial program designed to evaluate the efficacy and safety of tozorakimab added to standard-of-care therapy in patients with COPD. The program comprised four trials: OBERON, TITANIA, PROSPERO, and MIRANDA. The dosing frequencies and treatment durations varied among these trials. Here, we report the results from OBERON and TITANIA.

Patients

Eligible patients were 40 years of age or older, had COPD diagnosed at least 12 months before enrollment, and had received stable standard-of-care inhaled maintenance therapy (triple or dual therapy) for the previous 3 months. Patients had to have had at least two moderate or at least one severe COPD exacerbation (as defined below) in the previous 12 months, including at least one resulting in treatment with systemic glucocorticoids and at least one while receiving their most recent stable maintenance therapy.

Current or former smokers with a smoking history of at least 10 pack-years were eligible.

End Points

The primary end point was the annualized rate of moderate or severe exacerbations that occurred over a 52-week period in the prespecified cohort of former smokers. Moderate exacerbations were defined as worsening COPD symptoms resulting in treatment with systemic glucocorticoids for at least 3 days or antibiotics or both, or an ED visit lasting less than 24 hours with intensive treatment. Severe exacerbations were defined as worsening COPD symptoms resulting in hospitalization for at least 24 hours or death.

Characteristic	OBERON		TITANIA	
	Tozorakimab (N=446)	Placebo (N=431)	Tozorakimab (N=438)	Placebo (N=435)
Age — yr	67.3±7.8	67.1±7.8	68.0±7.3	67.8±7.2
Sex — no. (%)				
Male	296 (66.4)	273 (63.3)	301 (68.7)	293 (67.4)
Female	150 (33.6)	158 (36.7)	137 (31.3)	142 (32.6)
Smoking status — no. (%)				
Former smoker	342 (76.7)	337 (78.2)	350 (79.9)	344 (79.1)
Current smoker	104 (23.3)	94 (21.8)	88 (20.1)	91 (20.9)
Smoking history — pack-yr	40.9±21.7	42.4±21.3	44.6±24.7	43.8±24.3
Inhaled therapy for COPD — no. (%)†				
Triple therapy	406 (91.0)	393 (91.2)	396 (90.4)	390 (89.7)
Dual therapy‡	40 (9.0)	38 (8.8)	42 (9.6)	45 (10.3)
Inhaled glucocorticoid	416 (93.3)	409 (94.9)	414 (94.5)	407 (93.6)
No. of moderate or severe exacerbations in the 12 mo before enrollment§	2.5±1.2	2.4±1.2	2.3±1.0	2.3±1.2
Blood eosinophil count at screening — no. (%)				
<150 cells/μl	165 (37.0)	166 (38.5)	178 (40.6)	184 (42.3)
150 to <300 cells/μl	160 (35.9)	152 (35.3)	162 (37.0)	151 (34.7)
≥300 cells/μl	121 (27.1)	113 (26.2)	98 (22.4)	100 (23.0)
Severity of airflow obstruction — no. (%)¶				
Mild	12 (2.7)	21 (4.9)	17 (3.9)	21 (4.8)
Moderate	154 (34.5)	134 (31.1)	137 (31.3)	152 (34.9)
Severe	198 (44.4)	185 (42.9)	193 (44.1)	182 (41.8)
Very severe	82 (18.4)	89 (20.6)	91 (20.8)	80 (18.4)
Missing data	0	2 (0.5)	0	0
Postbronchodilator FEV_1:FVC ratio — %	43.4±11.8	44.0±13.1	43.2±12.6	44.1±12.3
SGRQ total score‖	54.0±17.2	54.2±16.8	54.3±18.3	55.3±18.5
E-RS–COPD total score**	14.8±6.0	14.4±6.3	15.2±5.9	14.4±6.4
CAT total score††	21.7±5.8	21.5±5.6	21.7±5.5	22.0±5.7

Adverse Events.

Event	OBERON		TITANIA	
	Tozorakimab (N=446)	Placebo (N=430)	Tozorakimab (N=438)	Placebo (N=435)
	number of patients (percent)			
Any adverse event†	314 (70.4)	332 (77.2)	351 (80.1)	347 (79.8)
Leading to discontinuation of trial regimen	14 (3.1)	12 (2.8)	16 (3.7)	23 (5.3)
Any serious adverse event	104 (23.3)	116 (27.0)	136 (31.1)	141 (32.4)
Any adverse event leading to death	6 (1.3)	5 (1.2)	11 (2.5)	4 (0.9)
Adverse events occurring in ≥5% of patients‡				
COPD	56 (12.6)	76 (17.7)	89 (20.3)	108 (24.8)
Nasopharyngitis	45 (10.1)	46 (10.7)	37 (8.4)	35 (8.0)
Upper respiratory tract infection	27 (6.1)	22 (5.1)	38 (8.7)	38 (8.7)
Injection-site reaction	23 (5.2)	6 (1.4)	29 (6.6)	7 (1.6)
Fall	21 (4.7)	24 (5.6)	28 (6.4)	24 (5.5)
Coronavirus disease 2019	23 (5.2)	16 (3.7)	25 (5.7)	39 (9.0)
Pneumonia	17 (3.8)	17 (4.0)	24 (5.5)	36 (8.3)
Headache	23 (5.2)	19 (4.4)	18 (4.1)	22 (5.1)
Respiratory failure	9 (2.0)	19 (4.4)	24 (5.5)	25 (5.7)
Urinary tract infection	21 (4.7)	24 (5.6)	12 (2.7)	17 (3.9)
Lower respiratory tract infection	11 (2.5)	11 (2.6)	21 (4.8)	22 (5.1)
Acute respiratory failure	7 (1.6)	11 (2.6)	9 (2.1)	23 (5.3)

Die Triple-Therapie setzt sich aus folgenden Bausteinen zusammen:

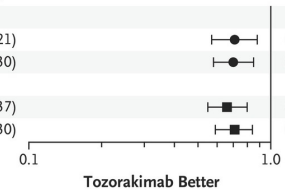
1. **LAMA (Langwirksame Anticholinergika):** Erweitern die Bronchien, indem sie die Verengung der Atemwegsmuskulatur blockieren (z. B. Glycopyrronium, Umeclidinium).

2. **LABA (Langwirksame Beta-2-Sympathomimetika):** Erweitern die Bronchien aktiv durch Entspannung der Atemwegsmuskulatur (z. B. Formoterol, Vilanterol).

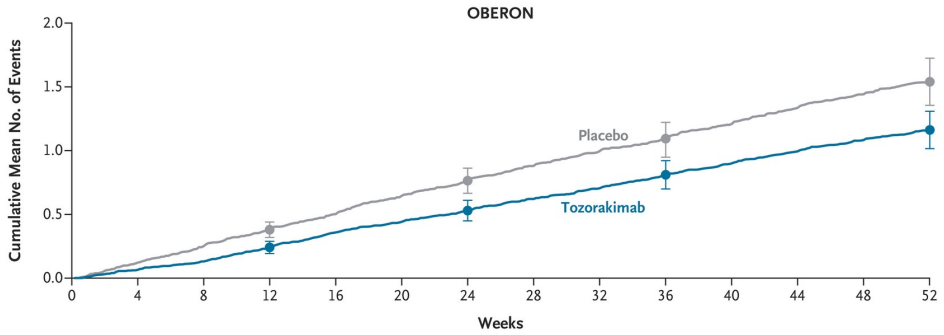
3. **ICS (Inhalative Kortikosteroide):** Inhalatives Kortison, das chronische Entzündungen in den Atemwegen bekämpft (z. B. Beclometason, Budesonid, Fluticasonfuroat)

A Annualized Rate of Moderate or Severe Exacerbations

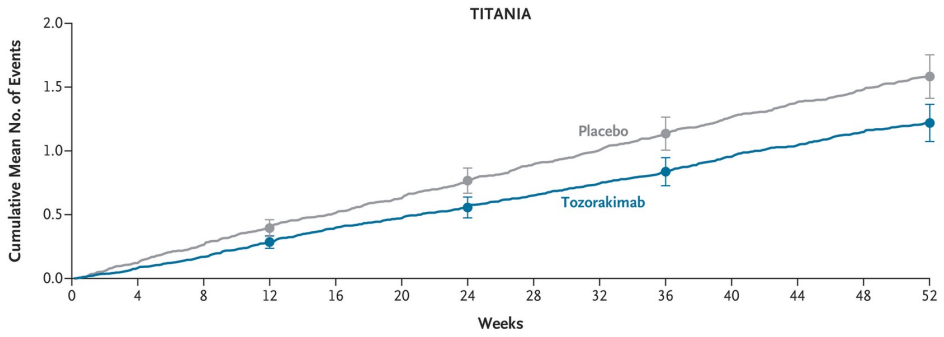
Population	Tozorakimab *total no. of patients*	Placebo *total no. of patients*	Tozorakimab *adjusted annualized rate (95% CI)*	Placebo *adjusted annualized rate (95% CI)*	Rate Ratio (95% CI)	P Value
OBERON						
Former smokers	342	337	1.34 (1.14–1.58)	1.90 (1.63–2.21)	0.71 (0.57–0.88)	0.002
Overall	446	431	1.41 (1.22–1.62)	2.00 (1.74–2.30)	0.70 (0.58–0.85)	<0.001
TITANIA						
Former smokers	350	344	1.37 (1.19–1.57)	2.07 (1.81–2.37)	0.66 (0.55–0.80)	<0.001
Overall	438	435	1.44 (1.27–1.63)	2.03 (1.80–2.30)	0.71 (0.59–0.84)	<0.001



B Cumulative Moderate or Severe Exacerbations

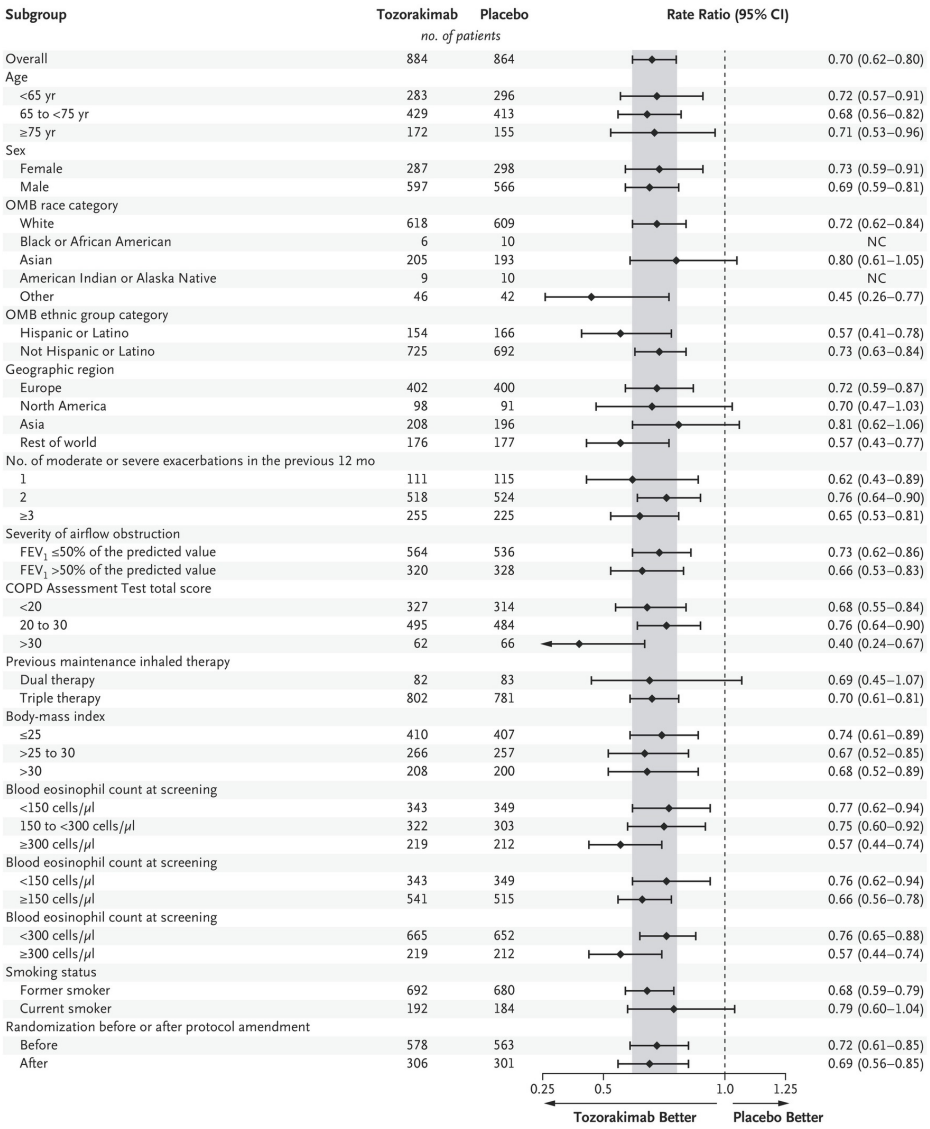


No. at Risk														
Placebo	431	429	424	423	418	417	414	412	407	403	399	396	390	349
Tozorakimab	446	445	443	440	436	431	429	423	422	417	417	417	415	371



Moderate or Severe Exacerbations.

Data are shown for the patients in the OBERON and TITANIA trials who were assigned to receive tozorakimab every 4 weeks and those who were assigned to receive placebo. Panel A shows the annualized rate of moderate or severe chronic obstructive pulmonary disease (COPD) exacerbations that had occurred over a 52-week period among former smokers (the primary end point) and in the overall population, which consisted of current and former smokers (the first key secondary end point). In the OBERON trial, two patients in the placebo group (one of whom was a former smoker) were excluded from the analyses because of missing lung-function data at screening. Panel B shows the cumulative mean number of moderate or severe exacerbations that occurred over a 52-week period in the overall population. The 95% confidence intervals (I bars) in Panel B have not been adjusted for multiplicity and should not be used to infer treatment effects.

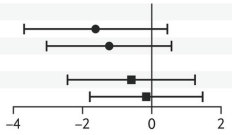


Subgroup Analysis of Moderate or Severe Exacerbations.

Shown is the annualized rate of moderate or severe COPD exacerbations in the pooled overall population from the OBERON and TITANIA trials, according to subgroup. Patients were originally assigned to receive tozorakimab once every 4 weeks or once every 8 weeks or placebo, but the protocol was later amended to stop assignment to the group receiving tozorakimab every 8 weeks. Data are shown for the patients who were assigned to receive tozorakimab every 4 weeks and those who were assigned to receive placebo. The gray shaded area indicates the 95% confidence interval for the pooled overall population. The 95% confidence intervals have not been adjusted for multiplicity and should not be used to infer treatment effects. All the subgroups were prespecified except for the subgroup defined according to a blood eosinophil count at screening of less than 150 cells per microliter or 150 cells or more per microliter, which combined the prespecified subgroups that were defined according to a blood eosinophil count of 150 to less than 300 cells per microliter or 300 cells or more per microliter; the modeled estimate among patients with a blood eosinophil count of less than 150 cells per microliter differs slightly between these analyses. Office of Management and Budget (OMB) race and ethnic group categories were reported by the patients. Total scores on the COPD Assessment Test range from 0 to 40, with higher scores indicating a greater effect of COPD on health status. The body-mass index is the weight in kilograms divided by the square of the height in meters. FEV_1 denotes the forced expiratory volume in 1 second, and NC could not be calculated.

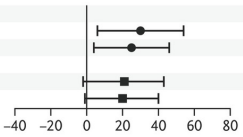
A Change in SGRQ Total Score

Population	Tozorakimab	Placebo	Tozorakimab	Placebo	Least-Squares Mean Difference (95% CI)
	no. of patients		*estimated change in points (95% CI)*		
OBERON					
Former smokers	298	304	−5.84 (−8.12 to −3.56)	−4.22 (−6.44 to −1.99)	−1.62 (−3.69 to 0.45)
Overall	392	386	−4.18 (−6.22 to −2.14)	−2.95 (−4.98 to −0.92)	−1.23 (−3.04 to 0.57)
TITANIA					
Former smokers	323	321	−3.33 (−5.20 to −1.45)	−2.73 (−4.64 to −0.83)	−0.59 (−2.43 to 1.25)
Overall	402	409	−3.68 (−5.39 to −1.98)	−3.53 (−5.22 to −1.83)	−0.16 (−1.79 to 1.47)



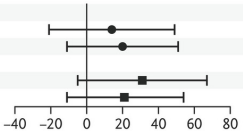
B Change in Prebronchodilator FEV_1

Population	Tozorakimab	Placebo	Tozorakimab	Placebo	Least-Squares Mean Difference (95% CI)
	no. of patients		*estimated change in ml (95% CI)*		
OBERON					
Former smokers	336	324	25 (0 to 51)	−5 (−30 to 21)	30 (6 to 54)
Overall	437	413	12 (−12 to 35)	−13 (−37 to 10)	25 (4 to 46)
TITANIA					
Former smokers	343	332	1 (−22 to 24)	−19 (−43 to 4)	21 (−2 to 43)
Overall	427	421	10 (−12 to 32)	−10 (−31 to 12)	20 (−1 to 40)



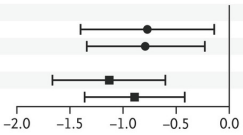
C Change in Postbronchodilator FEV_1

Population	Tozorakimab	Placebo	Tozorakimab	Placebo	Least-Squares Mean Difference (95% CI)
	no. of patients		*estimated change in ml (95% CI)*		
OBERON					
Former smokers	276	272	−7 (−40 to 26)	−21 (−54 to 12)	14 (−21 to 49)
Overall	363	342	−25 (−56 to 5)	−45 (−76 to −14)	20 (−11 to 51)
TITANIA					
Former smokers	271	280	−10 (−43 to 23)	−41 (−74 to −8)	31 (−5 to 67)
Overall	341	353	−23 (−53 to 7)	−44 (−75 to −14)	21 (−11 to 54)



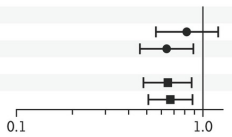
D Change in E-RS–COPD Total Score

Population	Tozorakimab	Placebo	Tozorakimab	Placebo	Least-Squares Mean Difference (95% CI)
	no. of patients		*estimated change in points (95% CI)*		
OBERON					
Former smokers	342	335	−2.58 (−3.23 to −1.92)	−1.80 (−2.45 to −1.15)	−0.77 (−1.40 to −0.14)
Overall	445	428	−2.10 (−2.69 to −1.51)	−1.31 (−1.91 to −0.72)	−0.79 (−1.34 to −0.23)
TITANIA					
Former smokers	349	343	−1.88 (−2.39 to −1.36)	−0.75 (−1.27 to −0.22)	−1.13 (−1.66 to −0.60)
Overall	437	434	−1.70 (−2.17 to −1.23)	−0.81 (−1.28 to −0.34)	−0.89 (−1.36 to −0.42)



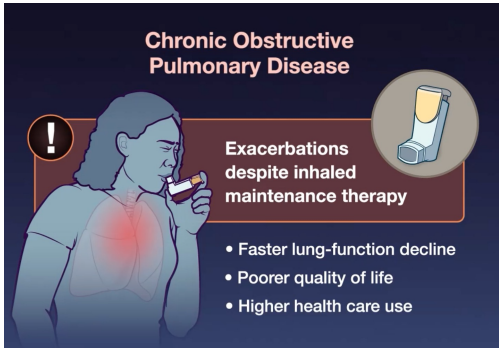
E Annualized Rate of Exacerbations Resulting in Hospitalization, Emergency Department Visit, or Both

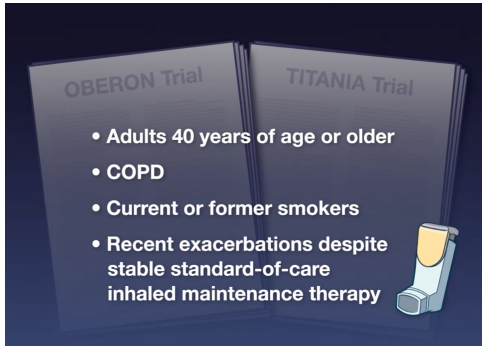
Population	Tozorakimab	Placebo	Tozorakimab	Placebo	Rate Ratio (95% CI)
	no. of patients		*estimated rate (95% CI)*		
OBERON					
Former smokers	342	336	0.31 (0.23 to 0.41)	0.38 (0.29 to 0.50)	0.82 (0.56 to 1.21)
Overall	446	429	0.30 (0.24 to 0.39)	0.48 (0.38 to 0.61)	0.64 (0.46 to 0.89)
TITANIA					
Former smokers	350	344	0.44 (0.35 to 0.56)	0.69 (0.55 to 0.85)	0.65 (0.48 to 0.87)
Overall	438	435	0.44 (0.36 to 0.55)	0.66 (0.54 to 0.80)	0.67 (0.51 to 0.88)

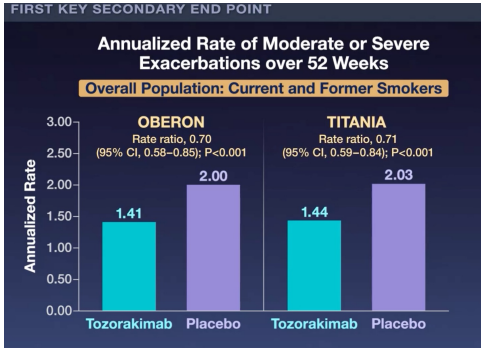


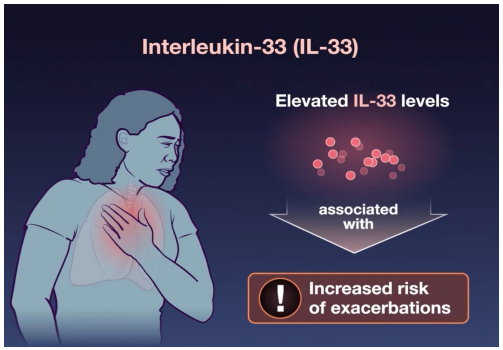
Other Key Secondary End Points.

Data are shown for the patients who were assigned to receive tozorakimab every 4 weeks and those who were assigned to receive placebo. The estimated changes were calculated with the use of a linear model for repeated measures. The changes in Panels A, B, and D are the estimated least-squares mean changes from baseline over a 52-week period, and the change in Panel C is the estimated least-squares mean change from baseline at week 52. Negative least-squares mean differences in Panels A and D and positive least-squares mean differences in Panels B and C favor tozorakimab. The estimated rate in Panel E is the adjusted annualized rate, calculated with the use of a negative binomial regression model. In both trials, the key secondary end points were tested hierarchically in the order shown. The difference in the change from baseline in the St. George's Respiratory Questionnaire (SGRQ) total score over a 52-week period between tozorakimab and placebo among former smokers was not significant; therefore, no formal hypothesis testing was performed for subsequent end points in the testing hierarchy. SGRQ total scores range from 0 to 100, with lower scores indicating better health-related quality of life. Evaluating Respiratory Symptoms in COPD (E-RS–COPD) total scores range from 0 to 40, with lower scores indicating less severe respiratory symptoms. COPD exacerbations resulting in hospitalization, an emergency department visit, or both were defined as exacerbations that resulted in inpatient hospitalization, an emergency department visit of any duration, or death. The 95% confidence intervals have not been adjusted for multiplicity and should not be used to infer treatment effects.

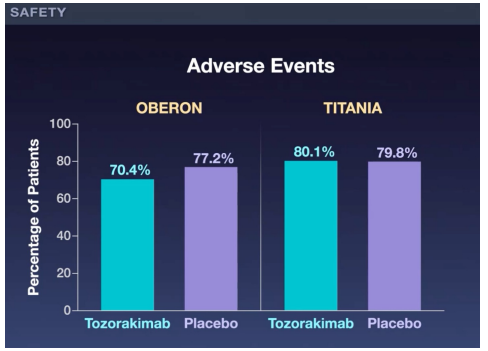

Chronic Obstructive Pulmonary Disease
Exacerbations despite inhaled maintenance therapy
• Faster lung-function decline
• Poorer quality of life
• Higher health care use

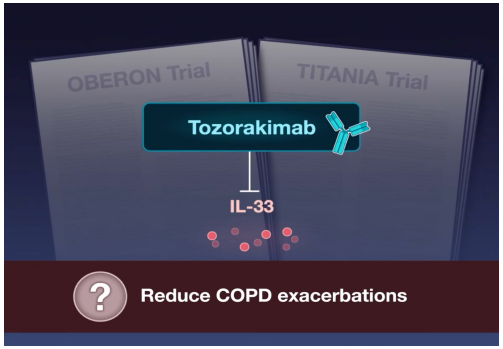

OBERON Trial
TITANIA Trial
• Adults 40 years of age or older
• COPD
• Current or former smokers
• Recent exacerbations despite stable standard-of-care inhaled maintenance therapy

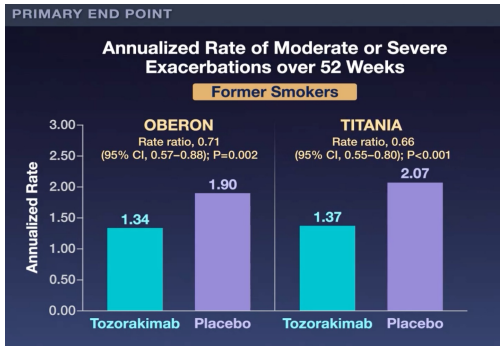

FIRST KEY SECONDARY END POINT
Annualized Rate of Moderate or Severe Exacerbations over 52 Weeks
Overall Population: Current and Former Smokers
OBERON
Rate ratio, 0.70
(95% CI, 0.58–0.85); P<0.001
TITANIA
Rate ratio, 0.71
(95% CI, 0.59–0.84); P<0.001
Annualized Rate
3.00
2.50
2.00
1.50
1.00
0.50
0.00
1.41
2.00
1.44
2.03
Tozorakimab
Placebo
Tozorakimab
Placebo

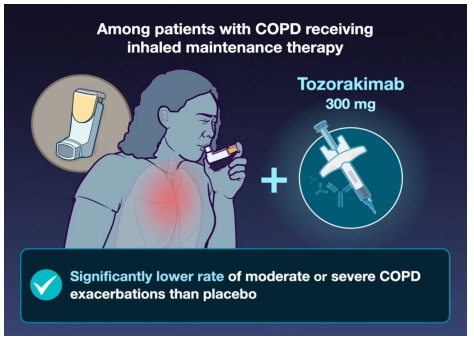

Interleukin-33 (IL-33)
Elevated IL-33 levels
associated with
Increased risk of exacerbations


OBERON
TITANIA
Tozorakimab 300 mg
Placebo
Tozorakimab 300 mg
Placebo
N=446
N=431
N=438
N=435
Every 4 weeks for 52 weeks


SAFETY
Adverse Events
OBERON
TITANIA
Percentage of Patients
100
80
60
40
20
0
70.4%
77.2%
80.1%
79.8%
Tozorakimab
Placebo
Tozorakimab
Placebo


OBERON Trial
TITANIA Trial
Tozorakimab
IL-33
Reduce COPD exacerbations


PRIMARY END POINT
Annualized Rate of Moderate or Severe Exacerbations over 52 Weeks
Former Smokers
OBERON
Rate ratio, 0.71
(95% CI, 0.57–0.88); P=0.002
TITANIA
Rate ratio, 0.66
(95% CI, 0.55–0.80); P<0.001
Annualized Rate
3.00
2.50
2.00
1.50
1.00
0.50
0.00
1.34
1.90
1.37
2.07
Tozorakimab
Placebo
Tozorakimab
Placebo

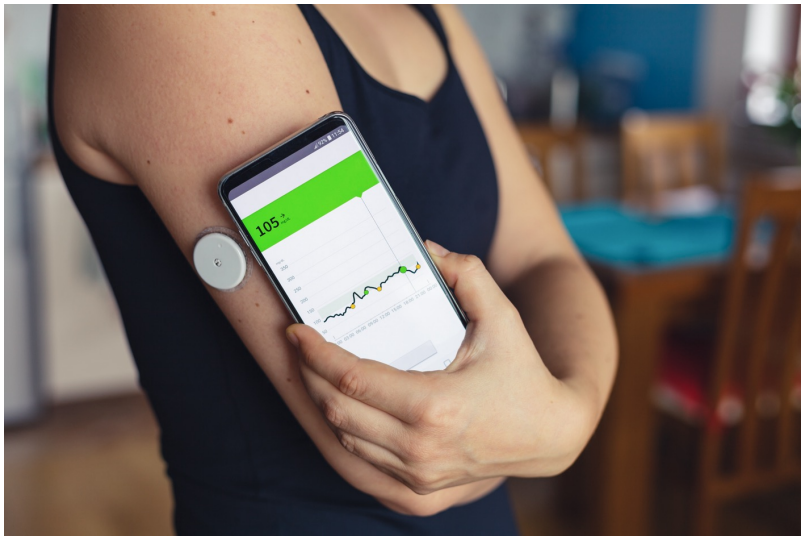

Among patients with COPD receiving inhaled maintenance therapy
Tozorakimab
300 mg
Significantly lower rate of moderate or severe COPD exacerbations than placebo

Ein **Continuous Glucose Monitoring (CGM)** – zu Deutsch: kontinuierliche Glucoseüberwachung – ist ein System, das rund um die Uhr den Zuckergehalt in der Gewebeflüssigkeit misst. Im Gegensatz zur klassischen Blutzuckermessung per Fingerstich liefert ein CGM ein lückenloses Bild des Glucosespiegels und zeigt Trends sowie Verläufe an.

Funktionsweise eines CGM-Systems

Ein CGM-System besteht aus drei wesentlichen Komponenten:

- **Sensor:** Ein winziger, flexibler Faden, der meist am Oberarm oder Bauch unter die Haut geschoben wird. Er misst den Zuckerwert in der Gewebeflüssigkeit (Interstitium).
- **Transmitter (Sender):** Ein flacher Clip, der auf dem Sensor sitzt. Er sendet die Messwerte drahtlos per Bluetooth.
- **Empfänger:** Ein eigenständiges Lesegerät oder (heute meistens) eine App auf dem Smartphone, die die Werte empfängt und grafisch darstellt.



FreeStyle Libre 3 PLUS

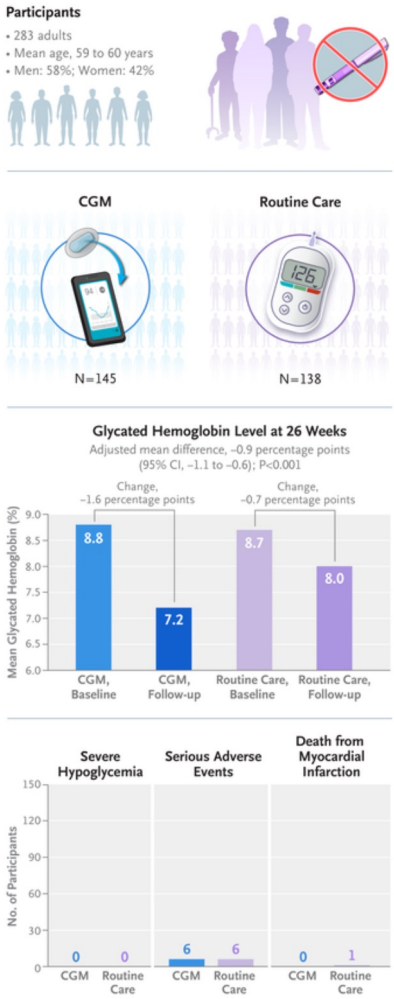


70,60€
Einmalig
inkl. 19% MwSt. / zzgl. 5,95€ Versandkosten
Funktioniert etwa 15 Tage

Continuous Glucose Monitoring in Non–Insulin-Treated Type 2 Diabetes

Continuous glucose monitoring (CGM) has been shown to be beneficial in persons with type 1 diabetes and others with insulin-treated type 2 diabetes, but its role in the treatment of persons with type 2 diabetes not being treated with insulin has needed further study.

In a 26-week trial conducted at 22 primary care practices in the United States, we randomly assigned adults with type 2 diabetes who were not using insulin to either CGM or routine care (control). The primary outcome was the glycated hemoglobin level at 26 weeks. Key CGM-measured secondary outcomes were tested hierarchically to control the type I error rate.



In randomized trials, continuous glucose monitoring (CGM) has been shown to be beneficial for persons with type 1 diabetes or insulin-treated type 2 diabetes. However, data on the effectiveness of CGM for persons with type 2 diabetes not being treated with insulin have been limited, although the existing literature suggests benefit. The 2026 American Diabetes Association Standards of Care cites level A evidence (clear evidence from well-conducted, generalizable, randomized, controlled trials) to recommend the use of CGM by persons with diabetes receiving insulin therapy but cites only level C evidence (supportive evidence from poorly controlled or uncontrolled studies) for the treatment of persons with non–insulin-treated diabetes. We conducted a multicenter, randomized, controlled trial (CONNECT) to evaluate the efficacy and safety of CGM in adults with non–insulin-treated type 2 diabetes. To maximize the generalizability of the results, only patients receiving diabetes care in primary care practices were included in the trial.

Trial Design and Participants

Trial participants were adults (≥18 years of age) who had had type 2 diabetes for at least 6 months (on the basis of clinical assessment) and were being treated in a primary care setting, with a locally measured glycated hemoglobin level at screening of at least 7.5%, no use of real-time CGM within the preceding 6 months, no use of insulin within the preceding 12 months, and stability of noninsulin glucose-lowering medications or weight-reduction medications for the previous month.

After completing a minimum 10-day blinded CGM run-in period to obtain baseline glucose data, participants were randomly assigned in a 1:1 ratio to either the CGM group or the routine-care group. Randomization was stratified according to clinical site and whether a GLP-1 receptor agonist was used (with or without a GLP-1–glucose-dependent insulinotropic polypeptide [GIP] dual agonist).

Outcomes

The primary efficacy outcome was the glycated hemoglobin level at 26 weeks. Key secondary outcomes, which were assessed in a hierarchical testing procedure to control the overall type I error, included the following glucose metrics as measured with CGM and were tested for superiority unless otherwise stated.

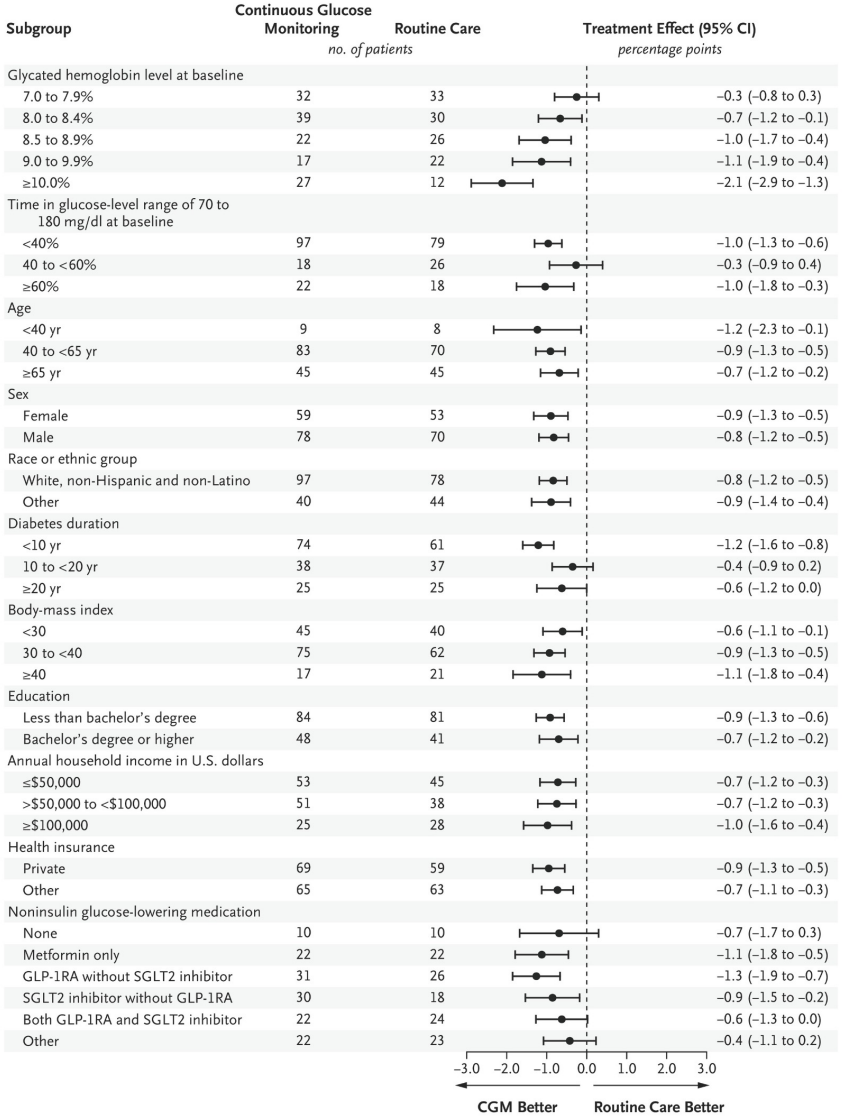
Characteristic	CGM (N=145)	Routine Care (N=138)
Age — yr		
Mean	59±13	60±12
Range	21–82	32–84
Female sex — no. (%)	63 (43)	57 (41)
Race or ethnic group — no. (%)†		
White	117 (81)	108 (78)
Black	20 (14)	17 (12)
Asian	2 (1)	6 (4)
American Indian or Alaska Native	1 (1)	0
Multiple	3 (2)	4 (3)
Hispanic or Latino ethnic group — no. (%)†	18 (12)	21 (15)
Body-mass index‡	33±7	34±8
Median duration of diabetes (IQR) — yr	9 (5–16)	10 (5–17)
Glycated hemoglobin — %§		
Mean	8.8±1.3	8.7±1.2
Range	7.1–14.2	7.3–14.9
Noninsulin glucose-lowering medication — no. (%)¶		
None	12 (8)	10 (7)
Metformin only	22 (15)	25 (18)
GLP-1 receptor agonist without SGLT2 inhibitor	33 (23)	28 (20)
SGLT2 inhibitor without GLP-1 receptor agonist	30 (21)	23 (17)
Both GLP-1 receptor agonist and SGLT2 inhibitor	24 (17)	27 (20)
Other	24 (17)	25 (18)
Median no. of blood-glucose-meter tests per week (IQR)	3 (0–7)	2 (0–7)

Primary and Secondary Hierarchical Efficacy Outcomes.

Outcome	At Baseline		At Follow-up†		Adjusted Difference (95% CI)※	P Value
	CGM (N=145)	Routine Care (N=138)	CGM (N=145)	Routine Care (N=138)		
Primary outcome						
Glycated hemoglobin — %	8.8±1.3	8.7±1.2	7.2±1.1	8.0±1.4	−0.9 (−1.1 to −0.6)	<0.001
Secondary outcomes						
No. of CGM readings included in analysis	3031±556	3096±623	5714±802	5687±1227		
Time with glucose level in range 70–180 mg/dl — %	29±26	31±23	62±25	42±26	21 (16 to 26)	<0.001
Mean glucose level — mg/dl§	229±58	225±49	175±40	207±47	−35 (−44 to −26)	<0.001
Time with glucose level >180 mg/dl — %	70±27	69±24	38±25	58±26	−21 (−26 to −15)	<0.001
Time with glucose level <54 mg/dl — %¶‖	0.21±0.31	0.26±0.44	0.02±0.04	0.19±0.25	−0.17 (−0.27 to −0.11)	<0.001
Time with glucose level <70 mg/dl — %¶‖	0.30±0.44	0.28±0.45	0.12±0.17	0.31±0.41	−0.20 (−0.43 to −0.09)	<0.001
Time with glucose level >250 mg/dl — %‖	33±27	31±25	7±8	22±18	−15 (−19 to −12)	0.002
Time with glucose level in range 70–140 mg/dl — %‖	8±10	8±8	28±19	15±15	13 (9 to 17)	0.002
Glucose coefficient of variation — %**	23±6	23±6	23±5	26±6	−2.1 (−3.3 to −0.9)	<0.001

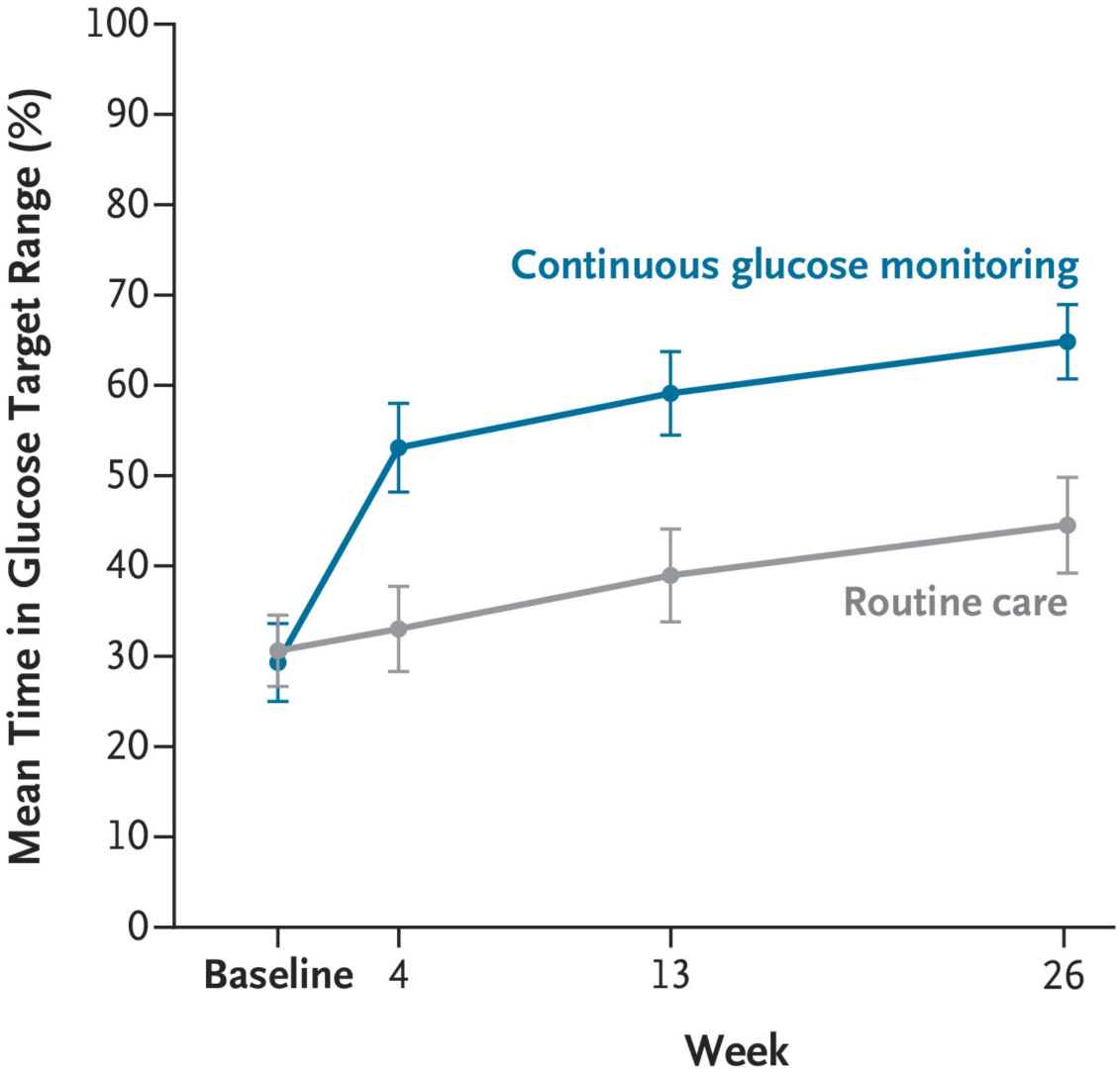
Safety Outcomes

Event	CGM (N=145)	Routine Care (N=138)
Any adverse event *		
No. of participants with event (%)	24 (17)	15 (11)
No. of events	33	24
Specific events		
Severe hypoglycemia — no. of events	0	0
Diabetic ketoacidosis or hyperosmolar hyperglycemic syndrome — no. of events	0	0
Other serious adverse events†		
No. of participants with event (%)	6 (4)	6 (4)
No. of events	7	7
Unanticipated adverse device-related effects — no. of events	0	0



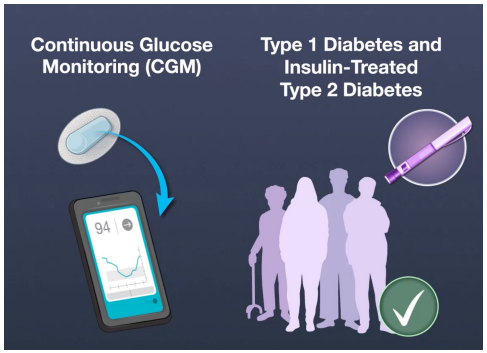
Treatment-Group Difference in Glycated Hemoglobin Level According to Baseline Subgroups.

The treatment effect on the glycated hemoglobin level is shown as the difference (in percentage points) in the mean glycated hemoglobin level at 26 weeks between the continuous glucose monitoring (CGM) group and the routine-care group, with adjustment for the baseline glycated hemoglobin level. The vertical dotted line represents a treatment-group difference of zero. Point estimates to the left of the vertical line indicate a lower glycated hemoglobin level in the CGM group than in the routine-care group. The confidence intervals should not be used for inference. To convert values for glucose to millimoles per liter, multiply by 0.05551. Race and ethnic group were reported by the participant. The body-mass index is the weight in kilograms divided by the square of the height in meters. Glucagon-like peptide-1 receptor agonist (GLP-1RA) use included use of a combined GLP-1RA and glucose-dependent insulinotropic polypeptide (GIP) dual agonist. SGLT2 denotes sodium–glucose cotransporter 2.

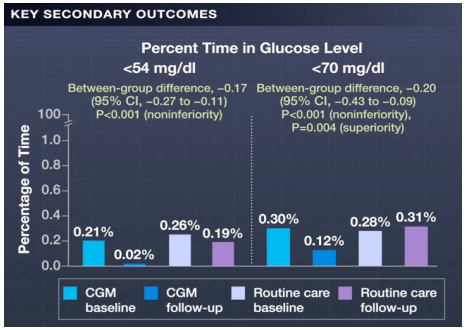


Mean Time in Glucose-Level Target Range at Baseline and at 4, 13, and 26 Weeks.

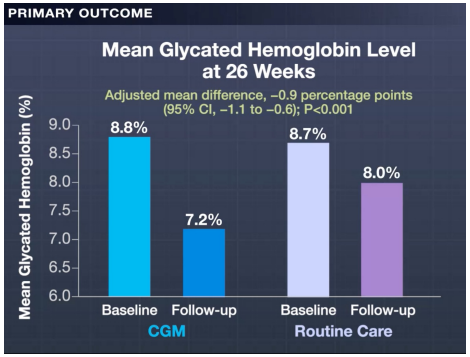
The glucose-level target range was defined as 70 to 180 mg per deciliter. I bars indicate the 95% confidence intervals.

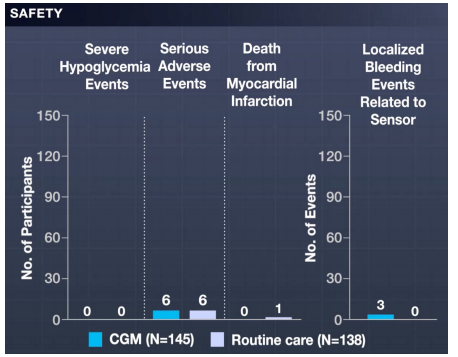

Continuous Glucose Monitoring (CGM)
Type 1 Diabetes and Insulin-Treated Type 2 Diabetes
94


CGM
Routine Care
94
126
N=145
N=138

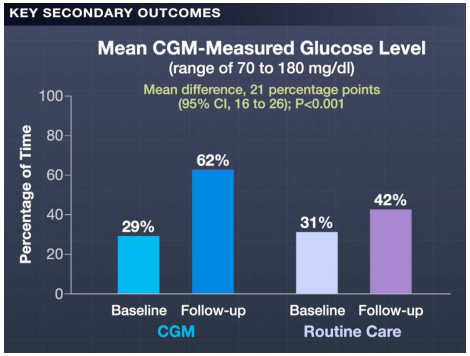

KEY SECONDARY OUTCOMES
Percent Time in Glucose Level
<54 mg/dl
<70 mg/dl
Between-group difference, −0.17 (95% CI, −0.27 to −0.11) P<0.001 (noninferiority)
Between-group difference, −0.20 (95% CI, −0.43 to −0.09) P<0.001 (noninferiority), P=0.004 (superiority)
Percentage of Time
100
1.0
0.8
0.6
0.4
0.2
0.0
0.21%
0.02%
0.26%
0.19%
0.30%
0.12%
0.28%
0.31%
CGM baseline
CGM follow-up
Routine care baseline
Routine care follow-up

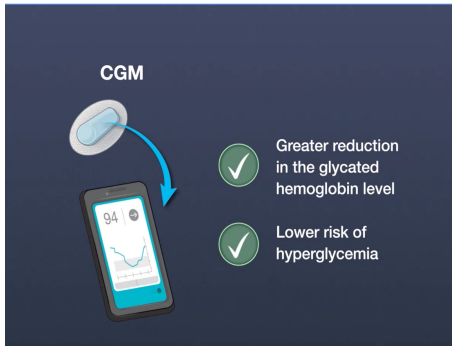

Continuous Glucose Monitoring (CGM)
Type 2 Diabetes Not Being Treated with Insulin
94


PRIMARY OUTCOME
Mean Glycated Hemoglobin Level at 26 Weeks
Adjusted mean difference, −0.9 percentage points (95% CI, −1.1 to −0.6); P<0.001
Mean Glycated Hemoglobin (%)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
8.8%
7.2%
8.7%
8.0%
Baseline
Follow-up
Baseline
Follow-up
CGM
Routine Care


SAFETY
Severe Hypoglycemia Events
Serious Adverse Events
Death from Myocardial Infarction
Localized Bleeding Events Related to Sensor
No. of Participants
No. of Events
150
120
90
60
30
0
0
0
6
6
0
1
3
0
CGM (N=145)
Routine care (N=138)


CONNECT Trial
• 283 Adults
• Type 2 diabetes
• Not using insulin


KEY SECONDARY OUTCOMES
Mean CGM-Measured Glucose Level
(range of 70 to 180 mg/dl)
Mean difference, 21 percentage points (95% CI, 16 to 26); P<0.001
Percentage of Time
100
80
60
40
20
0
29%
62%
31%
42%
Baseline
Follow-up
Baseline
Follow-up
CGM
Routine Care


CGM
94
Greater reduction in the glycated hemoglobin level
Lower risk of hyperglycemia

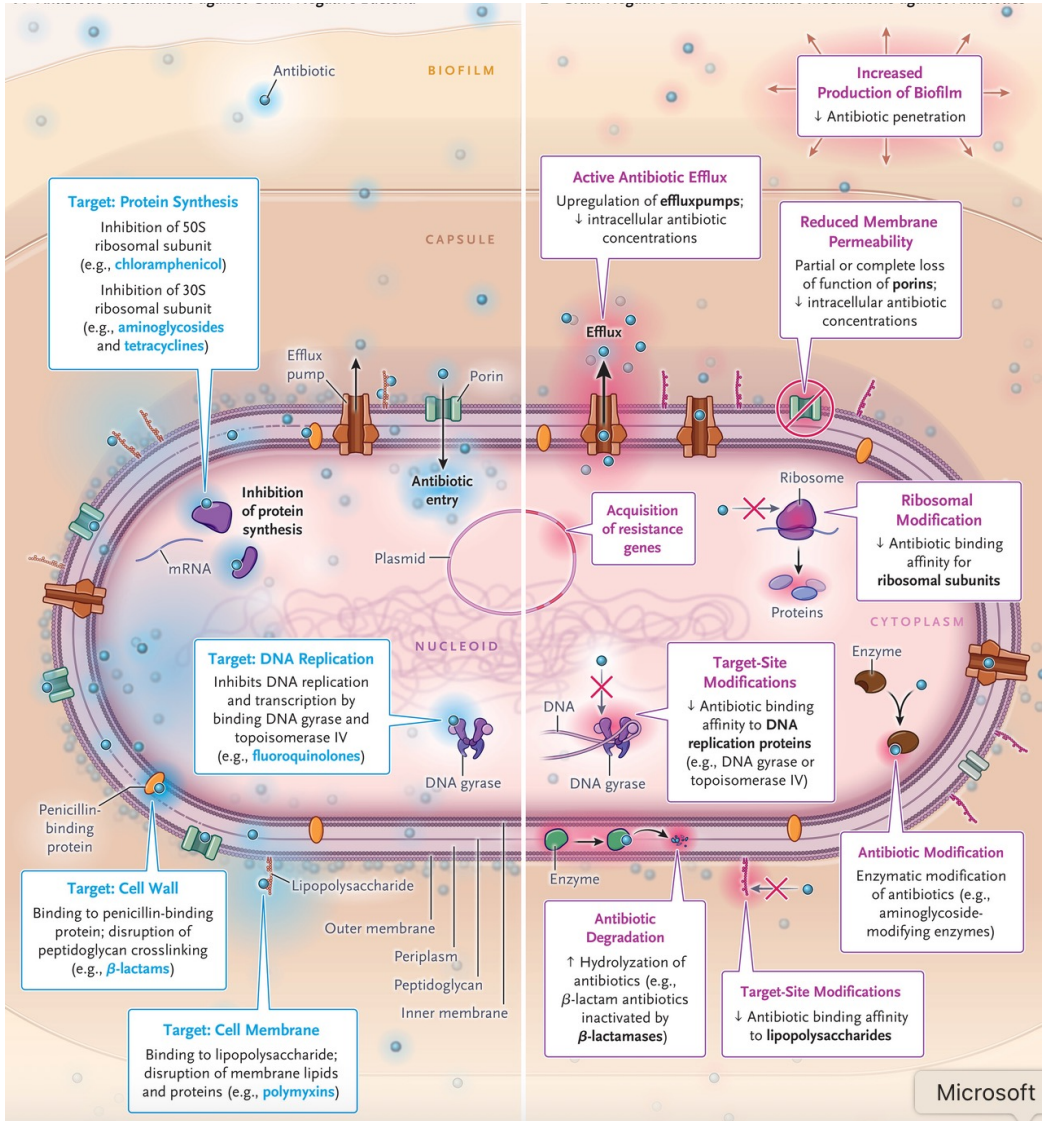
Gram-Negative Bacterial Resistance

Summary

The rapid worldwide spread of antimicrobial resistance among gram-negative bacteria is driven by a complex interplay of human, environmental, and health care–associated factors and accelerated by mobile genetic elements that facilitate the dissemination of resistance genes. Resistance in gram-negative bacteria arises primarily through reduced drug entry, active drug efflux, modification of antibiotic targets, and enzymatic drug inactivation, most notably through β-lactamase production. Clinically important resistant pathogens include extended-spectrum β-lactamase–producing Enterobacterales, carbapenem-resistant Enterobacterales, *Pseudomonas aeruginosa* with difficult-to-treat resistance, and carbapenem-resistant *Acinetobacter baumannii*. Limited access to effective antibiotics and the continued emergence of resistance to available agents pose substantial challenges to the management of these infections. Appropriate management requires timely and accurate diagnostics, targeted use of newer β-lactam agents, effective source control, and judicious selection of treatment durations.

Gram-Negative Bacterial Resistance

- The rapid worldwide spread of gram-negative antimicrobial resistance is driven by human, environmental, and health care–associated factors and accelerated by mobile genetic elements that facilitate the spread of resistance genes.
- Although several antibiotics are available to treat resistant gram-negative infections, limited access to these agents and the continued emergence of resistance constrain their clinical usefulness; nonantibiotic treatment strategies are under investigation.
- Resistance in gram-negative bacteria arises primarily through reduced drug entry, active drug efflux, modification of antibiotic targets, and enzymatic drug inactivation, most notably through β-lactamase production.
- Clinically important resistant pathogens include extended-spectrum β-lactamase–producing Enterobacterales, carbapenem-resistant Enterobacterales, *Pseudomonas aeruginosa* with difficult-to-treat resistance, and carbapenem-resistant *Acinetobacter baumannii*, with outcomes maximized when pathogen- and mechanism-informed treatment approaches are used.
- Appropriate management of resistant gram-negative infections requires timely and accurate diagnostics, targeted use of newer β-lactam agents, effective source control, and judicious selection of treatment durations.
- Sustained progress will depend on the revitalization of antibiotic development and implementation of economic models that support innovation while ensuring equitable global access.



Gram-Negative Bacterium.

Shown is a representative gram-negative bacterial cell and the principal mechanisms of antibiotic activity and resistance. Antibiotics reach their cellular targets through distinct pathways, including passage across the outer membrane through porin channels. Once they reach their targets, antibiotics disrupt essential bacterial processes. For example, β-lactam antibiotics bind to penicillin-binding proteins, inhibiting peptidoglycan cross-linking and ultimately leading to bacterial cell death (Panel A). Gram-negative bacteria use several mechanisms to evade antibiotic activity, including reduced expression or loss of outer-membrane porins, which restricts antibiotic entry; increased expression of efflux pumps, which expel antibiotics from the periplasm or cytoplasm and reduce drug accumulation; production of enzymes that modify or inactivate antibiotics; and alterations in antibiotic targets that diminish drug binding (Panel B).

Common Mechanisms of Antimicrobial Resistance to Antibiotics Frequently Used for the Treatment of Gram-Negative Infections.

General Categories and Examples	Bacterial Species Typically Involved	Antibiotics Typically Affected
Reduced membrane permeability		
Reduced production of OmpK35, OmpK36, and Ompk37	*Klebsiella pneumoniae*	Cephalosporins, carbapenems, ceftazidime–avibactam, and meropenem–vaborbactam
Reduced production of OmpC and OmpF	*Escherichia coli*	Penicillins, cephalosporins, aztreonam, carbapenems, and meropenem–vaborbactam
Reduced production of OprD porin	*Pseudomonas aeruginosa*	Carbapenems (imipenem more affected than meropenem)
Reduced production of CarO	*Acinetobacter baumannii* complex	Carbapenems (imipenem more affected than meropenem)
Mutations in the TonB-dependent transporter system (e.g., TonB, ExbB, ExbD, CirA, and FecA)	Enterobacterales, *P. aeruginosa*, *A. baumannii* complex	Cefiderocol
Active antibiotic efflux		
Increased expression of AcrAB–TolC efflux pump	*E. coli*	Ampicillin, cefazolin, fluoroquinolones, and tetracyclines
Increased expression of MexAB–OprM efflux pump	*P. aeruginosa*	Piperacillin–tazobactam, cefepime, meropenem, and fluoroquinolones
Increased expression of AdeABC efflux pump	*A. baumannii* complex	Aminoglycosides, fluoroquinolones, and tetracyclines
Increased expression of the major facilitator superfamily (e.g., TetA, TetB, TetC, and TetD)	Enterobacterales, *A. baumannii* complex	Tetracyclines
Target-site modification		
Modification of dihydrofolate reductase for trimethoprim (e.g., *dfrA*) and dihydropteroate synthase for sulfamethoxazole (e.g., *sul*)	Enterobacterales	TMP-SMX
Modifications of DNA gyrase (e.g., *gyrA*) and topoisomerase IV (e.g., *parC*)	Enterobacterales, *P. aeruginosa*, and *A. baumannii* complex	Fluoroquinolones
Modification of the lipid A component of lipopolysaccharide (e.g., *mcr*)	Enterobacterales	Polymyxins
Modification of PBP3 target	Enterobacterales and *P. aeruginosa*	Ceftazidime, cefepime, aztreonam, cefiderocol, aztreonam–avibactam, ceftazidime–avibactam, and ceftolozane–tazobactam
Modifications in the outer membrane (e.g., PhoPQ and PmrAB)	Enterobacterales, *P. aeruginosa*, and *A. baumannii* complex	Polymyxins
Enzymatic drug modification		
ESBL (e.g., CTX-M and SHV variants)	Enterobacterales	Ceftriaxone, ceftazidime, and aztreonam
Increased production of AmpC β-lactamases (e.g., AmpC, CMY, DHA, and FOX)	Enterobacterales	Ampicillin, cefazolin, ceftriaxone, ceftazidime, aztreonam, and piperacillin–tazobactam
Increased production of pseudomonas-derived cephalosporinases	*P. aeruginosa*	Piperacillin–tazobactam, ceftazidime, and aztreonam
Increased production of acinetobacter-derived cephalosporinases	*A. baumannii* complex	Ceftriaxone and aztreonam
Carbapenemases (e.g., KPC, NDM, VIM, IMP, OXA-48–like, and OXA-23)	Enterobacterales, *P. aeruginosa*, and *A. baumannii* complex	Penicillins, cephalosporins, and carbapenems
Aminoglycoside-modifying enzymes (e.g., AAC, ANT, and APH)	Enterobacterales, *P. aeruginosa*, and *A. baumannii* complex	Aminoglycosides

Preferred and Alternative Antibiotic Agents for the Treatment of Gram-Negative Antimicrobial-Resistant Infections.

Organism or Resistance Mechanism	Preferred Treatment	Alternative Treatment
ESBL-producing Enterobacterales	Uncomplicated UTI: Amikacin 15 mg/kg of body weight IV, 1 dose Gentamicin 5 mg/kg/dose IV, 1 dose Gepotidacin 1.5 g orally every 12 hr for 5 days Nitrofurantoin 100 mg orally every 12 hr for 5 days Pivmecillinam 370 mg orally every 8 hr for 3 days Sulopenem–etzadroxil (500 mg)–probenecid (500 mg) orally every 12 hr for 5 days Tobramycin 5 mg/kg/dose IV, 1 dose TMP-SMX 160 mg (trimethoprim component) IV or orally every 12 hr for 3 days Complicated UTI (7 days): Cefepime–enmetazobactam: cefepime 2 g IV plus enmetazobactam 0.5 g IV every 8 hr (infused over 2 hr) Ciprofloxacin 400 mg IV every 8 hr or 750 mg orally every 12 hr Ertapenem 1 g IV every 24 hr Imipenem–cilastatin 500 mg IV every 6 hr or 1000 mg IV every 8 hr† Levofloxacin 750 mg IV or orally every 24 hr Meropenem 1 g IV every 8 hr† TMP-SMX 8–15 mg per kg of body weight per day (trimethoprim component) IV or orally, divided every 8 to 12 hr Invasive infection (≥7 days): Imipenem–cilastatin 500 mg IV every 6 hr or 1000 mg IV every 8 hr Meropenem 1 g IV every 8 hr	Uncomplicated UTI: Cefepime–enmetazobactam: cefepime 2 g IV plus enmetazobactam 0.5 g IV every 8 hr (infused over 2 hr)† Ciprofloxacin 400 mg IV every 8 hr or 750 mg orally every 12 hr Ertapenem 1 g IV every 24 hr† Fosfomycin 3 g orally, 1 dose Levofloxacin 750 mg IV or orally every 24 hr Tebipenem 600 mg orally every 6 hr for 5 days† Complicated UTI (7 days): Fosfomycin 6 g IV every 8 hr Piperacillin–tazobactam 4.5 g IV every 6 hr (infused over ≥3 hr) Invasive infection (≥7 days): Cefepime–enmetazobactam: cefepime 2 g IV plus enmetazobactam 0.5 g IV every 8 hr (infused over 2 hr) Ciprofloxacin 400 mg IV every 8 hr or 750 mg orally every 12 hr Levofloxacin 750 mg IV or orally every 24 hr TMP-SMX 8–15 mg/kg/day (trimethoprim component) IV or orally, divided dose every 8 to 12 hr
KPC-producing Enterobacterales	Ceftazidime–avibactam: ceftazidime 2 g IV plus avibactam 0.5 g IV every 8 hr (infused over 3 hr) Meropenem–vaborbactam: meropenem 2 g IV plus vaborbactam 2 g IV every 8 hr (infused over 3 hr)	Aztreonam–avibactam: aztreonam 2 g IV plus avibactam 0.67 g IV loading dose (infused over 3 hr), then aztreonam 1.5 g IV plus avibactam 0.5 g IV every 6 hr (infused over 3 hr) Cefepime–zidebactam 3 g IV every 8 hr (infused over 1 hr)† Cefiderocol 2 g IV every 8 hours (infused over 3 hr)† Eravacycline 1 mg/kg per dose IV every 12 hr Tigecycline 200 mg IV as a single dose, then 100 mg IV every 12 hr
NDM-producing Enterobacterales	Aztreonam–avibactam: aztreonam 2 g IV plus avibactam 0.67 g IV loading dose (infused over 3 hr), then aztreonam 1.5 g IV plus avibactam 0.5 g IV every 6 hr (infused over 3 hr)‡ Cefepime–zidebactam 3 g IV every 8 hr (infused over 1 hr)† Cefiderocol 2 g IV every 8 hr (infused over 3 hr)	Eravacycline 1 mg/kg per dose IV every 12 hr Tigecycline 200 mg IV as a single dose, then 100 mg IV every 12 hr
OXA-48-like–producing Enterobacterales	Ceftazidime–avibactam: ceftazidime 2 g IV plus avibactam 0.5 g IV (infused over 3 hr)	Aztreonam–avibactam: aztreonam 2 g IV plus avibactam 0.67 g IV loading dose (infused over 3 hr), then aztreonam 1.5 g IV plus avibactam 0.5 g IV every 6 hr (infused over 3 hr) Cefepime–zidebactam 3 g IV every 8 hr (infused over 1 hr)† Cefiderocol 2 g IV every 8 hr (infused over 3 hr)† Eravacycline 1 mg/kg per dose IV every 12 hr Tigecycline 200 mg IV as a single dose, then 100 mg IV every 12 hr
P. aeruginosa with difficult-to-treat resistance	Ceftazidime–avibactam: ceftazidime 2 g IV plus avibactam 0.5 g IV every 8 hr (infused over 3 hr) Ceftolozane–tazobactam: ceftolozane 2 g IV plus tazobactam 1 g IV every 8 hr (infused over 1 hr)	Cefepime–zidebactam 3 g IV every 8 hr (infused over 1 hr)†§ Cefiderocol 2 g IV every 8 hr (infused over 3 hr)§
Carbapenem-resistant *A. baumannii* complex	Sulbactam–durlobactam: sulbactam 1 g plus durlobactam 1 g IV (2 g total) every 6 hr (infused over 3 hr) plus either imipenem or meropenem (infused over 3 hr)	High-dose ampicillin–sulbactam: 9 g of ampicillin–sulbactam (6 g ampicillin plus 3 g sulbactam) IV every 8 hr (infused over 4 hr) or 27 g of ampicillin–sulbactam (18 g ampicillin plus 9 g sulbactam) IV as a continuous infusion over 24 hr Plus at least one of the following: Minocycline 200 mg IV or orally every 12 hr Polymyxin B loading dose of 2.0–2.5 mg/kg (20,000–25,000 IU/kg) (infused over 1 hr) followed by 1.25–1.5 mg/kg (12,500–15,000 IU/kg) every 12 hr (infused over 1 hr) Tigecycline 200 mg IV as a single dose, followed by 100 mg IV every 12 hr Cefiderocol 2 g IV every 8 hr (infused over 3 hr)



Approved Intravenous β-Lactam Agents Available in the United States with Activity against Selected Gram-Negative Antimicrobial-Resistant Infections.

ESBL denotes extended-spectrum β-lactamase, FDA Food and Drug Administration, IMP imipenemase, KPC *Klebsiella pneumoniae* carbapenemase, NDM New Delhi metallo-β-lactamase, and VIM Verona integron-encoded metallo-β-lactamase.

Conclusions

The rise of gram-negative antimicrobial resistance threatens to erode the foundations of modern medicine, yet its trajectory is not predetermined. Recent innovations in diagnostics and therapeutics show that scientific solutions exist; what remains is constructing governance, financing, and research networks capable of deploying them where they are most needed. Because antimicrobial resistance is inherently global, its solutions must be collective — treating antibiotics as shared public goods and aligning incentives with stewardship and access. The salient question is whether the international community can act with sufficient urgency; if so, resistance may be contained well enough to preserve the gains of modern medicine.

An Element Out of Place



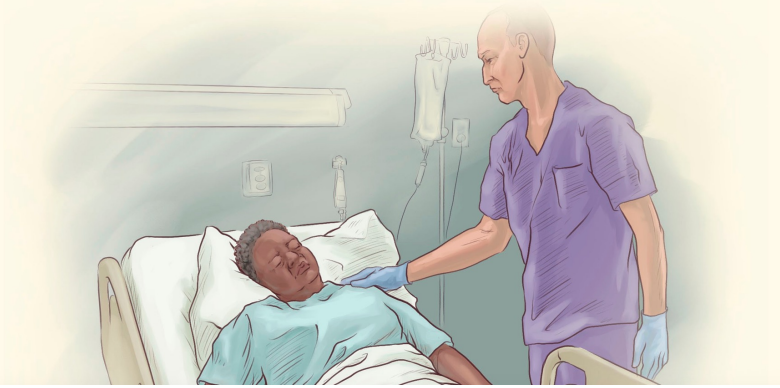
Case Presentation

A 55-year-old woman presented to the emergency department with a 10-day history of nausea, lightheadedness, and generalized abdominal pain.

In the days leading up to her presentation, she had had transient episodes of slurred speech, unsteady gait, and confusion.

She also reported a 5-day history of generalized weakness, constipation, polyuria, polydipsia, palpitations, decreased appetite and oral intake, and subjective weight loss. She noted pain in both knees that was consistent with existing chronic joint discomfort.

She reported no fevers, chills, cough, chest pain, shortness of breath, dysuria, diarrhea, rashes, or night sweats.



Patient History

Medical History

Hypertension

Type 2 diabetes complicated by peripheral neuropathy (glycated hemoglobin level, 7.4%, measured 2 months before presentation)

Fibromyalgia

Psoriatic arthritis

Remote Surgical History

Cholecystectomy

Total laparoscopic hysterectomy with bilateral salpingo-oophorectomy for atypical endometrial hyperplasia

Below-the-knee amputation of the right leg for diabetic ulcers complicated by necrotizing soft-tissue infection

Allergies

No known drug allergies

Medications

Duloxetine, 60 mg twice daily

Empagliflozin, 10 mg daily

Gabapentin, 300 mg three times daily

Insulin degludec, 28 units nightly

Ixekizumab subcutaneous injection (interleukin-17A inhibitor for treatment of psoriatic arthritis), 80 mg monthly (intermittently discontinued and resumed during the preceding year)

Social History

Worked at a residential program for women with substance use disorders, now retired

Reports no history of cigarette smoking

Reports no alcohol or illicit drug use

Family History

Mother and father with diabetes

Two paternal aunts with breast cancer

Paternal uncle with unknown cancer

Physical Examination

Vital signs

Heart rate, 90 beats per minute, regular

Blood pressure, 178/81 mm Hg

Temperature, 36.7°C

Respiratory rate, 16 breaths per minute

Oxygen saturation, 95% while the patient was breathing ambient air

Body-mass index, 34.8

General appearance

Fatigued and somnolent but easily arousable

Head, eyes, ears, nose, and throat

Mucous membranes dry

No scleral icterus or conjunctival injection

Hirsutism (chin), mild thinning of scalp hair

Neck

No cervical lymphadenopathy

No thyroid enlargement or nodularity

Heart

Regular rate and rhythm

No murmurs, rubs, or gallops

No jugular venous distention

Lungs

Clear on auscultation

Abdomen

Soft, nontender on palpation, and nondistended

Normal bowel sounds

No hepatosplenomegaly

Arms and legs

Tenderness over greater trochanteric bursae on both sides

Left leg warm and well perfused, without rash or cyanosis

Right leg with stump below the knee, well healed

2+ radial pulses

2+ dorsalis pedis pulse on the left side

No edema of the left leg

Skin

No rashes

No bruising or petechiae

No violaceous striae

Nervous system

Oriented to person, place, and time

No focal neurologic deficits

Cranial nerves II through XII intact on both sides

Normal strength in both arms and left leg

Normal sensation in both arms; diminished sensation in left leg

Difficulty performing tasks such as spelling "world" backwards and reciting the days of the week in reverse

Laboratory Evaluation

Laboratory test results obtained in the emergency department were notable for elevated creatinine and calcium levels. Six weeks before the current presentation, serum calcium was 9.5 mg per deciliter, creatinine 0.92 mg per deciliter, hemoglobin 11.4 g per deciliter, hematocrit 32%, and 25-hydroxyvitamin D_3 level less than 7 ng per milliliter (reference range, 20 to 80).

Variable*	Result	Normal Range	Flag
Sodium (mmol/liter)	135	136–145	Low
Potassium (mmol/liter)	4.6	3.3–4.5	High
Chloride (mmol/liter)	95	98–107	Low
Carbon dioxide (mmol/liter)	30	24–32	–
Urea nitrogen (mg/dl)	75	6–23	High
Creatinine (mg/dl)	3.9	0.5–1.2	High
Estimated glomerular filtration rate (ml/min/1.73 m^2)	13	>60	Low
Glucose (mg/dl)	177	70–100	High
Anion gap (mmol/liter)	10	7–17	–
Albumin (g/dl)	3.3	3.5–5.2	Low

Stage 4-5 Renal failure

Direct bilirubin (mg/dl)	0.3	0.0–0.4	–
Calcium (mg/dl)	18.9	8.8–10.7	High
Magnesium (mg/dl)	2.4	1.7–2.6	–
Phosphorus (mg/dl)	5.1	2.4–4.3	High
Ionized calcium (mmol/liter)	2.26	1.13–1.32	High
Total protein (g/dl)	6.9	6.0–8.5	–
Alanine aminotransferase (U/liter)	18	0–40	–
Aspartate aminotransferase (U/liter)	31	0–37	–
Alkaline phosphatase (U/liter)	152	35–130	High
White-cell count (per mm^3)	7910	4000–10,000	–
Hematocrit (%)	31	36–48	Low
Differential count (%)			
Neutrophils	69.4	40.0–80.0	–
Lymphocytes	15.7	7.0–36.0	–
Monocytes	6.6	4.0–8.0	–
Eosinophils	5.8	0.0–5.0	High
Basophils	2.5	0.0–1.5	High

*Hemoglobin, platelet count, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and red-cell distribution width could not be reported owing to red-cell agglutination.

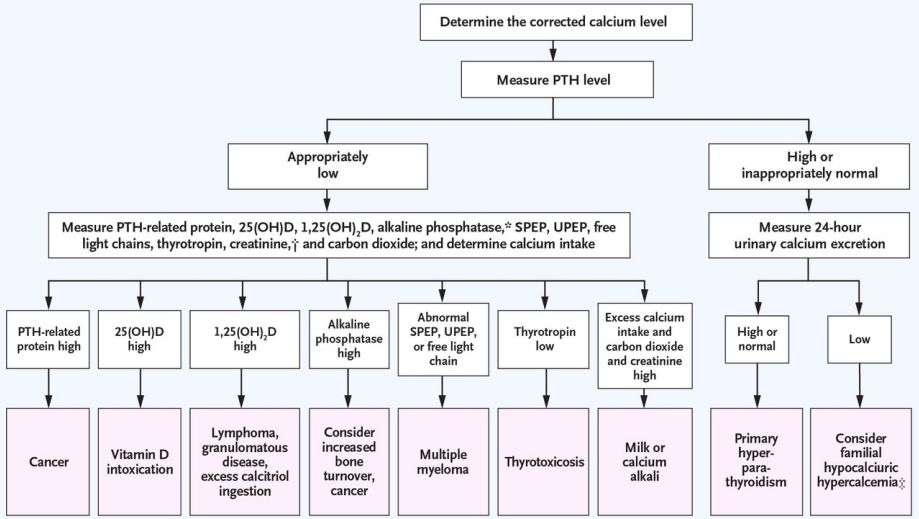
The results of initial imaging studies performed in the emergency department, including chest radiography and renal ultrasonography, were unremarkable.

Anemia and severe hypercalcemia (twice normal value)

Hypercalcemia

LEARNING MODULE

Diagnostic Approach



1,25(OH)$_2$D denotes 1,25-dihydroxyvitamin D, 25(OH)D 25-hydroxyvitamin D, PTH parathyroid hormone, SPEP serum protein electrophoresis, and UPEP urine protein electrophoresis.

* Consider measuring bone-specific alkaline phosphatase or fractionated alkaline phosphatase isoenzymes to confirm the origin in bone.

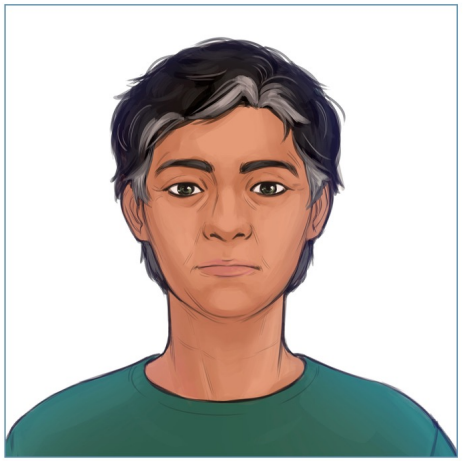
† Acute kidney injury or use of thiazide can worsen hypercalcemia by impairing calciuresis.

‡ Primary hyperparathyroidism in the context of vitamin D deficiency also may cause this pattern; low 25(OH)D should be replaced and 24-hr urine calcium rechecked before making the diagnosis of familial hypocalciuric hypercalcemia.

The diagnostic algorithm provides a framework for approaching the diagnosis of hypercalcemia.

Two practice cases

Scenario 1



A 55-year-old woman presents to her primary care physician with progressive fatigue.

Variable	Result	Normal Range
Calcium (mg/dl)	**12.0**	8.8–10.7
Albumin (g/dl)	4.1	3.5–5.2
PTH (pg/ml)	**8**	15–65
PTH-related protein (pmol/liter)	1.0	<4.2
25(OH)D (ng/ml)	**11**	20–80
$1,25(OH)_2D$ (pg/ml)	**110**	18–64
Alkaline phosphatase (U/liter)	50	40–130

Does the patient have true hypercalcemia?

- ✓ ◉ Yes
- ✗ ○ No

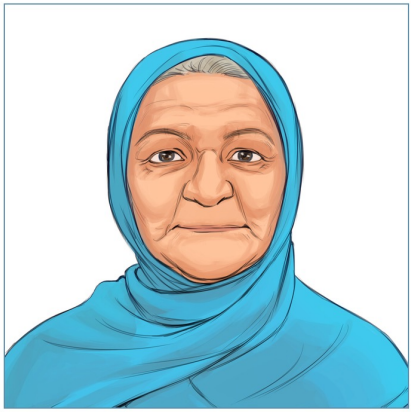
Is the hypercalcemia PTH dependent or PTH independent?

- ✗ ○ PTH dependent
- ✓ ◉ PTH independent

What condition or conditions could explain the hypercalcemia?

- ✗ ☐ PTH-related protein
- ✗ ☐ Vitamin D_3 intoxication
- ✓ ☑ An excess of $1,25(OH)_2D$
- ✗ ☐ A monoclonal gammopathy
- ✗ ☐ Thyrotoxicosis
- ✗ ☐ Increased bone turnover
- ✗ ☐ Milk alkali syndrome
- ✗ ☐ Primary hyperparathyroidism
- ✗ ☐ Familial hypocalciuric hypercalcemia

View detailed feedback below.



A 78-year-old woman presents to her primary care physician with progressive fatigue.

Variable	Result	Normal Range
Calcium (mg/dl)	**12.0**	8.8–10.7
Creatinine (mg/dl)	**2.3**	0.5–1.2
Albumin (g/dl)	**3.4**	3.5–5.2
PTH (pg/ml)	**8**	15–65
PTH-related protein (pmol/liter)	1.0	<4.2
25(OH)D (ng/ml)	**150**	20–80
$1,25(OH)_2D$ (pg/ml)	35	18–64
Alkaline phosphatase (U/liter)	50	40–130
Thyrotropin (uIU/ml)	2.0	0.5–5.7

Does the patient have true hypercalcemia?

- ✓ ◉ Yes
- ✗ ○ No

Is the hypercalcemia PTH dependent or PTH independent?

- ✗ ○ PTH dependent
- ✓ ◉ PTH independent

What condition or conditions could explain the hypercalcemia?

- ✗ ☐ PTH-related protein
- ✓ ☑ Vitamin D_3 intoxication
- ✗ ☐ An excess of $1,25(OH)_2D$
- ✗ ☐ A monoclonal gammopathy
- ✗ ☐ Thyrotoxicosis
- ✗ ☐ Increased bone turnover
- ✗ ☐ Milk alkali syndrome
- ✗ ☐ Primary hyperparathyroidism
- ✗ ☐ Familial hypocalciuric hypercalcemia

View detailed feedback below.

The Patient's Hypercalcemia



This patient, who is the focus of this interactive medical case, is a 55-year-old woman who presented to the emergency department with a 10-day history of nausea, lightheadedness, and generalized abdominal pain.

Variable	Result	Normal Range
Calcium (mg/dl)	**18.9**	8.8–10.7
Creatinine (mg/dl)	**3.9**	0.5–1.2
Albumin (g/dl)	**3.3**	3.5–5.2
Phosphorus (mg/dl)	**5.1**	2.4–4.3
Ionized calcium (mmol/liter)	**2.26**	1.13–1.32
PTH (pg/ml)	**9**	15–65
PTH-related protein (pmol/liter)	3.5	<4.2
25(OH)D (ng/ml)	**9**	20–80
$1,25(OH)_2D$ (pg/ml)	**<8**	18–64
Alkaline phosphatase (U/liter)	**152**	40–130
Thyrotropin (uIU/ml)	0.9	0.5–5.7

Does the patient have true hypercalcemia?

- ✓ (Yes)
- ✗ (No)

Is the hypercalcemia PTH dependent or PTH independent?

- ✗ PTH dependent
- ✓ PTH independent

What condition or conditions could explain the hypercalcemia?

- ✗ PTH-related protein
- ✗ Vitamin D_3 intoxication
- ✗ An excess of $1,25(OH)_2D$
- ✗ A monoclonal gammopathy
- ✗ Thyrotoxicosis
- ✓ Increased bone turnover
- ✗ Milk alkali syndrome
- ✗ Primary hyperparathyroidism
- ✗ Familial hypocalciuric hypercalcemia

View detailed feedback below.

Could not find it!

What Would You Do?

Which of the following management strategies would be most appropriate for this patient?

Select a strategy to see whether it is an appropriate choice and to learn about the probable outcome. You will be able to return to the list of choices to review the probable consequences of each choice.

- A Initiate volume expansion with normal saline ✓
- B Initiate treatment with calcitonin ✓
- C Initiate treatment with cinacalcet ✗
- D Initiate treatment with zoledronic acid ✗
- E Initiate treatment with denosumab ✓

Denosumab ist ein biotechnologisch hergestellter, humaner monoklonaler Antikörper (IgG2). Er wirkt als Inhibitor des Proteins **RANK-Ligand (RANKL)**. Durch die Bindung an RANKL verhindert er die Reifung, Aktivität und das Überleben von **Osteoklasten** (Knochen abbauenden Zellen), wodurch der Knochenabbau gehemmt und die Knochendichte gestärkt wird.

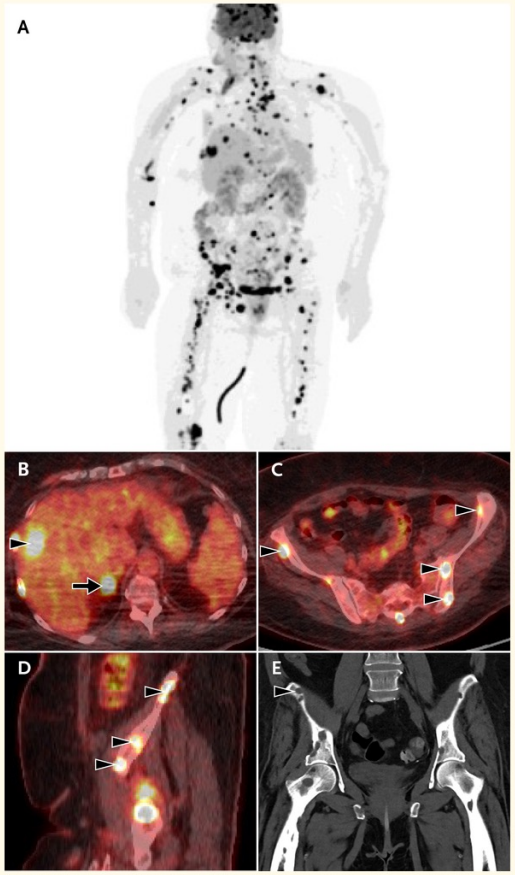
Hypercalcemia of malignancy (HCM) in lymphoma is commonly treated with intravenous bisphosphonates such as zoledronic acid (Zometa), alongside aggressive fluid resuscitation.

Imaging

CT revealed multiple lytic bone lesions involving the ribs, sternum, scapula, calvarium, skull base, and spine, all of which were suggestive of osseous metastases.

Whole-body positron emission tomography–computed tomography (PET-CT) confirmed numerous fluorodeoxyglucose-avid lytic lesions throughout the axial and appendicular skeleton, including the calvarium, as well as fluorodeoxyglucose-avid lesions in the liver and right adrenal gland, findings consistent with widespread metastatic disease (Panels A–E).

No primary tumor was identified.

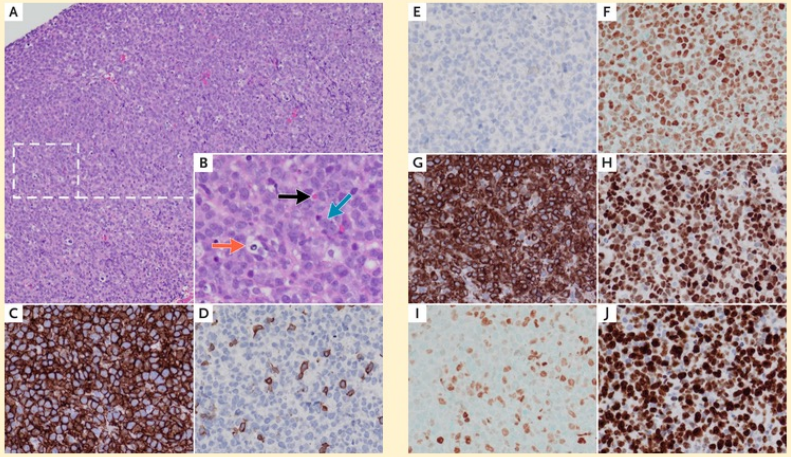


Representative PET-CT. A full-body coronal view shows numerous PET-avid lesions of the axial and appendicular skeleton (Panel A). The adrenal lesion (arrow) and one of multiple liver lesions (arrowhead) are seen in Panel B. Lesions of the pelvic bone, including the iliac crest (arrowheads), one of which was biopsied, are highlighted in Panels C and D. The lytic nature of the boney lesions can be seen in Panel E (non-PET image; right iliac crest lesion highlighted by arrowhead).

Diagnosis and Treatment

The patient underwent CT-guided core biopsy of the right iliac crest, which revealed diffuse large B-cell lymphoma (DLBCL) (Panels A–J). Cytogenetic analysis did not show a rearrangement of MYC.

Magnetic resonance imaging of the head showed no evidence of central nervous system involvement. On the basis of the pathological examination and imaging results, stage IV lymphoma was diagnosed. The patient was transferred to the oncology service for initiation of chemotherapy.



Hematoxylin and eosin staining reveals a diffuse pattern ("sheets") of large atypical lymphoid cells (Panel A). At higher magnification (Panel B), the cells have scant-to-moderate cytoplasm; large, irregular nuclear contours; vesicular chromatin, frequently with prominent nucleoli (blue arrow); and are clearly large compared to red cells (black arrow). Few scattered apoptotic bodies are seen, mostly within tangible body macrophages (orange arrow). The large, atypical cells are diffusely positive for CD20 (Panel C) and PAX5 (not shown) and are negative for T-cell markers CD3 (Panel D) and CD5 (not shown). CD3 marks scattered background small T cells. The neoplastic B cells are positive for BCL6, BCL2, and MUM1, are subset positive for c-MYC (30-40%), and are negative for CD10. The Ki-67 proliferative index is markedly elevated (approximately 95%). The combined morphologic and immunophenotypic features are consistent with DLBCL. The morphology and BCL2 expression, together with the non-diffuse c-MYC expression, lack of CD10 expression, and absence of a MYC rearrangement by fluorescent in-situ hybridization (not shown) excludes the possibility of Burkitt's lymphoma. In situ hybridization for Ebstein–Barr virus-encoded RNA was negative (not shown). Expression of BCL6 and MUM1 and lack of CD10 supports a diagnosis of DLBCL, not otherwise specified, of activated B-cell–like lineage. Magnification, 200× (Panels A and C–J) and 1000× (Panel B).

Click to view the learning module for more information about Diffuse Large B-Cell Lymphoma (DLBCL).

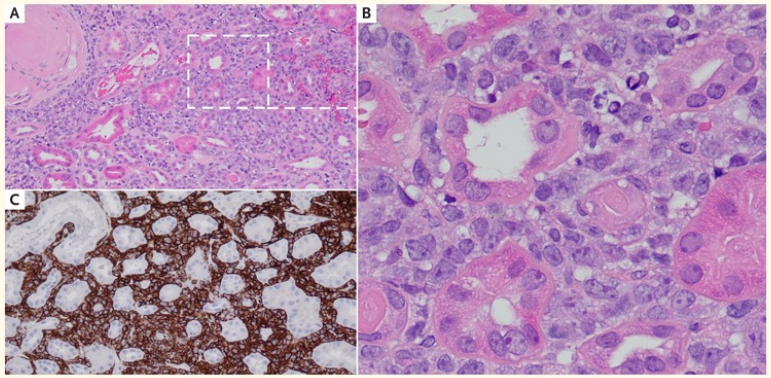
Case Outcome

The patient's hypercalcemia was attributed to extensive bone invasion by lymphoma, which was consistent with previous laboratory findings that indicated that the primary hypercalcemia was not mediated by PTH or 1,25-dihydroxyvitamin D.

The cornerstone of management of hypercalcemia for this patient was volume expansion with intravenous isotonic fluids. Fluid administration was begun at a rate of 200 ml per hour and adjusted to achieve a minimum urine output of 200 ml per hour. In addition to treating hypercalcemia, intravenous fluids also addressed the patient's volume depletion, which was likely due to hypercalcemia-induced polyuria and poor oral intake before presentation. Once euvolemia was reached, furosemide was added to prevent volume overload in the context of renal dysfunction. In addition to intravenous fluids, subcutaneous calcitonin, at a dose of 4 IU per kilogram of body weight, was administered every 12 hours, for a total of four doses. Given the severity and persistence of her hypercalcemia and the extent of the bone involvement, a single subcutaneous injection of denosumab, at a dose of 120 mg, was also administered. Once her calcium levels normalized, the patient received ergocalciferol at a dose of 50,000 IU weekly to treat her vitamin D deficiency and decrease the risk of hypocalcemia.

The patient's serum calcium level declined to 10.7 mg per deciliter by day 5 with this treatment strategy.

A comprehensive diagnostic evaluation — including tests for cryoglobulins, complement levels, anti–phospholipase A2 receptor antibodies, antinuclear antibodies, and antineutrophil cytoplasmic antibodies — did not reveal a clear cause of her kidney injury. A biopsy of the left kidney revealed diffuse and advanced nodular diabetic glomerulosclerosis, as well as involvement of her known DLBCL (Panels A–C). Her acute kidney injury abated modestly over the course of the next week after administration of the intravenous fluids and correction of hypercalcemia, with her creatinine level stabilizing at 1.97 mg per deciliter. Residual renal impairment was thought to be caused by a combination of diabetic nephropathy and lymphoma infiltration. Of note, there was no role for glucocorticoids in the treatment of hypercalcemia in this patient because, unlike many cases of lymphoma-associated hypercalcemia, the process was not mediated by 1,25-dihydroxyvitamin D.



Kidney-Biopsy Specimen. Hematoxylin and eosin staining (Panel A) shows a glomerulus with global glomerulosclerosis (at upper left) and adjacent tubular renal parenchyma with interstitial space infiltrated and expanded by an atypical lymphoid infiltrate. At higher magnification (Panel B), the infiltrating cells (between tubules) are large, with morphologic features similar to those seen in the biopsy specimen of the iliac crest. The infiltrating cells are diffusely positive for CD20 on immunostaining (Panel C) and are also positive for BCL6, BCL2, and MUM1 (not shown). Taken together, these findings are consistent with renal involvement by known DLBCL.

The patient began treatment with a glucocorticoid prophase consisting of prednisone and ultimately received pola-R-CHP (consisting of polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, and prednisone), with no complications reported. She was discharged home 3 weeks after admission with a plan for follow-up visits with an outpatient oncologist, a nephrologist, and an endocrinologist. Her anti–interleukin-17 therapy (ixekizumab) for psoriatic arthritis was discontinued owing to concerns for immunosuppression and associated infection risk during chemotherapy.

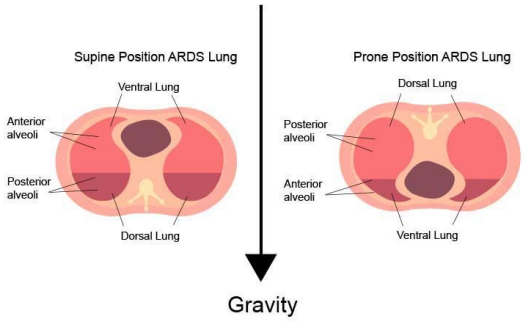


Hypercalcemia did not recur in the months after discharge, but the patient received a diagnosis of iatrogenic hypocalcemia caused by denosumab, which was treated with calcium and calcitriol supplementation. She ultimately completed six cycles of pola-R-CHP with curative intent.

Teaching Points

- Cancer-associated hypercalcemia can be caused by PTH-related protein secretion, osteolytic metastases, or ectopic vitamin D production. Understanding the etiology of cancer-associated hypercalcemia allows for treatment of the underlying cause but does not affect the initial approach to severe hypercalcemia.
- Severe hypercalcemia is a medical emergency. The cornerstone of treatment is isotonic fluid administration, with the possible addition of diuretics once euvolemia is achieved to prevent volume overload in the context of heart failure or renal disease. Medications, including calcitonin, denosumab, and bisphosphonates, are also used in more severe cases of hypercalcemia.
- DLBCL is often diagnosed at an advanced stage, but most patients are cured with systemic chemotherapy.

Prone Lagerung (Bauchlage) bei mechanischer Beatmung ist eine hochwirksame, evidenzbasierte Therapiemaßnahme, die vor allem bei Patientinnen und Patienten mit **schwerem akutem Atemnotsyndrom (ARDS)** eingesetzt wird. Durch das Wenden des Patienten von der Rücken- in die Bauchlage wird die Sauerstoffversorgung des Blutes signifikant verbessert und die Sterblichkeit nachweislich gesenkt.



In Rückenlage komprimieren das Eigengewicht des Herzens, das Mediastinum und die Bauchorgane die hinten liegenden (dorsalen) Lungenabschnitte. Die Bauchlage kehrt diese Effekte um:

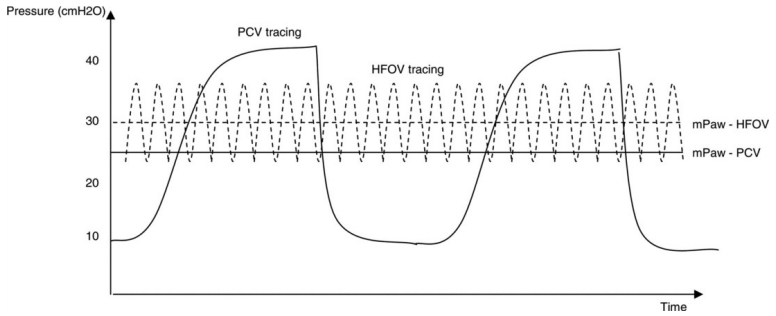
- **Optimierung des V/Q-Verhältnisses:** Die Belüftung (Ventilation) wird in den gut durchbluteten (perfundierten) dorsalen Lungenbereichen homogenisiert. Dies senkt den intrapulmonalen Shunt (Blutfluss durch nicht belüftete Alveolen).

- **Rekrutierung von Alveolen:** Kollabierte Lungenbläschen (Atelektasen) in den hinteren Abschnitten werden wieder eröffnet.

- **Lungenprotektion:** Der Beatmungsdruck verteilt sich gleichmäßiger über das gesamte Lungengewebe. Das verringert mechanischen Stress sowie beatmungsinduzierte Lungenschäden (VILI).

- **Entlastung des Herzens:** Das Herz verlagert sich nach vorne in Richtung Brustbein, wodurch der Druck auf den linken Lungenflügel nachlässt und die Nachlast der rechten Herzkammer (Vorderwand) optimiert wird.

High-Frequency Oscillatory Ventilation (HFOV) ist eine lungenprotektive Form der künstlichen Beatmung, bei der extrem kleine Atemzugvolumina mit sehr hohen Atemfrequenzen verabreicht werden**.** Im Gegensatz zur konventionellen mechanischen Beatmung liegt das Atemzugvolumen (Tidalvolumen) bei der HFOV oft unterhalb des anatomischen Totraums (ca. 1–3 ml/kg Körpergewicht). Sie wird vor allem in der Neonatologie sowie als "Rescue"-Therapie bei schwerem Lungenversagen eingesetzt.



Das Kernprinzip der HFOV basiert auf der Entkopplung von Oxygenierung und Ventilation (CO_2-Elimination):

- **Oxygenierung:** Ein konstanter Mitteldruck (Mean Airway Pressure, MAP) hält die Lungenbläschen (Alveolen) kontinuierlich offen. Dies verhindert das schädliche Kollabieren und Wiedereröffnen der Lungenstruktur (Atelektrauma).

- **Ventilation:** Ein oszillierender Kolben oder eine Membran erzeugt sinusförmige Druckwellen mit Frequenzen von **3 bis 15 Hertz** (180 bis 900 Schwingungen pro Minute). Sowohl die Einatmung als auch die Ausatmung erfolgen hierbei aktiv.

Prone and high frequency ventilation in newborns

Prone positioning and high-frequency oscillatory ventilation in early paediatric acute respiratory distress syndrome (PROSpect): an international, two-by-two factorial, response-adaptive, phase 3, randomised controlled trial

Summary

Background Data on prone positioning and high-frequency oscillatory ventilation (HFOV) used separately or in combination in patients with paediatric acute respiratory distress syndrome (PARDS) are inconclusive, leading to wide practice variability. We aimed to compare the effects of prone positioning with supine positioning and the effects of HFOV with conventional mechanical ventilation on ventilator-free days in children with early, moderate-to-severe PARDS.

Methods PROSpect was an international, two-by-two factorial, response-adaptive, phase 3, randomised controlled trial done in 75 paediatric intensive care units in 18 countries. Eligible patients were aged 2 weeks to 20 years, and were intubated and mechanically ventilated for less than 96 h before meeting criteria for moderate-to-severe PARDS. Patients were centrally randomly assigned using a web-based system to supine positioning and conventional mechanical ventilation, prone positioning and conventional mechanical ventilation, supine positioning and HFOV, or prone positioning and HFOV. Initially, the allocation was 1:1:1:1 stratified by age group and direct or indirect lung injury using a permuted block design with blocks of four and eight. Response-adaptive randomisation updates were planned to adjust allocation probabilities 28 days after 300 patients were randomly assigned and then 28 days after every 100 additional patients. Given the nature of the interventions, masking was not possible. The primary outcome was ventilator-free days through to day 28 among all randomly assigned participants. Safety was assessed prospectively by daily monitoring for the occurrence of prespecified adverse events. This study was registered with ClinicalTrials.gov (NCT03896763) and is closed to enrolment.

Findings Between May 1, 2019 and Jan 13, 2026, 1045 patients were eligible for enrolment. The trial was stopped early for futility and slow enrolment after 424 of 600 planned patients were recruited. 126 patients were randomly assigned to the supine and conventional mechanical ventilation group, 130 to the prone and conventional mechanical ventilation group, 90 to the supine and HFOV group, and 78 to the prone and HFOV group. Median age was 3·3 years (IQR 1·1–10·1), 211 (50%) patients were female, and 213 (50%) were male. There were no significant differences in ventilator-free days between prone and supine positioning (median 17·9 days [IQR 8·9–21·3] *vs* 17·4 days [6·4–21·9]; Hodges–Lehmann location shift adjusting for ventilation 0·0 [95% CI –0·8 to 1·0]) or between HFOV and conventional mechanical ventilation (17·3 [5·7–21·6] *vs* 18·0 [9·9–21·5]; Hodges–Lehmann location shift adjusting for positioning –0·3 [95% CI –1·5 to 0·5]). 41 (10%) patients had died at day 28, without group differences. Plugging or obstruction of the artificial airway occurred more frequently with prone than supine positioning (14 events in 12 [6%] of 188 patients *vs* three events in three [2%] of 197 patients; 0·74 [95% CI 0·44–1·26] *vs* 0·15 [0·05–0·47] events per 100 artificial airway days; rate ratio 4·83 [95% CI 1·38–16·82]). Stage 2 or worse immobility-related pressure injuries also occurred more frequently with prone versus supine positioning (12 [6%] *vs* two [1%]; relative risk 6·13 [95% CI 1·45–25·97]). Haemodynamic instability occurred more frequently with HFOV than conventional mechanical ventilation (41 events in 19 [13%] of 141 patients *vs* 38 events in 22 [9%] of 244 patients; 2·21 [95% CI 1·63–3·00] *vs* 1·22 [0·89–1·68] events per 100 paediatric intensive care unit days; rate ratio 1·84 [95% CI 1·18–2·87]). One serious adverse event, an unwitnessed self-extubation followed by cardiopulmonary arrest, occurred in a patient in the prone and conventional mechanical ventilation group.

Interpretation We found no evidence to support prone positioning or HFOV as first-line strategies to improve ventilator-free days in patients with early, moderate-to-severe PARDS. Thus, the routine use of these strategies in this population is not recommended.

	Overall (n=424)	Supine (n=216)	Prone (n=208)	Conventional mechanical ventilation (n=256)	HFOV (n=168)
Age at admission to paediatric intensive care unit, years	3·3 (1·1–10·1)	3·3 (1·1–10·4)	3·3 (1·1–10·1)	3·3 (1·2–10·0)	3·4 (1·0–10·6)
Age group					
2 weeks to <1 year	97 (23%)	49 (23%)	48 (23%)	56 (22%)	41 (24%)
1 year to 7 years	193 (46%)	98 (45%)	95 (46%)	122 (48%)	71 (42%)
8 years to 20 years	134 (32%)	69 (32%)	65 (31%)	78 (30%)	56 (33%)
Sex					
Female	211 (50%)	95 (44%)	116 (56%)	119 (46%)	92 (55%)
Male	213 (50%)	121 (56%)	92 (44%)	137 (54%)	76 (45%)
PCPC score of 1*	275 (65%)	142 (66%)	133 (64%)	162 (63%)	113 (67%)
POPC score of 1*	254 (60%)	132 (61%)	122 (59%)	148 (58%)	106 (63%)
Obesity†	106/327 (32%)	53/167 (32%)	53/160 (33%)	58/200 (29%)	48/127 (38%)
Primary diagnosis					
Direct lung injury	380 (90%)	193 (89%)	187 (90%)	228 (89%)	152 (90%)
Pneumonia	231 (54%)	117 (54%)	114 (55%)	134 (52%)	97 (58%)
Bronchiolitis (with pneumonia)	85 (20%)	46 (21%)	39 (19%)	55 (21%)	30 (18%)
Aspiration pneumonia	38 (9%)	18 (8%)	20 (10%)	22 (9%)	16 (10%)
Other direct lung injury‡	26 (6%)	12 (6%)	14 (7%)	17 (7%)	9 (5%)
Indirect lung injury	44 (10%)	23 (11%)	21 (10%)	28 (11%)	16 (10%)
Acute respiratory failure related to sepsis	31 (7%)	15 (7%)	16 (8%)	20 (8%)	11 (7%)
Other indirect lung injury‡	13 (3%)	8 (4%)	5 (2%)	8 (3%)	5 (3%)
Qualifying oxygenation parameters§					
Oxygenation index	20·8 (16·7–26·8)	20·2 (16·4–26·5)	21·4 (17·0–28·8)	20·8 (16·5–27·1)	20·9 (17·0–26·7)
PaO_2:FiO_2 ratio, mm Hg	83 (68–104)	86 (70–106)	81 (67–100)	83 (69–104)	83 (67–102)
Oxygen saturation index	16·3 (13·4–19·1)	15·1 (12·4–18·1)	16·6 (15·0–19·2)	16·0 (13·2–18·1)	16·4 (13·5–20·7)
Duration between intubation and randomisation, days	1·0 (0·4–2·0)	1·1 (0·5–2·0)	0·9 (0·4–1·9)	1·0 (0·4–1·9)	1·0 (0·5–2·1)
Organ dysfunction on day of randomisation					
PELOD-2 score¶	7 (6–9)	7 (6–9)	7 (6–10)	7 (6–9)	7 (6–10)
Number of organ dysfunctions	2 (2–3)	2 (2–3)	2 (2–3)	2 (2–3)	2 (2–3)

Data are median (IQR), n (%), or n/N (%). Data are complete for all baseline characteristics except that patients might have either an oxygenation index and PaO_2:FiO_2 ratio or an oxygen saturation index. There were no significant differences in baseline characteristics by positioning strategy, except for female sex (relative risk [prone *vs* supine] 1·27 [95% CI 1·05–1·54]). There were no significant differences in baseline characteristics by ventilation strategy. FiO_2=fractional concentration of O_2 in inspired air. HFOV=high-frequency oscillatory ventilation. PaO_2=partial pressure of O_2 in arterial blood. PCPC=Paediatric Cerebral Performance Category. PELOD-2=Paediatric Logistic Organ Dysfunction-2. POPC=Paediatric Overall Performance Category. *PCPC and POPC scores range from 1 to 6, with lower scores indicating less disability. †Obesity was calculated for 327 patients aged 1 year and older. Weight-for-height Z scores based on WHO growth charts for patients younger than 2 years and BMI-for-age Z scores based on US Centres for Disease Control and Prevention growth charts for children aged 2 years and older were calculated. Obesity was defined as having a Z score ≥1·65 (≥95th percentile). ‡Other direct lung injury includes pulmonary haemorrhage, near drowning, acute chest syndrome or sickle cell disease, inhalation burns, pertussis, vaping, and interstitial pneumonitis possibly related to paraquat poisoning. Other indirect lung injury includes acute respiratory distress syndrome caused by a clearly systemic process (eg, pancreatitis), pulmonary oedema, and acute respiratory failure related to multiple blood transfusions. §Oxygenation index and PaO_2:FiO_2 ratio were calculated for 358 patients with an arterial line. Oxygen saturation index was calculated for 66 patients without an arterial line. ¶PELOD-2 scores range from 0 to 33, with higher scores indicating more severe multiple organ dysfunction syndrome.

Table 1: **Baseline characteristics by positioning or ventilation strategy**

	Overall	Supine	Prone	Effect estimate comparing positioning strategies (95% CI)*	Conventional mechanical ventilation	HFOV	Effect estimate comparing ventilation strategies (95% CI)*
Intention-to-treat analysis	n=424	n=216	n=208	..	n=256	n=168	..
Ventilator-free days through to day 28	17·8 (7·6 to 21·6)	17·4 (6·4 to 21·9)	17·9 (8·9 to 21·3)	HL 0·0† (−0·8 to 1·0)	18·0 (9·9 to 21·5)	17·3 (5·7 to 21·6)	HL −0·3† (−1·5 to 0·5)
Assigned 0 ventilator-free days	86 (20%)	42 (19%)	44 (21%)	ReR 1·09 (0·74 to 1·58)	53 (21%)	33 (20%)	ReR 0·95 (0·65 to 1·40)
Still intubated on day 28	45 (11%)	20 (9%)	25 (12%)	..	27 (11%)	18 (11%)	..
Died by day 28	41 (10%)	22 (10%)	19 (9%)	..	26 (10%)	15 (9%)	..
Excluded from per-protocol analysis‡	39 (9%)	19 (9%)	20 (10%)	ReR 1·15 (0·64 to 2·07)	12 (5%)	27 (16%)	ReR 3·44 (1·79 to 6·59)
Per-protocol analysis	n=385	n=197	n=188	..	n=244	n=141	..
Ventilator-free days through to day 28	17·8 (9·3 to 21·7)	17·7 (9·2 to 22·0)	17·9 (9·6 to 21·3)	HL 0·0 (−1·2 to 0·8)	18·2 (10·5 to 21·9)	17·4 (6·1 to 21·5)	HL −0·3 (−1·9 to 0·2)
Assigned 0 ventilator-free days	75 (19%)	37 (19%)	38 (20%)	ReR 1·07 (0·72 to 1·61)	48 (20%)	27 (19%)	ReR 0·98 (0·64 to 1·49)
Still intubated on day 28	40 (10%)	20 (10%)	20 (11%)	..	24 (10%)	16 (11%)	..
Died by day 28	35 (9%)	17 (9%)	18 (10%)	..	24 (10%)	11 (8%)	..
Non-pulmonary organ failure-free days through to day 28	19 (11 to 23)	20 (11 to 23)	18 (12 to 23)	HL −1 (−2 to 1)	19 (11 to 23)	19 (11 to 23)	HL 0 (−2 to 1)
90-day hospital mortality	42 (11%)	20 (10%)	22 (12%)	ReR 1·14 (0·65 to 2·01)	28 (11%)	14 (10%)	ReR 0·87 (0·48 to 1·59)
Among survivors to day 90§	n=343	n=177	n=166	..	n=216	n=127	..
Duration of mechanical ventilation through to day 28, days	9·3 (6·0 to 14·6)	9·2 (5·8 to 15·3)	9·3 (6·3 to 13·9)	HR 1·03 (0·82 to 1·29)	8·9 (6·0 to 13·9)	10·0 (6·1 to 16·1)	HR 0·87 (0·69 to 1·09)
PICU length of stay through to day 90, days	13·7 (9·4 to 23·2)	13·5 (9·0 to 24·1)	14·1 (9·9 to 22·9)	HR 0·97 (0·78 to 1·21)	13·4 (9·2 to 22·5)	15·1 (9·5 to 25·6)	HR 0·92 (0·74 to 1·16)
Hospital length of stay through to day 90, days	21·8 (14·2 to 38·9)	21·1 (13·6 to 39·9)	22·0 (14·5 to 38·6)	HR 0·98 (0·78 to 1·23)	20·3 (13·7 to 38·6)	24·2 (15·9 to 42·1)	HR 0·91 (0·73 to 1·14)

Data are median (IQR) or n (%). Data are complete for all outcomes and adjusted analyses. See appendix p 10 for outcomes definitions. HFOV=high-frequency oscillatory ventilation. HL=Hodges–Lehmann location shift. HR=hazard ratio. PICU=paediatric intensive care unit. ReR=relative risk. *Effect estimates compare positioning strategies, stratifying by ventilation strategy, or compare ventilation strategies, stratifying by positioning strategy. HL estimates (median of pairwise differences; prone − supine, or HFOV − conventional mechanical ventilation) were calculated for ventilator-free days and organ failure-free days. ReRs and HRs (prone *vs* supine, or HFOV *vs* conventional mechanical ventilation) were calculated for binary and time-to-event outcomes, respectively. An HR<1 indicates a longer duration of mechanical ventilation or PICU or hospital length of stay for prone versus supine, or HFOV versus conventional mechanical ventilation. Effect estimates did not adjust for age group or lung injury category; see appendix p 37 for effect estimates adjusted for age group and lung injury category. †The primary analyses were performed on an intention-to-treat basis and compared ventilator-free days through to day 28 between positioning strategies using one-sided Wilcoxon rank-sum tests stratified by ventilation strategy and between ventilation strategies using one-sided Wilcoxon rank-sum tests stratified by positioning strategy: prone > supine p=0·48; supine > prone p=0·52; HFOV > conventional mechanical ventilation p=0·76; conventional mechanical ventilation > HFOV p=0·24. None of these p values were below the prespecified 0·022 threshold for statistical significance. HL estimates were also calculated within strata: prone versus supine in conventional mechanical ventilation 0·0 (95% CI −1·2 to 1·2), prone versus supine in HFOV 0·0 (−1·5 to 2·3), HFOV versus conventional mechanical ventilation in supine −0·2 (−2·4 to 0·9), HFOV versus conventional mechanical ventilation in prone 0·0 (−1·8 to 1·1). ‡25 patients were never transitioned to their randomly assigned positioning strategy, ventilation strategy, or both and 14 patients were withdrawn from study protocols during the first 24 h after randomisation without meeting protocol failure criteria. §Tests for the proportional-hazard assumption using Schoenfeld residuals yielded p>0·05 for positioning strategy and p>0·05 for ventilation strategy.

Table 2: **Outcomes by positioning or ventilation strategy**

	Overall (n=385)*	Supine (n=197)	Prone (n=188)	Conventional mechanical ventilation (n=244)	HFOV (n=141)
Study days on protocol	2376	1649	727	1902	474
Adherence to oxygenation goals, n study days (%)†	1785 (75%)	1214 (74%)	571 (79%)	1425 (75%)	360 (76%)
Adherence to ventilation goals, n study days (%)‡	1817 (76%)	1268 (77%)	549 (76%)	1470 (77%)	347 (73%)
Adherence to supine protocol					
Patient remained in the supine position, n study days (%)	..	1601 (97%)	..	..	..
Adherence to prone protocol					
Prone maintained for at least 16 h/day, n study days (%)§	..	..	641 (88%)	..	..
Prone positioning stopped when oxygenation index <8 for at least 4 h in the supine position, n/N (%)	..	..	154/188 (82%)	..	..
Adherence to ongoing conventional mechanical ventilation support					
Expired tidal volume 5–7 mL/kg of ideal bodyweight, n study days (%)¶	..	..	..	1297 (68%)	..
PIP ≤28 cm H_2O, n study days (%)‖	..	..	..	1651 (87%)	..
PEEP-FiO_2 titrated to table every 12 h, n study days (%)**	..	..	..	1385 (73%)	..
Adherence to ongoing HFOV support					
Maintained highest frequency (≥8 Hz), n study days (%)	..	..	..	..	461 (97%)
Amplitude (delta-P) within 60–90, n study days (%)	..	..	..	..	344 (73%)
Mean airway pressure titration manoeuvre performed every 12 h, n study days (%)**	..	..	..	..	344 (73%)
Converted to conventional mechanical ventilation when mean airway pressure <15 cm H_2O and FiO_2 <0·50, n/N (%)	..	..	..	..	141/141 (100%)
Continuous neuromuscular blockade administered for first 24 h on protocol, n (%)	339 (88%)	173 (88%)	166 (88%)	210 (86%)	129 (91%)
ERT completed, n/N patients who met ERT criteria (%)	192/203 (95%)	96/102 (94%)	96/101 (95%)	125/134 (93%)	67/69 (97%)
Extubated within 6 h of first passing ERT, n/N patients who passed ERT (%)††	200/223 (90%)	95/107 (89%)	105/116 (91%)	130/146 (89%)	70/77 (91%)
Removed from study protocol: met failure criteria, n (%)‡‡	82 (21%)	49 (25%)	33 (18%)	48 (20%)	34 (24%)
Persistent hypoxaemia	42 (11%)	30 (15%)	12 (6%)	19 (8%)	23 (16%)
Persistent hypoventilation	29 (8%)	13 (7%)	16 (9%)	24 (10%)	5 (4%)
Both persistent hypoxaemia and persistent hypoventilation	10 (3%)	6 (3%)	4 (2%)	5 (2%)	5 (4%)
Pattern of no effect of prone positioning for 3 days	1 (<1%)	0	1 (1%)	0	1 (1%)
Days to protocol failure, median (IQR)	0·7 (0·2–3·0)	0·6 (0·2–2·9)	0·8 (0·2–3·0)	0·3 (0·1–2·1)	1·9 (0·4–4·6)
Removed from study protocol: did not meet failure criteria, n (%)	54 (14%)	27 (14%)	27 (14%)	30 (12%)	24 (17%)
Clinical judgement by bedside care providers	36 (9%)	20 (10%)	16 (9%)	19 (8%)	17 (12%)
Developed PROSpect exclusion criterion	16 (4%)	7 (4%)	9 (5%)	10 (4%)	6 (4%)
Parent or guardian request	2 (1%)	0	2 (1%)	1 (<1%)	1 (1%)
Days to removal, median (IQR)	3·7 (2·4–7·6)	3·5 (2·6–7·1)	4·1 (2·0–7·6)	3·5 (2·4–7·6)	4·0 (2·4–6·5)
ECMO after removal from study protocol, n (%)	35 (9%)	15 (8%)	20 (11%)	17 (7%)	18 (13%)
Met failure criteria	24 (6%)	10 (5%)	14 (7%)	11 (5%)	13 (9%)
Did not meet failure criteria	11 (3%)	5 (3%)	6 (3%)	6 (2%)	5 (4%)

Data are n study days (%), n/N (%), n (%), or median (IQR). Data are complete for all protocol elements. ECMO=extracorporeal membrane oxygenation. ERT=extubation readiness test. FiO_2=fractional concentration of O_2 in inspired air. HFOV=high-frequency oscillatory ventilation. PEEP=positive end-expiratory pressure. PIP=peak inspiratory pressure. SpO_2=peripheral capillary O_2 saturation. *385 patients included in the per-protocol population. †Oxygenation goal defined as SpO_2 88–92% during the acute phase (oxygenation index ≥8 or oxygen saturation index ≥7·5) or SpO_2 92–97% during the titration phase (oxygenation index <8 or oxygen saturation index <7·5). Study days during which the clinician responded to out-of-range SpO_2 within 15 min were considered adherent. ‡Ventilation goal defined as pH 7·15–7·30 (irrespective of partial pressure of CO_2 in arterial blood) during the acute phase or pH 7·30–7·45 during the titration phase. Study days during which the clinician responded to out-of-range pH using ventilation manoeuvres within 15 min were considered adherent. §Study days during which the patient was positioned supine for a procedure or abdominal assessment or due to haemodynamic instability and the first and last study days following the prone protocol were considered adherent. ¶Study days with expired tidal volume as low as 3 mL/kg to maintain an acceptable PIP when oxygenation index ≥16 or oxygen saturation index ≥12·3 or as high as 8 mL/kg for primary respiratory acidaemia unresponsive to increased respiratory rate were considered adherent. The median expired tidal volume was 6·2 mL/kg (IQR 5·1–7·4). ‖Study days with PIP up to 32 cm H_2O for patients with clinical evidence of poor chest wall compliance were considered adherent. **Study days with PEEP titration manoeuvres or mean airway pressure recruitment manoeuvres up to 14 h apart were considered adherent. ††Not extubating within 6 h of first passing ERT due to patient-related factors was considered adherent. ‡‡Ventilation protocol failure was defined as a 2 h pattern of hypoxaemia (SpO_2 <85%; with FiO_2 1·0 and max PEEP per grid [16 cm <1 year; 18 cm ≥1 year; conventional mechanical ventilation] or mean airway pressure >35 cm H_2O [HFOV]) or hypoventilation (pH <7·15; with PIP >32 cm H_2O and a respiratory rate that does not cause intrinsic PEEP [conventional mechanical ventilation] or maximum power or amplitude at a frequency <8 Hz [HFOV]). Prone positioning protocol failure was defined as hypoxaemia per ventilation mode or a 3 consecutive day pattern of no effect.

***Table 3*: Protocol adherence by positioning or ventilation strategy**

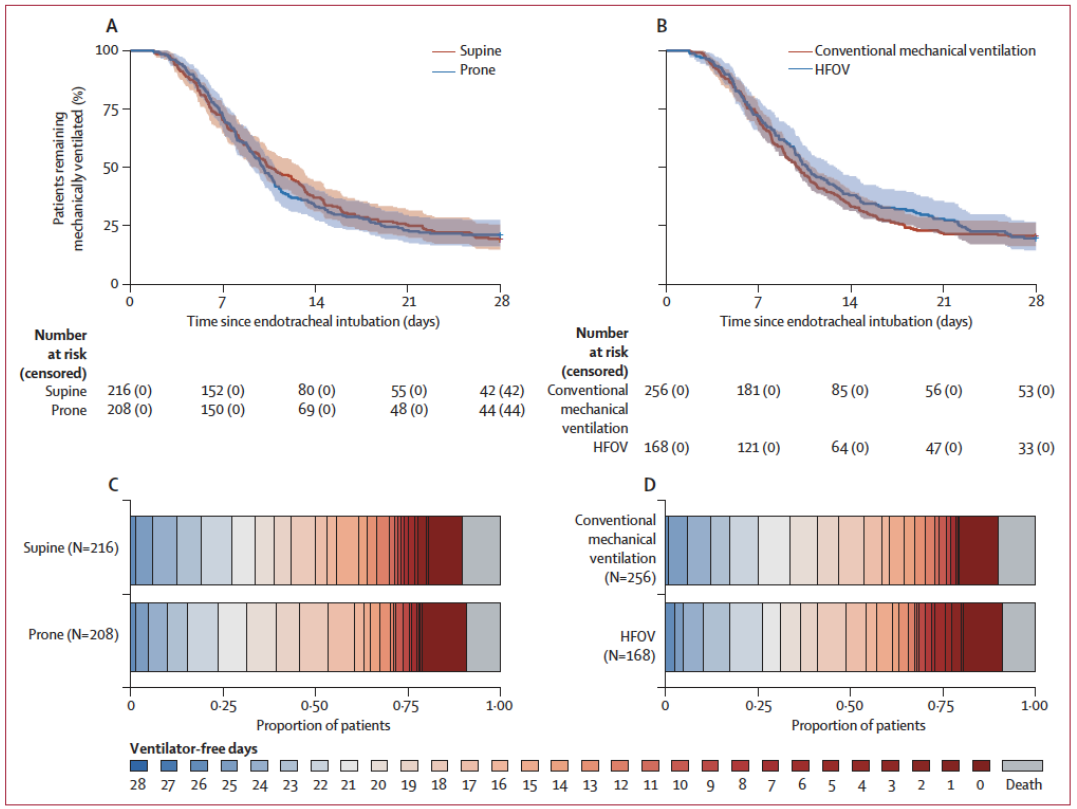


Figure 2: **Ventilator-free days by positioning or ventilation strategy**

(A) and (B) Kaplan–Meier curves with pointwise 95% CIs for remaining mechanically ventilated through to day 28 according to positioning strategy (A) or ventilation strategy (B). The only censored observations are at day 28 and include the 45 patients still intubated on day 28 and the 41 patients who died by day 28. The Hodges–Lehmann location-shift estimate for ventilator-free days comparing positioning strategies (prone–supine), stratifying by ventilation strategy, is 0·0 (95% CI −0·8 to 1·0; prone > supine one-sided Wilcoxon rank-sum p=0·48; supine > prone p=0·52). The estimate comparing ventilation strategies (HFOV–conventional mechanical ventilation), stratifying by positioning strategy, is −0·3 (95% CI −1·5 to 0·5; HFOV > conventional mechanical ventilation p=0·76; conventional mechanical ventilation > HFOV p=0·24). (C) and (D) Horizontally stacked bar plots of ventilator-free days (rounded to the nearest day) according to positioning strategy (C) or ventilation strategy (D). Blue represents better outcomes in survivors, red represents worse outcomes in survivors, and grey represents deaths. HFOV=high-frequency oscillatory ventilation.

	Overall (n=385)*	Supine (n=197)	Prone (n=188)	Effect estimate comparing positioning strategies (95% CI)†	Conventional mechanical ventilation (n=244)	HFOV (n=141)	Effect estimate comparing ventilation strategies (95% CI)†
Unplanned endotracheal tube extubation	9 (2%)	3 (2%)	6 (3%)	..	5 (2%)	4 (3%)	..
Events per 100 ventilator days (95% CI)	0·23 (0·12–0·45)	0·15 (0·05–0·47)	0·32 (0·14–0·71)	RR 2·15 (0·54–8·64)	0·21 (0·09–0·50)	0·27 (0·10–0·72)	RR 1·36 (0·36–5·07)
Unplanned removal of vascular line or invasive tube	8 (2%)	2 (1%)	6 (3%)	..	6 (2%)	2 (1%)	..
Events per 100 device days (95% CI)	0·05 (0·03–0·10)	0·03 (0·01–0·10)	0·07 (0·03–0·16)	RR 1·99 (0·50–7·98)	0·07 (0·03–0·14)	0·03 (0·01–0·12)	RR 0·46 (0·09–2·21)
Plugging or obstruction of the artificial airway with secretions, or blood, or both	15 (4%)	3 (2%)	12 (6%)	..	10 (4%)	5 (4%)	..
Events per 100 endotracheal tube or tracheostomy days (95% CI)	0·44 (0·27–0·71)	0·15 (0·05–0·47)	0·74 (0·44–1·26)	RR 4·83 (1·38–16·82)	0·50 (0·29–0·89)	0·34 (0·14–0·81)	RR 0·74 (0·26–2·10)
Main-stem bronchus intubation	3 (1%)	0	3 (2%)	ReR 8·40 (0·44–159·7)‡	0	3 (2%)	ReR 13·46 (0·71–256·7)‡
Air leak	42 (11%)	23 (12%)	19 (10%)	ReR 0·89 (0·50–1·57)	22 (9%)	20 (14%)	ReR 1·56 (0·88–2·77)
Haemodynamic instability	41 (11%)	18 (9%)	23 (12%)	..	22 (9%)	19 (13%)	..
Events per 100 paediatric intensive care unit days (95% CI)	1·59 (1·28–1·98)	1·52 (1·11–2·09)	1·66 (1·22–2·25)	RR 1·16 (0·74–1·81)	1·22 (0·89–1·68)	2·21 (1·63–3·00)	RR 1·84 (1·18–2·87)
Clinically significant agitation	10 (3%)	4 (2%)	6 (3%)	ReR 1·62 (0·47–5·63)	5 (2%)	5 (4%)	ReR 1·77 (0·52–6·00)
Pressure injury (immobility-related stage 2 or worse)	14 (4%)	2 (1%)	12 (6%)	ReR 6·13 (1·45–25·97)	8 (3%)	6 (4%)	ReR 1·40 (0·51–3·85)
Ventilator-associated event	5 (1%)	2 (1%)	3 (2%)	..	3 (1%)	2 (1%)	..
Events per 1000 ventilator days (95% CI)	1·29 (0·54–3·11)	1·01 (0·25–4·03)	1·59 (0·51–4·94)	RR 1·59 (0·27–9·58)	1·26 (0·41–3·90)	1·35 (0·34–5·40)	RR 1·11 (0·18–6·66)

Data are n (%) or rate (95% CI). Data are complete for all adverse events and adjusted analyses. See appendix pp 11–12 for adverse event definitions and expected rates. HFOV=high-frequency oscillatory ventilation. RR=rate ratio. ReR=relative risk. *385 patients included in the per-protocol population. †Effect estimates compare positioning strategies, stratifying by ventilation strategy, or compare ventilation strategies, stratifying by positioning strategy, except where noted. RRs and ReRs (prone *vs* supine, or HFOV *vs* conventional mechanical ventilation) are calculated for rate and binary outcomes, respectively. ‡Due to zero counts, a logit estimator, which used a correction of 0·5 in every cell, of the relative risk was calculated, ignoring a stratum with no events.

Table 4: **Adverse events by positioning or ventilation strategy**

Implications of all the available evidence

Our findings suggest that early use of prone positioning in patients with PARDS does not improve clinically relevant outcomes. Further research could identify individuals who might benefit from the rescue use of prone positioning. Based on our results in conjunction with the previously published literature, early or rescue use of HFOV does not improve clinically relevant outcomes.

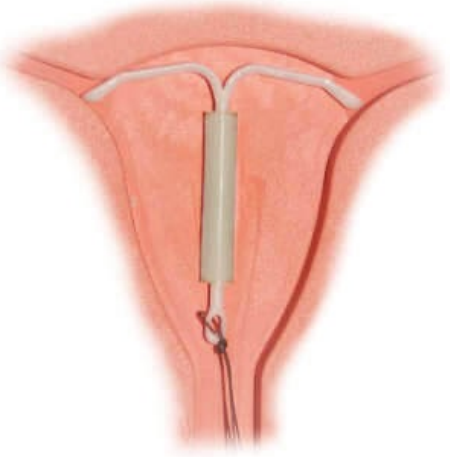
Sehr starke Regelblutungen (medizinisch **Hypermenorrhö** oder verlängerte Blutung als **Menorrhagie**) können sehr gut behandelt werden. Die Auswahl der Therapie richtet sich nach den Ursachen, dem Alter und ob noch ein Kinderwunsch besteht

Operative Therapien (bei organischen Ursachen oder wenn Medikamente nicht helfen)

- **Entfernung von Myomen oder Polypen:** Falls gutartige Wucherungen die Blutung auslösen, können diese minimal-invasiv (z. B. per Hysteroskopie) entfernt werden.
- **Endometriumablation (Schleimhautverödung):** Bei abgeschlossenem Kinderwunsch wird die Gebärmutterschleimhaut verödet (z. B. durch Hitze oder die *Goldnetz-Methode*), was die Blutung meist stark stoppt oder dauerhaft verringert.
- **Hysterektomie (Gebärmutterentfernung):** Die radikalste und endgültige Lösung, die bei sehr hohem Leidensdruck und abgeschlossener Familienplanung in Betracht gezogen wird



Levonorgestrel ist eine der wirksamsten medikamentösen Optionen zur Behandlung einer Menorrhagie (übermäßig starke und lang anhaltende Regelblutung). Der Wirkstoff ist ein synthetisches Gestagen (Gelbkörperhormon). Es sorgt dafür, dass sich die Gebärmutterschleimhaut deutlich weniger stark aufbaut, wodurch der monatliche Blutverlust drastisch sinkt.



Die Anwendung erfolgt in diesem Fall fast ausschließlich über eine **Hormonspirale (Intrauterines Wirkstofffreisetzungssystem, IUS)**.

Die Hormonspirale (LNG-IUS) als Goldstandard

Bei einer idiopathischen (ohne organische Ursache vorliegenden) Menorrhagie wird eine Hormonspirale mit Levonorgestrel eingesetzt.

- **Wirksamkeit:** Studien zeigen, dass der menstruelle Blutverlust bereits nach 3 Monaten um über 90 % und nach 6 Monaten um mehr als 97 % abnehmen kann. Bei vielen Frauen führt die Anwendung langfristig zu einer Amenorrhoe (vollständiges Ausbleiben der Periode), was medizinisch unbedenklich ist.
- **Wirkdauer:** Die Spirale schützt je nach Präparat über mehrere Jahre vor einer Schwangerschaft, wobei der therapeutische Nutzen bei Menorrhagie ebenfalls langfristig angelegt ist.

Endometrial ablation plus levonorgestrel-releasing intrauterine system versus endometrial ablation alone in women with heavy menstrual bleeding in The Netherlands (MIRA2): a multicentre, open-label, randomised, controlled, superiority trial

LNG-IUS + endometrial ablation against endometrial ablation alone (time to hysterectomy)

Summary

Background Endometrial ablation is an established and effective treatment for women with heavy menstrual bleeding, but many patients require further treatment, with approximately 10% ultimately undergoing a hysterectomy within 2 years. The insertion of a levonorgestrel-releasing intrauterine system (LNG-IUS) immediately after endometrial ablation might inactivate residual untreated endometrium or prevent its regeneration, thereby preventing recurrent symptoms necessitating a hysterectomy. The aim of the study was to assess whether LNG-IUS insertion immediately after endometrial ablation in women with heavy menstrual bleeding reduced the need for subsequent hysterectomy within 2 years compared with endometrial ablation alone.

Methods This multicentre, open-label, randomised, controlled, superiority trial was conducted in 34 hospitals in the Netherlands. Women younger than 60 years with heavy menstrual bleeding who were eligible for endometrial ablation were included and randomly assigned (1:1) to combined treatment comprising endometrial ablation plus LNG-IUS or to standard care comprising endometrial ablation alone (stratified by dysmenorrhoea and age). Masking was not applied. Endometrial ablation was done using electrical radiofrequency ablation or by transcervical resection of the endometrium. In participants allocated to combined treatment, intrauterine insertion of an LNG-IUS containing a total of 52 mg of levonorgestrel (releasing 20 µg per day in the first year) was done immediately after the ablative procedure. The primary outcome was the incidence of hysterectomy within 2 years, analysed on a modified intention-to-treat basis in all participants with available data. Serious adverse events were systematically assessed at 6 weeks, 12 months, and 24 months after the intervention. This study was registered on the International Clinical Trials Registry Platform (NL-OMON54839) and is complete.

Findings Between Nov 19, 2019, and April 5, 2023, 715 participants were randomly assigned to combined treatment (n=359) or endometrial ablation alone (n=356). The median age of all participants was 45 years (IQR 40–48). 42 (6%) participants had missing data for the primary outcome at 2 years of follow-up. A hysterectomy was done in 15 (4%) of 342 participants in the combined treatment group versus 34 (10%) of 331 participants in the endometrial ablation group, corresponding to a relative risk (RR) of 0·43 (95% CI 0·24 to 0·77; p=0·0050), with a risk difference of –0·06 (95% CI –0·10 to –0·02; p=0·0040). Serious adverse events were reported in 27 (8%) of 346 participants in the combined treatment group and 26 (8%) of 327 participants in the endometrial ablation alone group (RR 0·98, 95% CI 0·59–1·65; p=0·94), and there were no treatment-related deaths.

Interpretation The combination of endometrial ablation and LNG-IUS significantly reduced the incidence of hysterectomy compared with endometrial ablation alone. The combined treatment appears to be a safe adjunctive strategy for heavy menstrual bleeding that does not increase the risk of complications.

Funding The Netherlands Organization for Health Research and Development.

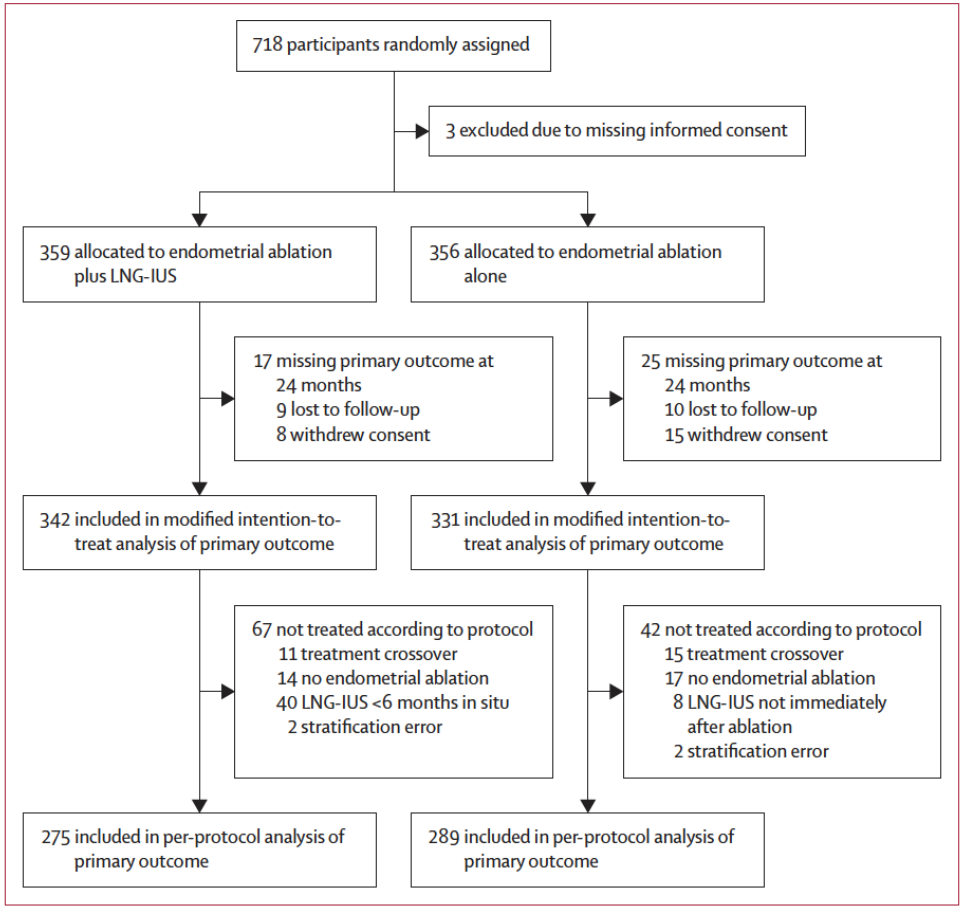


Figure 1: **Study profile**
LNG-IUS=levonorgestrel-releasing intrauterine system.

	Combined treatment (n=359)	Endometrial ablation alone (n=356)	Standardised mean difference
Mean age, years	44·3 (5·5)	44·4 (5·7)	0·02
BMI, kg/m²	27·3 (24·5–31·9)	26·8 (23·7–30·9)	0·11
Missing data	22	18	..
Nulliparous			
Yes	27/356 (8%)	29/353 (8%)	0·02
No	329/356 (92%)	324/353 (92%)	0·02
Missing data	3	3	..
Vaginal deliveries*	283/356 (80%)	270/347 (78%)	0·04
Caesarean section*	69/356 (19%)	80/347 (23%)	0·09
Missing data	3	9	..
Use of oestrogen or progesterone	100/357 (28%)	115/355 (32%)	0·10
Missing data	2	1	..
Tubal occlusion in history	19/357 (5%)	19/352 (5%)	0·00
Missing data	2	4	..
Smoking	52/304 (17%)	37/288 (13%)	0·12
Missing data	55	68	..
Duration of menstruation, days	10 (7–20)	10 (7–16)	0·09
Missing data	33	49	..
Median PBAC score	435 (240·5–825·3)	415 (249–813·5)	0·06
Missing data	43	56	..
PBAC <75	299/316 (95%)	284/300 (95%)	0·00
Missing data	43	56	..
Pre-existing dysmenorrhoea	123/359 (34%)	124/356 (35%)	0·01
Mild (NRS 1–3)	1/104 (1%)	3/101 (3%)	0·15
Moderate (NRS 4–6)	21/104 (20%)	18/101 (18%)	0·06
Severe (NRS 7–10)	82/104 (79%)	80/101 (79%)	0·01
Missing data	19	23	..
Non-cyclical pelvic pain	85/327 (26%)	94/313 (30%)	0·09
Missing data	32	43	..
Ultrasonography (two dimensional)			
Myomas	67/358 (19%)	64/354 (18%)	0·02
Missing data	1	2	..
One myoma	47/64 (73%)	43/59 (73%)	0·01
Two or more myomas	17/64 (27%)	16/59 (27%)	0·01
Missing data	3	5	..
Signs of adenomyosis	30/355 (8%)	28/355 (8%)	0·02
Missing data	4	1	..

Data are n/N (%), median (IQR), or mean (SD). PBAC=Pictorial Blood Assessment Chart. NRS=numeric rating scale.
*More than one response per participant was possible.

Table 1: **Baseline characteristics**

	Combined treatment (n=359)	Endometrial ablation alone (n=356)	Relative risk (95% CI)	p value
Hysterectomy (adjusted*)	15/342 (4%)	34/331 (10%)	0·43 (0·24–0·77)	0·0050
Missing data	17	25	..	..
Hysterectomy, per protocol (adjusted*)	8/275 (3%)	26/289 (9%)	0·32 (0·15–0·70)	0·0040
Mean time to hysterectomy, months	9·5 (6·8)	10·0 (6·1)	..	..
Reason for hysterectomy†				
Abnormal uterine bleeding	11/15 (73%)	22/34 (65%)	..	..
Cyclical pelvic pain	3/15 (20%)	12/34 (35%)	..	..
Other	4/15 (27%)	6/34 (18%)	..	..
Other subsequent treatment				
Re-ablation	0	1 (<1%)	NA	NA
Missing data	18	29	..	..
Pharmacological treatment*	20 (6%)	51 (16%)	0·37 (0·23–0·61)	0·0010
Oral hormonal medication	13 (4%)	41 (13%)	0·30 (0·17–0·54)	0·0010
Tranexamic acid	6 (2%)	16 (5%)	0·35 (0·14–0·89)	0·027
Gonadotropin-releasing hormone agonist	3 (1%)	4 (1%)	0·71 (0·16–3·14)	0·65
Missing data	23‡	39‡	..	..
LNG-IUS removal or expulsion	70/310 (23%)§	5/15 (33%)¶	..	..
Missing data	49	0	..	..
Time to LNG-IUS removal, months	3 (0–11)	6 (1–6)	..	..
Reason for removal*	..	..	..	..
Side-effects of LNG-IUS	33/70 (47%)	2/5 (40%)	..	..
Abnormal uterine bleeding	8/70 (11%)	0	..	..
Cyclical pelvic pain	6/70 (9%)	1/5 (20%)	..	..
Perforation in uterine wall	2/70 (3%)	0	..	..
Other	23/70 (33%)	2/5 (40%)	..	..
Spontaneous expulsion of LNG-IUS	6/70 (9%)	0	..	..
Re-insertion of LNG-IUS	2/70 (3%)	0	..	..
Later insertion of LNG-IUS after ablation¶	0	8/310 (3%)	..	..

Data are n (%), n/N (%), median (IQR), or mean (SD). Analysis was based on the modified intention-to-treat population (unless otherwise specified). LNG-IUS=levonorgestrel-releasing intrauterine system. NA=not applicable. *The primary outcome was adjusted for stratification factors (age and pre-existing dysmenorrhoea); crude analysis showed similar results. †More than one reason per participant was possible. ‡Data missing or misfiled. §Data missing or NA. ¶Deviation from allocated treatment.

Table 2: **Subsequent intervention within 24 months of follow-up**

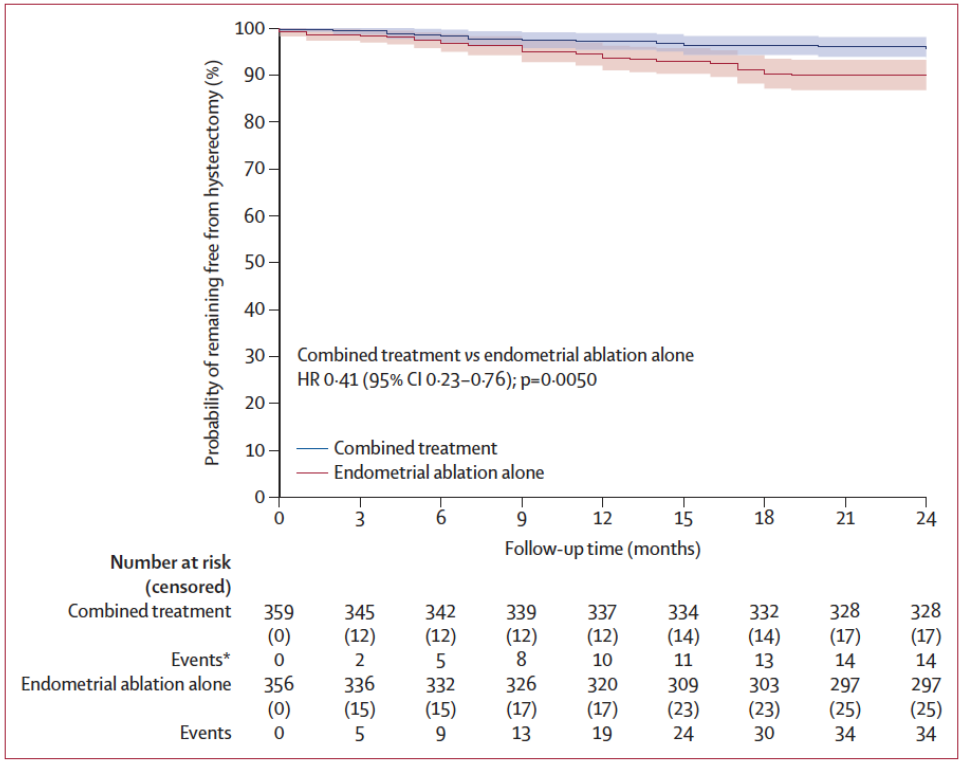


Figure 2: **Kaplan–Meier plot for time to hysterectomy**
HR=hazard ratio. *Deviation from number in intention-to-treat analysis due to one hysterectomy conducted 2 days after the 24-month follow-up (but within the prespecified margin of 1 month for inclusion in analysis).

	6 months	p value	12 months	p value	24 months	p value
Amenorrhoea						
Combined treatment	176/300 (59%)	..	155/274 (57%)	..	158/257 (61%)	..
Endometrial ablation alone	129/280 (46%)	..	128/257 (50%)	..	126/217 (58%)	..
Relative risk (95% CI)	1·27 (1·09–1·49)	0·0030	1·14 (0·97–1·33)	0·12	1·06 (0·91–1·23)	0·45
PBAC <75						
Combined treatment	260/296 (88%)	..	238/268 (89%)	..	235/252 (93%)	..
Endometrial ablation alone	213/275 (77%)	..	198/252 (79%)	..	185/212 (87%)	..
Relative risk (95% CI)	1·14 (1·05–1·23)	0·0010	1·13 (1·05–1·22)	0·0010	1·06 (1·00–1·13)	0·044
Cyclical pelvic pain						
Combined treatment	68/299 (23%)	..	60/274 (22%)	..	44/254 (17%)	..
Endometrial ablation alone	71/280 (25%)	..	71/256 (28%)	..	54/215 (25%)	..
Relative risk (95% CI)	0·90 (0·67–1·20)	0·46	0·79 (0·59–1·06)	0·12	0·69 (0·48–0·98)	0·040
Non-cyclical pelvic pain						
Combined treatment	41/299 (14%)	..	42/274 (15%)	..	36/255 (14%)	..
Endometrial ablation alone	39/280 (14%)	..	42/256 (16%)	..	25/215 (12%)	..
Relative risk (95% CI)	0·98 (0·66–1·48)	0·94	0·93 (0·63–1·38)	0·73	1·21 (0·75–1·96)	0·43

Data are n/N (%), unless otherwise specified. Analysis was based on the modified intention-to-treat population. PBAC=Pictorial Blood Assessment Chart.

Table 3: **Secondary outcomes: amenorrhoea, persistent vaginal bleeding, and cyclical and non-cyclical pelvic pain**

	Combined treatment (n=359)	Endometrial ablation alone (n=356)
Post-procedure complications within 6 weeks*	10/329 (3%)	7/320 (2%)
LNG-IUS perforation or migration	2/329 (1%)	..
Endometritis	5/329 (2%)	3/320 (1%)
Urinary tract infection	1/329 (<1%)	1/320 (<1%)
Pelvic inflammatory disease or tubo-ovarian abscess	2/329 (1%)	3/320 (1%)
Required treatment*		
Antibiotic treatment	9/10 (90%)	6/7 (86%)
Pain medication	4/10 (40%)	4/7 (57%)
Hospitalisation	4/10 (40%)	2/7 (29%)
LNG-IUS removal	5/10 (50%)	..
Side-effects of LNG-IUS within 24 months*		
All	155/256 (61%)	6/9 (67%)†
Bleeding	58/256 (23%)	1/9 (11%)
Tender breasts	64/256 (25%)	3/9 (33%)
Pelvic pain	84/256 (33%)	4/9 (44%)
Headache	64/256 (25%)	3/9 (33%)
Mood swings	78/256 (30%)	3/9 (33%)
Vaginal discharge	49/256 (19%)	2/9 (22%)
Other	53/256 (21%)	3/9 (33%)
Removal of LNG-IUS required	37/256 (14%)	1/9 (11%)
Serious adverse events within 24 months‡	28	26
Number of participants with one or more serious adverse events§	27/346 (8%)	26/327 (8%)
Related to study procedure	15	10
Not related to study procedure	13	16
Missing data	13	29

Data are n or n/N (%). Analysis was based on the modified intention-to-treat population. LNG-IUS=levonorgestrel-releasing intrauterine system. *More than one response per participant was possible. †Deviation from allocated treatment. ‡A more detailed overview is provided in the appendix (pp 5–6). §Relative risk 0·98 (95% CI 0·59–1·65; p=0·94).

Table 4: **Post-procedure complications, side-effects, and serious adverse events**

Implications of all the available evidence

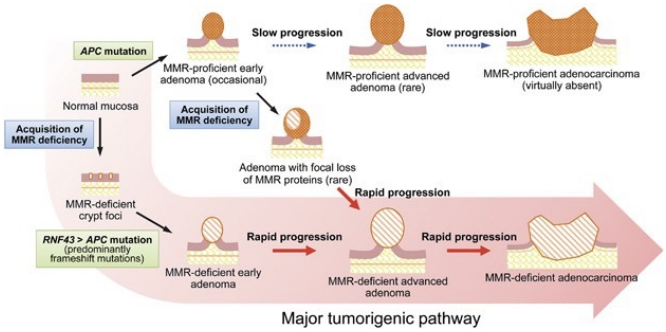
Together with existing literature, the results of this randomised trial support the adoption of a combined treatment strategy for heavy menstrual bleeding that has the potential to substantially reduce the need for hysterectomy. These findings provide robust evidence to inform clinical counselling for patients with heavy menstrual bleeding and to support shared decision making aimed at optimising patient-centred care. Future research should focus on cost-effectiveness and long-term outcomes beyond 2 years.

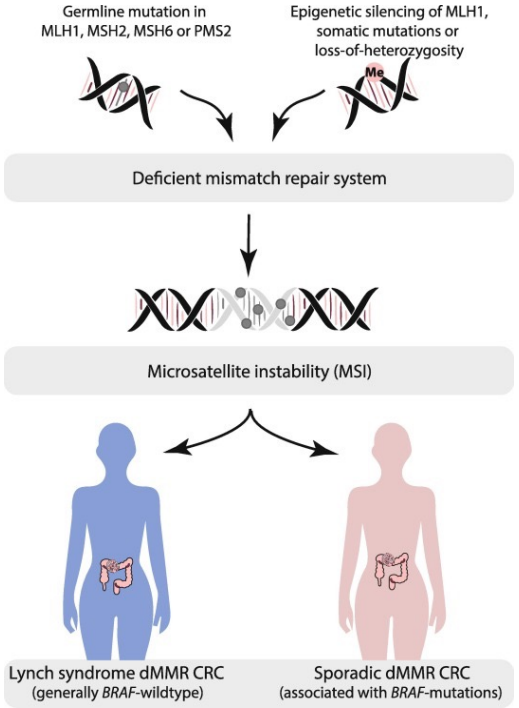
Mangelhafte DNA-Mismatch-Reparatur bei Darmkrebs (dMMR oder MSI-H Kolonkarzinom) bedeutet, dass den Tumorzellen ein wichtiges Enzymsystem zur Korrektur von Kopierfehlern in der DNA fehlt. Dies führt zu einer extrem hohen Anzahl von Mutationen (Hypermutation). Obwohl diese Krebsart dadurch aggressiv wachsen kann, macht genau diese Eigenschaft sie zu einem idealen Ziel für moderne **Immuntherapien**.

Dieses biologische Merkmal betrifft etwa 10–15 % aller Fälle von Dickdarmkrebs.

Normalerweise reparieren die Mismatch-Repair-Proteine (vor allem *MLH1, MSH2, MSH6* und *PMS2*) Fehler, die bei der Zellteilung entstehen. Fällt dieses System aus (defizient = dMMR):

- Entstehen unzählige Genmutationen in sogenannten Mikrosatelliten (daher der Name Mikrosatelliteninstabilität-High / MSI-H).
- Bildet der Tumor veränderte, Fremdeiweiße (Neoantigene).
- Erkennt das Immunsystem den Tumor dadurch als „fremd“ und wandert massiv in das Tumorgewebe ein. Krebszellen blockieren diese Immunzellen jedoch – eine Blockade, die medizinisch gelöst werden kann.





Microsatellite instability and checkpoint

Disease-free survival and overall survival after neoadjuvant immunotherapy in mismatch repair-deficient colon cancer in the Netherlands: results of the single-arm, multicentre, phase 2, NICHE-2 trial

Background Neoadjuvant immune checkpoint blockade induces high pathological response rates in patients with locally advanced mismatch repair-deficient (dMMR) colon cancer, yet long-term survival outcomes have not been established. Previously, we reported safety (a primary endpoint) and pathological response (a secondary endpoint) data from the NICHE-2 trial. Here, we report the primary efficacy endpoint of 3-year disease-free survival and the exploratory endpoint of 5-year overall survival.

Methods In this single-arm, multicentre, phase 2, NICHE-2 trial, patients with previously untreated, clinical stage 2 or 3, resectable dMMR colon cancer received a single dose of intravenous ipilimumab (1 mg per kg) on day 1, and two doses of intravenous nivolumab (3 mg per kg) on days 1 and 15, followed by surgery in one of the six participating hospitals in the Netherlands. Here, we report the independent primary efficacy endpoint of 3-year disease-free survival (time from surgery until disease recurrence or death from any cause) and the secondary endpoint of circulating tumour DNA (ctDNA) analysis. Overall survival (time from study enrolment until death from any cause) is reported as an exploratory post-hoc analysis. All endpoints were assessed in the per-protocol population (patients who met the eligibility criteria and received at least one cycle of therapy). The study is registered with ClinicalTrials.gov, NCT03026140, and has completed accrual.

Findings From July 4, 2017, to July 18, 2022, 123 patients were screened, of whom 115 were treated and 111 were included in the per-protocol population. At the data cutoff (June 19, 2026), the postoperative median follow-up was 58·7 months (IQR 49·0–72·9). The 3-year disease-free survival was 100% (97·5% CI 100–100). After a median follow-up of 60·4 months (IQR 50·6–74·1), calculated from time of study enrolment, the 5-year overall survival was 100% (95% CI 100–100). In patients with available plasma samples, ctDNA was detected in 99 (92%) of 108 patients at baseline, and ctDNA clearance was observed in 44 (45%) of 98 patients after the first cycle in week 2 and in 80 (82%) of 97 patients after the second cycle before surgery. In patients with a pathological near-complete response and complete response, presurgery ctDNA clearance was observed in 19 (70%) of 27 patients and 60 (92%) of 65 patients, respectively. Assessment for minimal residual disease after surgery revealed that all patients were ctDNA negative.

Interpretation In patients with locally advanced dMMR colon cancer, treatment with ipilimumab and nivolumab before surgery resulted in a 3-year disease-free survival and 5-year overall survival of 100%. These findings support neoadjuvant nivolumab plus ipilimumab as a potential standard of care for patients with locally advanced dMMR colon cancer.

Funding Bristol Myers Squibb.

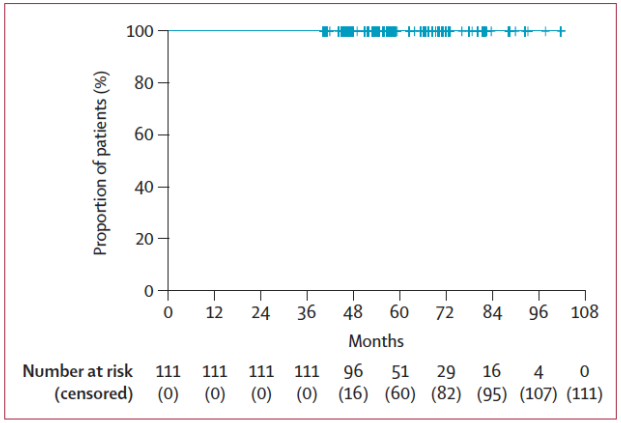


Figure 1: **Kaplan–Meier estimates of disease-free survival**
Time to event was calculated from date of surgery to the date of recurrence or death from any cause. Tick marks indicate data censored at the last moment the patient was known to be disease-free and alive. 3-year disease-free survival was 100% ([97·5% CI 100–100]; one sample log-rank test p<0·0001).

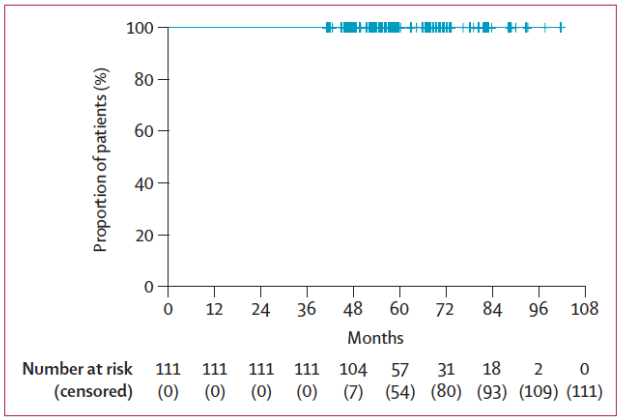


Figure 2: **Kaplan–Meier estimates of overall survival**
Time to event was measured from date of enrolment to date of death from any cause. Tick marks indicate data censored at the last moment the patient was known to be alive. 5-year overall survival was 100% (95% CI 100–100).

	ctDNA negative	ctDNA positive	ctDNA missing	Total
All patients (n=108)*				
Baseline	9 (8%)	99 (92%)	0	108
Dynamics in patients with detectable ctDNA at baseline				
Week 2	44 (45%)	54 (55%)	1	98
Presurgery	80 (82%)	17 (18%)	2	97
All patients with pathological response assessment (n=107)†				
Pathological complete response				
Baseline	7 (10%)	66 (90%)	0	73
Week 2	38 (58%)	27 (42%)	1	65
Presurgery	60 (92%)	5 (8%)	1	65
Near-pathological complete response				
Baseline	2 (7%)	27 (93%)	0	29
Week 2	5 (19%)	22 (81%)	0	27
Presurgery	19 (70%)	8 (30%)	0	27
Partial response				
Baseline	0	4 (100%)	0	4
Week 2	1 (25%)	3 (75%)	0	4
Presurgery	1 (33%)	2 (67%)	1	3
Non-response				
Baseline	0 (0%)	1 (100%)	0	1
Week 2	0 (0%)	1 (100%)	0	1
Presurgery	0 (0%)	1 (100%)	0	1

Of the 111 patients in the efficacy analysis, ctDNA could be evaluated in 108 patients (data were not available for two patients with pathological complete response and one patient with near-pathological complete response). All patients for whom ctDNA could be evaluated are included at the baseline timepoint. Subsequent timepoints (week 2 and presurgery) include only patients with detectable ctDNA at baseline. For some patients, plasma samples were not available for all timepoints, as indicated in the column ctDNA missing. Subgroups of pathological response include pathological complete response, defined as absence of residual viable tumour in both the primary tumour and lymph nodes; near-pathological complete response, defined as ≤10% residual viable tumour in the resection specimen; partial response, defined as ≤50% residual viable tumour in the resection specimen; and non-response, defined as ≥50% residual viable tumour in the resection specimen. ctDNA=circulating tumour DNA. *Contains all 108 patients for whom ctDNA could be evaluated. †ctDNA status is stratified by pathological response. The total number of patients stratified by pathological response equals 107, as pathological response was unavailable for one patient.

Table: **ctDNA status across treatment timepoints in all patients and by pathological response category**

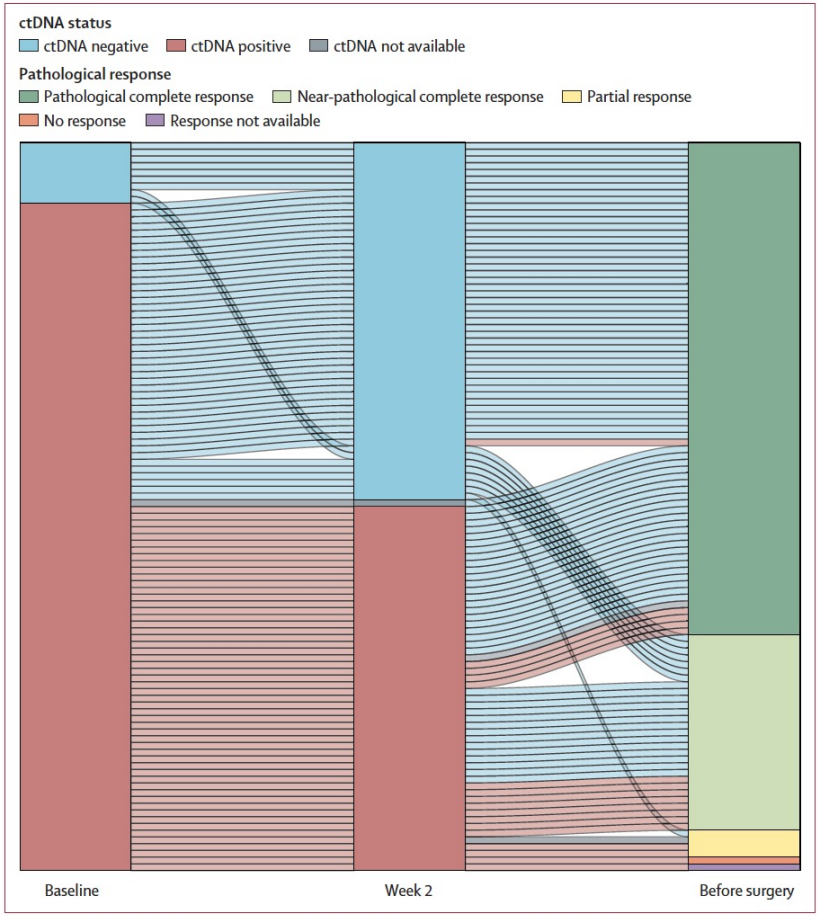


Figure 3: **Alluvial plot of ctDNA dynamics during neoadjuvant treatment**
Alluvial plot showing individual patient ctDNA dynamics across treatment time points for all patients for whom plasma samples were available at baseline. Each horizontal bar (flow) represents a single patient and depicts ctDNA status at baseline, after cycle 1 (week 2), and after cycle 2 (before surgery). Flows can be followed from left to right to track changes in ctDNA status for each patient over time. Flow colours indicate ctDNA positivity or negativity at the timepoint towards which the patient is transitioning. The vertical bars (strata) at each timepoint show ctDNA positivity or negativity at baseline and at week 2. At the presurgery timepoint, ctDNA status is linked to the patient's pathological response at surgery. ctDNA=circulating tumour DNA.

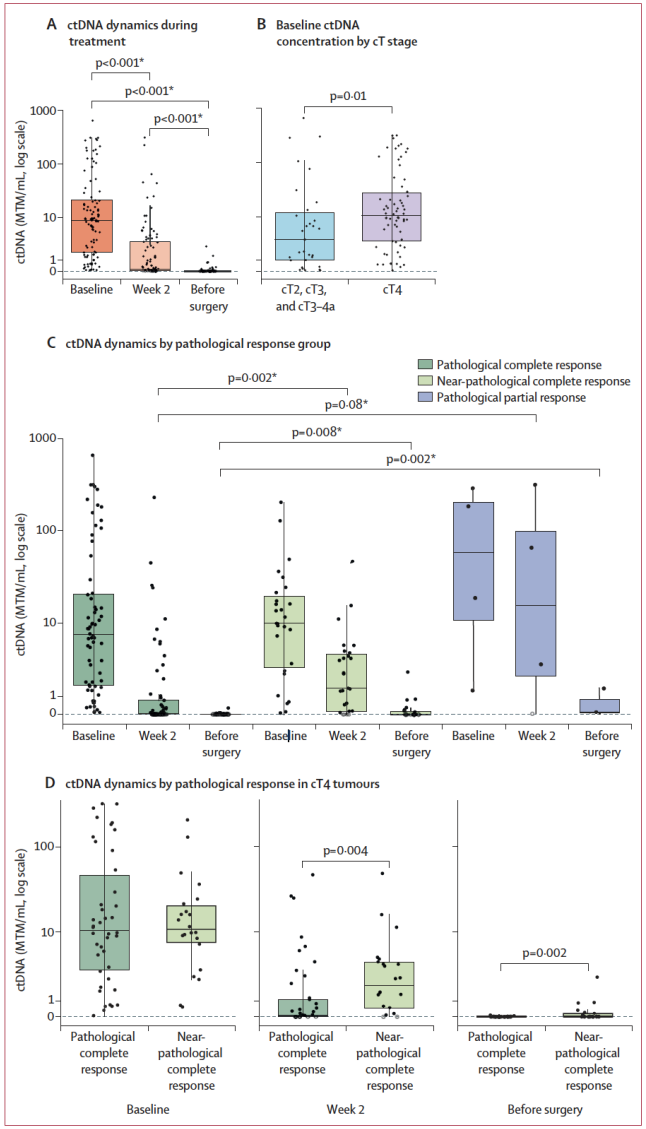


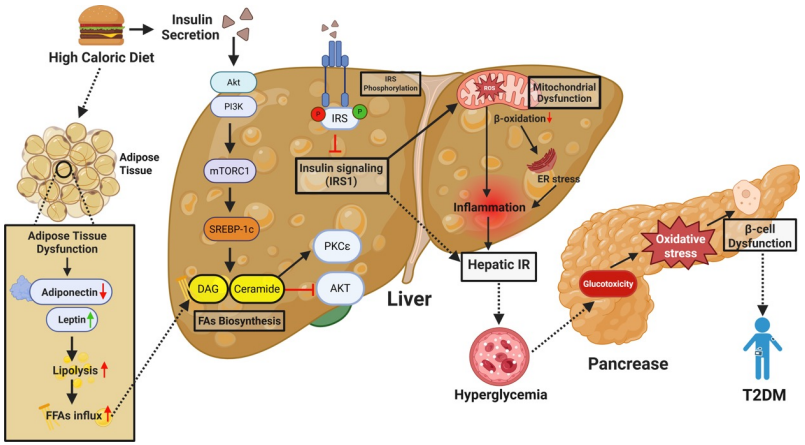
Figure 4: **ctDNA dynamics during neoadjuvant treatment**

(A) Longitudinal ctDNA concentration in all patients measured at baseline, after cycle 1 (week 2), and after cycle 2 at the presurgery timepoint. Overall differences across timepoints were assessed using the Friedman test, followed by pairwise Wilcoxon signed-rank tests. (B) Baseline ctDNA concentration stratified by clinical T stage based on radiographic staging at baseline. The cT2, cT3, and cT3–4a group includes patients classified as cT2, cT3, and cT3–4a (n=31). The cT4 group includes patients classified as cT4a and cT4b (n=66). A tumour was deemed cT3–4a when the radiologist could not differentiate between cT3 and cT4 disease. Consequently, these patients were assigned to the lower stage group (cT2, cT3 and cT3–4a). The cT4 group was reserved strictly for tumours that the radiologist unequivocally staged as cT4a or cT4b. Comparisons between groups were performed using the Wilcoxon rank-sum (Mann–Whitney *U*) test. (C) ctDNA dynamics according to pathological response category: pathological complete response (n=66), near-pathological complete response (n=27), and pathological partial response (n=4). Comparisons between response groups at each timepoint were first assessed using the Kruskal–Wallis test, followed by pairwise Wilcoxon rank-sum tests when appropriate. (D) ctDNA dynamics in cT4 tumours stratified by pathological response: pathological complete response (n=42) and near-pathological complete response (n=22). Comparisons between pathological complete response and near-pathological complete response at each timepoint were made using the Wilcoxon rank-sum test. ctDNA concentrations are shown on a logarithmic (log_{10}) scale. Dots represent individual patients. Boxplots indicate the median and interquartile range, with whiskers representing 1·5× the IQR. p values were adjusted for multiple testing using the Benjamini-Hochberg false discovery rate method for A, C, and D. Only (near) significant p values are shown. Patients with undetectable ctDNA at baseline (n=9) and one patient for whom pathological response was unavailable were excluded from this analysis. Due to the small sample size, comparisons involving the patient who had a pathological non-response (n=1) were not performed. ctDNA=circulating tumour DNA. MTM=mean tumour molecules. *Adjusted p values.

Implications of all the available evidence

This first report of a 3-year disease-free survival and 5-year overall survival of 100% in NICHE-2 supports the durability of previously reported pathological responses and reinforces neoadjuvant immune checkpoint blockade as a highly effective strategy for patients with locally advanced dMMR colon cancer. These results support neoadjuvant immune checkpoint blockade as a part of the standard of care, and the NICHE-2 approach has been included in guidelines such as the Dutch National Comprehensive Cancer Network guidelines, and has received several national regulatory approvals for the treatment of patients with locally advanced dMMR colon cancer.

Die **Metabolisch assoziierte Fettlebererkrankung** (offiziell als MASLD für *Metabolic dysfunction-associated steatotic liver disease* bezeichnet, früher bekannt als NAFLD) ist eine chronische Erkrankung, bei der sich **übermäßig viel Fett in den Leberzellen einlagert (Steatose > 5 %)**, gekoppelt mit mindestens einem metabolischen Risikofaktor wie Übergewicht oder Typ-2-Diabetes. Sie gilt als die häufigste chronische Lebererkrankung weltweit und betrifft fast ein Drittel der Weltbevölkerung.



Biomarker werden je nach Stadium der Erkrankung (Verfettung, Entzündung oder Vernarbung) in verschiedene Kategorien eingeteilt:

1. Steatose-Biomarker (Erkennung der Leberverfettung)
Diese Marker dienen dem Erstscreening, um festzustellen, ob überhaupt eine Fettleber vorliegt.

2. Steatohepatitis-Biomarker (Erkennung von Entzündung / MASH)
Wenn die reine Fettleber in eine entzündliche Form (MASH) übergeht, werden spezifische Marker im Blut messbar.

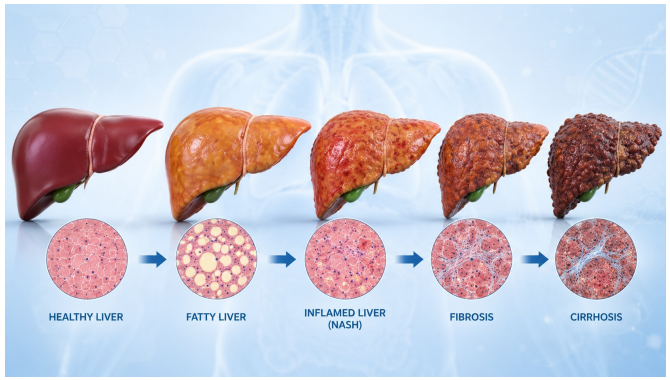
3. Fibrose-Biomarker (Erkennung von Vernarbung / Zirrhose)
Das Ausmaß der Fibrose (Vernarbung) bestimmt das Risiko für Folgeerkrankungen. Hierzu existiert eine klare Abstufung in der Diagnostik.

How MASH Is Actually Evaluated

Diagnosing and staging MASH typically requires a multi-step approach:

- **Blood Tests:** Checking liver enzymes (like ALT and AST) and calculating risk scores such as the **FIB-4 index** to assess the likelihood of liver scarring (fibrosis).
- **Specialized Imaging:** Using tools like **FibroScan** (vibration-controlled transient elastography) to measure liver stiffness and fat content, or MRI-based scans.
- **Liver Biopsy:** Considered the gold standard and definitive way to diagnose MASH by directly examining a small liver tissue sample under a microscope for inflammation, ballooning, and fibrosis





Multimarker panels for MASH

Non-invasive tests in metabolic dysfunction-associated steatotic liver disease: the LITMUS prospective multicentre diagnostic accuracy study

Summary

Background The advent of regulatory-approved pharmacological treatments for metabolic dysfunction-associated steatotic liver disease (MASLD) calls for precise, non-invasive biomarkers that facilitate early diagnosis, support therapy selection, and aid clinical trial enrolment. The European multicentre LITMUS study aimed to evaluate the diagnostic performance of a broad range of non-invasive biomarkers for identifying patients with metabolic dysfunction-associated steatohepatitis (MASH), at-risk MASH, advanced fibrosis, and cirrhosis.

Methods In this prospective, multicentre, diagnostic accuracy study, adults with biopsy-confirmed MASLD were prospectively recruited across 13 countries in Europe and the USA. We assessed 12 single markers and 18 multimarker panels. The reference standard was centrally scored liver histology according to the non-alcoholic steatohepatitis Clinical Research Network Scoring System. Target conditions included MASH (Non-Alcoholic Fatty Liver Disease Activity Score ≥4 with ≥1 point per component), at-risk MASH (MASH plus significant fibrosis [fibrosis stage F≥2]), advanced fibrosis (F≥3), and cirrhosis (F4). Performance was evaluated by area-under-the-receiver operating characteristic curve (AUC), with the minimum acceptable criterion (MAC) of AUC higher than 0·80 to indicate potential biopsy replacement.

Findings Between Jan 1, 2018, and June 30, 2023, we analysed data from 1590 participants with centrally scored liver biopsies and at least one biomarker measurement; 609 (38%) had biopsy-confirmed at-risk MASH, 678 (43%) had MASH, 585 (37%) had advanced fibrosis, and 164 (10%) had cirrhosis. For detecting at-risk MASH, SomaSignal showed the highest diagnostic performance (AUC 0·83 [95% CI 0·80–0·85]), significantly exceeding MAC, whereas no other test reached the MAC for MASH only. For advanced fibrosis, SomaSignal showed the highest performance (AUC 0·92 [0·90–0·94]), followed by FibroMeter-VCTE (AUC 0·87 [0·83–0·92]), Agile 3+ and TSP2 (both AUC 0·84 [0·82–0·86]), and NIS4 (0·82 [0·80–0·85]). For cirrhosis, FibroMeter-VCTE showed the highest diagnostic performance (AUC 0·94 [0·90–0·97]) followed by SomaSignal (AUC 0·92 [0·90–0·94]), followed by Agile 3+ (0·88 [0·85–0·91]), Agile 4 (0·87 [0·84–0·90]), ADAPT (0·85 [0·81–0·88]), and ELF, LSM-VCTE, and TSP2 (all 0·84 [0·81–0·87]). Sequential two-step approaches using gamma-glutamyl transferase as a first-line test met the MAC for both advanced fibrosis and at-risk MASH.

Interpretation Although single markers resulted in variable and limited performance when compared to histology for detecting at-risk MASH, multimarker panels showed great potential, with a proteomic panel showing strong diagnostic performance. These findings could support the selection and implementation of non-invasive testing strategies in MASLD and inform future clinical guidelines, regulatory evaluation, and clinical trial design.

	Total (N=1590)	At-risk MASH (N=609)	MASH (N=678)	Advanced Fibrosis (N=585)	Cirrhosis (N= 164)
Age, years	53·39 (12·64)	56·53 (11·68)	55·69 (11·95)	58·93 (10·60)	61·01 (9·15)
Sex					
Male	815 (51%)	293 (48%)	332 (49%)	293 (50%)	76 (46%)
Female	775 (49%)	316 (52%)	346 (51%)	292 (50%)	88 (54%)
White ethnicity	1399 (88%)	537 (88%)	595 (88%)	521 (89%)	147 (90%)
BMI, kg/m²	35·55 (7·60)	34·92 (6·80)	34·96 (6·74)	34·13 (6·09)	33·89 (5·48)
Type-2 diabetes	765 (48%)	360 (59%)	388 (57%)	401 (69%)	121 (74%)
Hypertension	929 (58%)	391 (64%)	423 (62%)	403 (69%)	121 (74%)
ALT, U/L	40 (25–67)	50 (32–82·5)	51 (32–84)	44 (28–72·3)	41 (26–60·3)
AST, U/L	35 (25–52)	45 (33–64)	44 (32–64)	43 (32–63)	44 (33·3–64·8)
GGT, U/L	48 (28–97)	65 (37–119)	63 (35·3–116)	71 (40–136)	94 (53–170)
Albumin, g/dL	4·36 (4·10–4·60)	4·30 (4–4·60)	4·30 (4·02–4·60)	4·30 (4– 4·60)	4·12 (3·90–4·50)
Glucose, mmol/L	5·90 (5·11–7·30)	6·50 (5·50–8·39)	6·44 (5·44–8·29)	6·61 (5·60–8·49)	6·97 (5·56–9·04)
Total cholesterol, mmol/L	4·65 (3·94–5·45)	4·65 (3·90–5·50)	4·67 (3·90–5·50)	4·50 (3·75–5·17)	4·44 (3·81–5·20)
Triglyceride, mmol/L	1·72 (1·35–2·30)	1·90 (1·41–2·48)	1·89 (1·42–2·44)	1·77 (1·39–2·37)	1·74 (1·31–2·34)
Platelet, 10⁹/L	233 (190–279)	222 (182–270)	227 (185–271)	213 (166–257)	178 (141–230)
Histology					
Steatosis					
0	183 (12%)	..	..	34 (6%)	14 (9%)
1	532 (34%)	78 (13%)	80 (12%)	182 (31%)	62 (38%)
2	505 (32%)	284 (47%)	320 (47%)	219 (37%)	53 (32%)
3	370 (23%)	247 (41%)	278 (41%)	150 (26%)	35 (21%)
Lobular inflammation					
0	283 (18%)	..	..	32 (5%)	11 (7%)
1	1026 (65%)	418 (69%)	475 (70%)	388 (66%)	117 (71%)
2	260 (16%)	171 (28%)	183 (27%)	149 (25%)	34 (21%)
3	21 (1%)	20 (3%)	20 (3%)	16 (3%)	2 (1%)
Hepatocyte ballooning					
0	744 (47%)	..	..	107 (18%)	31 (19%)
1	569 (36%)	349 (57%)	405 (60%)	274 (47%)	69 (42%)
2	277 (17%)	260 (43%)	273 (40%)	204 (35%)	64 (39%)
Fibrosis stage					
0	197 (12%)	..	3 (<1%)	..	..
1	313 (20%)	..	66 (10%)	..	..
2	495 (31%)	217 (36%)	217 (32%)	..	..
3	421 (26%)	287 (47%)	287 (42%)	421 (72%)	..
4	164 (10%)	105 (17%)	105 (15%)	164 (28%)	164 (100%)
NAS score					
0	106 (7%)	..	..	12 (2%)	6 (4%)
1	163 (10%)	..	..	23 (4%)	6 (4%)
2	232 (15%)	..	..	34 (6%)	15 (9%)
3	311 (20%)	..	..	104 (18%)	29 (18%)
4	309 (19%)	201 (33%)	226 (33%)	145 (25%)	41 (25%)
5	274 (17%)	222 (36%)	258 (38%)	136 (23%)	34 (21%)
6	150 (9%)	143 (23%)	149 (22%)	31 (5%)	27 (16%)
7	42 (3%)	40 (7%)	42 (6%)	9 (2%)	6 (4%)
8	3 (<1%)	3 (<1%)	3 (<1%)	2 (<1%)	0

Continuous variables are shown as mean (SD) or median (IQR), categorical variables are shown as n (%). Sex was recorded from medical records as sex at birth. Ethnicity was self-reported and collected according to local site procedures. Percentages might not total 100% because of rounding. ALT=alanine aminotransferase. AST=aspartate aminotransferase. BMI=body-mass index. GGT=gamma-glutamyl transferase. MASH=metabolic dysfunction-associated steatohepatitis. NAS=non-alcoholic fatty liver disease activity score.

Table 1: **LITMUS participant characteristics**

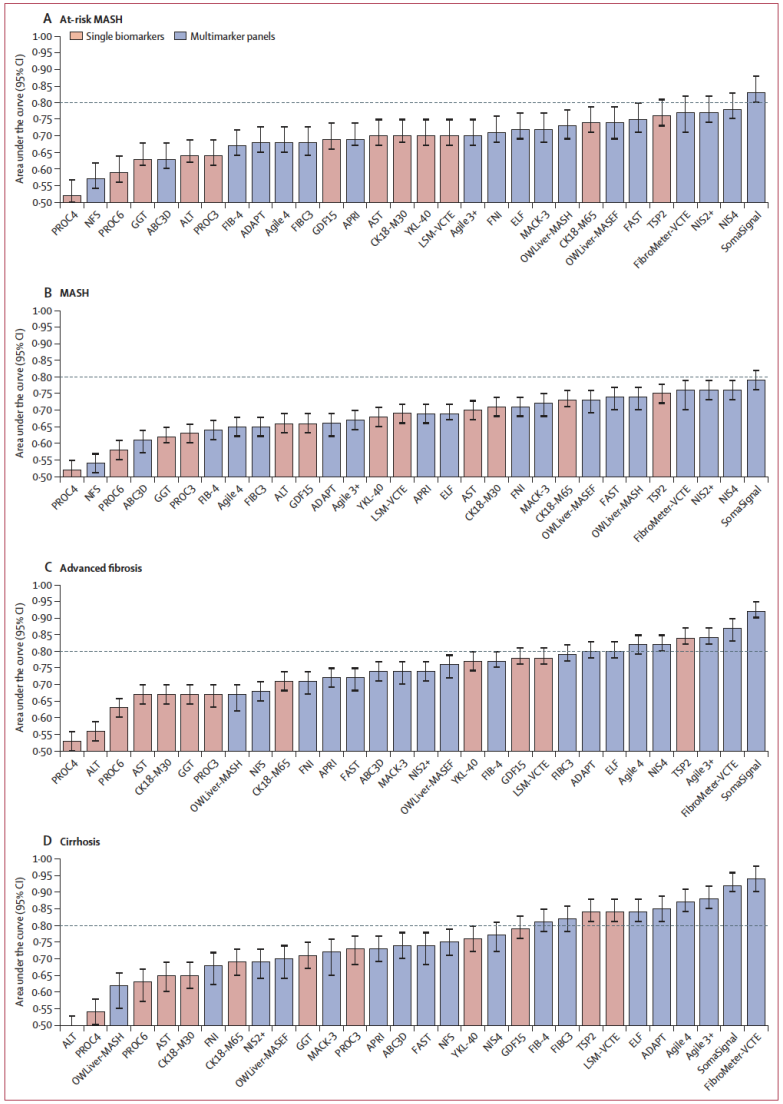


Figure 1: **Diagnostic performance of all markers in detecting at-risk MASH (A), MASH (B), advanced fibrosis (C), and cirrhosis (D)**
See appendix (pp 3, 52) for all definitions. MASH=metabolic dysfunction-associated steatohepatitis.

	At-risk MASH	MASH	Advanced fibrosis	Cirrhosis
Single markers				
ALT	0·68 (0·60–0·77)	0·68 (0·59–0·76)	0·60 (0·51–0·70)	0·51 (0·36–0·66)
AST	0·70 (0·61–0·78)	0·69 (0·61–0·77)	0·70 (0·62–0·79)	0·64 (0·51–0·78)
CK18-M30	0·74 (0·66–0·82)	0·74 (0·66–0·81)	0·69 (0·61–0·78)	0·62 (0·49–0·76)
CK18-M65	0·76 (0·68–0·83)	0·76 (0·69–0·83)	0·72 (0·64–0·80)	0·64 (0·50–0·78)
GDF15	0·75 (0·67–0·83)	0·71 (0·63–0·79)	0·80 (0·73–0·87)	0·79 (0·67–0·91)
GGT	0·62 (0·53–0·71)	0·63 (0·54–0·71)	0·61 (0·52–0·70)	0·54 (0·38–0·70)
PROC3	0·65 (0·56–0·74)	0·64 (0·56–0·73)	0·68 (0·59–0·78)	0·74 (0·58–0·90)
PROC6	0·63 (0·54–0·71)	0·61 (0·53–0·70)	0·67 (0·57–0·76)	0·49 (0·34–0·64)
PROC4	0·57 (0·48–0·66)	0·56 (0·47–0·65)	0·55 (0·45–0·64)	0·59 (0·43–0·74)
TSP2	0·73 (0·65–0·81)	0·74 (0·66–0·82)	0·87 (0·81–0·92)	0·84 (0·76–0·93)
YKL-40	0·68 (0·59–0·76)	0·67 (0·59–0·76)	0·76 (0·68–0·84)	0·65 (0·49–0·80)
LSM-VCTE	0·73 (0·65–0·81)	0·72 (0·64–0·80)	0·80 (0·73–0·88)	0·87 (0·80–0·93)
Multimarkers				
ABC3D	0·58 (0·50–0·67)	0·57 (0·48–0·66)	0·78 (0·70–0·85)	0·80 (0·69–0·91)
ADAPT	0·65 (0·57–0·74)	0·65 (0·57–0·74)	0·81 (0·75–0·88)	0·81 (0·68–0·94)
APRI	0·66 (0·57–0·75)	0·65 (0·57–0·74)	0·73 (0·64–0·81)	0·68 (0·58–0·78)
Agile 3+	0·66 (0·58–0·75)	0·66 (0·57–0·74)	0·83 (0·76–0·90)	0·86 (0·79–0·93)
Agile 4	0·65 (0·56–0·73)	0·65 (0·56–0·73)	0·80 (0·72–0·87)	0·83 (0·75–0·92)
ELF	0·71 (0·62–0·79)	0·70 (0·62–0·78)	0·80 (0·73–0·87)	0·86 (0·77–0·94)
FAST	0·76 (0·68–0·83)	0·76 (0·68–0·83)	0·79 (0·71–0·86)	0·78 (0·69–0·88)
FIBC3	0·63 (0·55–0·72)	0·63 (0·54–0·71)	0·83 (0·77–0·90)	0·81 (0·68–0·94)
FIB-4	0·62 (0·53–0·71)	0·61 (0·52–0·70)	0·73 (0·65–0·81)	0·73 (0·62–0·85)
FNI	0·74 (0·67–0·82)	0·72 (0·64–0·80)	0·76 (0·68–0·84)	0·71 (0·59–0·82)
NFS	0·50 (0·41–0·59)	0·52 (0·43–0·62)	0·66 (0·57–0·75)	0·68 (0·56–0·79)
NIS2+	0·79 (0·72–0·86)	0·79 (0·72–0·86)	0·77 (0·70–0·84)	0·63 (0·51–0·76)
NIS4	0·79 (0·72–0·86)	0·79 (0·72–0·86)	0·85 (0·79–0·91)	0·75 (0·64–0·86)
SomaSignal	0·84 (0·78–0·90)	0·82 (0·76–0·89)	0·91 (0·87–0·96)	0·90 (0·83–0·97)

Data are AUC (95% CI). A full list of the definitions is provided in the appendix (pp 3, 52). AUC=area under the receiver operating characteristic curve. ALT=alanine aminotransferase. AST=aspartate aminotransferase. GGT=gamma-glutamyl transferase. MASH=metabolic dysfunction-associated steatohepatitis.

Table 2: **Head-to-head comparison of the diagnostic performance of biomarkers in a subset of 157 patients**

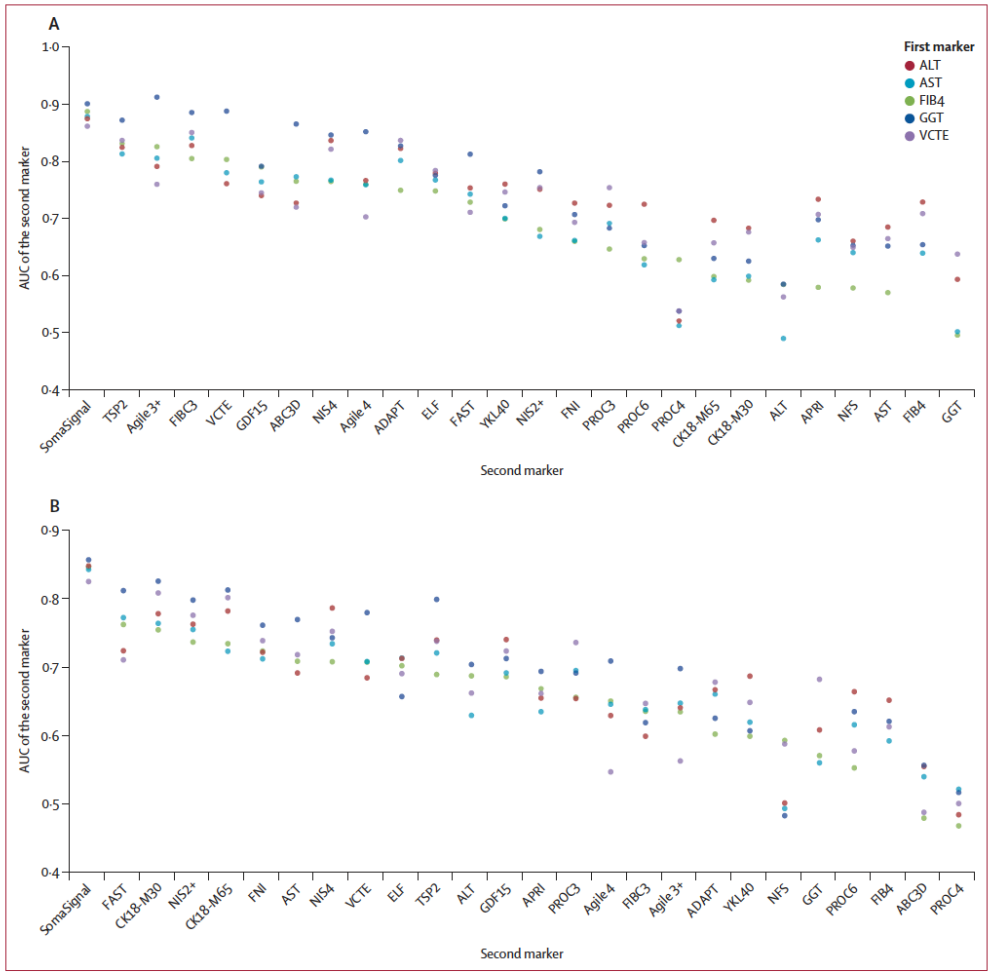


Figure 2: **Performance of biomarkers in different sequential testing scenarios for detecting advanced fibrosis (A) and at-risk MASH (B)**
Commonly used abnormal thresholds were applied to each first-line marker to determine when second-line testing was triggered as follows: AST higher than 30 U/L (n=90), ALT higher than 30 U/L (n=91), GGT higher than 55 U/L (n=66), FIB-4 of 1·3 (n=72), and VCTE higher than 9 kPa (n=74). Each dot represents the AUC of a second-line biomarker (x-axis) when applied after a first-line test (coloured by marker ALT, AST, GGT, FIB-4, or VCTE) in a subset of 157 participants with data on 26 biomarkers. ALT=alanine aminotransferase. AST=aspartate aminotransferase. AUC=area under the receiver operating characteristic curve. FIB-4=Fibrosis-4. GGT=gamma-glutamyl transferase. MASH=metabolic dysfunction-associated steatohepatitis. VCTE=vibration-controlled transient elastography.

	n	Threshold	PPV	Number of marker-positive participants undergoing biopsy (per 100)	Cirrhosis	Number of true positives confirmed by biopsy (per 100)	Number needed to test
SomaSignal	486	0·1	0·74 (0·66–0·80)	32	7	23	4
NIS2+	588	0·74	0·66 (0·59–0·73)	33	7	22	5
TSP2	606	90020·3	0·73 (0·64–0·80)	19	7	14	7
FAST	372	0·67	0·75 (0·64–0·84)	19	5	14	7
NIS4	506	0·77	0·75 (0·65–0·83)	19	6	14	7
OWLiver-MASH	169	0·75	0·79 (0·59–0·91)	14	3	11	9
ELF	738	10·49	0·70 (0·60–0·78)	14	5	10	10
OWLiver-MASEF	169	0·62	1·00 (0·76–1·00)	9	3	9	11
FNI	501	0·73	0·67 (0·55–0·78)	12	4	8	12
APRI	771	0·87	0·65 (0·54–0·76)	10	3	6	16
FIBC3	578	3·27	0·60 (0·47–0·71)	11	4	6	16
CK18-M65	652	1028·35	0·63 (0·50–0·74)	9	2	5	18
PROC3	611	60·83	0·60 (0·46–0·72)	9	3	5	19
ADAPT	579	11·7	0·56 (0·43–0·70)	9	3	5	21
AST	781	96·64	0·73 (0·58–0·86)	5	1	3	31
FIB-4	771	4·04	0·50 (0·33–0·64)	4	2	2	45
Agile 4	620	0·76	0·41 (0·20–0·64)	2	2	1	101
MACK-3	371	0·97	0·75 (0·38–1·00)	1	0	1	142
GDF15	651	4935·61	..	..	..	..	..

A full list of the definitions is provided in the appendix (pp 3, 52). The target condition is at-risk MASH. The selected threshold value from the development set was excessively high and did not align with the values present in the evaluation set. MASH=metabolic dysfunction-associated steatohepatitis. PPV=positive predictive value.

***Table 3*: Diagnostic screening performance of the markers at the selected thresholds in the evaluation set**

Implications of all the available evidence

Together with existing systematic reviews and previous LITMUS analyses, our findings indicate that several multimarker panels and fibrosis-focused tests have sufficient accuracy to identify patients with advanced fibrosis or cirrhosis and to support evidence-based pathways in specialised care. The results also support pragmatic sequential testing strategies that combine widely available first-line markers with more advanced second-line tests, improving efficiency while limiting unnecessary investigations. In clinical trial settings, selected biomarkers and thresholds can substantially reduce biopsy screen-failure rates, with potential implications for feasibility, patient burden, and costs. Future research should focus on validating these strategies across broader clinical populations, evaluating performance in diverse metabolic phenotypes, and refining thresholds to account for comorbidities. Continued prospective evaluation within the LITMUS programme will be essential to support regulatory qualification and routine integration into MASLD care.

Men's Health 1

Men's health: an intersectional and multilevel framework for understanding syndemic patterns of health

Men occupy a privileged position within gender power relations: the male body has been the default reference point for biomedical research and therapeutic development (with the historical exclusion of women from medical trials), and men dominate health services leadership and exercise well documented medical misogyny. Yet despite their privileged position, many aspects of men's health outcomes are neglected and undertheorised because they are not examined through an intersectional gender lens. Although consideration of gender and masculinity is important for understanding men's health, research thus far has focused predominantly on men's harmful health behaviours, overemphasising individual determinants of health, and a deficit-based approach. Little attention has been paid to the influence of structural determinants of men's health risks and vulnerabilities, or the gender-specific health outcomes of worsening social and economic inequalities. In this first paper of a *Lancet* Series on men's health, we present a conceptual framework for understanding men's health from an intersectional perspective, highlighting how structural, social, and commercial determinants of health, intersectionality, and syndemic theory can be combined to analyse men's health at different socioecological levels. We illustrate the framework using four selected case studies that show how the health outcomes of marginalised men are influenced by complex interactions. We provide a working definition of men's health that reflects existing literature and builds on the conceptual framework and case studies. Promotion of gender justice and health equity requires moving beyond one-dimensional approaches that construct men as problematic individuals, and towards better understanding and action on the broader set of power systems and structural determinants underpinning men's health.

Key messages

- The paradox of men's health—that men are privileged in gendered power relations, but their life expectancy and disability-adjusted life-year outcomes are generally poor compared with those of women—remains underexplored, and gender mainstreaming efforts have rarely explicitly included men's health.
- Much of the existing research on men's health has focused on hegemonic masculinities in isolation and paid insufficient attention to the influence of other intersecting systems of power and structural, social, and commercial determinants on men's health outcomes (explored in more detail in the second paper of this Series).
- We present a conceptual framework for understanding men's health that integrates structural, social, and commercial determinants of health with intersectionality and syndemic theory to show how the health experiences of marginalised men are shaped by complex interactions at different socioecological levels. We illustrate key aspects of the framework with four case studies, selected on the basis of their representation of different geographical locations, health conditions, and manifestations of men's marginality.
- Across different global contexts, historical and ongoing social and economic marginalisation and precarity interact with hegemonic masculinities to create clusters of poor health and wellbeing outcomes for groups of men disadvantaged by class, race, nationality, disability, and gender expression, sexuality, or both.
- Coordinated action at multiple levels on multiple systems of power is needed to address the determinants of men's health and ultimately achieve gender justice and health equity for all (explored in more detail in the third paper of this Series).

Men's Health 2

A global men's health epidemiology within an intersectional framework

Males have lower life expectancies and greater disability-adjusted life-years (DALYs) than females, and particularly poor outcomes are seen among males in marginalised contexts. In this paper, we provide an epidemiological overview and highlight the intersectional nature of men's health. We analyse mortality and DALYs data from the 1990–2023 Global Burden of Diseases, Injuries, and Risk Factors Studies to illustrate our intersectional framework and draw attention to how health varies in men and to show key themes. Conditions that contribute most to the poor health of males include non-communicable diseases (eg, cardiovascular diseases and cancers), substance use, suicide, injuries (eg, road traffic incidents and interpersonal violence), and respiratory infections (eg, tuberculosis and COVID-19). Although cardiovascular disease and cancer make the largest contributions to men's higher mortality rates, determinants of health such as violence and war, migration, economic stagnation, and labour market changes due to automation and new technologies will disproportionally affect their health in the future. Injuries, violence, and other external morbidity causes often occur at a young age and in unequal distributions across the sexes, making a large contribution to DALYs. Although biology plays a role, the pattern of many diseases contributing to health differences reflects the intersection of health behaviours, shaped by patriarchy, ideas of masculinity, and structural drivers (including commercial determinants of health); many of these are preventable. Although improvements in some health behaviours are seen, exceptions occur in marginalising social conditions (eg, incarcerated men, men experiencing homelessness, men with mental illnesses, men with substance use disorders, men with low income, men who have sex with men, and those who are gender non-conforming). Multiple data sources detail men's shorter life expectancies and the drivers compared with women, but going beyond sex disaggregation remains challenging and is an urgent priority for research and health monitoring.

Key messages

- Differences in life expectancies and disability-adjusted life years (DALYs) exist between males (especially in marginalised contexts) and compared with females; these reflect intersectional inequalities and the gaps are either persisting or increasing in most countries
- Conditions contributing to the greatest health differences (quantified using DALYs) between males and females include non-communicable diseases (ie, cardiovascular diseases and most cancers), liver failure, suicide and injuries (including road traffic incidents, falls, and violence), and respiratory infections (eg, tuberculosis and COVID-19)
- Poor health outcomes are often concentrated among marginalised and minoritised men, many of whom are experiencing intersecting social disadvantages
- The absence of of intersectionally disaggregated data currently limits systematic and comprehensive analyses, the understanding of which are needed to inform programmes and practices and develop robust approaches to improve men's health

Men's Health 3

Charting a course to men's health and wellbeing: applying a lens of power and politics to improve men's health outcomes

Despite long-standing evidence of poor health and life expectancy outcomes among men, particularly among men who are socially or structurally marginalised, men's health has generally received little and uneven attention in health policy and practice. Its gendered and intersectional aspects have been especially overlooked. This third paper in the *Lancet* Men's Health Series examines why men's health has received so little policy attention and proposes strategies to raise men's health on national and global agendas. We applied a gender lens to the 3-i theory-based framework and analysed how ideas, interests, and institutions shape the prioritisation of men's health within national and global policy agendas. We review the modest development of men's health policies and assess how power and politics, including the roles of a range of stakeholders from global and national health spaces, commercial actors, and civil society organisations, have shaped the construction of the problem as well as policy attention and framing, resource allocation, and interventions. The scarcity of attention paid to men's health on global and national agendas reflects how power operates through ideas and institutions which contribute to the conflation of gender with women, institutional inertia, and contested constructions of individual versus structural drivers of ill health. We highlight how this has created a space in which commercial actors, including the manosphere, can shape narratives and influence men's health in ways that align with commercial or ideological interests. We conclude by proposing politically informed strategies that recognise how power, institutional arrangements, and competing interests shape men's health policy within prevailing gender and structural orders. We identify entry points for advancing men's health equity and wellbeing that draw on empirical evidence and technical guidance, are grounded in political realities, and are consistent with a commitment to gender justice for all people.

Key messages

- Men—particularly those who live in socially and structurally marginalised environments—experience substantial premature mortality and avoidable disease burden, yet men's health remains largely absent from national and global health priorities. This situation reflects political choices about problem-framing and priority-setting rather than an absence of need.
- Globally, the first national men's health policy was not adopted until 2008, and only a small number of countries have followed the adoption since. In some countries where national policies and strategies have emerged, progress has been supported by civil society mobilisation and advanced through wider advocacy coalitions. Policy content, however, has been politically contested—particularly over whether responsibility lies with individual men or with the structural, environmental, and commercial determinants shaping risk exposure and access to their care.
- Policy attention to men's health is shaped by ideas, institutions, and interests, including the widespread conflation of gender with women, and path-dependent policy architectures contributing to institutional inertia within health systems and constraining the legitimacy of men's health as a governable policy issue.
- In the absence of sustained public health leadership and accountability, other powerful interests—including commercial actors and unregulated digital spaces such as the manosphere—have increasingly shaped and conflated narratives about men, masculinity, and grievance. Countervailing measures, including strengthened regulation of private-sector actors and support for civil society and public health stakeholders to promote gender justice and health equity, and contest harmful framings, are therefore crucial to sustaining rights-based, evidence-informed approaches to men's health.
- Progress on men's health is more likely to happen when it is framed as contributing to shared public goods (eg, safety, economic security, family wellbeing, and social cohesion) rather than as a siloed claim on public funds, and when it recognises the heterogeneity among men. Sustaining this progress requires embedding men's health within existing policy architectures (eg, universal health care, primary care, and non-communicable disease strategies), underpinned by clear institutional responsibilities and accountability mechanisms, and supported by cross-sector advocacy coalitions linking communities, civil society, researchers, and policy stakeholders across all stages of governance.

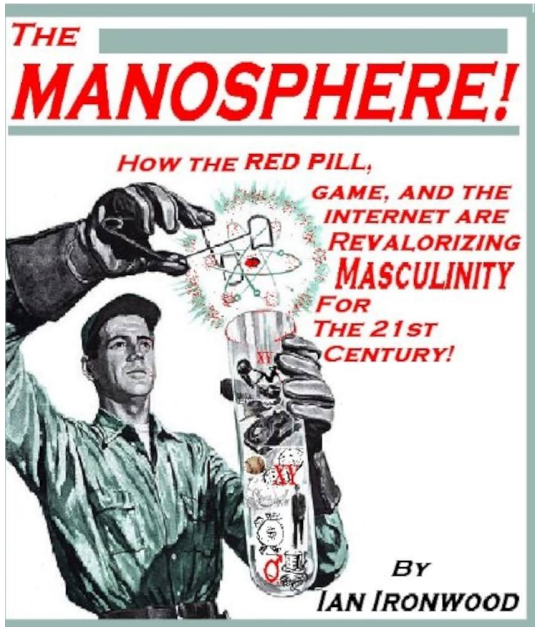
Reframing the manosphere: a public health response to a commercial ecosystem

The manosphere, a diffuse commercial ecosystem and loose collection of online communities united by shared beliefs about masculinity, misogyny, and male victimisation, is an under-recognised determinant of health harms. This network has been implicated in considerable health harms: widespread mental health impacts, especially in young people; violence against women, girls, and gender minorities; and delegitimising help-seeking in boys and men. In this Viewpoint, we argue that the manosphere is best understood and addressed as a public health problem.

Als **Manosphere** (deutsch *Mannosphäre*) bezeichnet man ein loses, internetbasiertes Netzwerk aus Blogs, Foren und Social-Media-Kanälen (u. a. TikTok, Instagram und YouTube), das sich um Themen wie Männlichkeit, Dating, Selbstoptimierung und Männerrechte dreht.







xeno-canto

Sharing bird sounds from around the world

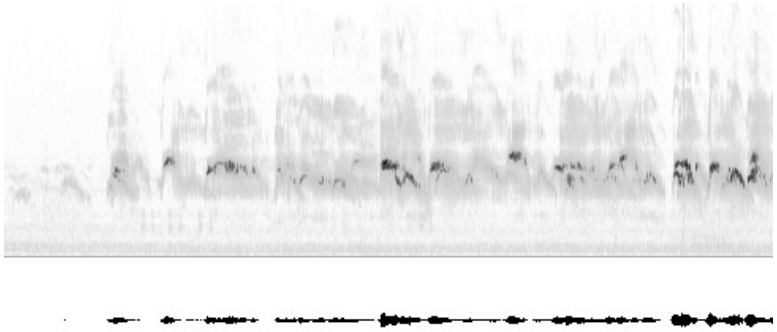


Xeno-canto (meaning "strange sound") is the world's largest crowdsourced, open-access online database of wildlife sounds, focusing primarily on birds, as well as bats, frogs, grasshoppers (orthoptera), and other land mammals.



Key Details

- **Launch & Purpose:** Launched on May 30, 2005, by Bob Planqué and Willem-Pier Vellinga, the platform aims to archive global wildlife recordings for researchers, birders, and the general public.
- **Scale:** It houses over **1.1 million recordings** covering more than **13,000 species** worldwide

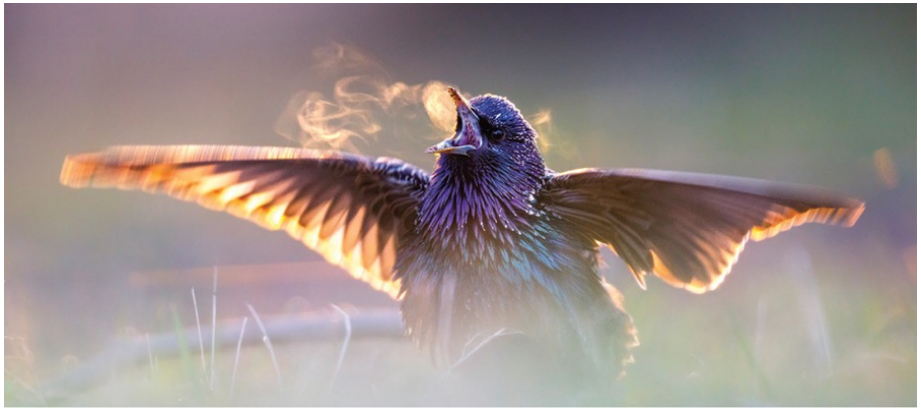


Key Analytical Methods

- **Dataset and Manual Annotation:** The researchers pulled audio recordings from **Xeno-canto** and manually annotated them into a dataset of ~70,000 bird vocal units. They compared these against a separate repository of over 15,000 human speech and song units spanning 52 languages.
- **Acoustic and Structural Metrics:** All frequency and duration values were log-transformed before normalization. The team evaluated specific patterns including:
    - **Frequency jumps:** Pitch intervals between notes (such as small pitch changes due to physiological constraints).
    - **Local isochrony:** Rhythmic regularity and predictable timing.
    - **Phrase-final elongation:** Extending the duration of the final element or phrase in a sequence (often tied to breathing patterns).
    - **Alternation:** Sequential ordering patterns of elements.
- **Principal Component Analysis (PCA):** They computed spectrotemporal modulations and measured the distance of each bird species in **PCA space** relative to the centroid of human speech and song.

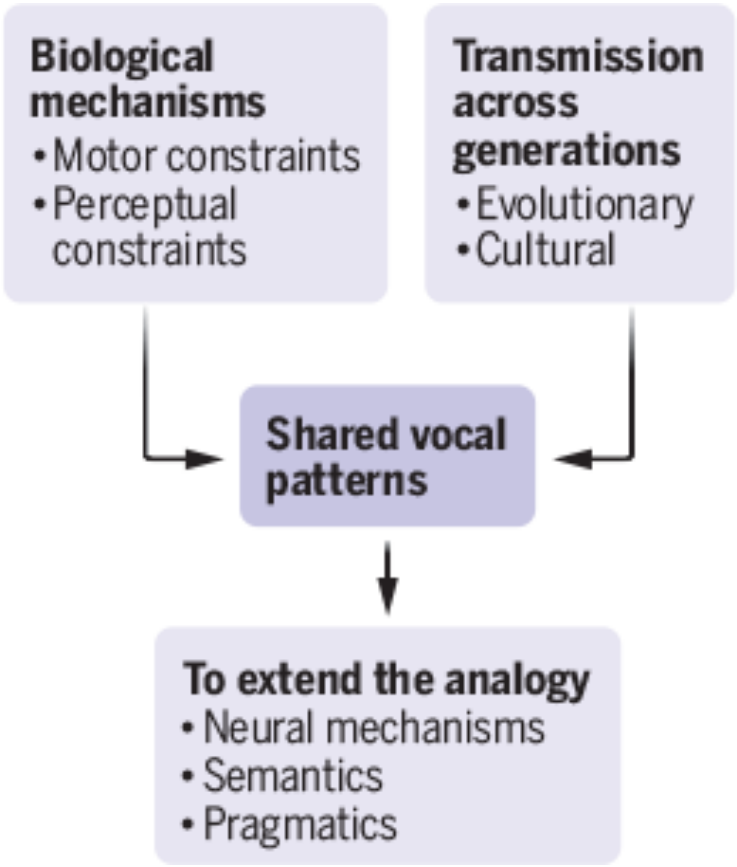


How comparable are bird and human sounds?



Many features of bird and human vocalizations are comparable—but some analogies lack evidence

James *et al*. compared songs from 367 bird species— including vocal learners (oscines and hummingbirds) and nonlearners (suboscines and nightjars)—with speech and song from 52 human languages. They analyzed the frequency, timing, duration, and loudness of these sound sequences, considering how closely related the species and languages are. Bird songs commonly contained small frequency changes between adjacent sounds, even spacing of the onsets of syllables within a song segment, and final sounds that were longer than those in the middle of a phrase. Frequency, duration, and loudness reversed direction less often in natural birdsong than in randomly reordered sound sequences. Because these patterns occur both in birds that are vocal learners and in nonlearners, their presence does not imply that the sounds were learned through imitation. James *et al*. found that the variation in the duration of individual sounds according to their position within a phrase resembled human song more than speech, whereas the combined variation of sounds across time and sound frequency was a feature that more closely resembled speech. These findings show that birdsong cannot simply be placed on a continuum from speech to music.



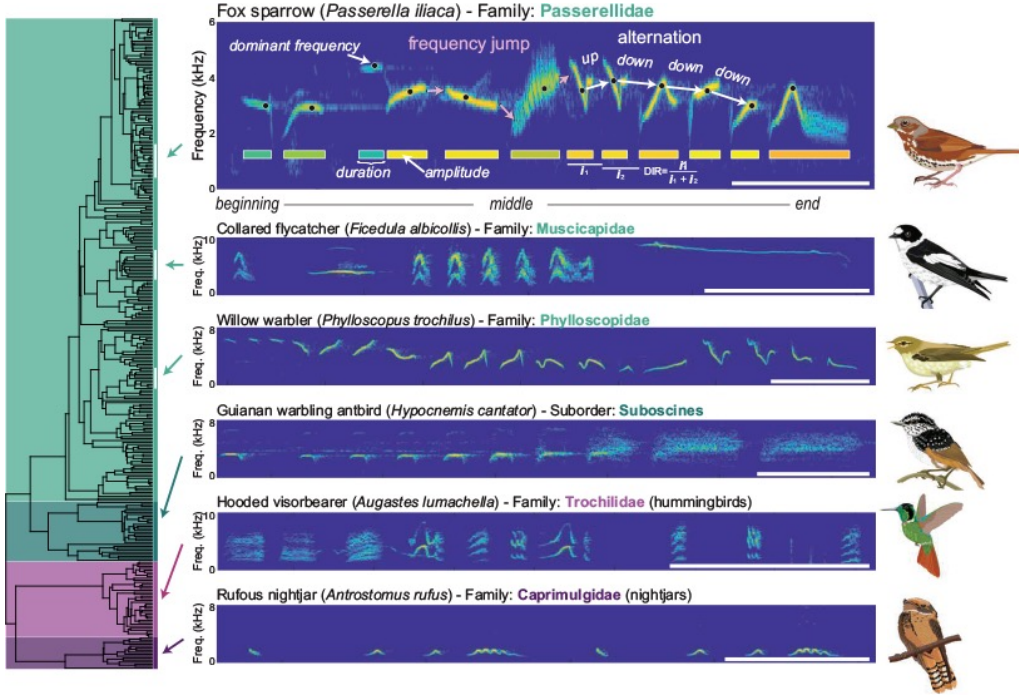
Singing similarities

Analogies between bird songs and human speech and song can be established on the basis of biological mechanisms and transmission processes. Notably, vocal learning is not a determinant of shared vocal patterns. Extending these analogies requires evidence beyond similarities in sound.

Pervasive patterns in bird songs resemble those in human speech and song and are independent of vocal learning

Bird songs are often described as analogs to human speech and songs, but expansive comparisons are necessary to determine analogy and mechanistic substrates. By analyzing global corpora consisting of 367 bird species (>74,500 vocal elements from ~5900 songs) within two clades of vocal learners (oscines and hummingbirds) and related nonlearners (suboscines and nightjars) and 52 human languages (>15,000 elements in >800 speech or song phrases), we revealed common patterns in bird songs that resemble prevalent patterns in human speech and song with variation in resemblance to speech or song. Vocal learning did not systematically affect acoustic patterning or similarity to human vocalizations. These data underscore the deep analogies between bird and human vocalizations and convergent motor mechanisms shaping communication.

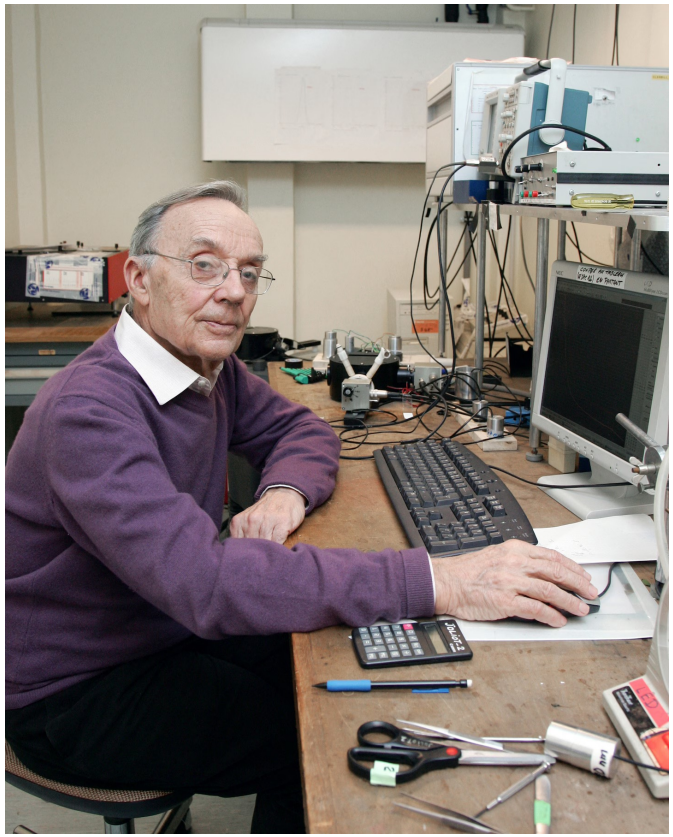
Analysis of acoustic features in the songs of passerines and Strisores. (**Left**) Phylogenetic tree used for analysis. (**Right**) Example spectrograms (frequency on the *y* axis, time on the *x* axis, color and lightness as amplitude) of bird songs. (**Top**) A spectrogram of one song rendition of a fox sparrow (*Passerella iliaca*) with annotations depicting the acoustic features we measured and analyses we conducted. Pink arrows depict our analysis of frequency jumps comparing the dominant frequency at the end (final 8 ms) of a syllable to the frequency at the beginning (initial 8 ms) of the next syllable. Black dots on each syllable indicate the dominant frequency of that syllable, and white arrows illustrate our analysis of alternation of frequency. Rectangles below each syllable indicate the duration (length) and amplitude (color and lightness) of each syllable. For positional variation, we compared feature values from across the beginning, middle, and end syllables. For rhythm, we analyzed the dyadic interval ratio by computing the ratio of adjacent interonset intervals throughout songs (i.e., i_1 and i_2). Note that all annotations are approximate and used for illustrative purposes only.



Discussion

We have documented that acoustic patterns prevalent in human speech and song are also common across the songs of hundreds of bird species, extending beyond oscines and integrating across two clades of vocal learners and nonlearners. Overall, birds demonstrated small frequency jumps, local isochrony, and phrase-final elongation regardless of vocal learning and clade, strongly suggesting that these vocal patterns represent “universals” in bird song. Further, because there were no or inconsistent effects of vocal learning, these data support motor origins underlying common vocal structure across birds and humans and suggest that these patterns might be prevalent in diverse taxa that rely on similar mechanisms of vocal production as well as in other motor sequences, including those that accompany vocalizations.

Born to a science dynasty, he broke away and made a photosynthesis breakthrough



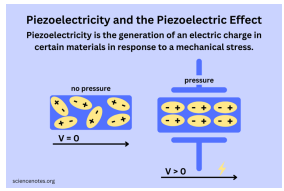
Born into a scientific dynasty that produced four Nobel laureates, including his grandparents, Marie and Pierre Curie, Pierre Joliot was the first researcher in his family to make the biological sciences his life's work.

As a pioneering French biophysicist, he walked a different path from his forebears, who conducted research into nuclear physics and physical chemistry. In choosing biology, he discovered how photosynthetic organisms split water to release oxygen.

Dr. Joliot died Oct. 10 in Paris. He was 94. His death was confirmed by the Curie Institute in a tribute on its website. The renowned research center in Paris was co-founded in 1909 as the Radium Institute by Dr. Joliot's maternal grandmother, Marie Curie.

Dr. Joliot was 3 when his parents, Irène and Frédéric Joliot-Curie, jointly won the 1935 Nobel Prize in chemistry for their discovery of artificial radioactivity.







Working at the Radium Institute, the couple bombarded nonradioactive substances, such as aluminum and magnesium, with alpha particles to induce radioactivity. They proved that radioactive isotopes could be inexpensively generated using the technique. Irène was the eldest of Marie and Pierre Curie's two daughters. Their other daughter, Ève, became a writer and pianist.

Dr. Joliot's grandparents shared the 1903 Nobel Prize in physics for their work involving "radiation phenomena," according to the Nobel Prize website. In 1911, Marie Curie won a second Nobel, this time in chemistry, for her discoveries of two radioactive elements, radium and polonium. She remains the only laureate to have won two Nobel Prizes in two scientific disciplines.

When he began doctoral studies in the mid-1950s, photosynthesis was only rudimentarily understood. What he discovered in a series of deceptively simple experiments answered one of the key questions in the cycle of life itself: how photosynthetic organisms split water to produce the very oxygen that sustains life on Earth.

"Pierre Joliot was one of the modern pioneers of photosynthesis research," said Robert Blankenship, a longtime friend and fellow member of the International Society of Photosynthesis Research. In 2013, the society honored Dr. Joliot with its Lifetime Achievement Award.

The Kok-Joliot Model & The "Four-Flash" Clock

Joliot's most celebrated achievement was elucidating how Photosystem II (PSII) splits water molecules to release oxygen. In his famous 1968 experiments, he exposed isolated chloroplasts to ultra-short, successive flashes of light and measured the precise oxygen output:

- **Period-Four Oscillation:** He discovered that oxygen release was not continuous but oscillated in a strict **period-of-four cycle**. Maximum oxygen yields always occurred after the 3rd flash, then the 7th, 11th, and so on.
- **The S-State Mechanism:** This discovery directly led to the formulation of the **Kok-Joliot Model** (developed alongside Bessel Kok). The model proved that the water-splitting complex acts like a biological battery, stepping through five distinct oxidation states (S_0 to S_4) by absorbing four successive photons of light before storing enough energy to execute the final chemical reaction that releases a molecule of O_2

