

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

The weekly Clinical Journal Club by Dr. Friedrich C. Luft

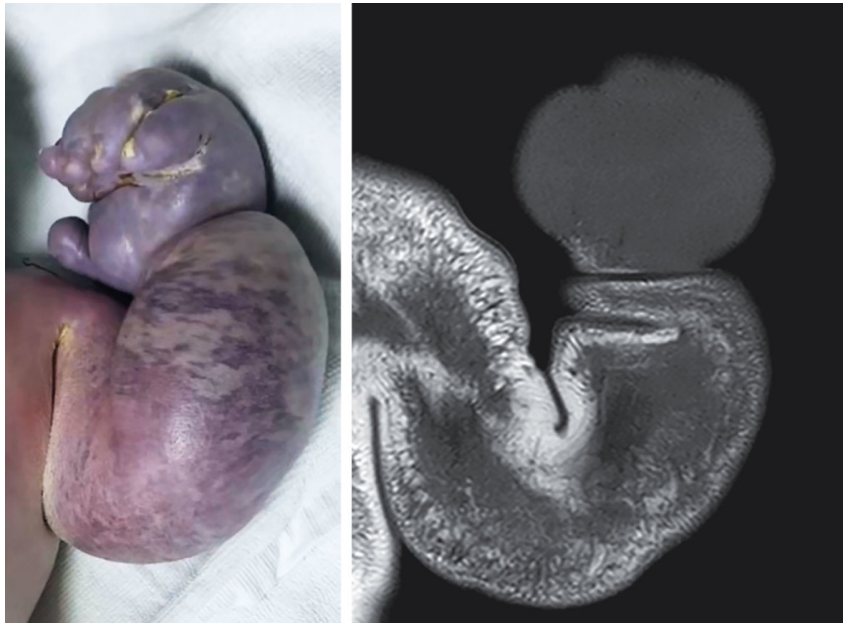
Usually every Wednesday 17:00 - 18:00



Klinische Forschung

Experimental and Clinical Research Center (ECRC) von MDC und Charité

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!](#)



Amniotic band sequence describes the cascade of events following early rupture of the amnion. Fetal body parts may project into the chorionic cavity, where they are at risk for deformation, constriction by fibrous amniotic bands, or amputation. The resulting abnormalities vary according to the timing, location, and severity of entrapment and may range from superficial constriction rings and distal edema to limb or digit defects.

A baby girl was noted to have severe swelling and discoloration of the left arm immediately after birth by cesarean section at 38 weeks' gestation. Prenatal ultrasonography at 28 weeks had shown soft-tissue swelling of the left arm of undetermined cause. Examination showed swelling, cyanosis, and limited movement of the left arm, shoulder, and chest. Two areas of constriction were present at the wrist and proximal forearm, although brachial and radial pulses remained detectable by Doppler ultrasonography. MRI showed two fibrous bands extending through the deep fascia. What is the most likely diagnosis?



Congenital amniotic band sequence

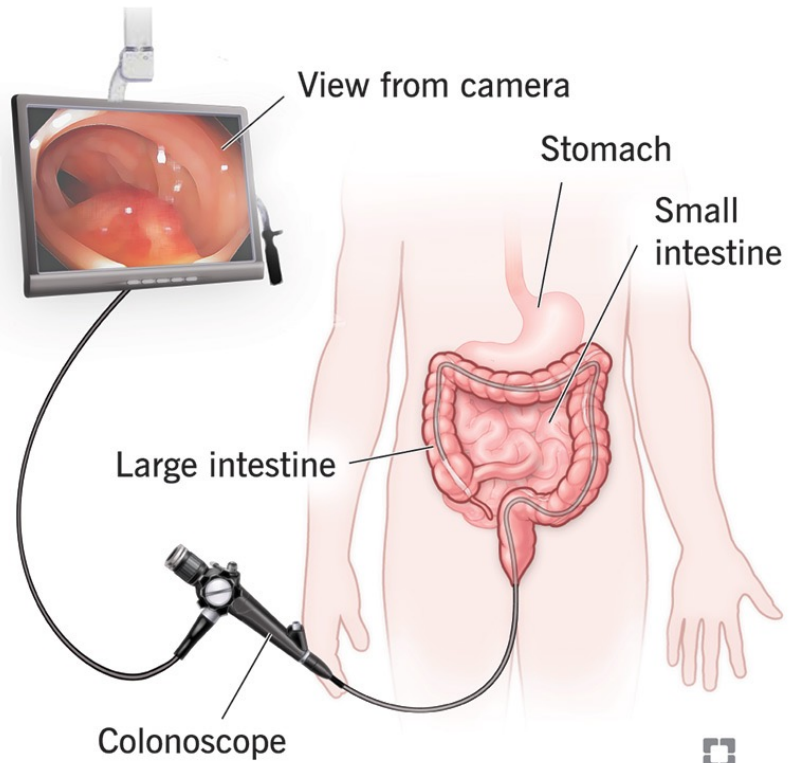
Congenital lymphedema

Klippel–Trenaunay syndrome

Neonatal compartment syndrome

Phlegmasia cerulea dolens due to upper-extremity venous thrombosis

Colonoscopy



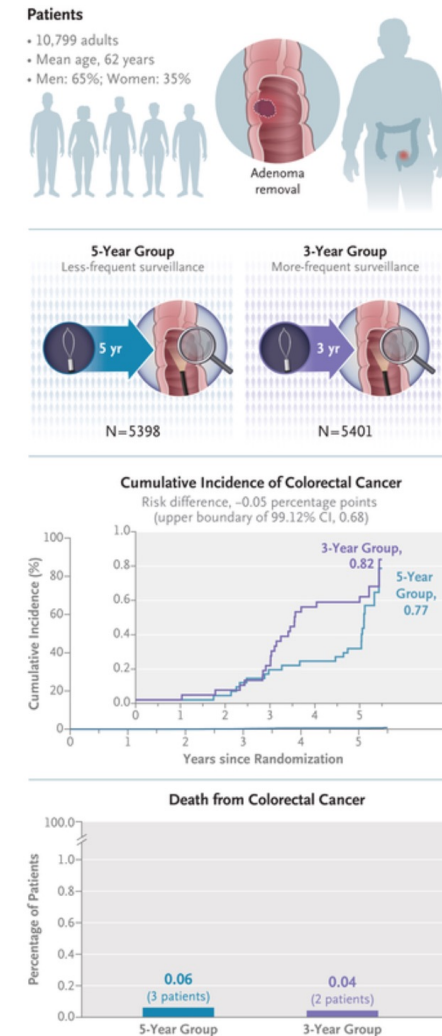
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Colonoscopy Intervals and Colorectal Cancer Incidence after Adenoma Removal

More evidence is needed to inform recommendations for intervals of colonoscopy surveillance after polyp removal.

In this ongoing noninferiority trial conducted in eight European countries, we randomly assigned patients with high-risk adenomas (defined as ≥ 1 adenoma with a diameter of ≥ 10 mm, high-grade dysplasia, or villous growth or 3 to 10 adenomas of any kind) to undergo a first colonoscopy at 5 years after polyp removal or at 3 years; surveillance at 3 years is currently recommended in guidelines. The 3-year group also underwent colonoscopy at 5 years. The primary end point is the cumulative incidence of colorectal cancer at 10 years, with a prespecified noninferiority margin of 0.7 percentage points for the upper boundary of the confidence interval for the difference between the two groups. Here, we report the results of an interim analysis conducted after 5.5 years of follow-up. Inverse probability weighting was used to account for missing data owing to nonparticipation in surveillance colonoscopy at 5 years. In this analysis, the incidence of colorectal cancer is reported with a one-sided 99.12% confidence interval; for the final analysis at 10 years, the plan is to calculate a 95.33% confidence interval to maintain an overall type I error of 5%.



After removal of polyps at colonoscopy, some patients are considered to be at high risk for new polyps or cancer. For patients with high-risk adenomas (defined as ≥ 1 adenoma with a diameter of ≥ 10 mm, high-grade dysplasia, or a villous growth pattern or 3 to 10 adenomas of any kind), current guidelines in the United States as well as international guidelines recommend frequent colonoscopies for surveillance, with the first surveillance colonoscopy at 3 years after polyp removal. However, the recommended intervals for surveillance are based on data from observational studies and two small, randomized trials with imprecise estimates, and the guidelines emphasize the need for long-term, high-quality, randomized trials.

Methods

Patients eligible for the EPoS trials were men and women 40 to 74 years of age who underwent colonoscopy with complete removal of polyps. Colonoscopies had to be performed with completed cecal intubation and adequate colonic cleansing, with a score on the Boston bowel preparation scale of at least 2 in all colonic segments; scores for each segment range from 0 to 3, with higher scores indicating better visualization.

Trial End Points

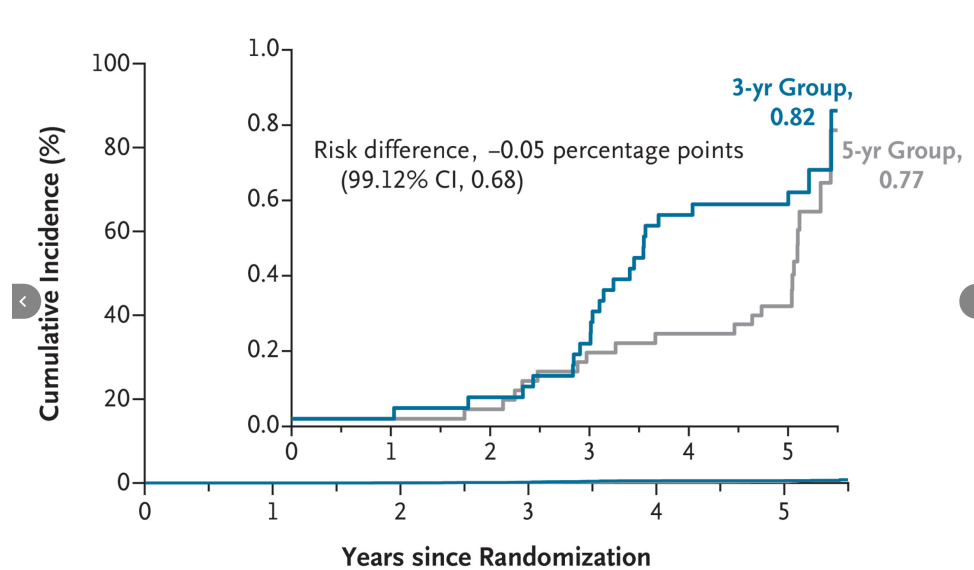
The primary end point in all the EPoS trials is the cumulative incidence of colorectal cancer at 10 years.

Surveillance at 3 years is currently recommended in guidelines

Characteristic	Surveillance at 5 Yr (N = 5398)	Surveillance at 3 and 5 Yr (N = 5401)
Age — yr†	62.2±6.7	62.2±6.8
Sex — no. (%)		
Female	1885 (34.9)	1873 (34.7)
Male	3513 (65.1)	3528 (65.3)
BMI category — no./total no. (%)‡		
Underweight or normal weight: <25.0	1437/5094 (28.2)	1376/5082 (27.1)
Overweight: 25.0–29.9	2380/5094 (46.7)	2395/5082 (47.1)
Obese: ≥30	1277/5094 (25.1)	1311/5082 (25.8)
Missing	304/5398 (5.6)	319/5401 (5.9)
Country — no. (%)		
Spain	2830 (52.4)	2839 (52.6)
Norway	989 (18.3)	985 (18.2)
Denmark	524 (9.7)	523 (9.7)
Poland	503 (9.3)	503 (9.3)
The Netherlands	481 (8.9)	476 (8.8)
Sweden	58 (1.1)	58 (1.1)
Portugal	8 (0.1)	10 (0.2)
Austria	5 (0.1)	7 (0.1)
Indication for colonoscopy at enrollment — no./total no. (%)		
Primary screening	689/5389 (12.8)	688/5390 (12.8)
Positive FIT	3513/5389 (65.2)	3520/5390 (65.3)
Symptoms	1092/5389 (20.3)	1093/5390 (20.3)
Other	95/5389 (1.8)	89/5390 (1.7)
Missing	9/5398 (0.2)	11/5401 (0.2)
Had adverse event within 30 days after enrollment colonoscopy — no. (%)	71 (1.3)	60 (1.1)

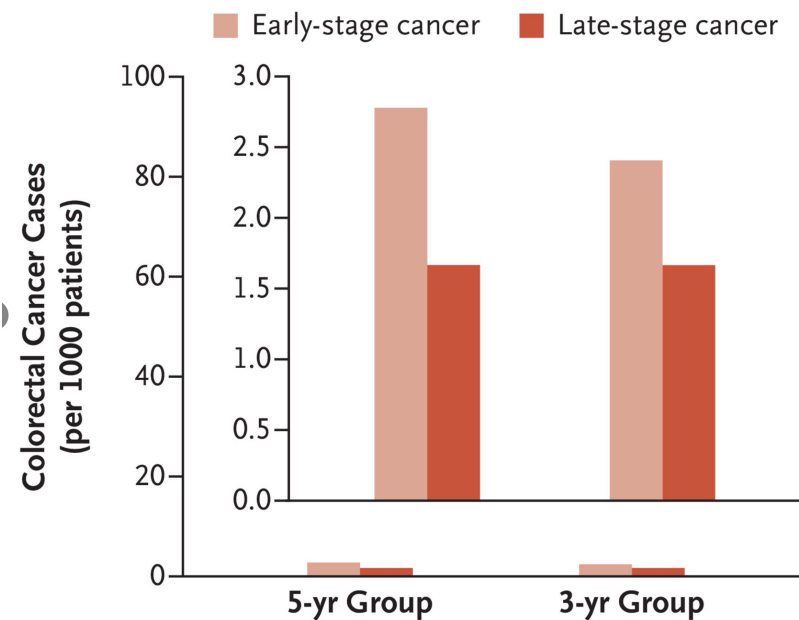
End Points.

End Point	Overall (N = 10,786)	Surveillance at 5 Yr (N = 5389)	Surveillance at 3 and 5 Yr (N = 5397)	Difference in Risk (99.12% or 95% CI)† percentage points
Diagnosis of colorectal cancer‡				
No. of patients	48	25	23	
Cumulative incidence with IPW — %	0.79	0.77	0.82	–0.05 (0.68)
Death from colorectal cancer — no. of patients/ total no. (%)§	5/10,799 (0.05)	3/5398 (0.06)	2/5401 (0.04)	
Death from any cause — no. of patients/total no. (%)§	366/10,799 (3.55)	183/5398 (3.60)	183/5401 (3.50)	
Identification of advanced adenoma				
No. of patients	934	421	513	
Cumulative incidence with IPW — %	12.74	11.07	14.55	–3.48 (–4.98 to –1.96)
Identification of adenoma				
No. of patients	5055	2133	2922	
Cumulative incidence with IPW — %	63.44	54.82	71.77	–16.95 (–19.02 to –14.86)
Identification of serrated polyps				
No. of patients	2563	987	1576	
Cumulative incidence with IPW — %	33.69	25.95	41.63	–15.68 (–17.89 to –13.41)
Colonoscopy-related adverse event¶				
No. of patients	42	24	18	
Cumulative incidence with IPW — %	0.57	0.63	0.52	0.11 (–0.24 to 0.47)



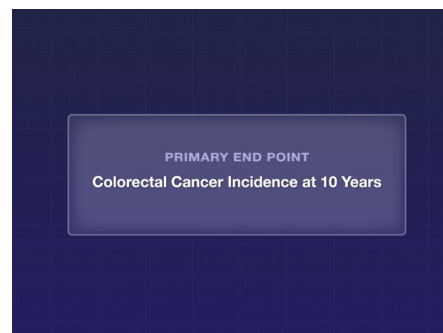
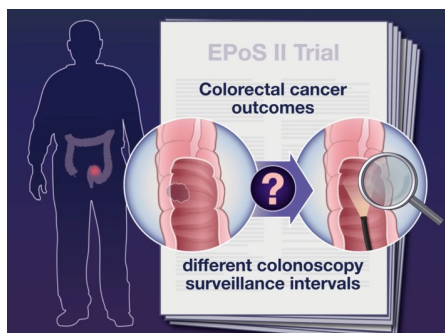
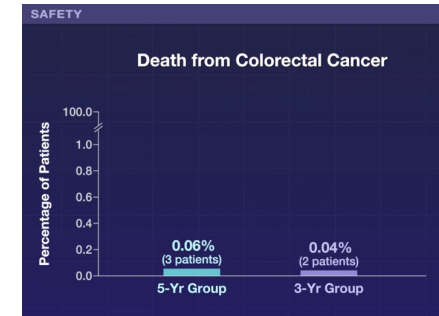
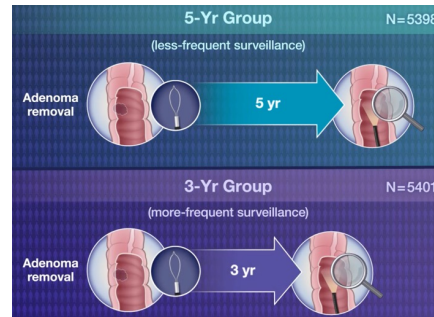
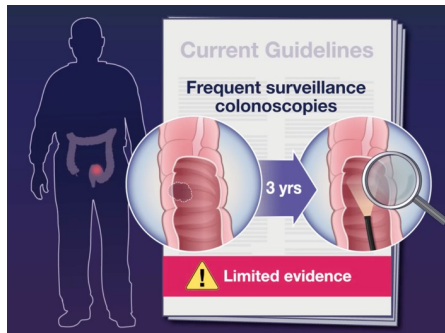
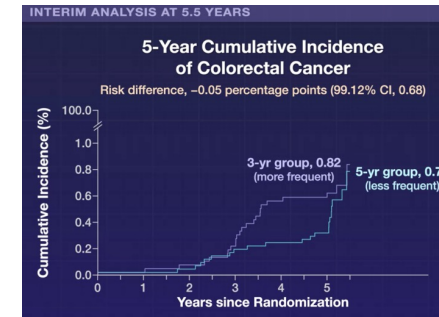
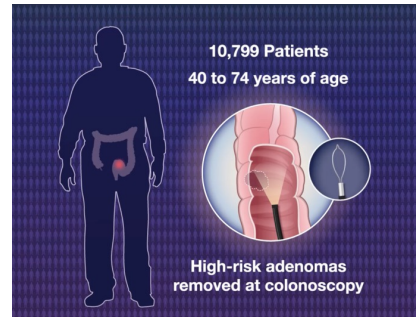
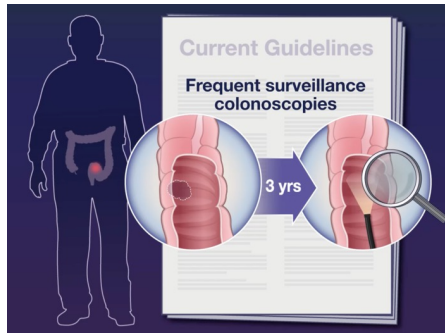
Cumulative Incidence of Colorectal Cancer in the Two Trial Groups.

Inverse probability weighting was used for the analysis. The upper boundary of the one-sided 99.12% confidence interval is shown. The inset shows the same data on an expanded y axis. CI denotes confidence interval.



Incidence of Colorectal Cancer Classified as Early Stage or Late Stage at Diagnosis.

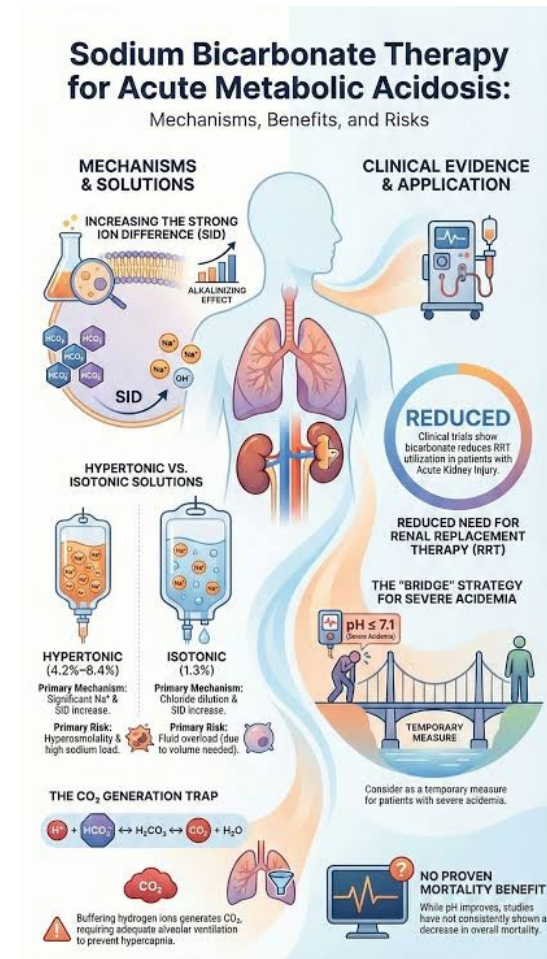
Shown are numbers of cases of early-stage cancer and of late-stage cancer per 1000 patients according to trial group. Two cases of colorectal cancer with unknown stage at diagnosis (one in each group) are excluded. The inset shows the same data on an expanded y axis.



Sodium bicarbonate is used selectively in severe metabolic acidosis to transiently raise arterial pH and counteract life-threatening cardiovascular instability.

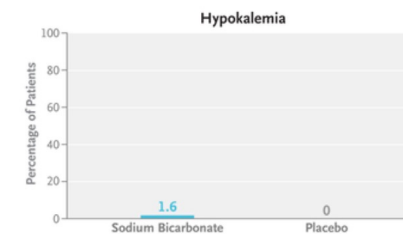
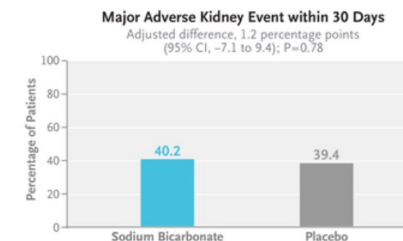
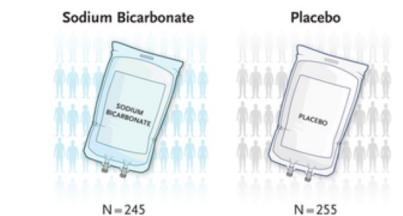
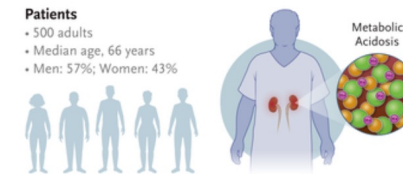
Indications and Clinical Use

- **Severe Acidity:** Considered primarily when arterial pH drops below 7.10 to 7.20, particularly in settings of shock or severe hypoperfusion.
- **Renal Protection:** Clinical trials like the [BICARICU 2 Trial overview](#) indicate that while sodium bicarbonate does not lower overall mortality in critically ill patients, it can reduce or delay the need for renal replacement therapy.
- **Specific Toxicities:** Useful in managing severe metabolic acidosis tied to specific poisonings or sodium channel blocker toxicities and severe hyperkalemia.



Sodium Bicarbonate for Critically Ill Adults with Metabolic Acidosis and Shock

Metabolic acidosis is common in critically ill patients and is associated with organ dysfunction and death. Sodium bicarbonate is used to correct acidemia, but its benefit in patients with metabolic acidosis who are receiving vasopressors remains uncertain. In this pragmatic, adaptive, double-blind, randomized trial, we assigned adults with metabolic acidosis (pH, <7.30; base excess, no more than -4 mmol per liter; and partial pressure of arterial carbon dioxide, ≤ 45 mm Hg without intubation or ≤ 50 mm Hg with intubation) who were receiving vasopressors in the intensive care unit (ICU) to receive either sodium bicarbonate or placebo (5% dextrose). Sodium bicarbonate or placebo was infused for up to 5 hours, with the infusion rate adjusted for a target pH of at least 7.30 and base excess of at least 0 mmol per liter. The primary outcome was a major adverse kidney event, defined as death, use of renal-replacement therapy, or persistent renal dysfunction, within 30 days.



Sodium bicarbonate is widely used to treat metabolic acidosis, but evidence supporting such use remains uncertain. In a randomized trial involving patients with severe metabolic acidosis, sodium bicarbonate did not lead to lower 90-day mortality than control but did lead to a lower risk of renal-replacement therapy. A second trial, which involved patients with acute kidney injury, showed no difference in mortality but suggested lower use of renal-replacement therapy with sodium bicarbonate than with control. These findings suggest possible renal benefits of sodium bicarbonate treatment; however, because these trials were open-label, knowledge of the treatment assignment may have influenced the decision to initiate renal-replacement therapy. Moreover, these trials included patients with severe acidosis and therefore do not inform treatment decisions for the broader population of patients in the intensive care unit (ICU) who have less severe acidosis. Guideline recommendations on sodium bicarbonate use are based on low-certainty evidence and focused on narrow clinical scenarios.

Methods

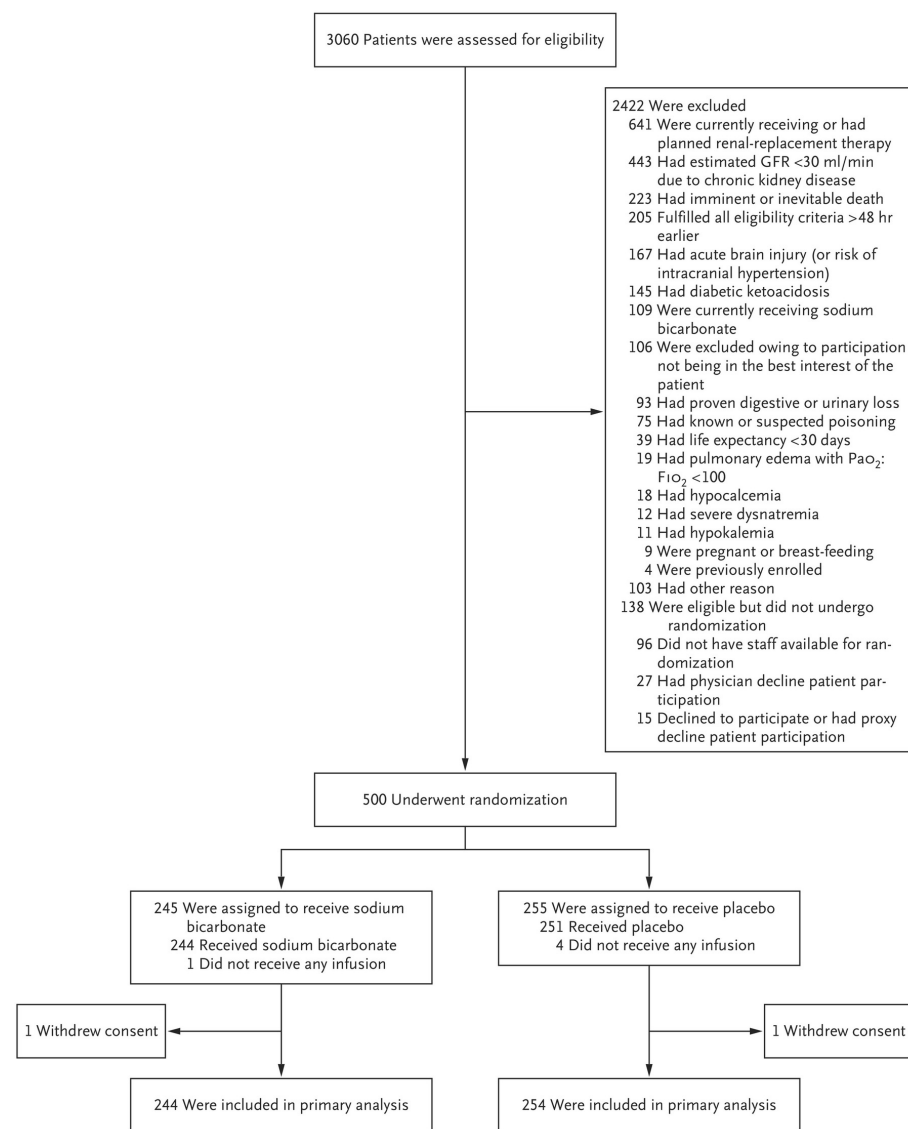
Trial Design and Oversight

We conducted a pragmatic, adaptive, double-blind, randomized clinical trial. Adults (≥ 18 years of age) who were receiving a continuous infusion of a vasopressor to correct hypotension and who had metabolic acidosis, defined as a pH below 7.30, a base excess of no more than -4 mmol per liter, and a partial pressure of arterial carbon dioxide (P_{aCO_2}) of no more than 45 mm Hg (without intubation) or of no more than 50 mm Hg (with intubation), were eligible for inclusion. Patients were excluded if they had diabetic ketoacidosis, major bicarbonate losses, or an estimated glomerular filtration rate of less than 30 ml per minute due to chronic kidney disease.

Randomization and Interventions

Randomization was performed, in a 1:1 ratio, with the use of permuted blocks of varying sizes, with stratification according to trial center, pH level (< 7.25 or ≥ 7.25), and serum creatinine level (< 1.7 mg per deciliter [< 150 μ mol per liter] or ≥ 1.7 mg per deciliter), and was conducted with the use of a secure website. Sodium bicarbonate or placebo had to be started within 1 hour after randomization. Sodium bicarbonate or placebo was infused according to a prespecified algorithm and always commenced at a rate of 100 ml per hour. Blood gases were assessed at 1 hour and 3 hours after the start of the infusion, and the infusion rate was adjusted by the bedside clinical team. The infusion rate was maintained at 100 ml per hour if the pH was below 7.30 or the base excess was less than 0 mmol per liter, the rate was adjusted to 25 ml per hour if the pH was 7.30 to 7.35 with a base excess of at least 0 mmol per liter, or the infusion was discontinued if the pH was above 7.35 with a base excess of more than 0 mmol per liter.

Characteristic	Sodium Bicarbonate (N = 244)	Placebo (N = 254)
Median age (IQR) — yr	65.0 (51.8 to 74.0)	68.0 (55.2 to 76.0)
Sex — no. (%)		
Female	111 (45.5)	104 (40.9)
Male	133 (54.5)	150 (59.1)
Median time between eligibility determination and randomization (IQR) — min	39.9 (15.0 to 73.3)	37.8 (12.0 to 70.6)
Type of admission — no. (%)		
Medical	119 (48.8)	123 (48.4)
Emergency surgery	64 (26.2)	66 (26.0)
Elective surgery	61 (25.0)	65 (25.6)
Median APACHE II score on ICU admission (IQR) [†]	21 (16 to 26)	22 (17 to 27)
Median SOFA score closest to randomization (IQR) [‡]	7 (6 to 9)	7 (6 to 9)
Cause of metabolic acidosis — no. (%) [§]		
Sepsis or septic shock	122 (50.0)	119 (46.9)
Cardiogenic shock	40 (16.4)	56 (22.0)
Hypovolemia or dehydration	32 (13.1)	20 (7.9)
Cardiac arrest	19 (7.8)	28 (11.0)
Postoperative condition	9 (3.7)	15 (5.9)
Vasoplegia	6 (2.5)	5 (2.0)
Acute kidney injury [¶]	3 (1.2)	5 (2.0)
Hemorrhage	3 (1.2)	3 (1.2)
Anaphylaxis or anaphylactic shock	1 (0.4)	1 (0.4)
Other	9 (3.7)	2 (0.8)
Blood gas variables at eligibility determination		
Median pH (IQR)	7.26 (7.22 to 7.28)	7.26 (7.23 to 7.28)
pH <7.25 — no. (%)	93 (38.1)	99 (39.0)
Median base excess (IQR) — mmol/liter	-9.2 (-11.5 to -7.0)	-8.8 (-11.0 to -7.0)
Median Paco ₂ (IQR) — mm Hg	41 (35 to 44)	41 (36 to 44)
Median bicarbonate (IQR) — mmol/liter	17.0 (15.0 to 19.2)	18.0 (15.9 to 19.1)
Median creatinine before ICU admission (IQR) — mg/dl	1.05 (0.80 to 1.40)	1.04 (0.81 to 1.41)
Prerandomization variables		
Median creatinine (IQR) — mg/dl	1.46 (1.07 to 2.18)	1.42 (1.05 to 2.14)
Median lactate (IQR) — mmol/liter	2.5 (1.4 to 4.5)	2.5 (1.5 to 4.5)
Median sodium (IQR) — mmol/liter	137 (133 to 140)	137 (134 to 139)
Received sodium bicarbonate — no. (%)	35 (14.3)	23 (9.1)
Acute kidney injury — no./total no. (%) ^{**}	113/243 (46.5)	115/251 (45.8)
Mechanical ventilation — no. (%)	191 (78.3)	207 (81.5)
Sepsis — no. (%) ^{††}	163 (66.8)	174 (68.5)
Septic shock — no. (%) ^{††}	95 (38.9)	104 (40.9)
Median norepinephrine dose (IQR) — µg/kg/min	0.14 (0.07 to 0.23)	0.15 (0.07 to 0.23)



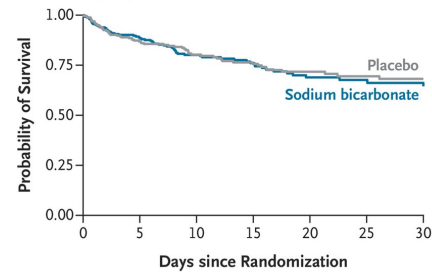
Characteristics of the Intervention in the First 24 Hours.

Characteristic	Sodium Bicarbonate (N = 244)	Placebo (N = 254)	Adjusted Absolute Difference (95% CI) ^a
Median time between randomization and start of infusion (IQR) — hr	0.5 (0.4 to 0.7)	0.4 (0.3 to 0.5)	0.1 (0.1 to 0.2)
Median duration of infusion (IQR) — hr	5.0 (4.7 to 5.0)	5.0 (5.0 to 5.0)	0.0 (0.0 to 0.0)
Median volume infused (IQR) — ml	500 (329 to 500)	500 (500 to 500)	0.0 (−32.0 to 32.0)
Median total sodium bicarbonate dose (IQR) — mmol	300.0 (197.4 to 300.0)	0.0 (0.0 to 0.0)	300.0 (292.4 to 307.6)
Adjustment of infusion — no./total no. (%) [†]	121/243 (49.8)	58/250 (23.2)	27.0 (19.5 to 34.5)
Use of open-label sodium bicarbonate — no./total no. (%)	17/243 (7.0)	38/250 (15.2)	−8.2 (−13.6 to −2.8)
Blood gas analysis during the first 24 hr [‡]			
Median pH (IQR)			
Lowest	7.31 (7.26 to 7.34)	7.26 (7.22 to 7.30)	0.05 (0.04 to 0.06)
Highest	7.43 (7.39 to 7.46)	7.37 (7.33 to 7.41)	0.05 (0.04 to 0.06)
Median bicarbonate (IQR) — mmol/liter			
Lowest	19.0 (17.0 to 22.0)	17.0 (15.0 to 19.0)	2.6 (1.7 to 3.4)
Highest	26.0 (23.8 to 27.9)	21.0 (19.0 to 23.0)	4.5 (3.8 to 5.2)
Median base excess (IQR) — mmol/liter			
Lowest	−6.0 (−9.0 to −3.5)	−9.0 (−12.0 to −7.0)	3.1 (2.4 to 3.7)
Highest	1.5 (−1.0 to 3.0)	−4.2 (−6.2 to −1.8)	5.1 (4.4 to 5.8)
Median Paco ₂ (IQR) — mm Hg			
Lowest	35.0 (32.0 to 38.9)	33.9 (30.0 to 37.0)	1.0 (−0.2 to 2.2)
Highest	44.0 (40.0 to 48.0)	41.8 (38.0 to 46.0)	2.0 (0.6 to 3.4)
Median lactate (IQR) — mmol/liter			
Lowest	1.3 (1.0 to 2.2)	1.3 (0.9 to 1.9)	0.1 (0.0 to 0.2)
Highest	3.1 (2.1 to 5.4)	2.9 (1.8 to 5.1)	0.2 (−0.1 to 0.5)
Median sodium (IQR) — mmol/liter			
Lowest	136.5 (134.0 to 140.0)	133.0 (131.0 to 136.0)	4.0 (2.6 to 5.4)
Highest	141.0 (138.0 to 144.0)	137.0 (134.0 to 140.0)	4.0 (2.6 to 5.4)
Median norepinephrine infusion rate (IQR) — µg/min			
Lowest	0.06 (0.03 to 0.10)	0.05 (0.02 to 0.12)	0.00 (−0.01 to 0.01)
Highest	0.18 (0.10 to 0.31)	0.19 (0.11 to 0.30)	−0.01 (−0.04 to 0.02)

Trial Outcomes.

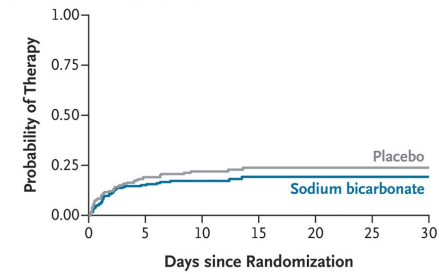
Outcome	Sodium Bicarbonate (N = 244)	Placebo (N = 254)	Adjusted Absolute Difference (95% CI)	Adjusted Hazard Ratio (95% CI)
Primary outcome				
Major adverse kidney event within 30 days — no. (%)	98 (40.2)	100 (39.4)	1.2 (−7.1 to 9.4) [†]	—
Secondary outcomes				
Components of primary outcome [‡]				
In-hospital death by day 30 — no. (%)	62 (25.4)	61 (24.0)	1.8 (−5.6 to 9.2)	1.09 (0.76 to 1.56)
Receipt of renal-replacement therapy within 30 days — no. (%)	41 (16.8)	53 (20.9)	−3.9 (−10.6 to 2.7)	—
Persistent renal dysfunction within 30 days — no./total no. (%) [§]	34/243 (14.0)	46/251 (18.3)	−4.3 (−10.7 to 2.1)	—
Renal-replacement therapy dependence at day 30 — no. (%) [¶]	14 (5.7)	23 (9.1)	−3.3 (−7.8 to 1.3)	—
In-ICU death by day 30 — no. (%)	49 (20.1)	56 (22.0)	−1.7 (−8.6 to 5.3)	—
In-hospital death by day 90 — no. (%)	64 (26.2)	65 (25.6)	1.2 (−6.3 to 8.6)	1.06 (0.75 to 1.51)
Physiological outcomes				
Recurrence of metabolic acidosis — no./total no. (%)	78/244 (32.0)	141/253 (55.7)	−23.3 (−31.4 to −15.1)	—
Acute kidney injury — no./total no. (%) ^{**}	156/242 (64.5)	162/250 (64.8)	−0.0 (−7.7 to 7.6)	—
Stage 1	64/156 (41.0)	58/162 (35.8)		
Stage 2	35/156 (22.4)	44/162 (27.2)		
Stage 3	57/156 (36.5)	60/162 (37.0)		
Process-of-care measures^{††}				
Median no. of vasopressor-free days at day 30 (IQR)	27.2 (0.0 to 28.9)	27.6 (6.1 to 28.9)	−0.5 (−1.3 to 0.4)	
Median no. of days free from renal-replacement therapy at day 30 (IQR)	30.0 (0.0 to 30.0)	30.0 (10.4 to 30.0)	−0.0 (−0.6 to 0.6)	
Median no. of ICU-free days at day 30 (IQR)	23.7 (0.0 to 26.9)	24.0 (0.0 to 27.0)	−0.5 (−2.3 to 1.3)	
Median no. of hospital-free days at day 90 (IQR)	69.3 (0.0 to 79.8)	69.2 (0.0 to 80.6)	1.1 (−6.4 to 8.6)	

A In-Hospital Survival by Day 30



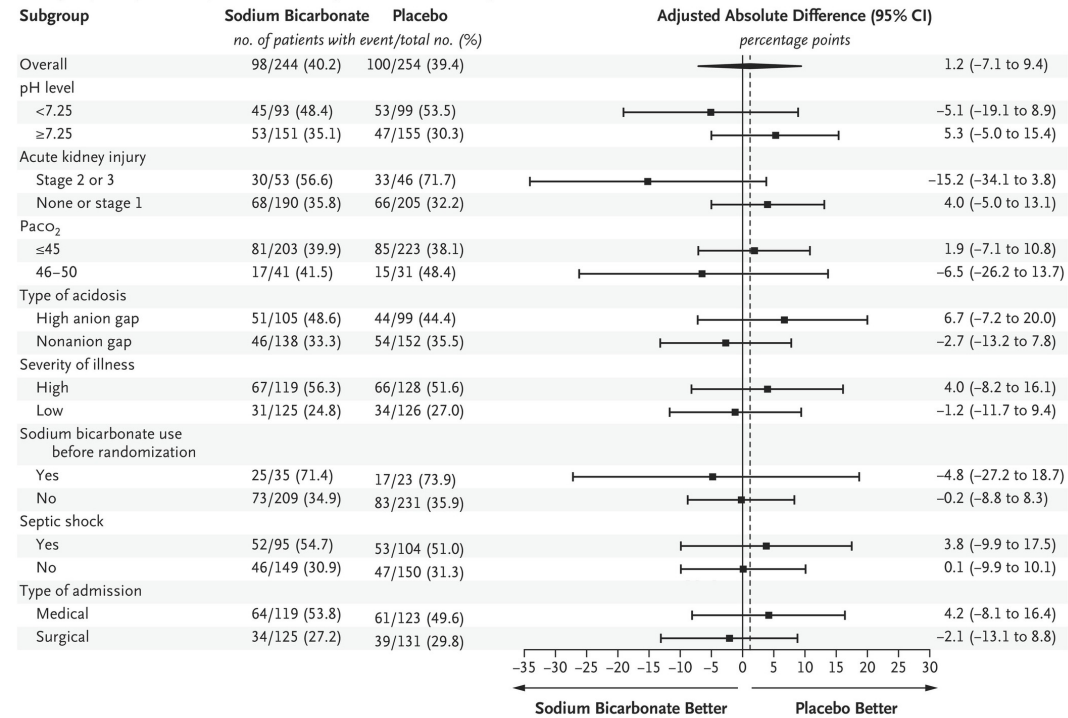
No. at Risk							
Sodium bicarbonate	244	205	141	97	66	46	39
Placebo	254	208	140	103	76	55	48

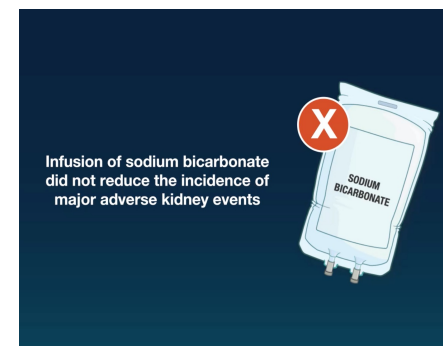
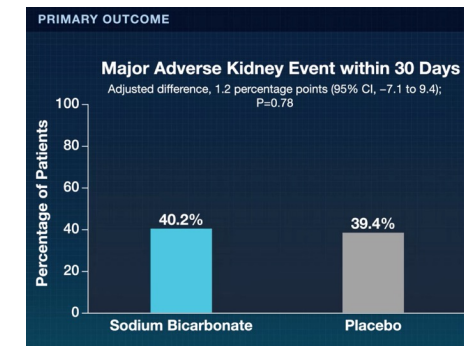
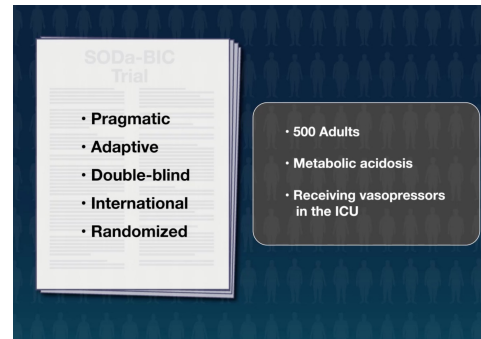
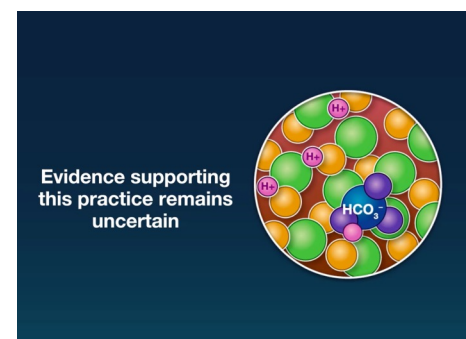
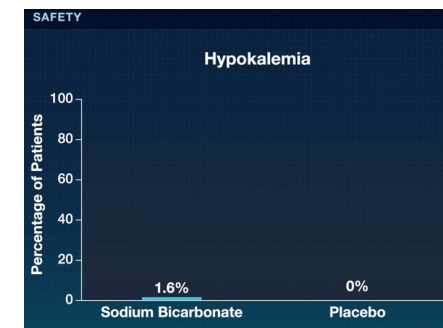
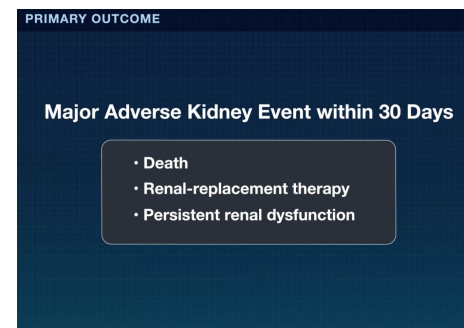
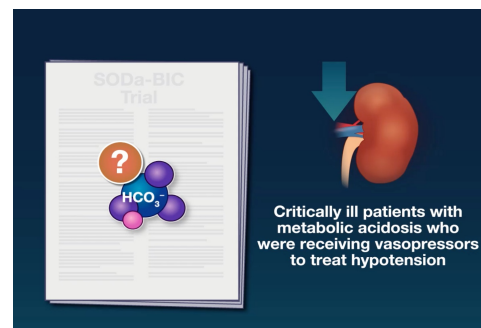
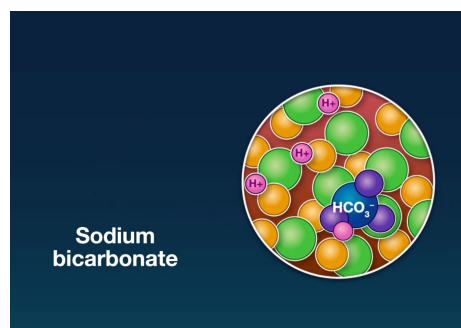
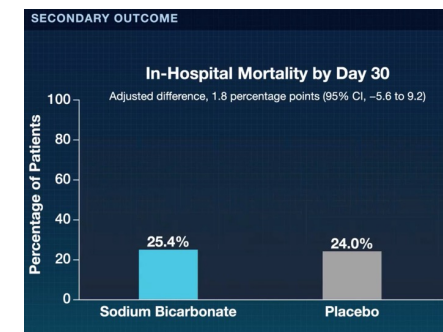
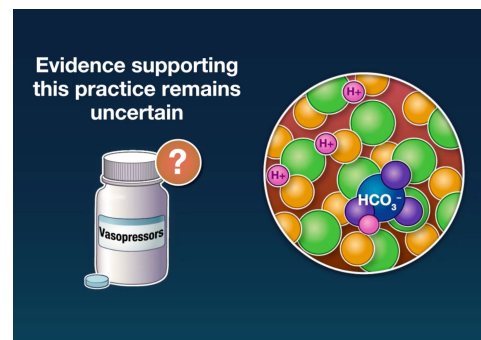
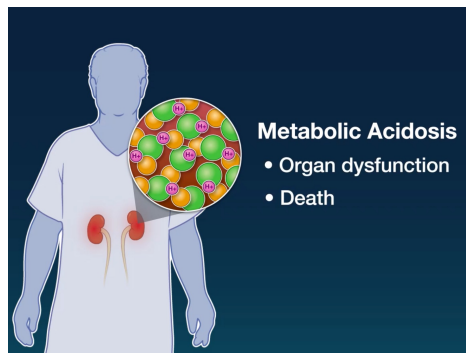
B Renal-Replacement Therapy by Day 30



No. at Risk							
Sodium bicarbonate	244	175	109	67	45	32	27
Placebo	254	174	106	73	56	36	32

C Subgroup Analysis of Major Adverse Kidney Events within 30 Days

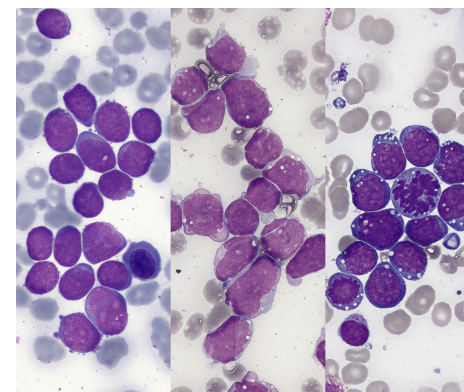




Chemotherapy for high-risk acute lymphoblastic leukemia (ALL) in children involves intensive, multi-drug regimens given in structured phases to destroy cancer cells while managing severe toxicities.

Treatment Phases

- **Induction:** Lasts about 4 weeks using drugs like vincristine, corticosteroids (dexamethasone or prednisone), asparaginase, and an anthracycline (such as daunorubicin or doxorubicin) to achieve remission.
- **Consolidation/Intensification:** Uses higher doses and high-risk blocks with agents like high-intensity methotrexate, cytarabine, cyclophosphamide, and pegaspargase.
- **Maintenance:** Lasts for about 2 years using lower-intensity oral medications like 6-mercaptopurine and weekly methotrexate to prevent relapse.
- **CNS-Directed Therapy:** Includes chemotherapy injected directly into the cerebrospinal fluid to protect or treat the central nervous system.



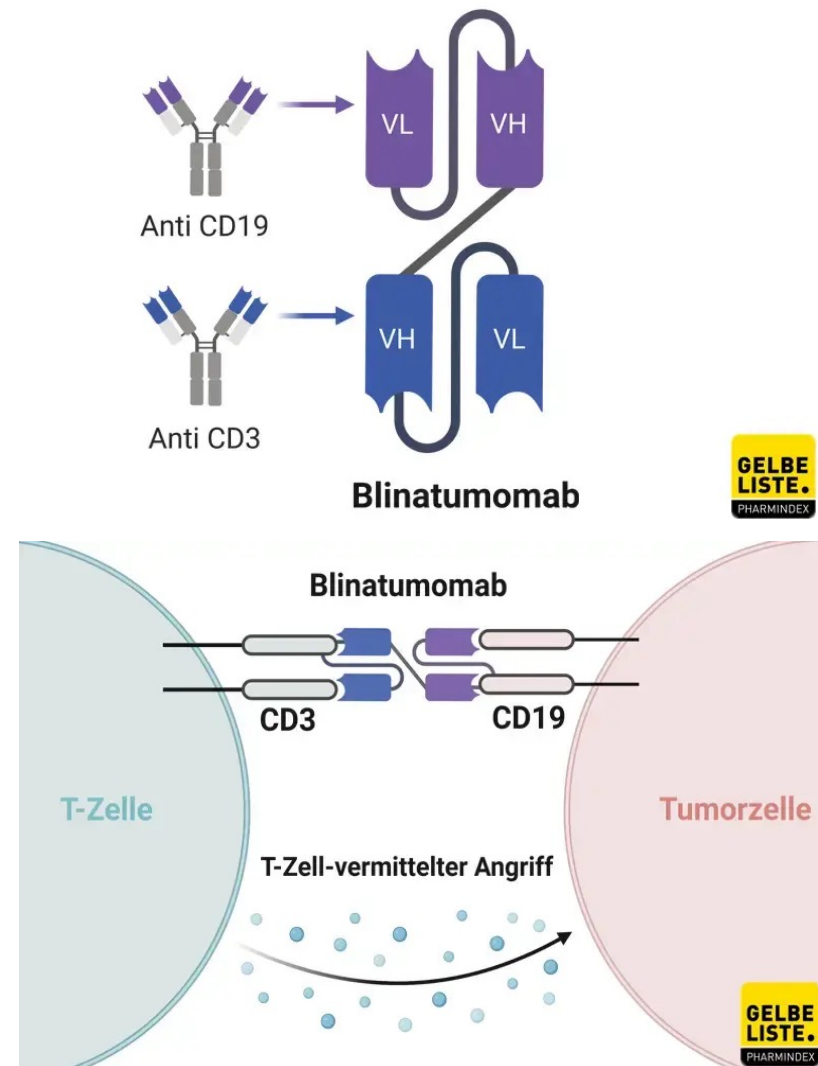
Phase	Chemotherapy Agents	Schedule
Induction (35 days)	Dexamethasone PO (< 10 years of age) ^a Prednisone PO (≥ 10 years of age) ^a Vincristine IV Daunorubicin IV Pegaspargase IM/IV Cytarabine IT Methotrexate IT	Days 1–14 Days 1–28 Days 1, 8, 15, 22 Days 1, 8, 15, 22 Day 4 Day 1 (B-ALL CNS2 require more) Days 8, 29 (also Days 15, 22 for CNS3)
Consolidation ^b (56 days for B-ALL;	Mercaptopurine PO Cyclophosphamide IV	B-ALL: Days 1–14 and 29–42 T-ALL: Days 8–21 and 50–63 B-ALL: Days 1, 29

Blinatumomab (Handelsname [Blincyto](#)) ist ein innovativer, bispezifischer monoklonaler Antikörper aus der Klasse der sogenannten BiTE-Antikörper (Bi-specific T-cell engagers). Er wird in der Onkologie zur spezifischen Immuntherapie bei bestimmten Formen der akuten lymphatischen Leukämie (ALL) eingesetzt.

Wirkungsweise und Prinzip

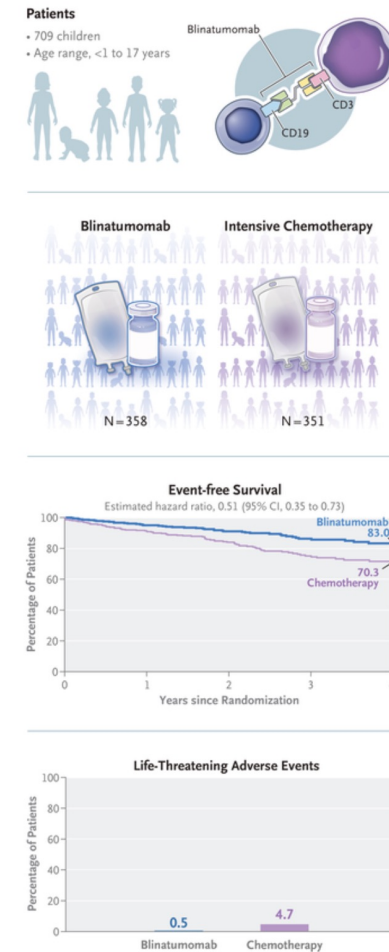
Blinatumomab fungiert als molekulare Brücke zwischen den körpereigenen Abwehrzellen des Patienten und den bösartigen Krebszellen.

- **Doppelbindung:** Der Antikörper bindet gleichzeitig an das Oberflächenprotein **CD19** auf den bösartigen B-Vorläuferzellen und an den **CD3-Rezeptor** auf zytotoxischen T-Zellen.
- **T-Zell-Aktivierung:** Durch die räumliche Annäherung werden die T-Zellen aktiviert, vermehren sich und zerstören die Leukämiezellen gezielt über einen seriellen Abtötungsmechanismus.



Blinatumomab for Replacing Chemotherapy in Pediatric Acute Lymphoblastic Leukemia

Blinatumomab, a bispecific T-cell engager targeting the CD19 antigen on B cells, may offer an option to safely replace cycles of traditional chemotherapy in pediatric patients with newly diagnosed high-risk B-cell acute lymphoblastic leukemia (ALL). We randomly assigned, in a 1:1 ratio, children with high-risk B-cell ALL to receive two cycles of blinatumomab (blinatumomab group) or two cycles of chemotherapy (control group) after consolidation. The primary end point was event-free survival as evaluated in a time-to-event analysis; the duration of event-free survival was defined as the time from randomization to the first event among resistance to protocol treatment, relapse, second cancer, or death from any cause. Our primary objective was to evaluate whether the 4-year event-free survival would be 10 percentage points higher in the blinatumomab group than in the control group.



The introduction of blinatumomab, a novel bispecific T-cell engager directed against the CD19 antigen expressed on B cells, has led to improved outcomes. Blinatumomab has shown increased efficacy against leukemia in patients with relapse, despite reductions in chemotherapy. A recent large prospective trial involving children with newly diagnosed standard-risk B-cell ALL (as defined by the National Cancer Institute [NCI]) showed that the addition of two cycles of blinatumomab to a common chemotherapy backbone led to improved disease-free survival. Several studies involving adults with B-cell ALL have had excellent results, confirming the efficacy of this new agent. We performed the AIEOP-BFM ALL (Associazione Italiana di Ematologia e Oncologia Pediatrica and Berlin–Frankfurt–Münster Group Acute Lymphoblastic Leukemia) 2017 trial to assess whether replacement of two cycles of highly toxic chemotherapy with two cycles of blinatumomab as first-line treatment can still improve outcomes while reducing adverse events in pediatric patients with high-risk B-cell ALL.

Methods

Trial Design and Oversight

Participating centers in this phase 3 randomized trial were located in Australia, Austria, the Czech Republic, Germany, Israel, Italy, Slovakia, and Switzerland.

Patients who had newly diagnosed Philadelphia chromosome–negative ALL and were younger than 18 years at the time of diagnosis were enrolled in the risk-stratified AIEOP-BFM ALL 2017 trial; results for the patients with high-risk B-cell ALL are reported here.

The high-risk group was defined by documentation of at least one of the following features: the absence of complete remission on day 33 after the start of treatment; a positive test for the fusion gene *KMT2A::AFF1* (also known as *MLL-AF4*); a positive test for the fusion gene *TCF3::HLF* (which encodes E2A-HLF); hypodiploidy; minimal residual disease (MRD) positivity at a leukemic blast level of at least 10% in bone marrow on day 15, as assessed by flow cytometry, and the absence of a positive test for the fusion gene *ETV6::RUNX1* (also known as *TEL-AML1*); a positive test for *IKZF1*^{plus} and positive or inconclusive MRD status at the end of induction as assessed by polymerase-chain-reaction (PCR) assay and the absence of a positive test for *ETV6::RUNX1*, the fusion gene *TCF3::PBX1*, and *KMT2A* (formerly known as *MLL*) rearrangements other than *KMT2A::AFF1*; MRD at a level of at least 5×10^{-4} (≥ 5 cancer cells per 10,000 bone marrow cells) at the end of induction and MRD at a level of less than 5×10^{-4} at the end of consolidation as assessed by PCR assay; MRD at a level of at least 5×10^{-4} at the end of consolidation as assessed by PCR assay; or an age of less than 1 year and a positive test for any *KMT2A* rearrangement.

Treatment

All the patients with newly diagnosed Philadelphia chromosome–negative ALL received four-drug induction treatment (induction phase 1A; see the protocol for details) plus intrathecal methotrexate. Patients who met the eligibility criteria for early high-risk B-cell ALL after induction were randomly assigned to receive four doses of bortezomib plus standard consolidation chemotherapy or standard consolidation chemotherapy alone. Of these patients, those who met the eligibility criteria for high-risk B-cell ALL then received cycle one of intensive chemotherapy.

Blinatumomab was administered as a continuous infusion of 15 µg per square meter of body-surface area per day (capped at 28 µg) with a 14-day interval between treatment cycles. Two additional doses of intrathecal methotrexate were administered as central nervous system (CNS) prophylaxis on days 1 and 29 of each blinatumomab cycle. A poor response to the first cycle of blinatumomab was defined as MRD at a level of at least 1×10^{-4} or MRD at a nonquantifiable level (threshold for quantification, $\geq 5 \times 10^{-4}$).

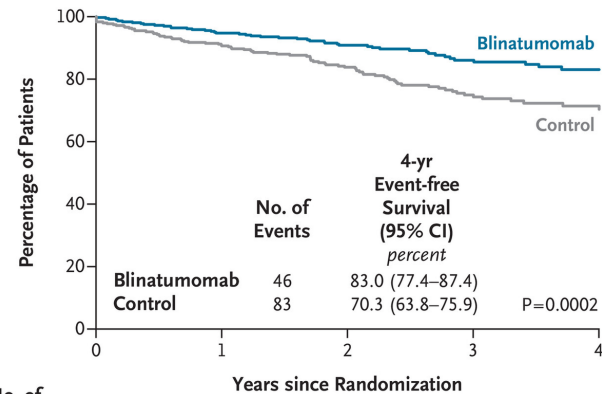
End Points

The primary end point was event-free survival as evaluated in a time-to-event analysis; the duration of event-free survival was defined as the time from randomization to the first event among resistance to protocol treatment, relapse, second cancer, or death from any cause.

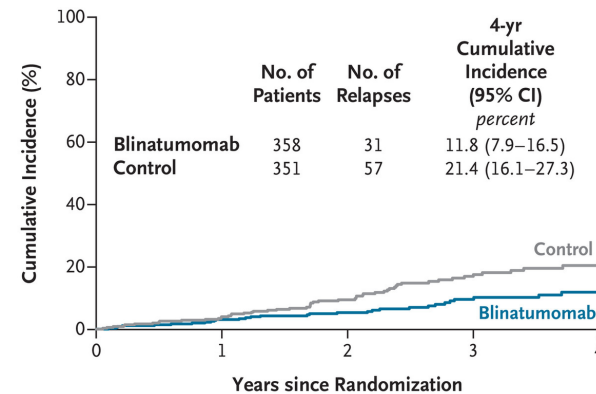
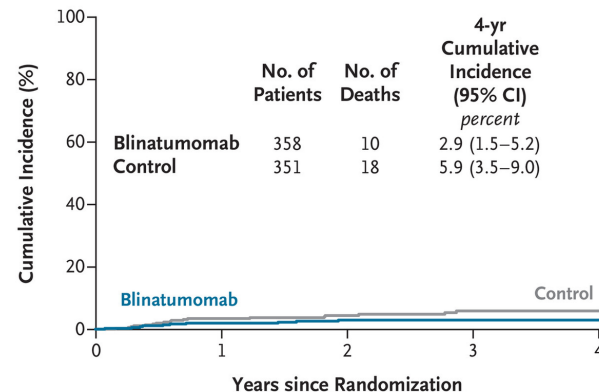
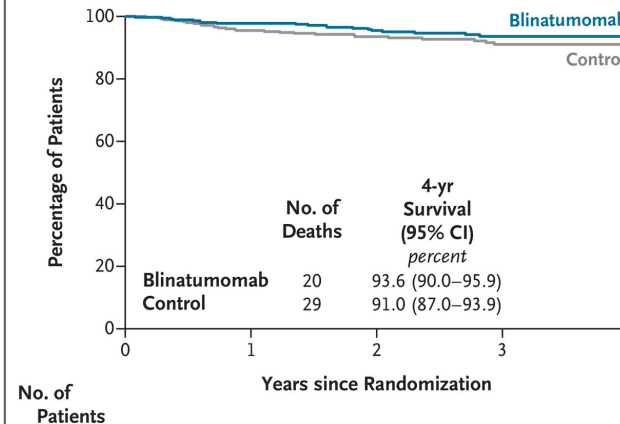
Characteristic	Blinatumomab (N = 358)	Control (N = 351)
<i>number of patients (percent)</i>		
Demographic characteristics		
Age		
<1 yr	26 (7.3)	22 (6.3)
1–9 yr	213 (59.5)	210 (59.8)
10–17 yr	119 (33.2)	119 (33.9)
Medical history		
White-cell count		
<20,000 per μl	205 (57.3)	204 (58.1)
20,000 to <100,000 per μl	97 (27.1)	91 (25.9)
$\geq 100,000$ per μl	56 (15.6)	56 (16.0)
NCI risk category†		
Standard risk	164 (45.8)	167 (47.6)
High risk	194 (54.2)	184 (52.4)
CNS-3 involvement‡	7 (2.0)	13 (3.7)
Genetic features		
Positive for ETV6::RUNX1	12 (3.4)	11 (3.1)
KMT2A status		
Positive for KMT2A::AFF1	22 (6.1)	21 (6.0)
Positive for other KMT2A fusion	16 (4.5)	16 (4.6)
Hypodiploidy	26 (7.3)	25 (7.1)
IKZF1 ^{high} profile§		
Present	78 (21.8)	66 (18.8)
Absent	252 (70.4)	252 (71.8)
Unknown	28 (7.8)	33 (9.4)
Response		
MRD on day 15 of induction, assessed by flow cytometry		
<0.1%	30 (8.4)	30 (8.5)
0.1 to <10%	128 (35.8)	154 (43.9)
$\geq 10\%$	187 (52.2)	162 (46.2)
Unknown	13 (3.6)	5 (1.4)
Morphologic complete remission at the end of induction¶	335 (93.6)	327 (93.2)
MRD status at the end of induction, assessed by PCR		
Negative	16 (4.5)	20 (5.7)
Positive at a level of $<5 \times 10^{-4}$	119 (33.2)	91 (25.9)
Positive at a level of $\geq 5 \times 10^{-4}$	222 (62.0)	238 (67.8)
PCR not performed or data not available	1 (0.3)	2 (0.6)
MRD status at the end of consolidation, assessed by PCR		
Negative	156 (43.6)	142 (40.5)
Positive at a level of $<5 \times 10^{-4}$	163 (45.5)	177 (50.4)
Positive at a level of $\geq 5 \times 10^{-4}$	37 (10.3)	31 (8.8)
PCR not performed or data not available	2 (0.6)	1 (0.3)
MRD status after cycle one of chemotherapy, assessed by PCR‖		
Negative	243 (67.9)	220 (62.7)
Positive at a level of $<5 \times 10^{-4}$	97 (27.1)	90 (25.6)
Positive at a level of $\geq 5 \times 10^{-4}$	13 (3.6)	15 (4.3)
PCR not performed or data not available	5 (1.4)	26 (7.4)

Selected Medically Relevant Adverse Events during the Treatment Period (As-Treated Population).

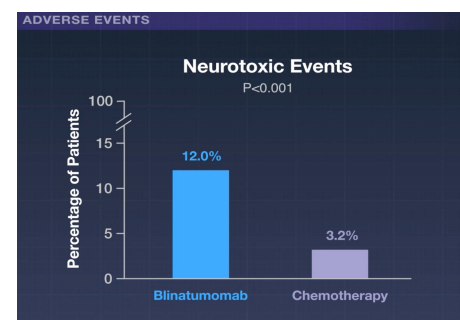
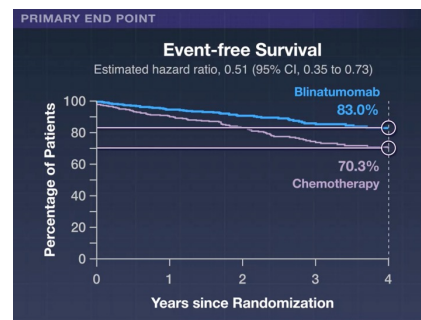
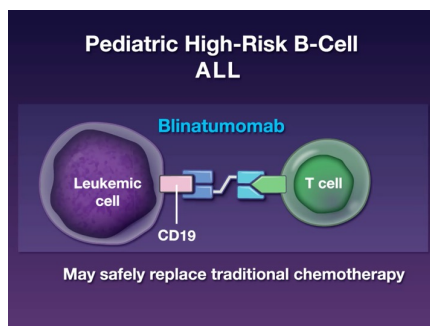
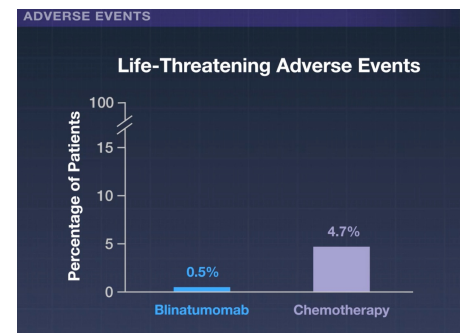
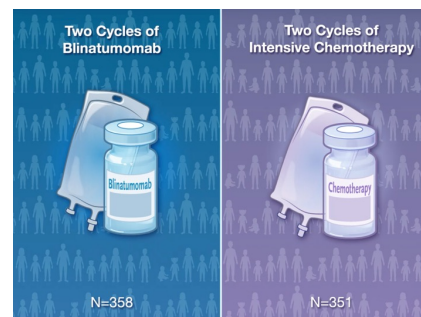
Event	Event of Special Interest or Serious Event					Life-Threatening Event†					P Value
	Blinatumomab (N = 368)		Control (N = 340)		P Value	Blinatumomab (N = 368)		Control (N = 340)			
	no. of patients (%)	no. of events	no. of patients (%)	no. of events		no. of patients (%)	no. of events	no. of patients (%)	no. of events		
Infections and infestations											
Overall	88 (23.9)	119	236 (69.4)	368	<0.001	0	0	11 (3.2)	11	<0.001	
Neutropenic enterocolitis	1 (0.3)	1‡	6 (1.8)	6	0.06	0	0	0	0		
Proven, probable, or possible invasive fungal infection	0	0	7 (2.1)	7	0.006	0	0	1 (0.3)	1	0.48	
Severe invasive soft-tissue infection of grade ≥3	2 (0.5)	2	4 (1.2)	4	0.43	0	0	0	0		
Serious other infection or febrile neutropenia§	86 (23.4)	116‡	233 (68.5)	351	<0.001	0	0	10 (2.9)	10	<0.001	
Neurotoxic events											
Overall	45 (12.2)	48	11 (3.2)	12	<0.001	0	0	1 (0.3)	1	0.48	
Posterior reversible encephalopathy syndrome	0	0	3 (0.9)	3	0.11	0	0	1 (0.3)	1	0.48	
Seizure of grade ≥2¶	17 (4.6)	17	3 (0.9)	3	0.001	0	0	0	0		
Other neurotoxic events‖	28 (7.6)	31	6 (1.8)	6	<0.001	0	0	0	0		
Other adverse events											
Acute pancreatitis of grade ≥2	1 (0.3)	1	7 (2.1)	7	0.03	1 (0.3)	1	0	0	1.00	
Gastrointestinal perforation	0	0	1 (0.3)	1	0.48	0	0	1 (0.3)	1	0.48	
Allergic reaction to investigational product of grade ≥2***	2 (0.5)	3‡	27 (7.9)	31	<0.001	0	0	3 (0.9)	3	0.11	
Severe hepatic failure with biochemical evidence of liver injury	0	0	1 (0.3)	1	0.48	0	0	1 (0.3)	1	0.48	
Serious mucositis††	1 (0.3)	1‡	34 (10.0)	35	<0.001	0	0	0	0		
Cytokine release syndrome of grade ≥2	4 (1.1)	4	0	0	0.12	0	0	0	0		
Complication due to sedation	1 (0.3)	1	0	0	1.00	1 (0.3)	1	0	0	1.00	

A Event-free Survival

No. of Patients	Years since Randomization				
Blinatumomab	358	335	247	147	77
Control	351	318	224	129	67

B Relapse**C Death During First Complete Remission****D Overall Survival****End Points (Intention-to-Treat-Population).**

Shown are estimates of end-point events between randomization and year 4. Panel A shows event-free survival over the 4-year period. After a median follow-up of 2.9 years, 46 primary end-point events (resistance to the protocol treatment in 1 patient, relapse in 31, secondary cancer in 4, and death during the first complete remission in 10) had occurred in the blinatumomab group, and 83 primary end-point events (resistance to the protocol treatment in 6 patients, relapse in 57, secondary cancer in 2, and death during the first complete remission in 18) had occurred in the control group. The estimated hazard ratio for a primary end-point event (blinatumomab vs. control) was 0.51 (95% confidence interval, 0.35 to 0.73) as assessed with a Cox model. Panel B shows the cumulative incidence of relapse, Panel C the cumulative incidence of death during the first complete remission, and Panel D freedom from death from any cause. Complete remission was assessed as morphologic complete remission (defined by a regenerating bone marrow with a leukemic-blast level of less than 5% and no evidence of extramedullary involvement). Additional details about end-point events are provided in Table S3.

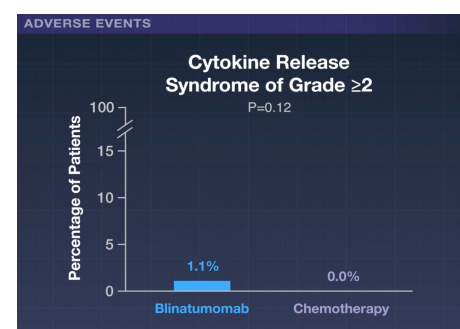
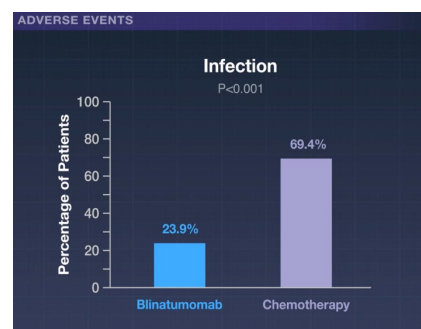


AIEOP-BFM ALL 2017 Trial

- Phase 3
- International
- Randomized

709 Patients

- Newly diagnosed high-risk B-cell ALL
- Younger than 18 years at the time of diagnosis



A peanut allergy is an abnormal, IgE-mediated immune system response to specific proteins found in peanuts, classifying them as one of the most common and severe food allergies. Because peanuts are legumes rather than tree nuts, an allergy to them involves distinct protein profiles (such as Ara h 1, Ara h 2, and Ara h 3) that can trigger rapid, potentially life-threatening reactions even with trace exposures.

Symptoms and Anaphylaxis

Reactions to peanuts typically occur **within minutes up to two hours** after ingestion or direct exposure.

- **Mild to Moderate Symptoms:** Hives, skin redness, itching, tingling around the mouth, runny nose, and gastrointestinal upset like stomach cramps, nausea, or vomiting.
- **Anaphylaxis Signs:** Airway constriction, severe swelling of the lips, tongue, and throat, a sharp drop in blood pressure (shock), rapid pulse, dizziness, and loss of consciousness. This is a medical emergency requiring immediate treatment with an [Epinephrine Auto-Injector](#) and emergency services.



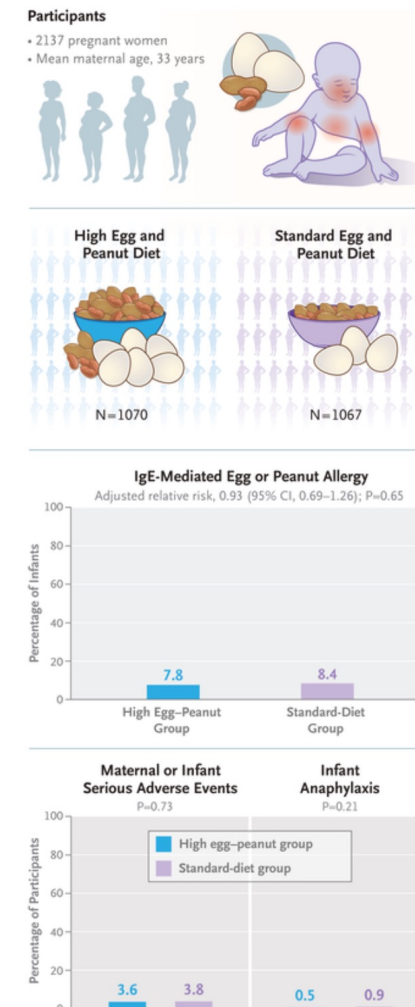
\$550 to \$814

Trial of a Maternal Diet Rich in Eggs and Peanuts to Reduce Infant Allergy

Immune responses leading to food allergy may develop early in life, potentially before the introduction of solid foods.

Exposures to food allergens in utero and through breast milk have been proposed as a strategy to prevent food allergies in infants, but evidence from randomized trials is lacking.

In this multisite, randomized trial, pregnant women whose unborn child had at least two biologic family members with medically diagnosed allergic disease were eligible to participate. Participants were assigned in a 1:1 ratio to follow either a diet high in eggs and peanuts that included at least 6 eggs and 60 peanuts per week (high egg-peanut group) or a standard (control) egg and peanut diet that included no more than 3 eggs and 30 peanuts per week (standard-diet group), from before 23 weeks' gestation until 4 months postnatally during lactation. The primary outcome was IgE-mediated egg or peanut allergy in the infant at 1 year of age.



A 2018 meta-analysis showed that maternal avoidance of allergenic foods during pregnancy or lactation did not reduce the risk of child allergic disease. Evidence is lacking on recommended amounts of maternal dietary intake of food allergens, and the frequency and dose of fetal and early-infancy food-allergen exposure may be important. For infant solid-food intakes of peanut and egg, higher consumption has been associated with a lower prevalence of these food allergies than lower consumption. In previous human trials during lactation, higher maternal egg consumption has been associated with an increased concentration of egg protein in breast milk. One large observational study (8205 participants) in the United States showed that higher maternal peripregnancy consumption of peanuts and tree nuts was associated with a lower risk of allergy to peanuts and tree nuts in children. We conducted a randomized trial (PrEggNut Study) to determine the effectiveness of high maternal dietary intake of eggs and peanuts during pregnancy and lactation, as compared with low intake of these foods, as a strategy for infant food-allergy prevention.

Methods

Trial Design and Oversight

PrEggNut was a two-group (1:1 ratio), parallel-design, multisite, single-blind, randomized, controlled superiority trial conducted across four Australian cities.

Trial Participants

Pregnant women at less than 23 weeks' gestation with a singleton pregnancy who were able to give informed consent and who were planning to breast-feed for at least 4 months were eligible to participate. In addition, the fetus needed to have at least two biologic family members (mother, father, or siblings) with medically diagnosed allergic disease (asthma, eczema or atopic dermatitis, allergic rhinitis, or IgE-mediated food allergy). Women with egg or peanut allergies were ineligible to participate, because they would not be able to safely follow the intervention without allergic reactions.

Interventions

Participating women were randomly assigned to follow either a diet high in eggs and peanuts (high egg-peanut group) or a standard (control) egg and peanut diet (standard-diet group). Participants in the high egg-peanut group were asked to consume at least 6 eggs and 60 peanuts per week, as compared with no more than 3 eggs and 30 peanuts per week in the standard-diet group, commencing from enrollment until 4 months postnatally during lactation, unless breast-feeding ceased earlier. The standard-diet group was considered to represent current best practice, because the latest guidelines for food-allergy prevention do not recommend maternal avoidance of common food allergens during pregnancy or lactation.

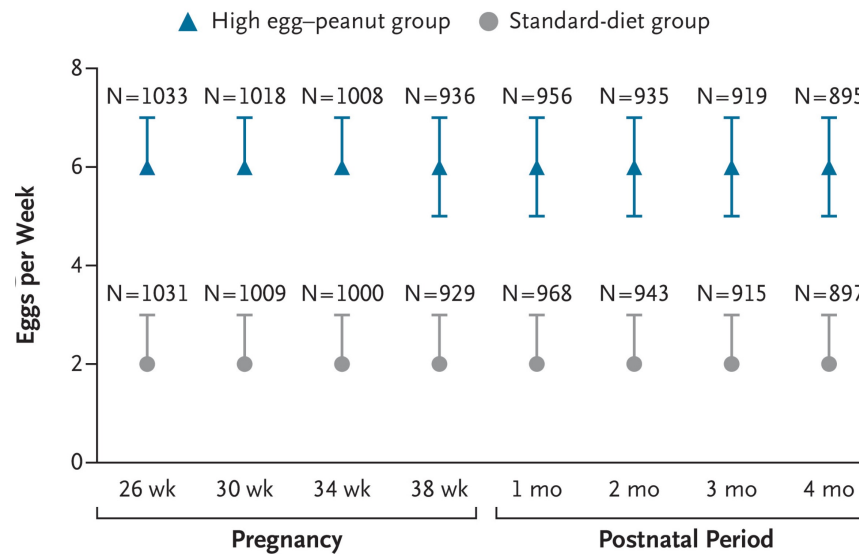
Outcomes

The primary outcome was infant IgE-mediated egg or peanut allergy at 1 year of age, which was assessed at major tertiary pediatric hospitals in each city.

Characteristic	High Egg–Peanut Group (N = 1070)	Standard-Diet Group (N = 1067)
Median gestation at randomization (IQR) — wk	20.6 (19.6–21.7)	20.6 (19.6–21.7)
Maternal age — yr	33.3±4.1	33.2±4.1
Maternal race — no./total no. (%)†		
White	886/1067 (83.0)	887/1063 (83.4)
Asian	109/1067 (10.2)	101/1063 (9.5)
Other	72/1067 (6.7)	75/1063 (7.1)
Educational level — no./total no. (%)		
Secondary school completion	998/1067 (93.5)	1003/1063 (94.4)
University degree	788/1067 (73.9)	799/1063 (75.2)
Median maternal prepregnancy body-mass index (IQR)‡	24.6 (21.8–28.4)	24.2 (21.7–28.6)
Allergic disease — no./total no. (%)§		
In mother of fetus	978/1068 (91.6)	973/1063 (91.5)
In father of fetus	928/1066 (87.1)	930/1063 (87.5)
In sibling of fetus	485/1067 (45.5)	488/1061 (46.0)
Food allergy — no./total no. (%)§		
In mother of fetus	68/1068 (6.4)	78/1063 (7.3)
In father of fetus	67/1066 (6.3)	90/1063 (8.5)
In sibling of fetus	224/1067 (21.0)	212/1061 (20.0)
Median peanut intake per week (IQR)		
Maternal intake	40 (17–83)	33 (15–63)
Household intake	100 (40–180)	80 (35–146)
Median egg intake per week (IQR)		
Maternal intake	4.0 (2.5–6.0)	3.4 (2.2–5.1)
Household intake	9.8 (6.2–15.1)	8.8 (5.4–13.2)
Infant male sex — no./total no. (%)	547/1034 (52.9)	527/1029 (51.2)

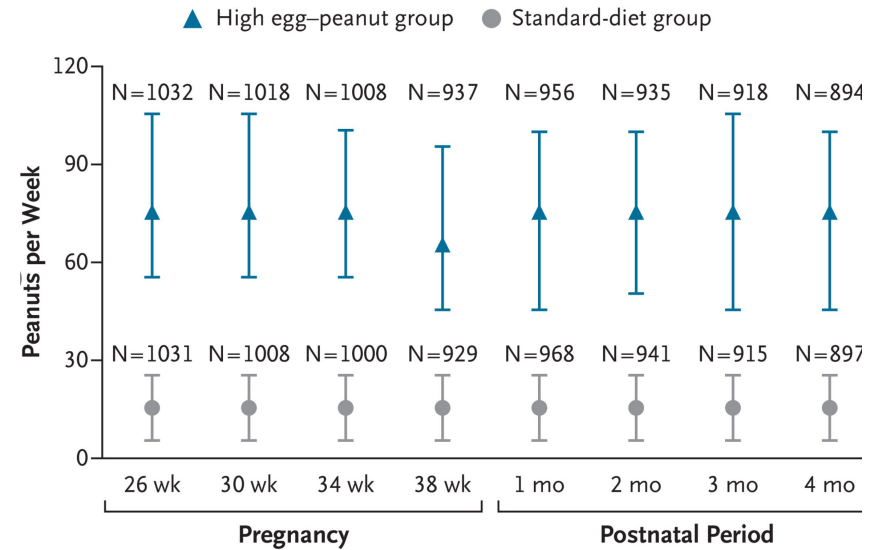
Infant Primary and Secondary Clinical Allergic Disease Outcomes.

Outcome	High Egg– Peanut Group (N = 1066)	Standard-Diet Group (N = 1064)	Relative Risk (95% CI)	
			Unadjusted	Adjusted†
no. of infants (%)				
Primary outcome				
IgE-mediated egg or peanut allergy	83 (7.8)	89 (8.4)	0.93 (0.69–1.26)	0.93 (0.69–1.26)‡
Secondary outcomes				
Sensitization to egg	122 (11.4)	133 (12.5)	0.91 (0.72–1.17)	0.92 (0.72–1.18)
Sensitization to peanut	80 (7.5)	66 (6.2)	1.21 (0.86–1.70)	1.21 (0.86–1.70)
IgE-mediated egg allergy	66 (6.2)	76 (7.2)	0.87 (0.62–1.21)	0.87 (0.62–1.21)
IgE-mediated peanut allergy	28 (2.6)	27 (2.6)	1.03 (0.60–1.77)	1.02 (0.60–1.76)
Medical diagnosis of eczema by 4 mo	175 (16.4)	192 (18.1)	0.91 (0.75–1.10)	0.91 (0.75–1.10)
Medical diagnosis of eczema by 12 mo	457 (42.8)	492 (46.2)	0.93 (0.84–1.02)	0.93 (0.84–1.02)



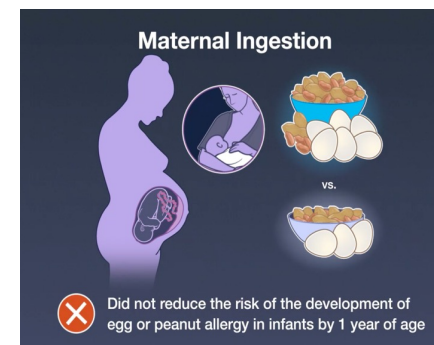
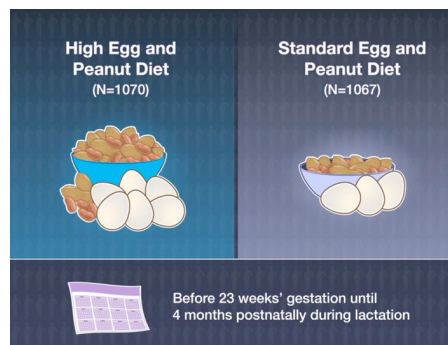
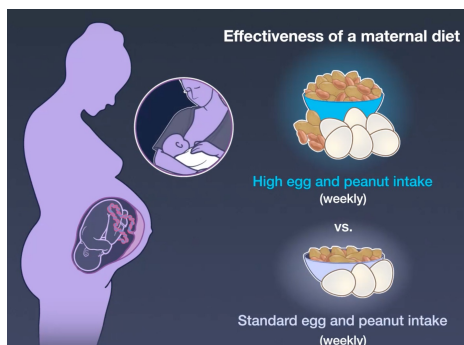
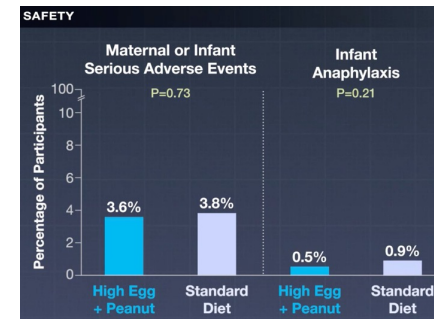
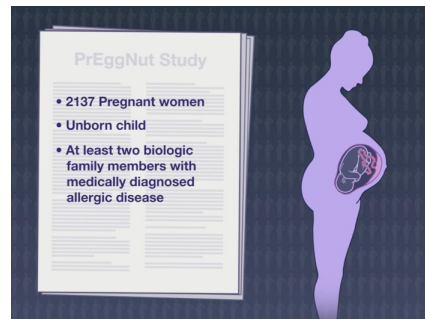
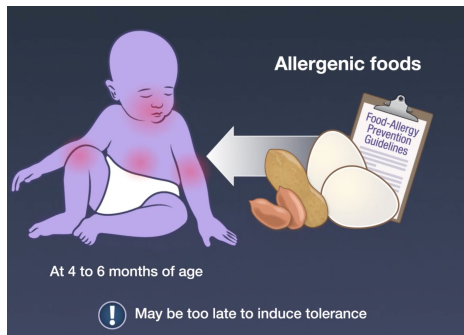
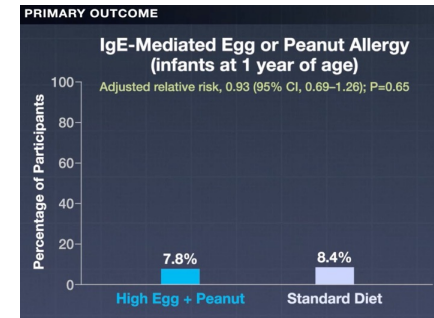
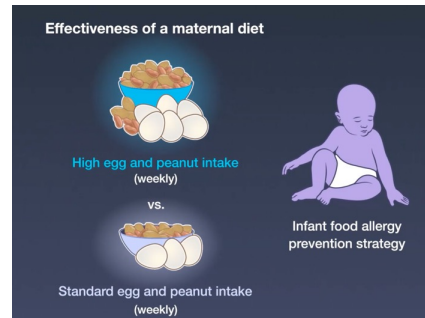
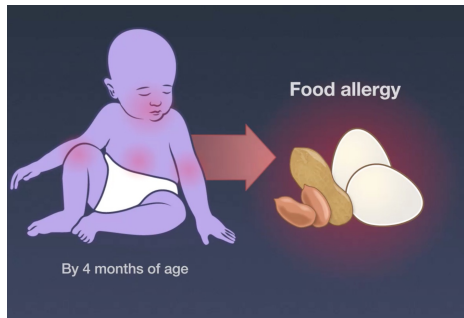
Weekly Egg Intake.

Shown are the median weekly egg intake values (surveyed each month) across the intervention period for each trial group. Error bars indicate the interquartile range; the absence of a lower whisker indicates that the 25th percentile and median values were the same.



Weekly Peanut Intake.

Shown are the median weekly peanut intake values (surveyed each month) across the intervention period for each trial group. Error bars indicate the interquartile range.

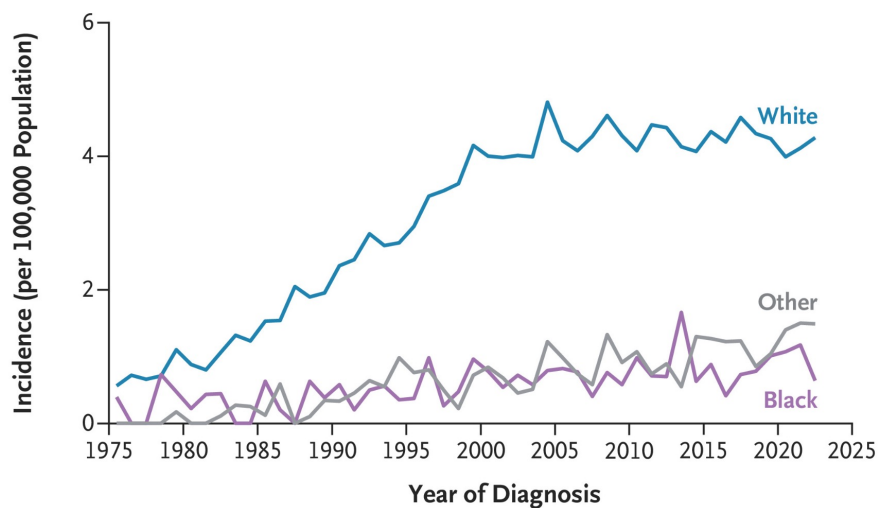


Esophageal Cancer

Summary

Cancer of the esophagus is the thirteenth most common cancer and the seventh leading cause of cancer-related death worldwide, resulting in approximately 500,000 deaths annually. Population-based 5-year survival has improved in recent decades but rarely exceeds 20%. The main histologic types of esophageal cancer, adenocarcinoma and squamous-cell carcinoma, have different incidence patterns. The past four decades have witnessed a rapidly increasing incidence of esophageal adenocarcinoma in many Western countries, especially among White men, and a decreasing incidence of esophageal squamous-cell carcinoma. In contrast, the opposite is true for most other populations, in which esophageal squamous-cell carcinoma remains the most frequent form. This review focuses on recent developments in the epidemiologic characteristics, risk factors, prevention, and clinical management of esophageal cancer.

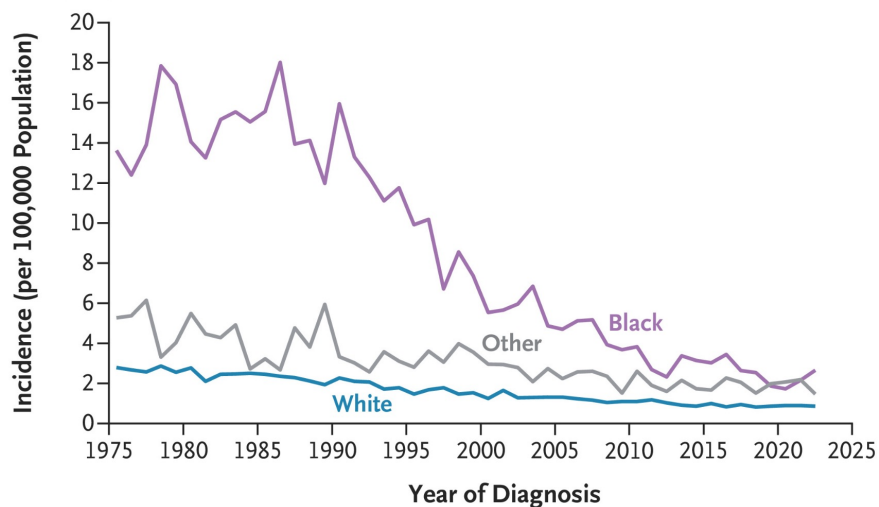
A Esophageal Adenocarcinoma



Race-Specific and Age-Standardized Incidence of Esophageal Cancer among Men in the United States.

Shown are the incidence of esophageal adenocarcinoma (Panel A) and that of esophageal squamous-cell carcinoma (Panel B) among men in the United States from 1975 through 2022, with stratification according to race. Data were obtained from eight registries of the Surveillance, Epidemiology, and End Results program.³

B Esophageal Squamous-Cell Carcinoma



**Established Nongenetic Risk Factors for Esophageal
Adenocarcinoma and Esophageal Squamous-Cell Carcinoma.**

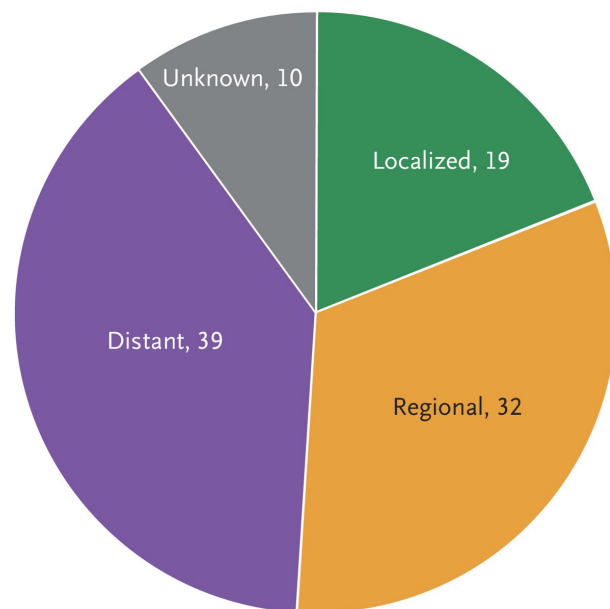
Risk Factor	Esophageal Adenocarcinoma	Esophageal Squamous-Cell Carcinoma
Older age	Increased risk with age	Increased risk with age
Male sex	Incidence 6 times as high among men as among women	Incidence >2 times as high among men as among women
Gastroesophageal reflux disease	Increased risk with longer symptom duration and greater frequency and severity	No association
Obesity	Increased risk with greater body-mass index	No increased risk with greater body-mass index
Tobacco smoking	Moderately increased risk; no clear risk reduction after quitting	Increased risk with longer duration and greater amount per day; clear risk reduction after quitting
Alcohol consumption	No association	Increased risk with greater consumption
<i>Helicobacter pylori</i> infection	Inverse association	No association

KEY POINTS

Esophageal Cancer

- The two main histologic types of esophageal cancer, adenocarcinoma and squamous-cell carcinoma, have markedly different incidence patterns, causes, and treatment and should be regarded as separate disease entities.
- The main risk factors for esophageal cancer are nongenetic and include gastroesophageal reflux disease and obesity for adenocarcinoma and smoking and overconsumption of alcohol for squamous-cell carcinoma.
- Endoscopic screening for premalignant conditions and early esophageal cancer may be considered for persons at high risk, and whether endoscopic surveillance is warranted in persons with premalignant conditions, as well as the appropriate time intervals, should be determined by the histologic findings.
- Centralization of surgery for esophageal cancer (i.e., performing the surgery at a center where there is a high volume of procedures performed) improves patient outcomes and facilitates a tailored surgical approach that is based on patient and tumor characteristics.
- The multimodal treatment of esophageal cancer has progressed substantially, owing in part to the increased use of immunotherapy.

A Percentage of Cases According to Stage



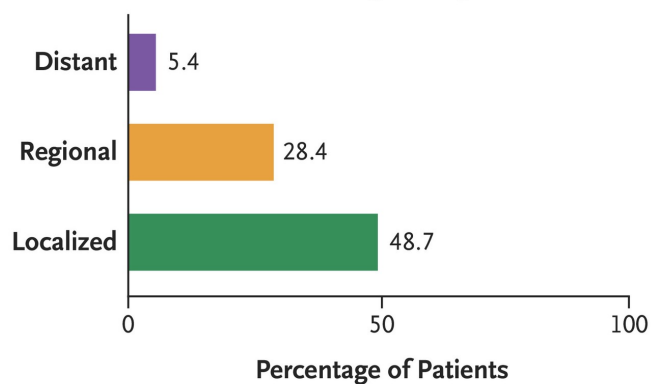
Disease Incidence and 5-Year Survival among Persons with Esophageal Cancer in the United States.

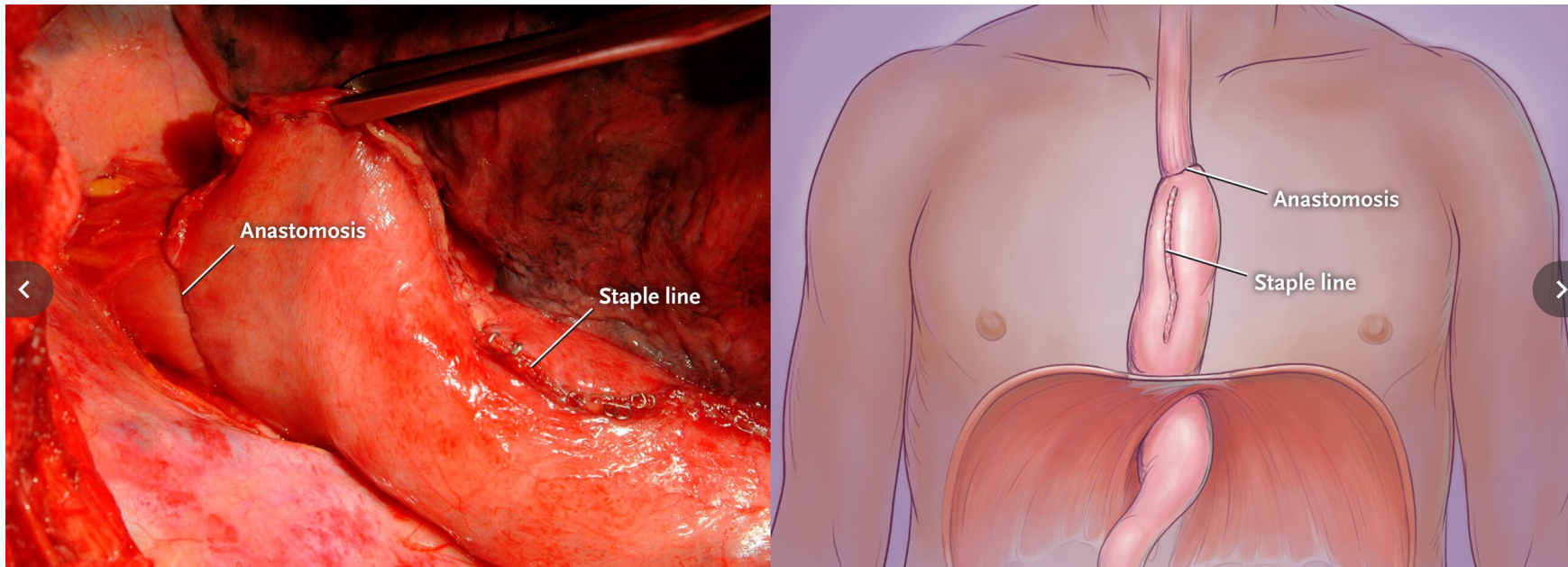
Shown are the incidence of esophageal cancer according to tumor stage (Panel A) and the 5-year survival among persons with esophageal cancer (Panel B) in the United States from 2015 through 2021. Data were obtained from 21 registries of the Surveillance, Epidemiology, and End Results program.²⁷

Localized esophageal cancer means the cancer is growing only inside the esophagus and has not spread to nearby tissues, lymph nodes, or distant organs.

A regional esophageal cancer means the disease has grown through the lining or muscle of the esophagus and spread into nearby tissues or local lymph nodes, but it has not reached distant organs

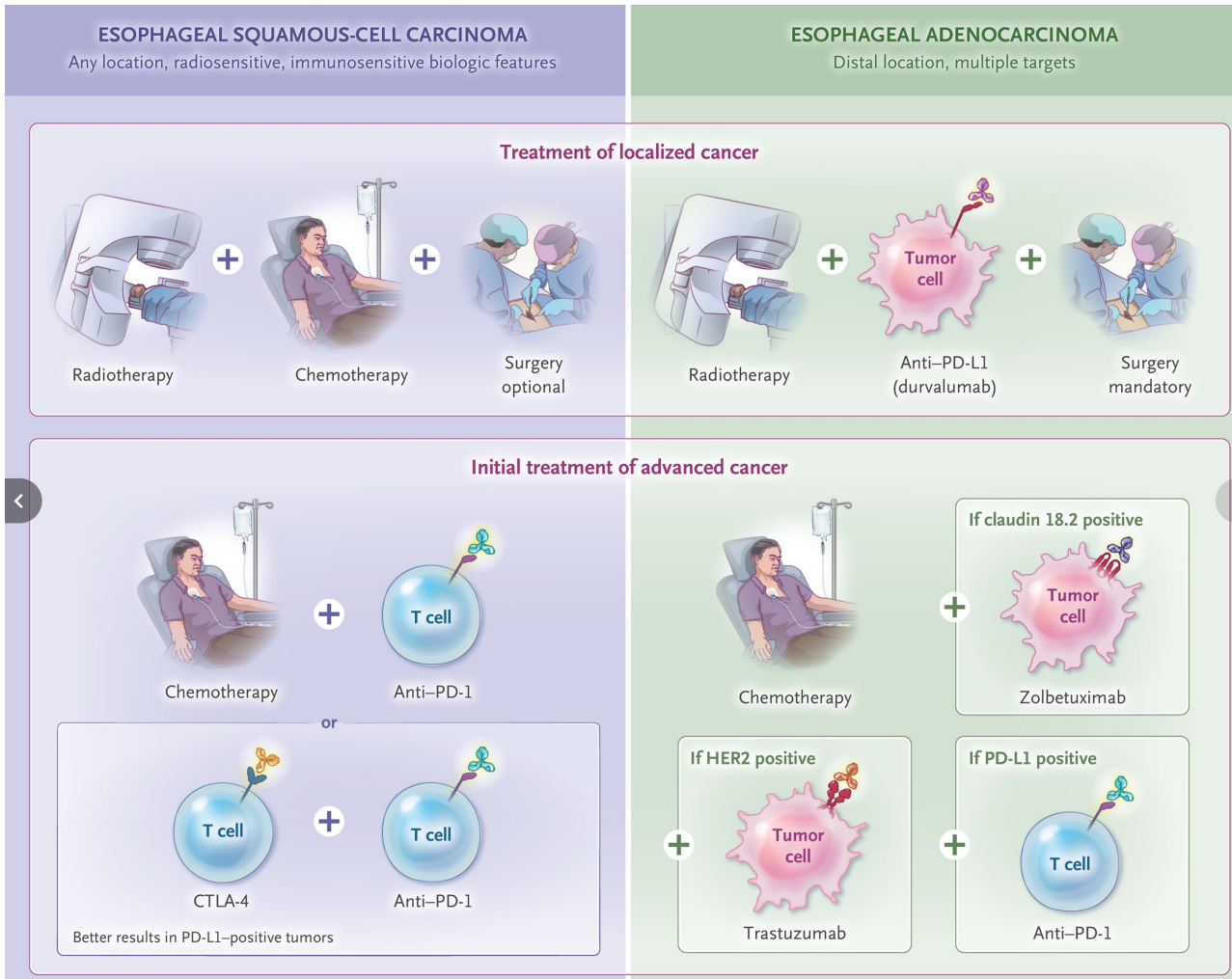
B 5-Yr Relative Survival According to Stage





Esophagectomy in Esophageal Cancer.

Shown is a picture of an esophagectomy (left image) and a diagram showing the corresponding anatomy (right image). The main part of the esophagus (with the tumor) has been removed and replaced by a gastric tube, which has been pulled up into the upper part of the chest. The sutured anastomosis links the remaining upper part of the esophagus with the gastric tube. The longitudinal line of staples is used to form the stomach into a tube.



Treatment Paradigms for Esophageal Cancer According to Histologic Type.

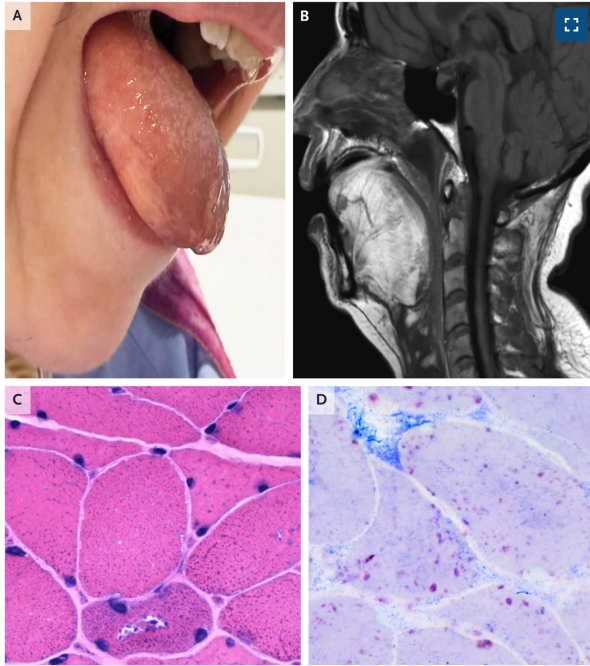
Shown are the recommended treatment approaches for esophageal squamous-cell carcinoma and esophageal adenocarcinoma. CTLA-4 denotes cytotoxic T-lymphocyte antigen 4, HER2 human epidermal growth factor receptor 2, PD-1 programmed cell death protein 1, and PD-L1 programmed death ligand 1.

Chemotherapy for squamous cell esophageal cancer (ESCC) typically combines a platinum drug (like cisplatin or oxaliplatin) with a fluoropyrimidine (like 5-fluorouracil or capecitabine), often alongside radiation or immunotherapy depending on the stage.

Conclusions and Future Perspectives

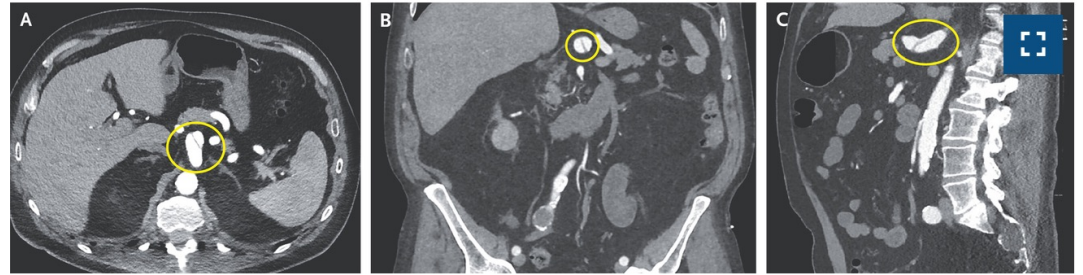
Recent advances in the detection and treatment of esophageal cancer and in the identification of the causes of the disease have improved patient survival and quality of life. The marked etiologic and biologic differences between esophageal squamous-cell carcinoma and esophageal adenocarcinoma indicate that these subtypes should be regarded as separate disease entities. However, more research is needed for a better understanding of the causes of both esophageal squamous-cell carcinoma, particularly in developing countries, and esophageal adenocarcinoma. Future preventive measures and screening efforts need to be directed toward persons at a well-defined high risk for esophageal cancer rather than the population at large.

Late-Onset Pompe Disease



A 54-year-old woman presented to the emergency department with a 4-month history of progressively worsening asthenia and falls and 5 days of dyspnea. Physical examination was notable for macroglossia (Panel A), head drop, and mild symmetric weakness of the proximal upper and lower limbs. The creatine kinase level was 373 U per liter (reference range, 24 to 173). Magnetic resonance imaging of the head and cervical spine was notable for fatty infiltration of the tongue (Panel B) and paravertebral muscles. Owing to clinical suspicion of an underlying metabolic myopathy, biopsy of the deltoid muscle was performed while results of enzymatic and genetic testing were pending. Hematoxylin and eosin staining of skeletal muscle (Panel C) showed vacuolar myopathy, and acid phosphatase staining (Panel D) showed increased acid phosphatase activity suggestive of lysosomal dysfunction. Enzymatic activity of acid α -glucosidase in leukocytes was low, and genetic testing identified compound heterozygosity for pathogenic variants in GAA. A diagnosis of late-onset Pompe disease, an autosomal recessive lysosomal disorder that manifests as a skeletal myopathy, was made. Treatment with alglucosidase alfa, an enzyme-replacement therapy, was administered while respiratory failure from ventilatory-muscle weakness and pneumonia was managed. The patient was discharged to an inpatient rehabilitation facility 2 months after presentation.

Celiac-Artery Dissection



A 72-year-old man with well-controlled hypertension, hyperlipidemia, and a stable ascending aortic aneurysm presented to the emergency department with sudden-onset, severe epigastric pain after moving boxes in his house. The pain had lasted for 10 to 15 minutes before hospital arrival and was not associated with nausea, vomiting, or abdominal discomfort. The patient had no history of smoking. His blood pressure was 164/89 mm Hg. The physical examination was unremarkable. The troponin level was normal, and an electrocardiogram showed no ischemic changes. The serum lactate level was not checked during the admission. Owing to concern for aortic dissection, computed tomographic angiography (CTA) of the chest, abdomen, and pelvis was performed. These scans showed a dissection of the celiac artery with an underlying aneurysmal dilatation (Panel A, axial view; Panel B, coronal view; and Panel C, sagittal view). Aneurysmal dilatations of the infrarenal abdominal aorta and distal right common iliac artery were also seen. A diagnosis of a spontaneous, isolated celiac-artery dissection — an uncommon vascular phenomenon with a favorable prognosis that typically improves with conservative treatment — was made. A vascular surgeon evaluated the patient and recommended medical management. Treatment with clopidogrel and antihypertensive medications was prescribed, and the pain did not recur. At discharge, a 6-month follow-up CTA was scheduled to monitor for thrombosis, stenosis, or worsening of the aneurysmal dilatation.

Das Wernicke-Korsakow-Syndrom ist eine schwere neurologische Erkrankung, die durch einen akuten oder chronischen Mangel an Vitamin B1 (Thiamin) ausgelöst wird.

Ursachen

- **Vitamin-B1-Mangel:** Thiamin ist lebenswichtig für den Energiestoffwechsel der Gehirnzellen.
- **Alkoholmissbrauch:** Die häufigste Ursache ist langjährige Alkoholabhängigkeit, da Alkohol die Aufnahme von Vitamin B1 im Darm stört und oft eine Mangelernährung begünstigt.
- **Weitere Auslöser:** In seltenen Fällen führen starkes, anhaltendes Erbrechen, Essstörungen oder schwere Mangelernährung zu dem Defizit.

Symptome der Wernicke-Enzephalopathie

- Bewusstseinsstörungen
- Ophthalmoplegien
- Ataxie

Symptome des Korsakow-Syndroms:^[5]

- anterograde Gedächtnisstörungen
- Konfabulationen
- Orientierungsstörungen



Case 26-2026: A 62-Year-Old Woman with Memory Loss, Anhedonia, and Temporal Wasting

The patient had been in her usual state of health until 1 month before the current presentation, when **anorexia, dysgeusia, and xerostomia** developed, which resulted in decreased oral intake. Two weeks before the current presentation, the patient was seen in the oncology clinic at this hospital for ongoing **breast cancer treatment**. She reported altered taste, a profound lack of appetite, and severe exertional intolerance; she stated that she had previously been able to walk 2 to 3 miles continuously but now felt **too tired and unstable while walking** to proceed for more than a block. She reported no depression, but her son had observed that she seemed apathetic and disengaged and was sleeping for most of the day. In addition, the son described the patient as confused and having progressively **worsening short-term memory loss**. Treatment with intravenous hydration was administered.

Three days before the current presentation, the son noticed that the patient had progressive inability to walk. She had severe imbalance and often used the wall or furniture as support to move around the house; she had not sustained any falls. In addition, the patient was eating minimal amounts of food, and her memory loss had continued to progress. Owing to these symptoms, she was referred to the emergency department of this hospital for further evaluation.

The **medical history** was notable for **infarction in the posterior aspect of the left temporal lobe and left occipital lobe that had occurred 3 years before** the current presentation, with an associated seizure disorder. The patient also had a history of **metastatic adenoid cystic carcinoma** of the breast for which she was receiving treatment with pembrolizumab and an agonist of stimulator of interferon genes. On presentation to the emergency department, the vital signs were normal. The patient was oriented to person, place, and time. The mucous membranes were dry, but the remainder of a complete physical examination was normal. Computed tomography (**CT**) of the head and radiography of the chest showed no acute findings, and **electroencephalography (EEG)** showed no epileptiform discharges. Treatment with intravenous normal saline and thiamine was administered, and the patient was admitted to the oncology service for further evaluation.

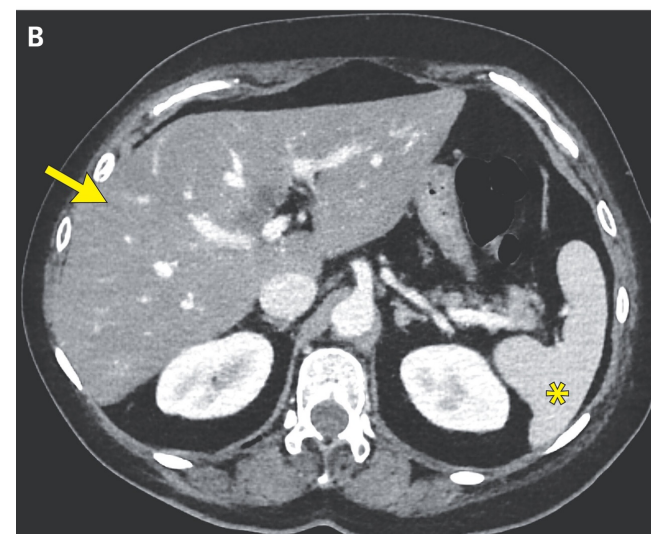
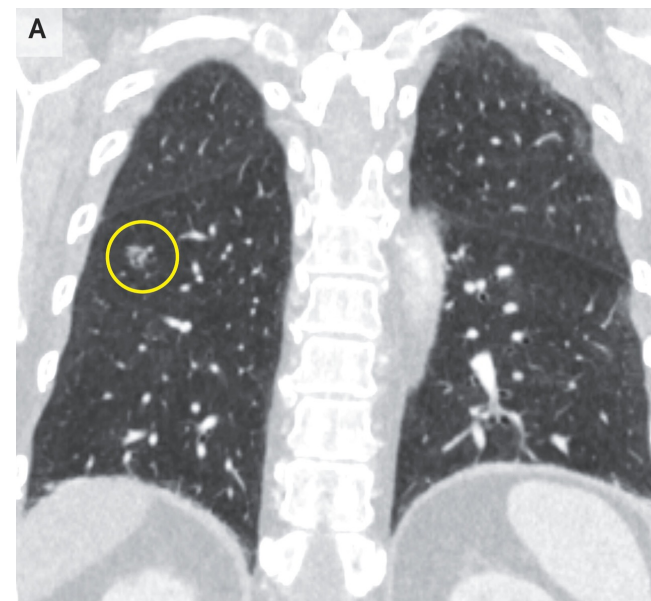
On admission, the patient noted ongoing fatigue and a weight loss of 5 kg during the previous month. She acknowledged her memory deficits and described disinterest in her hobbies, such as arts and crafts, along with feelings of **hopelessness surrounding her declining health**. She reported that, at times, she lacked the will to live but continued to attend medical visits; she reported no active suicidal ideation. A review of systems was negative for recent seizures, headache, fever, change in the character of her chronic cough, dysuria, diarrhea, abdominal pain, rash, dizziness with standing, vertigo, dysphagia, numbness and tingling, **(no) diplopia**, and focal weakness.

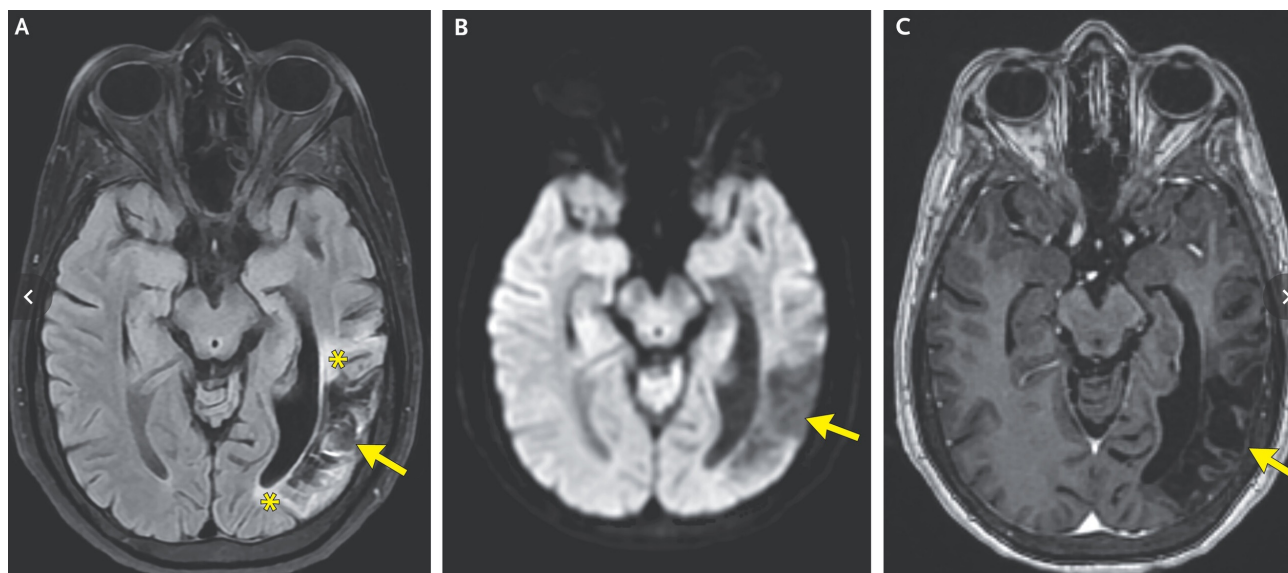
Medications included aspirin, amlodipine, and levetiracetam, as well as dextromethorphan–guaifenesin as needed for cough. The patient had had no recent changes to these medications. She lived in New England with her adult son, who was her primary caretaker. She had previously been a small-business owner but had retired when she received the breast cancer diagnosis. She drank one glass of wine per week and occasionally used edible cannabis for nausea and low appetite; she did not smoke cigarettes. Her family history was notable for breast cancer in a maternal aunt.

On examination, the oral temperature was 36.1°C, the blood pressure 163/88 mm Hg, the heart rate 94 beats per minute, the respiratory rate 18 breaths per minute, and the oxygen saturation 96% while the patient was breathing ambient air. The weight was 64.9 kg, and the body-mass index (the weight in kilograms divided by the square of the height in meters) was 24. Temporal wasting was noted. The patient was able to speak in full sentences and was alert and oriented to person and time. However, she had episodes of confabulation, in which she reported that she was at her business, stated that the business was located in this hospital, and referred to the examiner as her coworker. She was noted to be forgetful; she was unable to recall three out of three objects at 5 minutes, even with cueing. She was able to state the days of the week backward. Her affect was bright and concordant with her stated mood.

The patient's cranial-nerve function was normal and symmetric. She had no pronator drift or other motor deficits. She performed finger-to-nose testing smoothly. The brachioradialis, patellar, and ankle reflexes were normal and symmetric.

Variable	Reference Range, Adults†	On Presentation
Hemoglobin (g/dl)	12.0–16.0	12.4
Hematocrit (%)	36.0–46.0	37.5
White-cell count (per μ l)	4500–11,000	5460
Platelet count (per μ l)	150,000–400,000	327,000
Sodium (mmol/liter)	135–145	138
Potassium (mmol/liter)	3.4–5.0	3.6
Chloride (mmol/liter)	98–108	100
Carbon dioxide (mmol/liter)	23–32	24
Urea nitrogen (mg/dl)	8–25	7
Creatinine (mg/dl)	0.60–1.50	0.40
Calcium (mg/dl)	8.5–10.5	9.2
Glucose (mg/dl)	70–110	66
Aspartate aminotransferase (IU/liter)	9–32	▶ 182
Alanine aminotransferase (IU/liter)	7–33	▶ 165
Alkaline phosphatase (IU/liter)	30–100	▶ 120
Total bilirubin (mg/dl)	0.0–1.0	0.3
Albumin (g/dl)	3.3–5.0	3.7
Globulin (g/dl)	1.9–4.1	1.0
Vitamin B ₁₂ (pg/ml)	>231	1320
Thyrotropin (μ IU/liter)	0.40–5.90	2.68
C-reactive protein (mg/liter)	<8.0	1.0
Ammonia (μ mol/liter)	12–48	25





Magnetic resonance imaging (MRI), performed with and without the administration of intravenous contrast material, showed stable encephalomalacia and gliosis in the posterior aspect of the left temporal lobe and left occipital lobe. No acute infarct, mass lesion, or abnormal enhancement was identified.

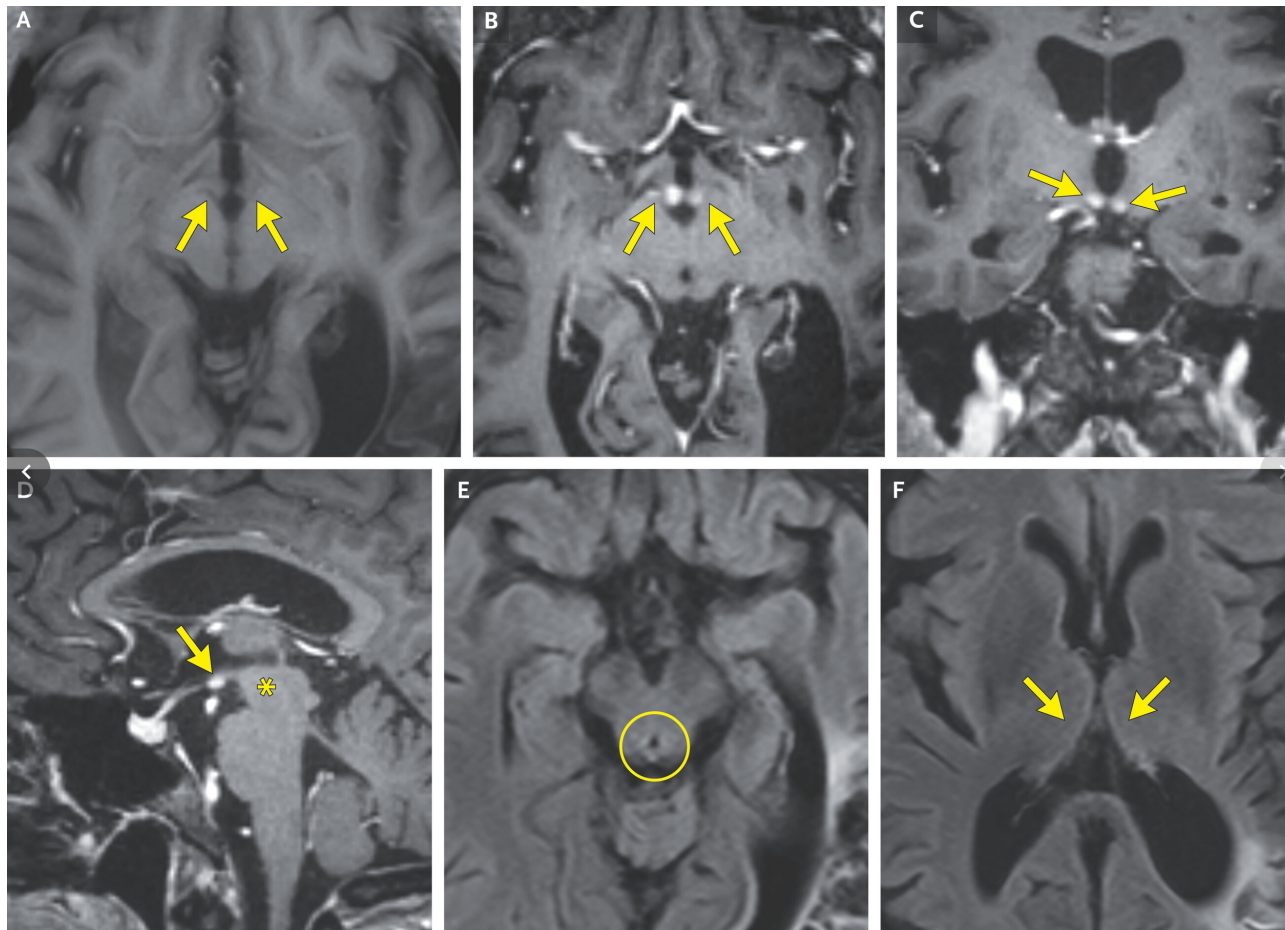
Wernicke Encephalopathy

The classic triad of mental-status changes, ataxia, and ophthalmoparesis is present in only 10 to 16% of patients with Wernicke encephalopathy. A majority of patients with Wernicke encephalopathy (71%) have no ophthalmoparesis or other ocular abnormalities; of note, the most common ocular abnormality seen in patients with Wernicke encephalopathy is horizontal nystagmus. Approximately 19% of patients with Wernicke encephalopathy present without any classic symptoms.

The diagnosis in this patient's case is the Wernicke–Korsakoff syndrome due to **malnutrition** associated with **side effects caused by immunomodulator** therapy. I would recommend additional MRI of the head, with a focus on the medial mammillary bodies for signs of degeneration. I would expect this imaging to show hyperintensity involving the medial thalami, mammillary bodies, periaqueductal gray matter, and periventricular region. Such imaging has poor sensitivity (53%) but high specificity (93%) for the diagnosis. Given the catastrophic consequences of untreated Wernicke encephalopathy, including high mortality, I would also recommend immediate initiation of treatment with **high-dose intravenous thiamine to ensure neuronal preservation**.

Follow-up

The patient completed an extended course of intravenous thiamine administered three times per day for 1 week, given the severity of her deficits. The thiamine level that had been measured early in the hospital course, after intravenous thiamine administration, was normal (156 nmol per liter; reference range, 70 to 180). The patient's condition improved somewhat, although persistent confusion and anterograde memory impairment were noted on formal testing performed during occupational therapy sessions. She was discharged home with visiting services under her son's care.



Repeat MRI of the Head.

Axial T1-weighted images obtained before and after the administration of contrast material (Panels A and B, respectively) show marked enhancement involving the mammillary bodies on both sides (arrows). T1-weighted contrast-enhanced images in the coronal and sagittal planes (Panel C and D, respectively) also show avid enhancement involving the mammillary bodies (arrows), which can be seen anterior to the midbrain (Panel D, asterisk). Axial T2-weighted FLAIR images at the level of the midbrain and thalami (Panels E and F, respectively) show no definitive signal abnormality in the periaqueductal gray matter (Panel E, circle) or medial thalami (Panel F, arrows).

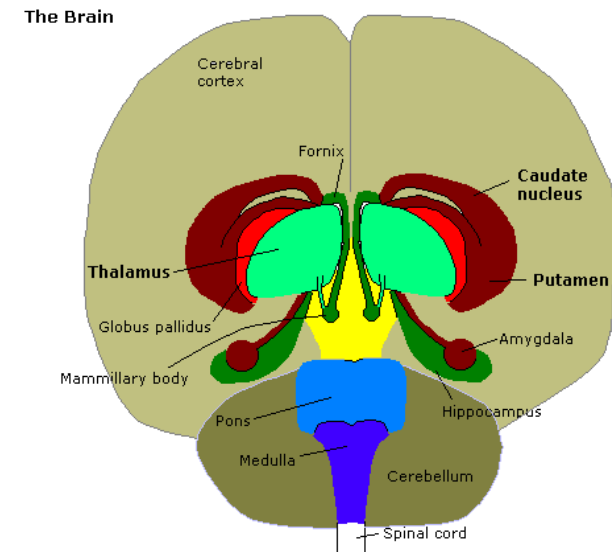
Die **Mammillarkörper** (lateinisch *Corpora mamillaria*, Singular *Corpus mamillare*) sind zwei kleine, paarige, brustwarzenförmige Erhebungen an der Unterseite des Gehirns. Sie gehören anatomisch zum **Hypothalamus** (Teil des Zwischenhirns) und sind funktionell ein wichtiger Bestandteil des **limbischen Systems**.

Hier ist eine Übersicht zu ihrer Anatomie, Funktion und klinischen Relevanz:

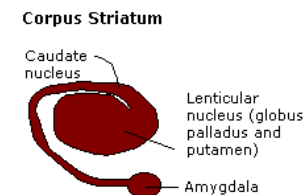
Episodisches Gedächtnis: Sie sind essenziell für das **Fakten- und Ereignisgedächtnis** (recollective memory). Sie helfen dabei, Informationen über Zeitpunkte, Orte und Erlebnisse miteinander zu verknüpfen und abzurufen.

Räumliche Orientierung: Durch Verbindungen zum Hirnstamm (Gudden-Kerne) sind sie vermutlich auch an der Verarbeitung von Kopfrichtungs- und Navigationssignalen beteiligt.

Emotions- und Verhaltensregulation: Als Teil des limbischen Systems wirken sie moduliert an emotionalen Reaktionen und dem Belohnungssystem mit.



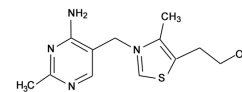
The brain as viewed from the underside and front. The thalamus and Corpus Striatum (Putamen, caudate and amygdala) have been splayed out to show detail.



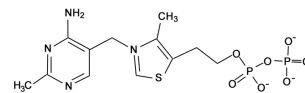
Thiamin, auch bekannt als **Vitamin B1**, ist ein wasserlösliches Vitamin, das für den Energiestoffwechsel und das Nervensystem unentbehrlich ist.

Funktion und Wirkung

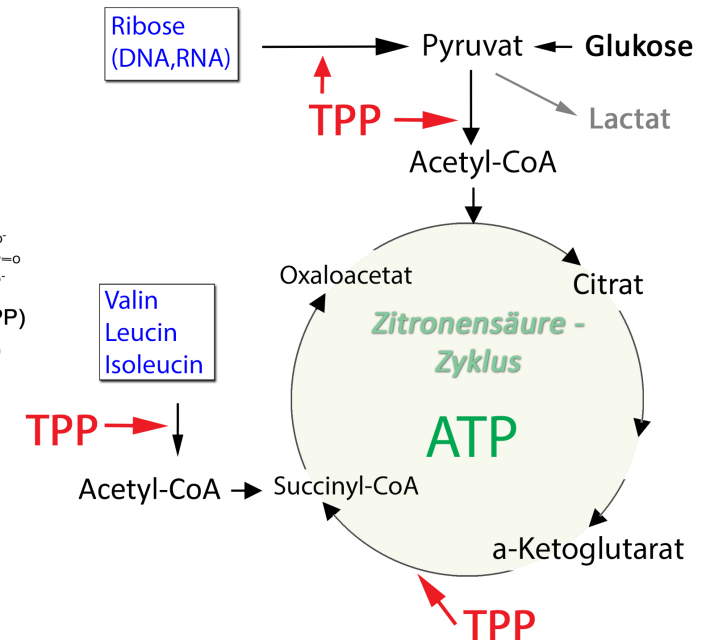
- **Energiegewinnung:** Es hilft dem Körper, Kohlenhydrate aus der Nahrung in nutzbare Energie umzuwandeln. Das ist besonders wichtig für Organe mit hohem Energiebedarf wie das Gehirn und das Herz.
- **Nervensystem:** Es unterstützt die normale Funktion der Nerven und die Reizweiterleitung.
- **Psychische Funktion:** Es trägt zu einer normalen psychischen Verfassung bei



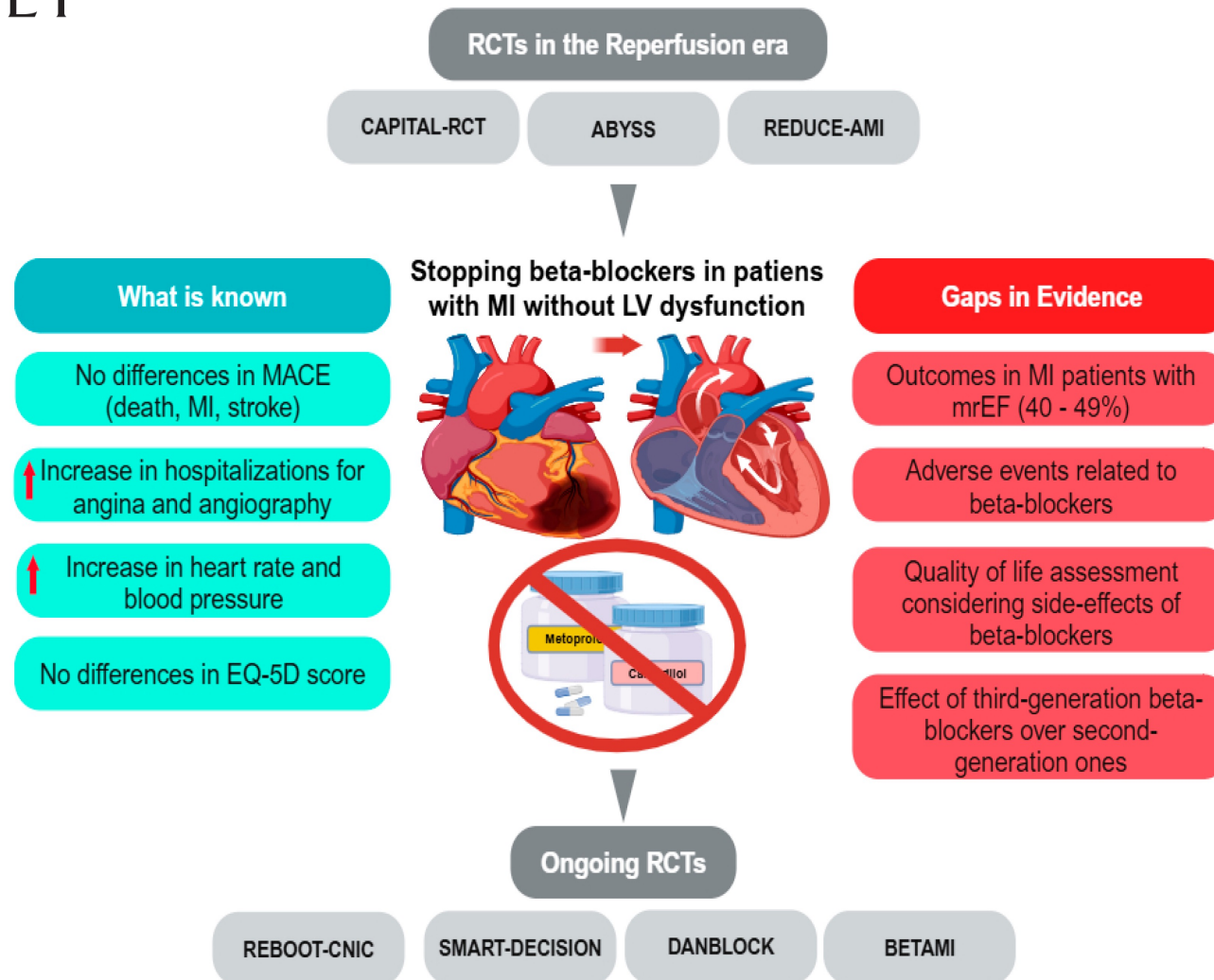
Thiamin (Vitamin B1)



Thiamin-Diphosphat (TPP)
(Thiamin-Pyrophosphat)



THE LANCET



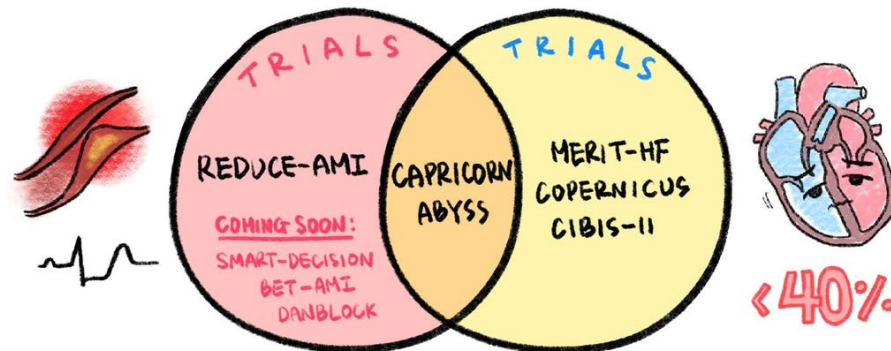


DOES THIS PATIENT NEED BETA BLOCKERS? 🧐



POST-ACUTE
CORONARY SYNDROME

HEART FAILURE WITH
REDUCED EJECTION FRACTION



OTHER INDICATIONS

β 1-SELECTIVE AGENTS

NONSELECTIVE BETA BLOCKERS
(e.g. PROPRANOLOL)



Rate control
for
Tachyarrhythmias
(Afib, Aflutter, ...)



Anginal
Relief



Tremors



Migraines

Discontinuation of β -blockers in stable patients with previous myocardial infarction, preserved left ventricular ejection fraction, and no heart failure: a pooled analysis of individual patient data

EF>40%

Are beta-blockers necessary?

Probably not

Summary

Background Many stable patients with chronic coronary syndrome continue β -blocker therapy for years after a myocardial infarction, despite having no clear ongoing indication. Whether β -blockers can be safely discontinued in such patients remains uncertain. The objective of this analysis was to assess the non-inferiority of β -blocker discontinuation versus continuation in patients with previous myocardial infarction and no remaining indication.

Methods We performed a pooled analysis of individual patient data from the ABYSS and SMART-DECISION randomised trials in stable patients over 6 months after a myocardial infarction with a left ventricular ejection fraction of $\geq 40\%$ and no heart failure. Non-inferiority was assessed for the composite primary endpoint of all-cause death, myocardial infarction, stroke, or hospitalisation for cardiovascular reasons, and for the key secondary endpoint of all-cause death, myocardial infarction, or hospitalisation for heart failure. Analyses used a one-stage mixed-effects Cox proportional hazards model including trial as a random effect with margins of 1.25 for the primary endpoint and 1.40 for the key secondary endpoint. The review protocol was registered with PROSPERO, number CRD420261299839.

Findings Among 6238 patients (3698 from ABYSS and 2540 from SMART-DECISION), 3092 were assigned to β -blocker discontinuation and 3146 to continuation. Median time from index myocardial infarction to randomisation was 3.6 years (IQR 1.6–7.5) and median follow-up was 3.0 years (2.3–3.8). The primary endpoint occurred in 532 (17.2%) of 3092 patients in the β -blocker discontinuation group and 500 (15.9%) of 3146 in the continuation group (hazard ratio 1.09 [95% CI 0.97–1.24]; $p_{\text{non-inferiority}}=0.016$). The key secondary endpoint occurred in 201 (6.5%) of 3092 patients in the discontinuation group and 201 (6.4%) of 3146 patients in the continuation group (1.01 [0.83–1.23]; $p_{\text{non-inferiority}}=0.0006$). Findings were consistent irrespective of background left ventricular ejection fraction.

Interpretation In stable patients with previous myocardial infarction, left ventricular ejection fraction $\geq 40\%$, no heart failure, and no other indication for β -blocker therapy, discontinuation met the non-inferiority criteria for the primary and key secondary endpoints. Interpretation of the primary endpoint is limited by its hospitalisation-heavy and trial-dependent composition.

	β-blocker discontinuation (n=3092)	β-blocker continuation (n=3146)
Demographic and cardiovascular risk		
Age, years	63.3 (56.0–70.6)	63.0 (56.0–70.6)
Sex		
Male	2618 (84.7%)	2657 (84.5%)
Female	474 (15.3%)	489 (15.5%)
BMI, kg/m ²	25.8 (23.7–28.4)	25.8 (23.7–28.4)
Current smoker	751 (24.3%)	694 (22.1%)
Hypertension	1540 (49.8%)	1571 (49.9%)
Diabetes	873 (28.2%)	843 (26.8%)
Dyslipidaemia	1733 (56.0%)	1782 (56.6%)
Medical history		
ST-segment elevation myocardial infarction	1882 (60.9%)	1891 (60.1%)
Duration between last myocardial infarction and random assignment, years	3.6 (1.6–7.4)	3.6 (1.5–7.5)
Multivessel disease	1707 (55.2%)	1737 (55.2%)
Revascularisation for index myocardial infarction (PCI or CABG)	2963 (95.8%)	3011 (95.7%)
Peripheral vascular disease	115 (3.7%)	95 (3.0%)
Stroke or transient ischemic attack	86 (2.8%)	104 (3.3%)
Health status		
Ejection fraction at randomisation	59.4% (53.0–62.0)	59.0% (53.0–63.0)
Systolic blood pressure at baseline, mm Hg	130 (120–140)	130 (120–140)
Diastolic blood pressure at baseline, mm Hg	75 (69–81)	75 (69–82)
Heart rate at baseline, bpm	67 (60–75)	67 (60–75)
Data are median (IQR) or n (%). Percentages and summary statistics were calculated among patients with available data. Missing values were 228 of 6238 for BMI, 15 of 6238 for time from index myocardial infarction to random assignment, 80 of 6238 for left ventricular ejection fraction, 91 of 6238 for systolic blood pressure, 91 of 6238 for diastolic blood pressure, and 98 of 6238 for heart rate. CABG=coronary artery bypass grafting. PCI=percutaneous coronary intervention.		
Table 1: Baseline characteristics of the patients		

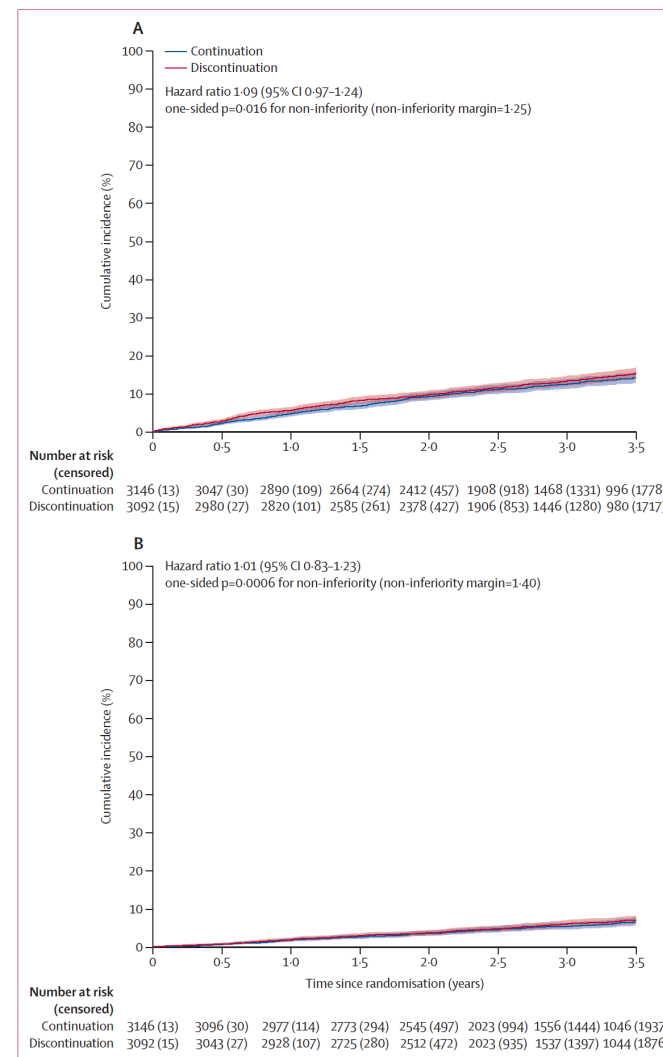


Figure 1: Kaplan-Meier estimates for the cumulative incidence of the primary composite endpoint of death, myocardial infarction, stroke, or hospitalisation for cardiovascular reasons (A) and the key secondary composite endpoint of death, myocardial infarction, or heart failure hospitalisation (B)

	Total (n=6238)	β-blocker discontinuation (n=3092)	β-blocker continuation (n=3146)	Risk difference* (95% CI)	Hazard ratio† (95% CI)	Non-inferiority p value‡
Primary endpoint						
Death, myocardial infarction, stroke, or hospitalisation for cardiovascular reason	1032 (16.5%)	532 (17.2%)	500 (15.9%)	0.50 (−1.19 to 2.20)	1.09 (0.97 to 1.24)	0.016
Key secondary endpoint						
Death, myocardial infarction, or hospitalisation for heart failure	402 (6.4%)	201 (6.5%)	201 (6.4%)	−0.03 (−1.24 to 1.18)	1.01 (0.83 to 1.23)	0.0006
Other secondary endpoints						
Death, myocardial infarction, or stroke	387 (6.2%)	189 (6.1%)	198 (6.3%)	−0.27 (−1.46 to 0.92)	0.96 (0.79 to 1.17)	..
Death, myocardial infarction, stroke, or hospitalisation for heart failure	448 (7.2%)	220 (7.1%)	228 (7.2%)	−0.27 (−1.54 to 1.01)	0.98 (0.81 to 1.17)	..
Death or hospitalisation for heart failure	289 (4.6%)	140 (4.5%)	149 (4.7%)	−0.34 (−1.38 to 0.71)	0.95 (0.75 to 1.20)	..
Death, myocardial infarction, stroke, or coronary revascularisation	569 (9.1%)	282 (9.1%)	287 (9.1%)	−0.33 (−1.73 to 1.06)	0.99 (0.84 to 1.17)	..
Individual components of endpoints						
Death	216 (3.5%)	103 (3.3%)	113 (3.6%)	−0.36 (−1.25 to 0.54)	0.92 (0.70 to 1.20)	..
Myocardial infarction	138 (2.2%)	71 (2.3%)	67 (2.1%)	0.17 (−0.57 to 0.90)	1.07 (0.77 to 1.49)§	..
Stroke	64 (1.0%)	26 (0.8%)	38 (1.2%)	−0.37 (−0.89 to 0.15)	0.69 (0.42 to 1.14)§	..
Hospitalisation for cardiovascular reasons	821 (13.2%)	427 (13.8%)	394 (12.5%)	0.60 (−0.92 to 2.12)	1.11 (0.97 to 1.28)§	..
Hospitalisation for heart failure	93 (1.5%)	50 (1.6%)	43 (1.4%)	0.25 (−0.35 to 0.85)	1.18 (0.78 to 1.77)§	..
Coronary revascularisation (PCI or CABG)	264 (4.2%)	131 (4.2%)	133 (4.2%)	−0.06 (−1.04 to 0.93)	1.00 (0.78 to 1.27)§	..

Data are n (%), unless otherwise specified. Wald-type 95% CIs are presented. Confidence intervals for secondary endpoints have not been adjusted for multiplicity and should therefore be regarded as descriptive. CABG=coronary artery bypass grafting. PCI=percutaneous coronary intervention. *Risk difference in proportion calculated with a generalised linear mixed model and including trial as a random effect. †Hazard ratio estimated with a one-stage mixed-effects Cox proportional-hazards model and included trial as a random effect. ‡Non-inferiority was assessed using a one-sided type 1 error of 0.025, with margins corresponding to an upper 97.5% confidence limit of 1.25 for the primary endpoint and 1.40 for the key secondary endpoint, as specified in the statistical analysis plan. §Cause-specific proportional hazards regression model was used with death as competing risk.

Table 2: Primary and secondary endpoints in the intention-to-treat population

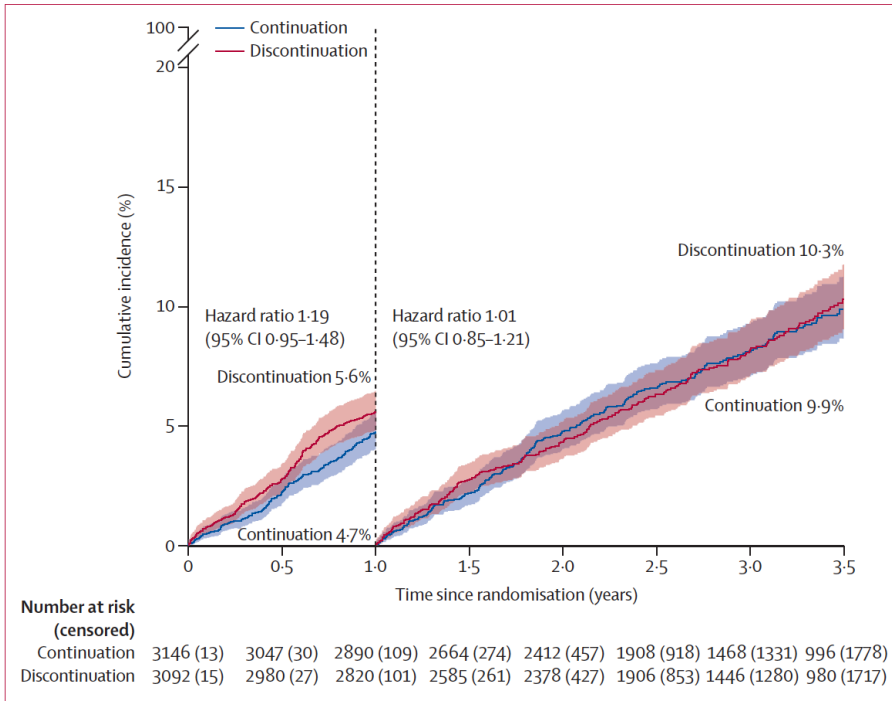


Figure 2: Landmark analysis at 12 months for the primary composite endpoint of death, myocardial infarction, stroke, or hospitalisation for cardiovascular reasons

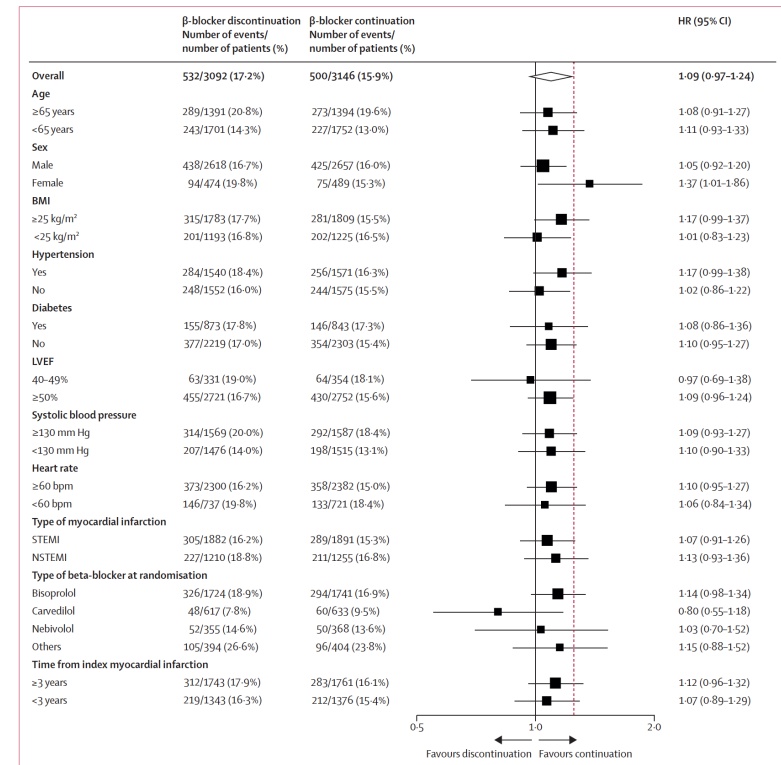


Figure 3: Subgroup analysis for the primary composite endpoint of death, myocardial infarction, stroke, or hospitalisation for cardiovascular reasons
The solid black vertical line indicates an HR of 1 and the dashed red vertical line indicates the non-inferiority margin. HR=hazard ratio. LVEF=left ventricular ejection fraction. NSTEMI=non-ST-segment elevation myocardial infarction. STEMI=ST-segment elevation myocardial infarction.

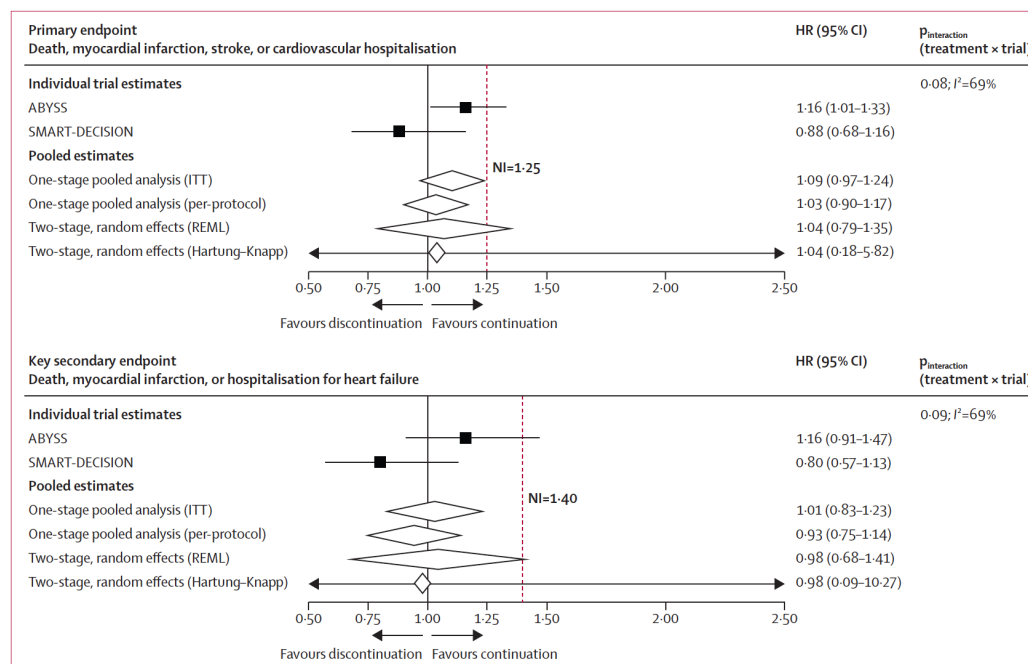


Figure 4: Effect estimates of the primary and key secondary endpoint and its corresponding sensitivity analyses

Data show the composite primary endpoint (death, myocardial infarction, stroke, or cardiovascular hospitalisation) and the key secondary endpoint (death, myocardial infarction, or heart failure hospitalisation). Filled squares represent individual trial estimates (area proportional to weight); diamonds represent pooled estimates. The primary analysis is the one-stage mixed-effects Cox proportional-hazards with trial included as a random effect. Dashed vertical lines indicate non-inferiority margins (primary endpoint: HR 1.25; key secondary endpoint: HR 1.40). For the two-stage random-effects model, the Hartung-Knapp correction (df=1) yields markedly wide confidence intervals; arrowheads indicate bounds exceeding axis limits (primary: 0.18-5.82; key secondary: 0.09-10.27). Interaction p values are from the one-stage model and are exploratory. HR=hazard ratio. ITT=intention to treat. NI=non-inferiority. REML=restricted maximum likelihood.

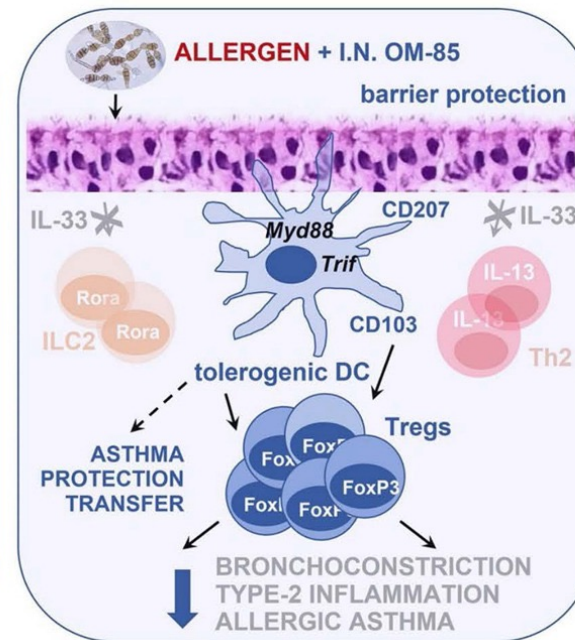
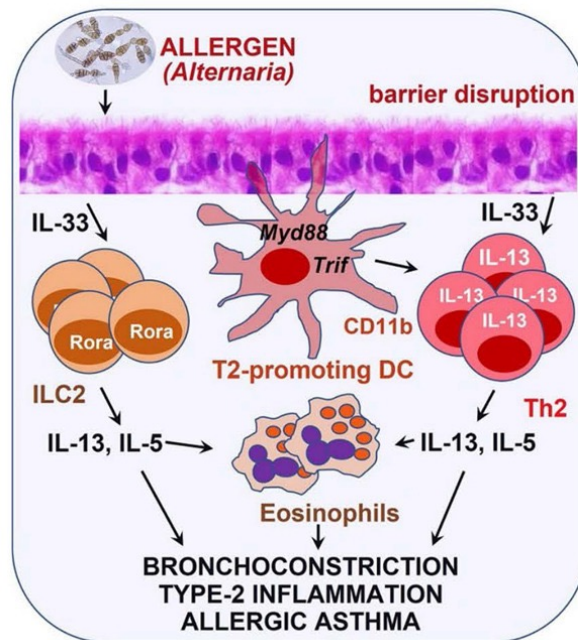
Implications of all the available evidence

β -blocker discontinuation was found to be non-inferior to a strategy of β -blocker continuation in stable patients after myocardial infarction and LVEF $\geq 40\%$. Taken together, the available evidence supports a stage-specific and individualised approach to β -blocker therapy after myocardial infarction. Late discontinuation after initial treatment in the early post-acute phase can be considered with appropriate clinical monitoring.

A bacterial lysate is a preparation made from broken-down bacterial cells used to stimulate the immune system against common infections



Airway administration of the OM-85 bacterial lysate blocks experimental asthma by targeting dendritic cells and the epithelium/IL-33/ILC2 axis



DC: dendritic cells
FoxP3: forkhead box P3
IL: interleukin
ILC2: innate type-2 lymphoid cells
i.n.: intra-nasal
Rora: retinoic acid receptor-related orphan receptor-alpha
T2: type-2
Tregs: T regulatory cells



OM-85 (meist bekannt unter dem Handelsnamen **Broncho-Vaxom**) ist ein Immunstimulanz aus Bakterienextrakten, das zur Vorbeugung von wiederkehrenden Atemwegsinfektionen eingesetzt wird. **Was ist OM-85?**

- **Zusammensetzung:** Ein Lysat (extrahierte Moleküle) aus Zellwänden von acht häufigen Atemwegsbakterien (wie *Streptococcus pneumoniae* oder *Haemophilus influenzae*).
- **Wirkweise:** Es ist kein Antibiotikum, sondern ein Immunmodulator. Es stärkt das körpereigene Immunsystem (angeborene und adaptive Abwehr).
- **Anwendung:** Es wird meist oral (als Kapsel) eingenommen. Neuere Forschungen testen auch Verabreichungen als Nasenspray.

Wofür wird es genutzt?

- **Vorbeugung:** Zur Verringerung von Infektionen der Atemwege (Nase, Hals, Lunge) bei Kindern und Erwachsenen.
- **Weniger Antibiotika:** Studien zeigen, dass Patienten nach der Einnahme seltener Antibiotika benötigen.
- **Einsatzbereiche:** Häufig bei Kindern mit wiederkehrenden Infekten oder bei Patienten mit chronischen Atemwegserkrankungen.

Use of the bacterial lysate OM-85 for the primary prevention of wheezing lower respiratory illness in preschool children: a randomised, placebo-controlled trial

Summary

Background Wheezing lower respiratory tract illnesses are a major health concern in preschool children. We report the results of the ORBEX trial which evaluated the safety and efficacy of the bacterial lysate, OM-85, in the primary prevention of wheezing lower respiratory tract illness.

Methods ORBEX is a parallel-arm, double-blind, placebo-controlled trial for the primary prevention of wheezing lower respiratory tract illness in young children at increased risk for asthma due to atopic dermatitis, parental asthma, or asthma in a blood sibling aged 4 years or older. Children aged 6–18 months were centrally randomly assigned (1:1) at 11 academic clinical sites with experience in recruiting young children in the USA to receive OM-85 3·5 mg or placebo orally for 10 days each month for 24 months and then followed for an additional 36 months to evaluate outcomes while they were off the study drug. Identical openable capsules were used for active drug and placebo, and staff, investigators, and participants were masked to treatment assignment. Participants received usual treatment for wheezing illness as per US guidelines. Randomisation was stratified by sex, age group, family history of asthma, and clinical site. The primary outcome was the time to first wheezing lower respiratory tract illness during the 36-month observation period off the study drug analysed in the intention-to-treat population, which included all randomly assigned participants. The trial is registered with clinicaltrials.gov, NCT02148796, and is completed.

Findings Between Jan 3, 2017, and Nov 30, 2020, 984 children were screened for eligibility, 162 were excluded, and 822 were randomly assigned (411 to the OM-85 intervention group and 411 to the placebo group). 492 participants were male (59·9%) and 330 (40·1%) were female and the mean age of participants was 11·8 months (SD 3·8). 681 children completed the 24-month treatment period, and 596 children completed the 36-month observation period. 132 children experienced at least one wheezing lower respiratory tract illness during the observation period; 71 (21%) of 342 in the OM-85 group and 61 (18%) of 339 in the placebo group. There was no significant difference between OM-85 and placebo with respect to the time to first wheezing lower respiratory tract illness (log-rank test p value 0·35; hazard ratio 1·16 [95% CI 0·82–1·64]). The most frequent adverse events, fevers, coughs, and colds, did not differ between groups.

Interpretation Oral administration of OM-85 in early life did not decrease the incidence of wheezing lower respiratory tract illness in this high-risk population. Bacterial lysates are not efficacious for the primary prevention of asthma-like symptoms during the preschool years.

Funding National Heart, Lung, and Blood Institute and OM Pharma with supplemental funding and provision of study drug and placebo from OM Pharma.

Is OM-85
any good?

No

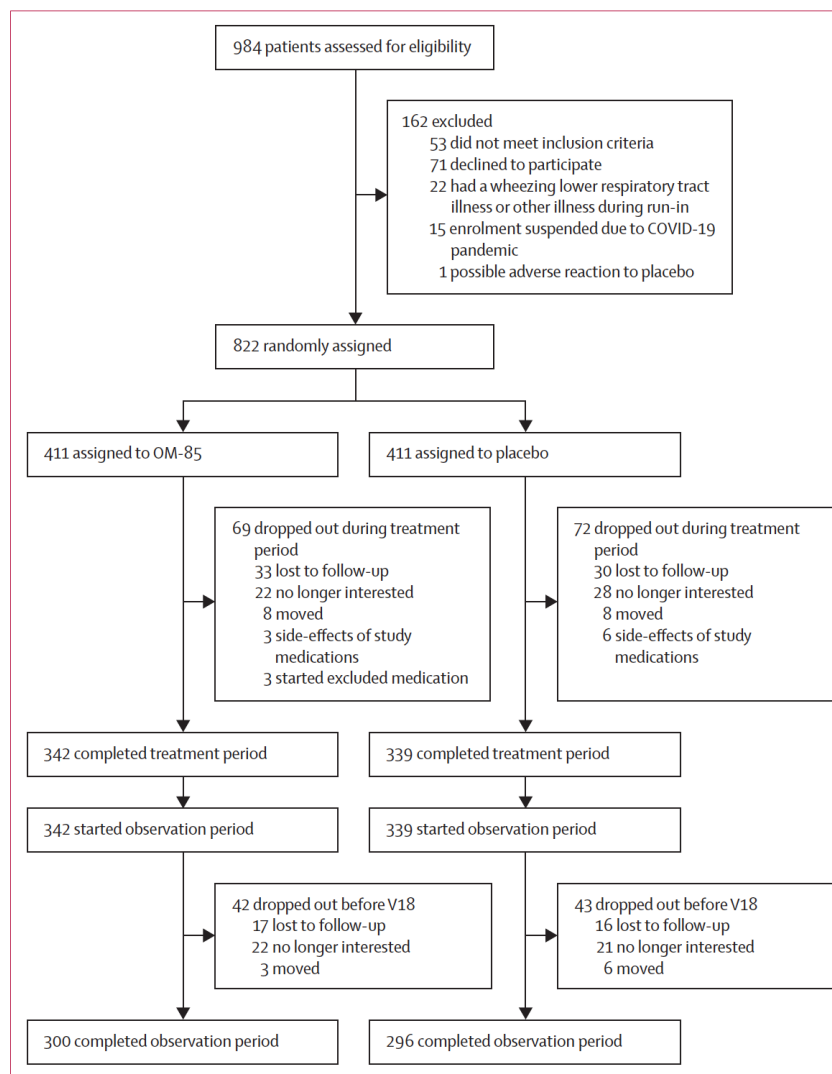


Figure 1: Trial profile

	Placebo (n=411)	OM-85 (n=411)	Total (N=822)
Age (months)	11.7 (3.8)	11.9 (3.8)	11.8 (3.8)
Age group			
6–12 months	216 (52.6%)	216 (52.6%)	432 (52.6%)
12–18 months	195 (47.4%)	195 (47.4%)	390 (47.4%)
Sex			
Male	246 (59.9%)	246 (59.9%)	492 (59.9%)
Female	165 (39.4%)	165 (39.4%)	330 (40.1%)
Race			
American Indian or Alaskan Native	2 (0.5%)	1 (0.2%)	3 (0.4%)
Asian	7 (1.7%)	4 (1.0%)	11 (1.3%)
Black or African American	91 (22.1%)	94 (22.9%)	185 (22.5%)
White	246 (59.9%)	241 (58.6%)	487 (59.2%)
Mixed race	65 (15.8%)	71 (17.3%)	136 (16.5%)
Hispanic or Latino ethnicity	60 (14.6%)	53 (12.9%)	113 (13.7%)
Parental history of asthma	287 (69.8%)	283 (68.9%)	570 (69.3%)
Sibling history of asthma			
No	179 (43.6%)	182 (44.3%)	361 (43.9%)
Yes	109 (26.5%)	112 (27.3%)	221 (26.9%)
Missing	123 (29.9%)	117 (28.5%)	240 (29.2%)
History of eczema	287 (69.8%)	283 (68.9%)	570 (69.3%)
History of food or airborne allergies			
No	239 (58.2%)	229 (55.7%)	468 (56.9%)
Yes	126 (30.7%)	129 (31.4%)	255 (31.0%)
Missing	46 (11.2%)	53 (12.9%)	99 (12.0%)
History of food allergy			
No	268 (65.2%)	263 (64.0%)	531 (64.6%)
Yes	112 (27.3%)	113 (27.5%)	225 (27.4%)
Missing	31 (7.5%)	35 (8.5%)	66 (8.0%)
History of airborne allergy			
No	325 (79.1%)	315 (76.6%)	640 (77.9%)
Yes	33 (8.0%)	38 (9.2%)	71 (8.6%)
Missing	53 (12.9%)	58 (14.1%)	111 (13.5%)
Attends daycare	154 (37.5%)	142 (34.5%)	296 (36.0%)
Number of wheezing lower respiratory illnesses before enrolment			
0	358 (87.1%)	348 (84.7%)	706 (85.9%)
1	46 (11.2%)	55 (13.4%)	101 (12.3%)
2	7 (1.7%)	8 (1.9%)	15 (1.8%)
BMI group			
<10th percentile	13 (3.2%)	7 (1.7%)	20 (2.4%)
10th–84th percentile	249 (60.6%)	251 (61.1%)	500 (60.8%)
≥85th percentile	149 (36.3%)	153 (37.2%)	302 (36.7%)
BMI percentile	69.0 (27.1)	69.9 (25.1)	69.5 (26.1)
Eosinophils (cells per μ L)			
<300	174 (42.3%)	187 (45.5%)	361 (43.9%)
≥300	155 (37.7%)	164 (39.9%)	319 (38.8%)
Missing	82 (20.0%)	60 (14.6%)	142 (17.3%)
Treatment adherence*	100.0 (85.7–100.0)	100.0 (83.3–100.0)	100.0 (83.3–100.0)
Included in per-protocol population	325 (79.1%)	320 (77.9%)	645 (78.5%)

Data are n (%), mean (SD), or median (IQR). *Percentage of prescribed doses taken during the treatment period.

Table 1: Baseline characteristics

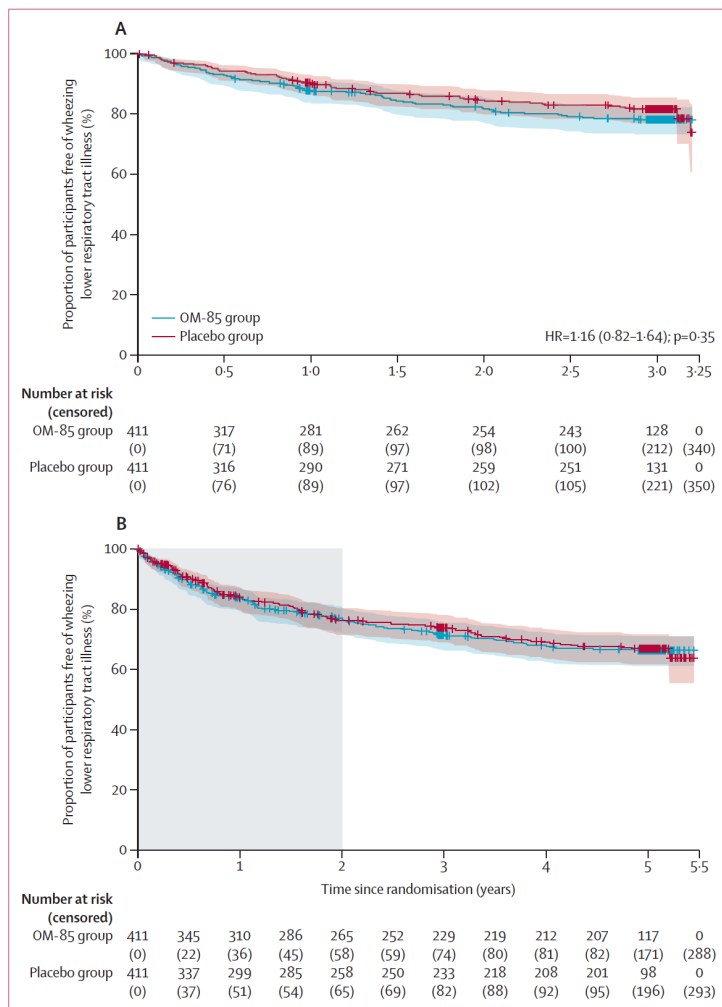


Figure 2: Kaplan–Meier estimates of time to first wheezing lower respiratory tract illness, by treatment group (A) Data from observation period. (B) Data from entire 5-year study, with the shaded section corresponding to the 24-month treatment period. Shaded bands indicate 95% CIs. Tick marks indicate censoring events. Numbers at risk and censored are shown at half-year intervals below each x-axis. Curves and numbers extend past nominal end of study time due to visit windows. HR=hazard ratio.

	OM-85	Placebo	OM-85 vs placebo (effect size; 95% CI)
Observation period			
Number of participants entering; number of participants completing	342; 300	339; 296	..
Total follow-up time, years	967 years	954 years	..
Wheezing lower respiratory illnesses: primary outcome			
Cumulative incidence	71/342 (21%)	61/339 (18%)	HR 1.16 (0.82–1.64)
Annualised rate	0.18 (0.13–0.25)	0.16 (0.11–0.22)	RR 1.16 (0.74–1.80)
Severe wheezing lower respiratory illnesses			
Cumulative incidence	28/342 (8%)	24/342 (7%)	HR 1.11 (0.65–1.93)
Annualised rate	0.04 (0.02–0.06)	0.03 (0.02–0.05)	RR 1.10 (0.59–2.06)
Systemic corticosteroids for wheezing			
Cumulative incidence	42/342 (12%)	42/342 (12%)	HR 0.98 (0.64–1.51)
Annualised rate	0.07 (0.05–0.11)	0.07 (0.05–0.11)	RR 1.00 (0.60–1.66)
Any wheeze			
Cumulative incidence	101/342 (30%)	95/339 (28%)	HR 1.08 (0.81–1.43)
Annualised rate	0.36 (0.28–0.47)	0.28 (0.22–0.37)	RR 1.27 (0.88–1.84)
Asthma incidence	21% (16–27)	21% (16–27)	OR 0.99 (0.67–1.48)
Treatment period			
Number of participants entering; number of participants completing	411; 342	411; 339	..
Total follow-up time, years	742 years	729 years	..
Wheezing lower respiratory illnesses			
Cumulative incidence	90/411 (22%)	88/411 (21%)	HR 0.99 (0.74–1.34)
Annualised Rate	0.28 (0.21–0.36)	0.24 (0.18–0.31)	RR 1.17 (0.81–1.69)
Severe wheezing lower respiratory illnesses			
Cumulative incidence	20/411 (5%)	24/411 (6%)	HR 0.81 (0.45–1.46)
Annualised rate	0.05 (0.03–0.07)	0.04 (0.02–0.06)	RR 1.18 (0.60–2.32)
Systemic corticosteroids for wheezing			
Cumulative incidence	44/411 (8%)	42/411 (10%)	HR 0.80 (0.51–1.25)
Annualised rate	0.08 (0.06–0.12)	0.09 (0.06–0.12)	RR 0.98 (0.57–1.68)
Any wheeze			
Cumulative incidence	141/411 (34%)	135/411 (33%)	HR 1.02 (0.81–1.30)
Annualised rate	0.51 (0.41–0.62)	0.44 (0.35–0.54)	RR 1.17 (0.87–1.56)

Frequency is denoted in rate per child-year (95% CI) and asthma incidence is shown as proportion of participants (95% CI) who developed asthma. HR=hazard ratio. RR=rate ratio. OR=odds ratio.

Table 2: Primary and secondary outcomes during observation and treatment periods

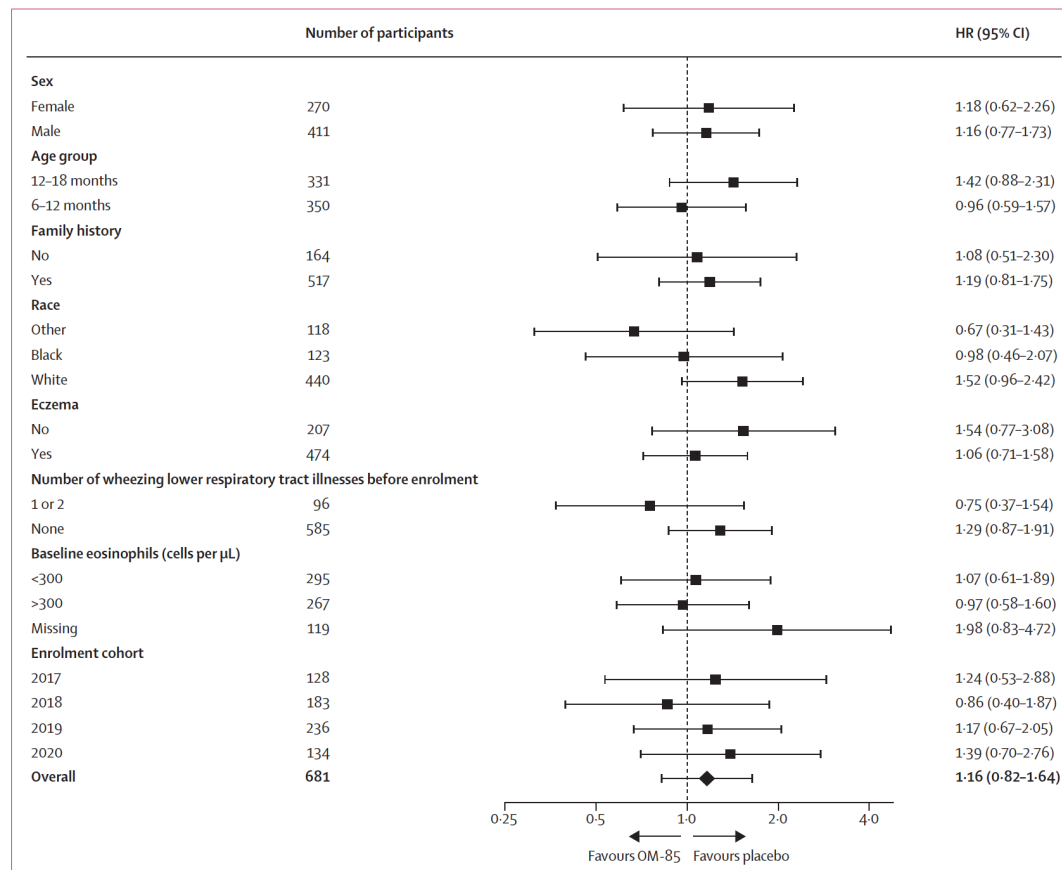


Figure 3: Observation period time to first wheezing lower respiratory tract illness, across prespecified subgroups
Squares represent the point estimate, and horizontal lines represent the 95% CI for each subgroup level. The diamond represents the overall estimate. The dashed vertical line indicates HR=1 (no treatment effect). Values less than 1 favour OM-85; values greater than 1 favour placebo. HR=hazard ratio.

	Treatment period		Observation period	
	OM-85 (n=411)	Placebo (n=411)	OM-85 (n=342)	Placebo (n=339)
Gastrointestinal disorders				
Diarrhoea	104 (25.3%)	100 (24.3%)	36 (10.5%)	51 (15.0%)
Teething	180 (43.7%)	199 (48.4%)	4 (1.2%)	5 (1.5%)
Vomiting	118 (28.7%)	102 (24.8%)	102 (29.8%)	109 (32.1%)
General disorders and administration site conditions				
Fever	346 (84.2%)	344 (83.6%)	271 (79.2%)	274 (80.8%)
Pain	49 (11.9%)	33 (8.0%)	27 (7.9%)	36 (10.6%)
Immune system disorders				
Seasonal allergy	48 (11.6%)	49 (11.9%)	63 (18.4%)	64 (18.9%)
Infections and infestations				
COVID-19	38 (9.2%)	47 (11.4%)	135 (39.5%)	132 (38.9%)
Conjunctivitis	43 (10.4%)	50 (12.1%)	73 (21.3%)	56 (16.5%)
Croup infectious	61 (14.8%)	55 (13.3%)	37 (10.8%)	38 (11.2%)
Gastroenteritis	47 (11.4%)	58 (14.1%)	62 (18.1%)	70 (20.6%)
Hand-foot-and-mouth disease	61 (14.8%)	66 (16.0%)	29 (8.5%)	28 (8.3%)
Influenza	49 (11.9%)	36 (8.7%)	56 (16.4%)	60 (17.7%)
Otitis media	204 (49.6%)	213 (51.8%)	157 (45.9%)	145 (42.8%)
Pharyngitis streptococcal	25 (6.0%)	25 (6.1%)	77 (22.5%)	85 (25.1%)
Upper respiratory tract infection	271 (65.9%)	284 (69.1%)	238 (69.6%)	243 (71.7%)
Nervous system disorders				
Headache	5 (1.2%)	8 (1.9%)	35 (10.2%)	34 (10.0%)
Respiratory, thoracic, and mediastinal disorders				
Cough	251 (61.0%)	243 (59.1%)	247 (72.2%)	236 (69.6%)
Nasal congestion	92 (22.3%)	86 (20.9%)	68 (19.9%)	67 (19.8%)
Rhinitis allergic	51 (12.4%)	49 (11.9%)	32 (9.4%)	36 (10.6%)
Rhinorrhoea	145 (35.3%)	145 (35.2%)	106 (31.0%)	97 (28.6%)
Skin and subcutaneous tissue disorders				
Eczema or atopic dermatitis	68 (16.5%)	57 (13.9%)	34 (9.9%)	27 (7.9%)
Rash (non-atopic or non-allergic)	44 (10.7%)	51 (12.4%)	14 (4.0%)	22 (6.4%)
Urticaria	51 (12.4%)	32 (7.8%)	32 (9.3%)	17 (5.0%)

Data are n (%).

Table 3: Adverse events

Research in context

Evidence before this study

We searched PubMed and the Cochrane Library from database inception to April 1, 2016, for randomised controlled trials, with no language restrictions using MeSH terms: ("bacterial lysates" OR "OM-85" OR "probiotics") AND ("prevention" OR "prophylaxis") AND ("asthma" OR "wheezing") AND ("children") AND ("randomized clinical trial"). There were many trials on a range of probiotics aimed at preventing atopic disease including asthma and wheeze. By contrast to epidemiological evidence that high microbial burden is associated with a reduction in atopy and asthma, clinical trials of probiotics have not demonstrated convincing evidence that these interventions are effective in the primary prevention of wheezing or asthma in children. However, a clinical trial of OM-85, a lysate of common respiratory bacterial pathogens, in children with recurrent wheeze demonstrated a notable reduction in both frequency and duration of wheezing attacks. Although OM-85 was only given for 3 consecutive months at study onset, the effect was demonstrated over the 12 months of the trial suggesting immunomodulation and the potential for the primary prevention of wheezing illness and asthma. Furthermore, meta-analyses of OM-85 clinical trials have suggested a reduction in respiratory illnesses in children.

Added value of this study

ORBEX is the first large, long-term, randomised controlled trial to evaluate the use of OM-85 as an intervention for the primary prevention of asthma and wheeze in previously healthy children aged 6–18 months at high risk for these respiratory outcomes. Exposure to OM-85 was moderately intensive and lasted for 2 years. This was followed by a 3-year observational period off OM-85 during which there was no difference seen between placebo and OM-85 groups in time to first wheezing lower respiratory illness or the frequency of wheezing lower respiratory illness. No difference was observed in the development of asthma by age 6 years.

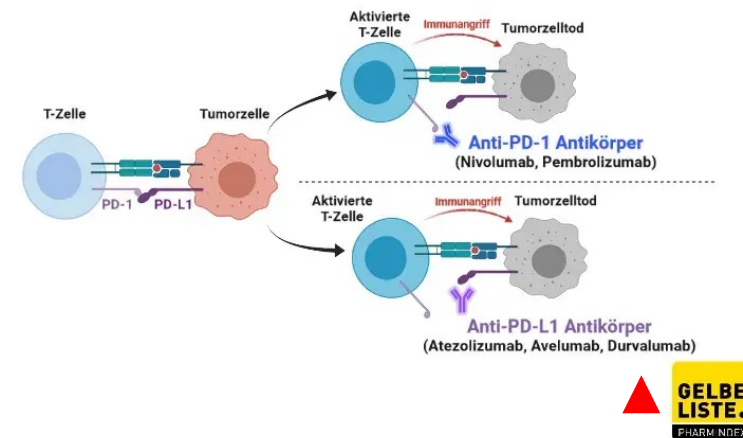
Implications of all the available evidence

Despite compelling observational evidence that exposure to a high microbial burden reduces subsequent allergy and asthma, there is no evidence that administering bacterial lysates in early life can reduce subsequent wheezing illness. This suggests the need for continued mechanistic research to determine both the maternal and infant mechanisms involved in the apparent protection in epidemiological cohorts afforded by natural exposures to environmental microbes.

Als PD-L1-Inhibitor bindet Durvalumab an das Protein PD-L1 auf Zellen. Dadurch verhindert es, dass Tumorzellen das körpereigene Immunsystem über das PD-1-Signal bremsen. Immunzellen (T-Zellen) können den Krebs so wieder besser erkennen und bekämpfen.

Anwendungsgebiete (Indikationen)

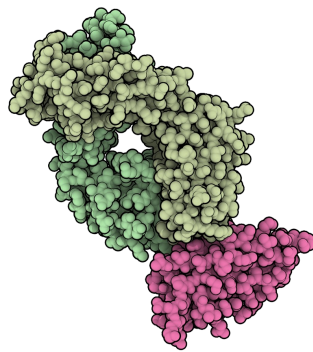
- **Lungenkrebs:** Sowohl bei nicht-kleinzelligem Lungenkrebs (NSCLC) als auch bei kleinzelligem Lungenkrebs (SCLC) in unterschiedlichen Stadien – oft als Kombination mit Chemotherapie oder als Erhaltungstherapie nach einer Bestrahlung/Operation.
- **Gallenwegstumoren (BTC):** In Kombination mit Chemotherapie (Gemcitabin und Cisplatin).
- **Hepatozelluläres Karzinom (HCC):** Leberzellkrebs, als Monotherapie oder in Kombination.
- Weitere Zulassungen umfassen bestimmte Formen des Endometrium-, Blasen- und Magenkarzinoms.



Perioperative durvalumab plus fluorouracil, leucovorin, oxaliplatin, and docetaxel for resectable gastric and gastro-oesophageal junction adenocarcinoma (MATTERHORN): final results of overall survival and event-free survival by pathological response in a global, randomised, double-blind, placebo-controlled, multicentre, phase 3 trial

Summary

Background Durvalumab plus perioperative fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) previously improved event-free survival and pathological complete response in resectable gastric and gastro-oesophageal junction adenocarcinoma. We aimed to examine its effect on overall survival.



[Antigen-binding fragment](#) of durvalumab (pale green) in complex with PD-L1 (pink).

Does
PDL1
blockade
help?

Yes

Methods MATTERHORN is a global, randomised, double-blind, placebo-controlled, multicentre, phase 3 trial that took place in 147 medical centres in 20 countries (representing Asia, Europe, North America, and South America). Adults with histologically documented resectable gastric or gastro-oesophageal junction adenocarcinoma (eligible for radical surgery; stage II–IVa) not previously treated with anticancer therapy were eligible. Participants were randomly assigned (1:1) to perioperative durvalumab plus FLOT or placebo plus FLOT. Blocked randomisation (unique randomisation number via an interactive response technology system and randomisation and trial supply management system) was stratified by geographical region, clinical lymph node status, and PD-L1 expression. Participants were centrally assigned using the interactive response technology system and randomisation and trial supply management system. Participants received durvalumab 1500 mg or placebo intravenously every 4 weeks on day 1 of each cycle plus FLOT intravenously every 2 weeks on days 1 and 15 of each cycle for four cycles (two neoadjuvant and two adjuvant), followed by durvalumab 1500 mg or placebo intravenously every 4 weeks on day 1 of each cycle for ten additional cycles. Participants, investigators, and those assessing outcomes were masked. The previously reported primary outcome was event-free survival; overall survival in the intention-to-treat population was a key secondary endpoint and is the main endpoint reported here. Safety data were collected throughout treatment and the follow-up period (up to and including 90 days after the last dose of the trial drug) and were analysed in participants who received at least one dose of trial treatment; these data were reported previously and are summarised here. MATTERHORN is closed to recruitment but is ongoing and registered with ClinicalTrials.gov (NCT04592913).

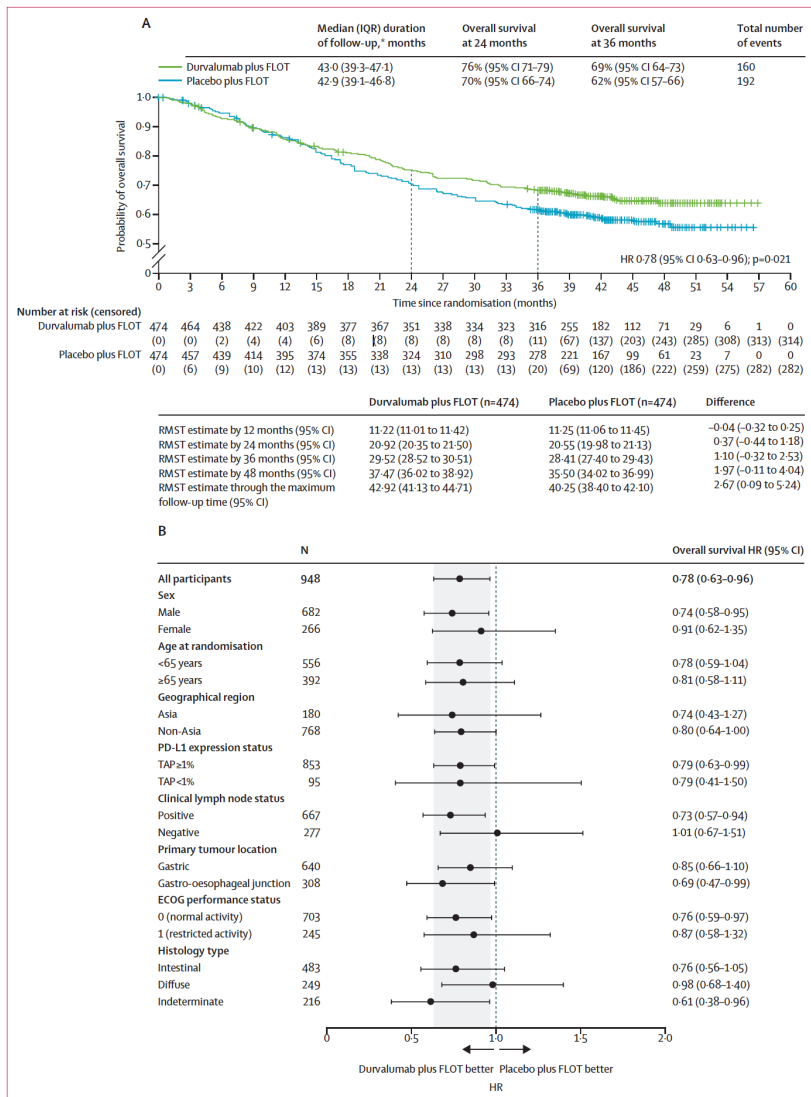
Findings From Nov 17, 2020, to Sept 2, 2022, 1258 participants were enrolled and 948 were randomly assigned; 474 were randomly assigned to durvalumab and 474 to placebo. In a total of 948 participants, the median age was 62 years (IQR 54–68), 682 (72%) were male, and 266 (28%) were female. Overall survival significantly improved in the durvalumab versus placebo group (hazard ratio 0·78, 95% CI 0·63–0·96; $p=0·021$; significance threshold $p<0·0499$). Adverse events with the outcome of death possibly related to any trial treatment occurred in 6 (1%) of 475 participants in the durvalumab group and 2 (<1%) of 469 participants in the placebo group.

Interpretation Perioperative durvalumab plus FLOT improved overall survival versus placebo plus FLOT and is a new standard treatment option for patients with resectable gastric or gastro-oesophageal junction adenocarcinoma.

	Durvalumab plus FLOT (n=474)	Placebo plus FLOT (n=474)	Total (n=948)
Age, years	62 (53–68)	63 (55–69)	62 (54–68)
<50	86 (18%)	57 (12%)	143 (15%)
≥50 to <65	205 (43%)	208 (44%)	413 (44%)
≥65 to <75	146 (31%)	166 (35%)	312 (33%)
≥75	37 (8%)	43 (9%)	80 (8%)
Sex			
Male	326 (69%)	356 (75%)	682 (72%)
Female	148 (31%)	118 (25%)	266 (28%)
Geographical region			
Non-Asia	384 (81%)	384 (81%)	768 (81%)
Asia	90 (19%)	90 (19%)	180 (19%)
Race			
White	321 (68%)	322 (68%)	643 (68%)
Asian	96 (20%)	97 (20%)	193 (20%)
American Indian or Alaska Native	18 (4%)	20 (4%)	38 (4%)
Black or African American	7 (1%)	3 (1%)	10 (1%)
Other	8 (2%)	8 (2%)	16 (2%)
Not reported	24 (5%)	24 (5%)	48 (5%)
ECOG performance status			
0 (normal activity)	337 (71%)	366 (77%)	703 (74%)
1 (restricted activity)	137 (29%)	108 (23%)	245 (26%)
Primary tumour location			
Gastric	324 (68%)	316 (67%)	640 (68%)
Gastro-oesophageal junction	150 (32%)	158 (33%)	308 (32%)
Siewert status type 1	44 (9%)	55 (12%)	99 (10%)
Siewert status type 2	72 (15%)	68 (14%)	140 (15%)
Siewert status type 3	34 (7%)	35 (7%)	69 (7%)
Primary tumour stage			
T4	117 (25%)	117 (25%)	234 (25%)
T4a	101 (21%)	103 (22%)	204 (22%)
T4b	16 (3%)	14 (3%)	30 (3%)
Non-T4	357 (75%)	357 (75%)	714 (75%)
T0	1 (<1%)	0	1 (<1%)
Tis	1 (<1%)	0	1 (<1%)
T1	7 (1%)	4 (1%)	11 (1%)
T2	41 (9%)	32 (7%)	73 (8%)
T3	307 (65%)	321 (68%)	628 (66%)
Positive clinical lymph node status*	329 (69%)	330 (70%)	659 (70%)
PD-L1 expression status by TAP†			
<1%	48 (10%)	47 (10%)	95 (10%)
≥1%	426 (90%)	427 (90%)	853 (90%)
MSI status‡			
MSI-high	25 (5%)	24 (5%)	49 (5%)
Not MSI-high	301 (64%)	310 (65%)	611 (64%)
Not evaluable	69 (15%)	52 (11%)	121 (13%)
Missing	79 (17%)	88 (19%)	167 (18%)

(Table 1 continues on next page)

	Durvalumab plus FLOT (n=474)	Placebo plus FLOT (n=474)	Total (n=948)
(Continued from previous page)			
Histology type			
Intestinal	245 (52%)	238 (50%)	483 (51%)
Diffuse	130 (27%)	119 (25%)	249 (26%)
Indeterminate	99 (21%)	117 (25%)	216 (23%)
Data are median (IQR) or n (%). Data cutoff: Dec 20, 2024. From The New England Journal of Medicine, Janjigian YY, Al-Batran SE, Wainberg ZA, Muro K, Molena D, Van Cutsem E, Hyung WJ, Wyrwicz L, Oh DY, Omori T, Moehler M, Garrido M, Oliveira SCS, Liberman M, Oliden VC, Smyth EC, Stein A, Bilici M, Alvarenga ML, Kozlov V, Rivera F, Kawazoe A, Serrano O, Heilbron E, Negro A, Kurland JF, Tabernero J, for the MATTERHORN Investigators, Perioperative Durvalumab in Gastric and Gastroesophageal Junction Cancer, 393, 217–230, Copyright © 2025, Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. ECOG=Eastern Cooperative Oncology Group. FLOT=fluorouracil, leucovorin, oxaliplatin, and docetaxel. ITT=intention-to-treat. MSI=microsatellite instability. TAP=tumour area positivity. *As recorded at randomisation on the interactive response technology system or randomisation and trial supply management system. †Measured by immunohistochemistry using the investigational VENTANA PD-L1 (SP263) Assay (Roche Diagnostics, Indianapolis, IN, USA) and recorded at randomisation on the interactive response technology system, randomisation and trial supply management system, electronic case report form, or from external vendor data from samples collected on or before randomisation. Participants provided a tumour tissue sample at screening to determine PD-L1 expression status using the TAP scoring method. ‡MSI was measured by a clinical trial assay based on FoundationOne CDx (Foundation Medicine, Boston, MA, USA) in a research use-only capacity.			
Table 1: Baseline demographics and clinical characteristics, ITT population			



(Figure 2 continues on next page)

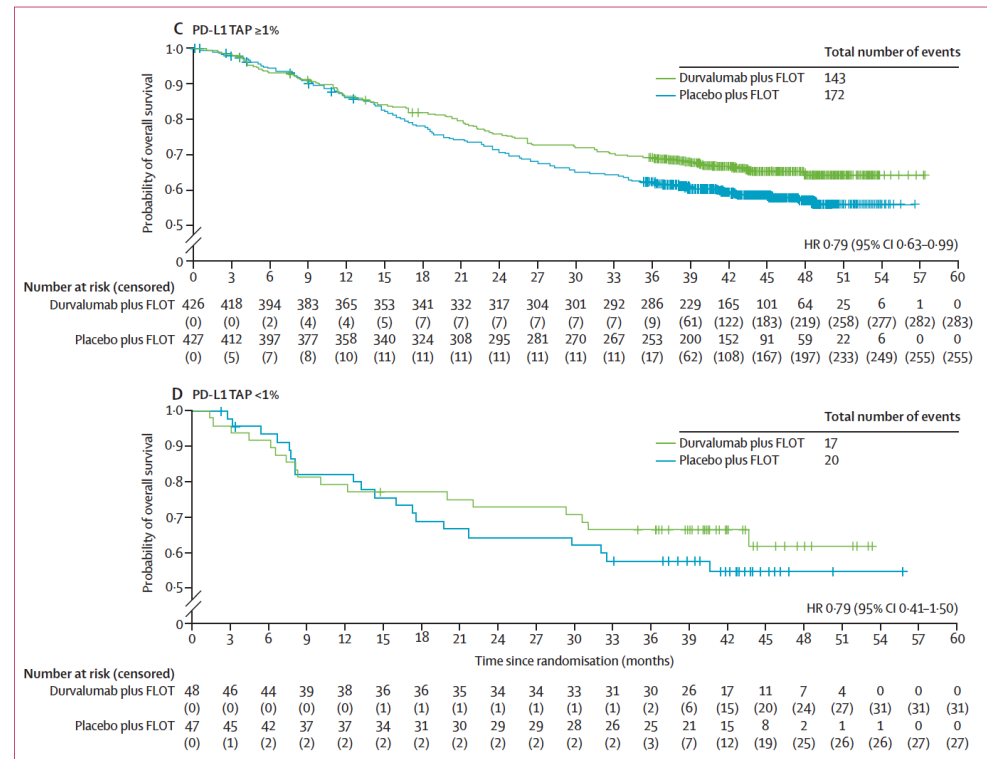
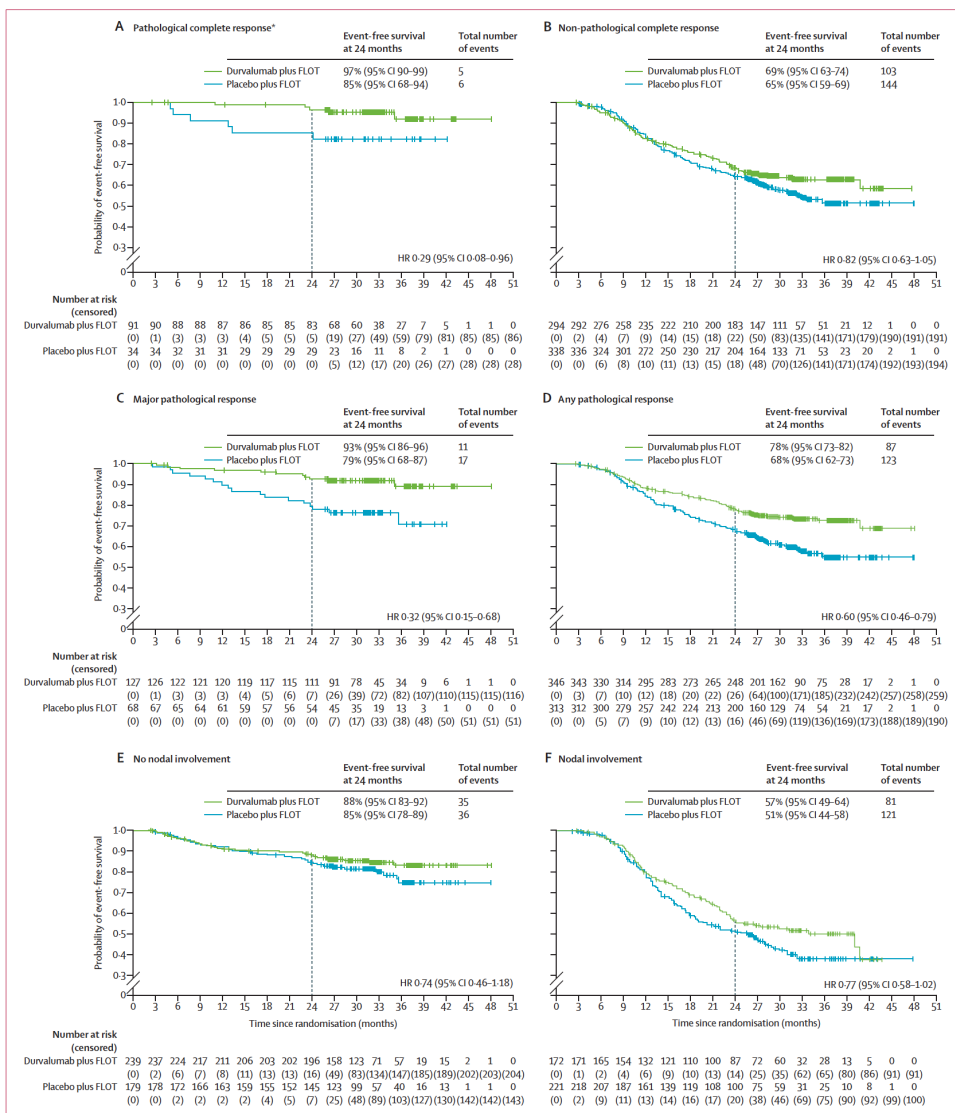


Figure 2: Overall survival and overall survival among participant subgroups, including participants with PD-L1 TAP ≥1% or <1%, in the durvalumab plus FLOT group versus the placebo plus FLOT group in the ITT population

Overall survival (A), subgroup analysis of overall survival (B), and overall survival among participants with PD-L1 TAP ≥1% (C) and PD-L1 TAP <1% (D) in the durvalumab plus FLOT group versus the placebo plus FLOT group. Data cutoff: Sept 1, 2025. An HR of <1 favours durvalumab plus FLOT. (A) Overall survival maturity was 37%. Median overall survival was NR (95% CI NR-NR) in either treatment group. (B) The grey band represents the 95% CI for the HR for the ITT population. (C) Median overall survival was NR (95% CI NR-NR) in either treatment group. (D) Median overall survival in months was NR (95% CI 43.66-NR) with durvalumab plus FLOT and NR (95% CI 21.72-NR) with placebo plus FLOT. ECOG=Eastern Cooperative Oncology Group. FLOT=fluorouracil, leucovorin, oxaliplatin, and docetaxel. HR=hazard ratio. ITT=intention-to-treat. NR=not reached. RMST=restricted mean survival time. TAP=tumour area positivity. *In censored participants.



	Durvalumab plus FLOT (n=475)*	Placebo plus FLOT (n=469)	Total (n=944)
Any-grade adverse event	471 (99%)	463 (99%)	934 (99%)
Possibly related to any trial treatment	453 (95%)	444 (95%)	897 (95%)
Possibly related to durvalumab or placebo	282 (59%)	244 (52%)	526 (56%)
Possibly related to FLOT	450 (95%)	438 (93%)	888 (94%)
Maximum grade 3 or 4 adverse event	340 (72%)	334 (71%)	674 (71%)
Possibly related to any trial treatment	283 (60%)	277 (59%)	560 (59%)
Possibly related to durvalumab or placebo	67 (14%)	58 (12%)	125 (13%)
Possibly related to FLOT	272 (57%)	268 (57%)	540 (57%)
Serious adverse event	229 (48%)	207 (44%)	436 (46%)
Adverse event leading to discontinuation of any trial treatment	142 (30%)	107 (23%)	249 (26%)
Leading to discontinuation of durvalumab or placebo	48 (10%)	30 (6%)	78 (8%)
Leading to discontinuation of any FLOT	121 (25%)	95 (20%)	216 (23%)
Adverse event with outcome of death	24 (5%)	20 (4%)	44 (5%)
Possibly related to any trial treatment	6 (1%)	2 (<1%)†	8 (1%)
Possibly related to durvalumab or placebo	3 (1%)	1 (<1%)	4 (<1%)
Possibly related to FLOT	3 (1%)	2 (<1%)	5 (1%)
Immune-mediated adverse event (any grade)‡	110 (23%)	34 (7%)	144 (15%)
Maximum grade 3 or 4 immune-mediated adverse event	34 (7%)	17 (4%)	51 (5%)
Serious immune-mediated adverse event (including events with outcome of death)	23 (5%)	13 (3%)	36 (4%)
Immune-mediated adverse event with outcome of death	2 (<1%)	0	2 (<1%)
Any adverse event leading to surgery not being performed	3 (1%)	2 (<1%)	5 (1%)
Any adverse event leading to a delay in surgery§	11 (2%)	12 (3%)	23 (2%)
Any adverse event possibly related to surgery	182 (38%)	173 (37%)	355 (38%)
Most common adverse events (any grade) occurring in ≥20% of participants in ≥1 treatment group			
Diarrhoea	296 (62%)	270 (58%)	566 (60%)
Nausea	241 (51%)	237 (51%)	478 (51%)
Neutropenia	153 (32%)	155 (33%)	308 (33%)
Alopecia	145 (31%)	149 (32%)	294 (31%)
Decreased appetite	145 (31%)	141 (30%)	286 (30%)
Fatigue	137 (29%)	146 (31%)	283 (30%)
Anaemia	119 (25%)	147 (31%)	266 (28%)
Neutrophil count decreased	119 (25%)	138 (29%)	257 (27%)
Vomiting	124 (26%)	120 (26%)	244 (26%)
Peripheral sensory neuropathy	96 (20%)	88 (19%)	184 (19%)
Abdominal pain	82 (17%)	96 (20%)	178 (19%)
Asthenia	95 (20%)	71 (15%)	166 (18%)
Pyrexia	95 (20%)	71 (15%)	166 (18%)

(Table 2 continues on next page)

	Durvalumab plus FLOT (n=475)*	Placebo plus FLOT (n=469)	Total (n=944)
(Continued from previous page)			
Most common adverse events (maximum grade 3 or 4) occurring in ≥5% of participants in ≥1 treatment group			
Neutropenia	101 (21%)	104 (22%)	205 (22%)
Neutrophil count decreased	93 (20%)	105 (22%)	198 (21%)
Diarrhoea	30 (6%)	28 (6%)	58 (6%)
White blood cell count decreased	25 (5%)	28 (6%)	53 (6%)
Anaemia	24 (5%)	24 (5%)	48 (5%)
Data are n (%). Data cutoff: Dec 20, 2024. From The New England Journal of Medicine, Janjigian YY, Al-Batran SE, Wainberg ZA, Muro K, Molena D, Van Cutsem E, Hyung WJ, Wyrwicz L, Oh DY, Omori T, Moehler M, Garrido M, Oliveira SCS, Liberman M, Oliden VC, Smyth EC, Stein A, Bilici M, Alvarenga ML, Kozlov V, Rivera F, Kawazoe A, Serrano O, Heilbron E, Negro A, Kurland JF, Tabernero J, for the MATTERHORN Investigators, Perioperative Durvalumab in Gastric and Gastroesophageal Junction Cancer, 393, 217-230, Copyright © 2025, Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. Included are adverse events reported during the overall treatment period that had an onset date on or after the first dose of investigational treatment, as well as adverse events that had an onset date before the first dose but increased in severity on or after the first dose, up to and including 90 days after the last dose or until initiation of the first subsequent anticancer therapy (excluding palliative radiotherapy), whichever occurred first. Participants with multiple events in the same category were counted only once per category. Participants with events in more than one category were counted once in each of those categories. Relatedness of adverse events to trial treatment was determined by the investigator; missing responses were counted as related. Any trial treatment indicates durvalumab or placebo, FLOT, or both. FLOT=fluorouracil, leucovorin, oxaliplatin, and docetaxel. *One participant in the placebo plus FLOT group received a single dose of durvalumab and was therefore included in the durvalumab plus FLOT group for the safety analysis. †In the placebo plus FLOT group, one adverse event with the outcome of death was determined by the investigator to be related to both placebo and FLOT. ‡Excluding infusion or hypersensitivity reactions. §Defined as surgery occurring more than 8 weeks (56 days) after the last dose of neoadjuvant treatment.			
Table 2: Adverse event summary, safety analysis set			

Added value of this study

To our knowledge, the MATTERHORN trial is the first phase 3 study to show definitive evidence that perioperative treatment with an anti-PD-L1 antibody (durvalumab) combined with FLOT improves outcomes across all three key efficacy endpoints of event-free survival, overall survival, and pathological complete response in resectable gastric and gastro-oesophageal junction adenocarcinoma. The incorporation of durvalumab did not compromise surgical feasibility or increase treatment-related adverse events.

Implications of all the available evidence

The totality of evidence supports perioperative durvalumab combined with FLOT as a new standard treatment option for people with resectable gastric or gastro-oesophageal junction adenocarcinoma.



Wildfire smoke and health: current evidence, mechanisms, and future challenges

In the era of climate change, numerous regions worldwide are facing a surge in both the frequency and unprecedented scale of wildfires. Exposure to wildfire smoke poses substantial risks to health, especially for vulnerable populations. Although previous studies have shed light on health effects of wildfire smoke, crucial research gaps persist, including long-term health effects, interactions with pre-existing health conditions, and health disparities. Closing these gaps is vital to enhancing the ability to safeguard public health during wildfire events and to formulate effective strategies for prevention, mitigation, and response. This Review synthesises global evidence on the trends, health effects, and physical and chemical characteristics of wildfire smoke, exploring potential biological mechanisms and challenges in health risk assessment. Acknowledging the global impact of wildfires and their health effects is essential for mitigating environmental, social, and economic challenges. Safeguarding public health requires an interdisciplinary approach to comprehensively address the public health burden from wildfires. This integrated strategy is essential to systematically assess and mitigate the substantial public health burden posed by wildfires, as well as promoting resilience and sustainable solutions for affected communities.

Particulate matter 2.5 micrometers or less in diameter (**PM_{2.5}**) is a major air pollutant that poses severe risks to human health because it bypasses the body's natural defenses to reach deep into the lungs and bloodstream.

Key messages

- Climate change is increasing wildfire activity globally, leading to rising population exposure to wildfire smoke and associated health risks
- Wildfire smoke contains a unique mix of pollutants, with toxicity varying by fuel type, combustion conditions, and ageing processes, requiring further investigation
- Unlike stable pollution sources, wildfire smoke is highly variable, and its long-term health effects, including cumulative exposure effects, remain unclear
- Research on wildfire smoke and health has expanded, revealing acute effects, especially on the respiratory system, but key gaps remain in long-term impacts, early-life effects, and interventions
- Exposure during pregnancy and early childhood might have lasting health impacts, but more research is needed to understand long-term risks
- Some groups, including Indigenous Peoples communities and outdoor workers, face greater risks, yet research on vulnerable populations remains scarce
- Long-term cohort studies are essential for understanding wildfire smoke impacts, and recent extreme events highlight the need for new research efforts

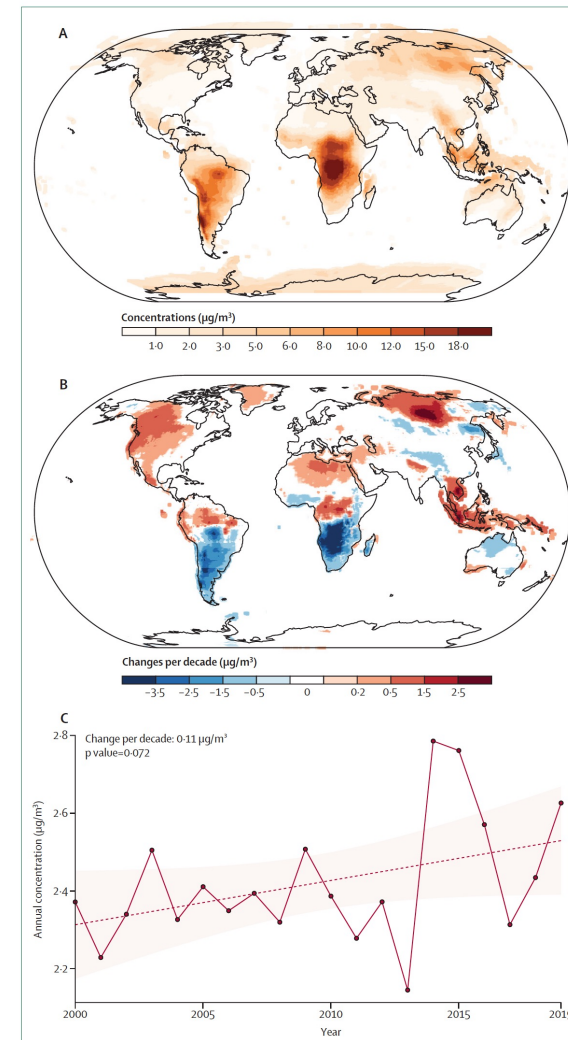


Figure 1: Global patterns of estimated wildfire-related PM_{2.5} during 2000–19
 (A) Average wildfire PM_{2.5} during 2000–19. (B) Trends of wildfire PM_{2.5} from 2000 to 2019. (C) Global population-weighted average wildfire PM_{2.5} from 2000 to 2019. Data sourced from Xu and colleagues.* PM_{2.5}=particulate matter with an aerodynamic diameter of 2.5 μm or less.

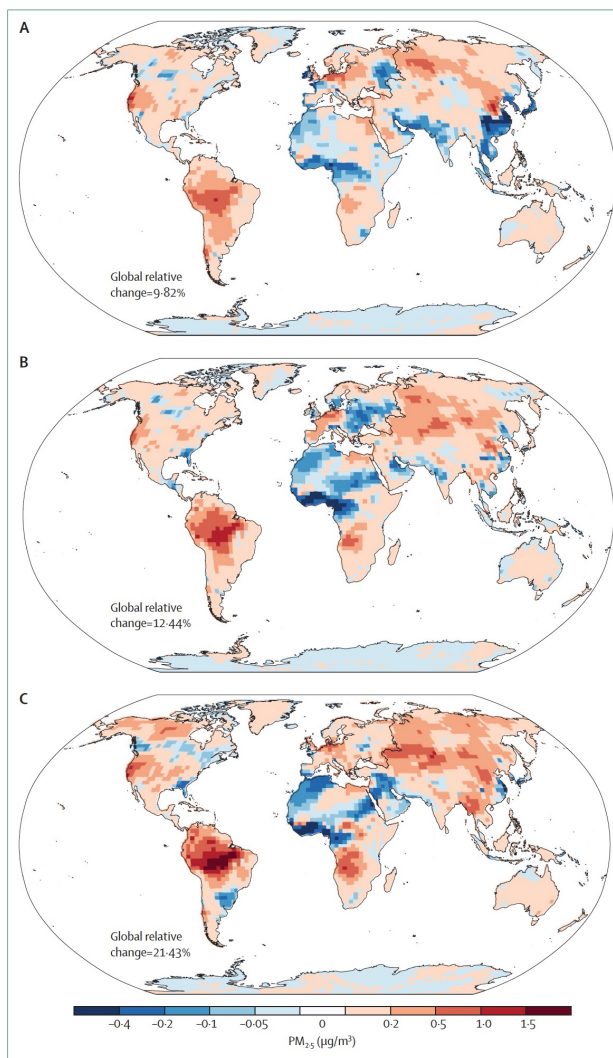


Figure 2: Annual mean changes in wildfire-related surface $PM_{2.5}$ concentrations
Concentrations by (A) 1.5°C, (B) 2°C, and (C) 3°C warming compared with present day. Data sourced from Tian and colleagues.¹⁴ $PM_{2.5}$ =particulate matter with an aerodynamic diameter of 2.5 μm or less.

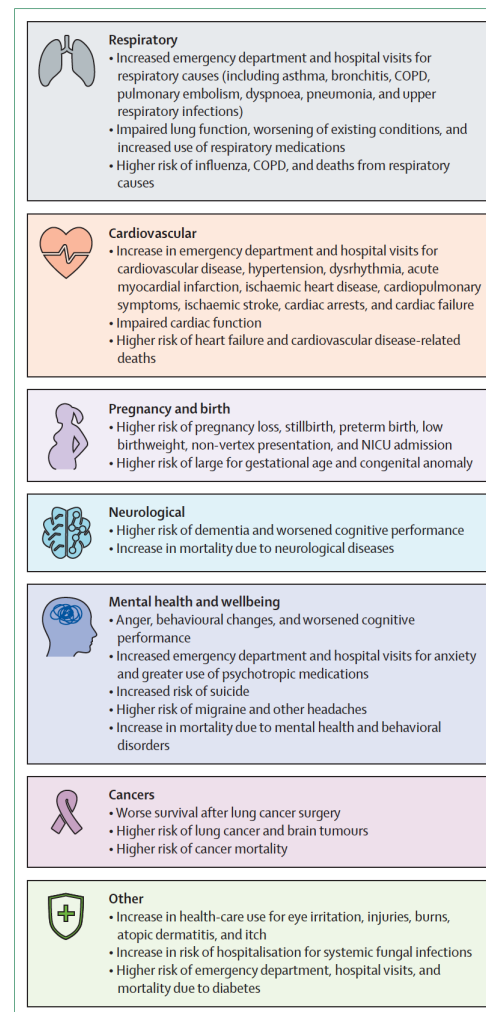


Figure 3: Health outcomes associated with wildfire smoke in the epidemiological literature
Details of literature search and references are available in the appendix (pp 7, 8). COPD=chronic obstructive pulmonary disease. NICU=neonatal intensive care unit.

Particulate matter 2.5 micrometers or less in diameter (**PM_{2.5}**) is a major air pollutant that poses severe risks to human health because it bypasses the body's natural defenses to reach deep into the lungs and bloodstream.

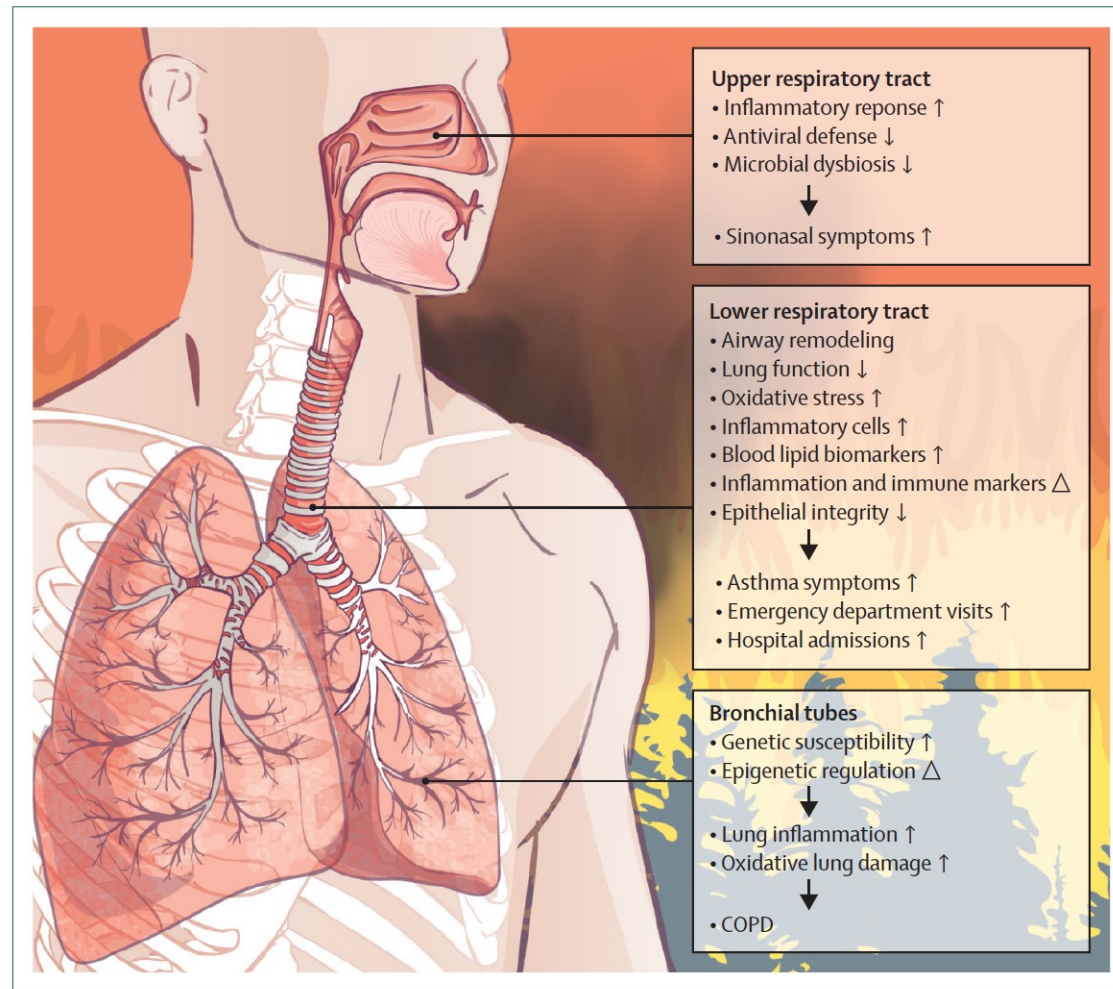


Figure 4: Potential mechanisms for respiratory effects of wildfire smoke

Each category shows the progression of health outcomes. Triangles represent changes in the level of biomarkers. COPD=chronic obstructive pulmonary disease.

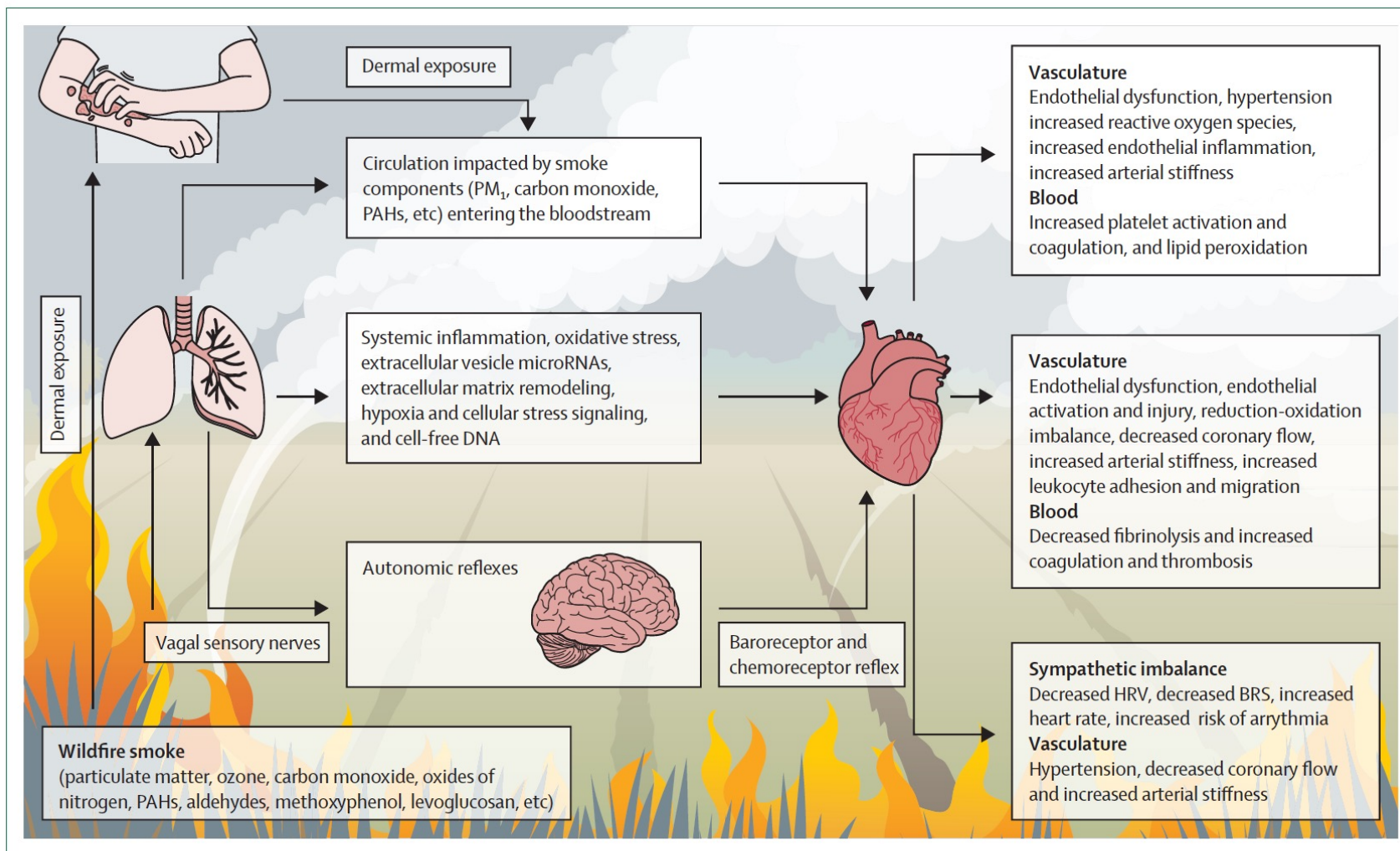


Figure 5: Schematic pathway showing proposed pathophysiological mechanisms of cardiovascular effects induced by wildfire smoke exposure
BRS=baroreflex sensitivity. HRV=heart rate variability. PAHs=polycyclic aromatic hydrocarbons. PM₁=particulate matter with a diameter $\leq 1 \mu\text{m}$.

Conclusions

In conclusion, the growing evidence on wildfire smoke highlights urgent research gaps, particularly long-term health effects amid climate change. Key priorities include clarifying links to chronic diseases, early-life outcomes, and smoke composition. Cohort studies leveraging recent extreme wildfire events could provide crucial insights to inform public health strategies and protect vulnerable communities.

META-ANALYSIS

Built upon a
systematic
review framework



Resolve
discrepancies
between high-
quality RCTs



Typical goal is
a single effect
estimate or
direction



Not inherently
a higher level
of evidence



BROOKBUSH
INSTITUTE

What makes a meta-analysis believable?

Introduction

Meta-analysis, from Greek μετά (meta, after) and ἀνά-λυσις (ana-lysis, breaking up), refers to the analysis of analyses. Meta-analyses address what existing studies collectively allow to be inferred, rather than answering a primary research question. The use of meta-analysis has expanded rapidly, with more than 400 000 meta-analyses indexed in PubMed between 1980 and 2025 (appendix p 9). Yet the trustworthiness of meta-analyses varies widely. Some have reshaped clinical practice and policy; others have added noise or conveyed false certainty. The key question is not whether meta-analyses are influential, but which deserve clinical confidence.

Often positioned near the apex of the evidence-based medicine hierarchy (appendix p 10), meta-analyses can help to guide clinical decision making, inform guidelines, and identify effects not evident in individual trials. High-quality meta-analyses also refine existing knowledge, identify gaps, and generate hypotheses for future confirmation. However, visibility and citation do not necessarily reflect clinical value (appendix p 11). True impact depends on the quality and coherence of the evidence, the appropriateness of the methods, and the validity of the inferences drawn. To quote William Bruce Cameron, “not everything that can be counted counts, and not everything that counts can be counted”.¹

Metaphysics is the branch of philosophy that examines the fundamental nature of reality, existence, and the structure of the world.

It studies what is there and how it is, exploring features of reality that go beyond standard empirical observation. : The word comes from Aristotle's works, originally titled *meta ta physika*, meaning "after the physics"



An expert-level generalist AI for abdominal CT diagnosis

INTRODUCTION: Radiology is critical for modern clinical diagnosis, enabling the detection and characterization of diverse diseases. A long-standing vision in the field is to realize a generalist artificial intelligence (AI) capable of expert-level diagnostic support for varied real-world scenarios. Contrast-enhanced abdominal computed tomography (CT) poses one of the most complex challenges, requiring assessment of dozens of organs and hundreds of conditions. Despite milestones in AI for specific domains, current AI solutions remain limited in disease coverage and accuracy. They largely depend on supervised learning with expensive manual annotation, restricting scalability and applicability in open-ended clinical contexts.

RATIONALE: Vision-language learning offers an alternative to annotation-intensive supervised learning by training models on paired image-text data, with the core principle of pulling visual and textual embeddings from the same patient closer in a shared representation space while separating those from different patients. However, methods successful in natural image domains do not readily transfer to abdominal CT because of its anatomical complexity and sparse diagnostic signals. To address these barriers, we developed **RADAR (Rapid Abdominal Diagnosis with AI and Radiology)**, a fine-grained vision-language framework that decomposes CT volumes into anatomical units; aligns them with diagnostic textual reports via adaptive contrastive learning; and achieves scalable, versatile, and interpretable diagnosis without additional manual labeling.

RESULTS: We constructed **RAD-CT**, a large abdominal CT dataset, consisting of **424,911 examinations** and **15 million anatomy-wise pairs** for fine-grained, large-scale training. Evaluated across 18 anatomical structures and 146 imaging findings, RADAR achieved an area under the receiver operating characteristic curve (AUC) of 0.913 (95% confidence interval, 0.911 to 0.915) for the diagnosis of 146 findings in a real-world internal cohort of 39,160 examinations and AUCs of 0.874 to 0.912 across eight external centers. In pathology confirmed evaluation for **four types of cancers (liver, pancreas, stomach, and colorectum)**, performance reached AUCs of 0.891 to 0.984. In another cross-population cohort, RADAR achieved an AUC of 0.883 without any fine-tuning. In **acute abdominal conditions**, which had been excluded from initial training, RADAR maintained high performance with an AUC of 0.904, underscoring strong generalization to urgent, unfamiliar scenarios.

In a reader study with **26 radiologists** from 14 centers, **RADAR outperformed most participants** and increased sensitivity by $\sim 10\%$ in collaborative use. RADAR also provided attention maps to highlight diagnosticrelevant visual cues, thereby facilitating better interpretation, a feature of considerable value in clinical practice.

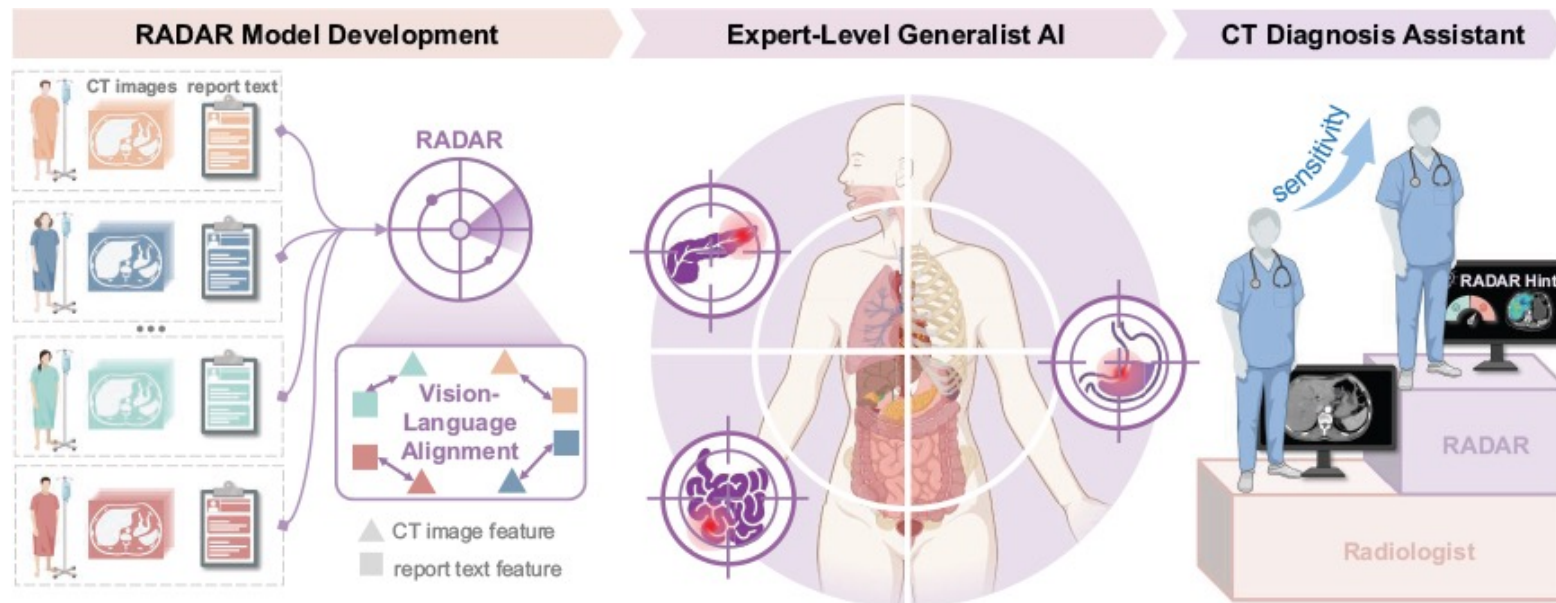


Illustration of the RADAR model development and deployment. Applying vision-language learning to a large, unannotated dataset of abdominal CT images and reports, **RADAR provides expert-level diagnosis** across a wide range of anatomies and findings. It serves as a generalist AI assistant, empowering radiologists and enhancing their diagnostic performance.

CONCLUSION: RADAR is a generalist AI model built on a scalable vision-language framework trained directly on large-scale clinical reports without manual annotation. It achieved broad diagnostic coverage and high accuracy in abdominal CT interpretation and improved radiologists' sensitivity when used as an assistive reading tool. This work suggests that large-scale vision-language learning may provide a practical path toward efficiently developing generalist AI systems for complex and diverse radiologic interpretation tasks.

*The T790M variant leads to low-level constituent kinase activation. While T790M *per se* increases baseline kinase activity over wild-type EGFR, its kinetic behavior changes drastically when it co-occurs with classical primary activating mutations (like L858R or Exon 19 deletions)*

Germline *EGFR* T790M mutation and lung cancer risk

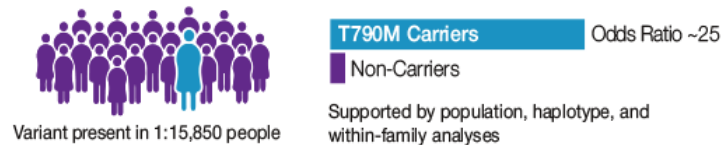
INTRODUCTION: Lung cancer in individuals who have never smoked is an increasingly recognized global health concern and is predicted to remain prevalent even as tobacco-related disease continues to decline. Although most lung cancers are attributable to smoking, with genetic contributors influencing smoking behavior identified through genome wide association studies, the genetic basis of lung cancer in those who have not smoked, particularly inherited risk, is poorly understood. Familial clustering has long been observed, yet only a few risk-associated germline variants have been described. Among these, the germline *EGFR* T790M variant stands out, associated with lung tumorigenesis in conjunction with a somatic activating *EGFR* mutation. Clarifying its population frequency and associated risk is essential for both clinical management and understanding how risk-associated alleles propagate in human populations.

RATIONALE: Because of the rarity of the *EGFR* T790M variant, prior studies have been limited to small case series, preventing reliable quantification of lung cancer risk or evaluation of potential risk modifiers. We conducted a case-control study of more than 3.3 million genotyped research participants through the direct-to-consumer genetic testing company 23andMe, enabling quantification of the magnitude and specificity of lung cancer risk associated with this variant, assessment of whether risk is modified by smoking or by polygenic susceptibility, evaluation of its frequency and geographic distribution across global ancestries, and tracing of the evolutionary, demographic, and geographic origins of the variant.

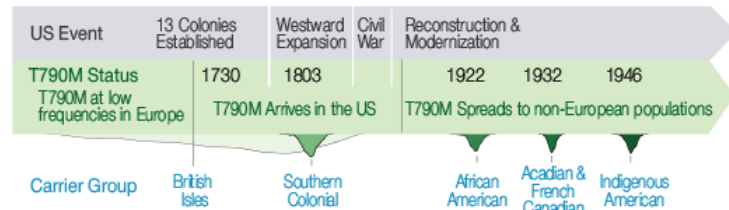
RESULTS: Among 3,372,531 individuals, the germline *EGFR* T790M variant was present in 1 of 15,850 individuals and strongly associated with lung cancer (odds ratio = 25.18; $P = 1.9 \times 10^{-24}$). No significant associations were observed for 17 non–lung cancer types or noncancerous pulmonary conditions evaluated. Across three independent polygenic risk score models, no significant interactions were detected between T790M and genome-wide lung cancer susceptibility, indicating that the association is largely independent of polygenic background. Effect size differed by smoking status, with higher estimates in individuals who had not smoked than in those who had reported smoking. Global ancestry analyses showed that *EGFR* T790M is significantly enriched in the US (carrier frequency 1 in 8,920) relative to British-and Irish-descendant populations. Fine-scale geographic and ancestry analyses revealed a recent founder effect in the Southern Appalachian region approximately 200 to 225 years ago, with a regional carrier frequency of 1 in 2078. This was followed by expansion into additional populations after the Civil War, including those with African and Indigenous American ancestry.

IN OVER 3.3 MILLION INDIVIDUALS

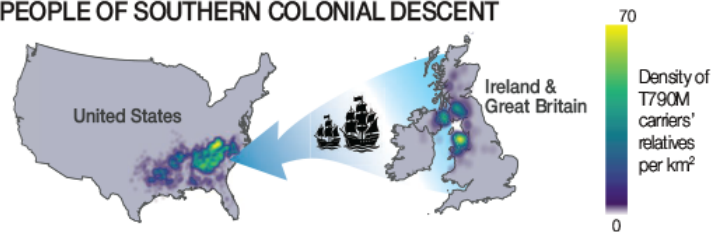
EGFR T790M ASSOCIATION WITH LUNG CANCER



HISTORY OF EGFR T790M



EGFR T790M VARIANT IS SIX TIMES MORE COMMON IN PEOPLE OF SOUTHERN COLONIAL DESCENT



Lung cancer risk, genetic history, and population distribution of the **EGFR T790M** variant. Shown is the population frequency of the **EGFR T790M** variant and its association with lung cancer risk supported by complementary analyses. A historical timeline traces **the variant's origins, introduction into the US**, and spread across ancestral groups. Population-level maps illustrate the geographic distribution and relative density of individuals genetically related to T790M carriers, highlighting **elevated frequencies among those with Southern Colonial ancestry**.

CONCLUSION: The germline *EGFR* T790M variant is a rare lung cancer–specific susceptibility allele that is strongly associated with lung cancer risk and enriched in individuals of Southern Appalachian ancestry through a recent founder event. Recognition of individuals more likely to carry *EGFR* T790M, including those with family history of lung cancer, multifocal lung cancer, or lung nodules or Southeastern US ancestry, may help to inform future screening and prevention strategies for those at highest risk.

Trump says he's banning CNN, MS NOW and Politico from the White House



„Headed towards state-controlled media“

President Donald Trump said he is banning CNN, MS NOW and Politico from the White House for reporting what he called “fake news,” breaking with long-running protocol for relations between the executive office and the press.

“Media Outlets shouldn’t be able to constantly write or report FICTION and LIES when they’re covering the President of the United States, the Trump Administration, or the United States of America,” Trump wrote in a Friday post on Truth Social. “Other Fake News Media Outlets to follow.”

When pressed about the nature of the order, Trump told reporters it’d be “a very simple ban.”

“I don’t want him in my office. I don’t want them here. I would say the ban would go as far as you can,” he said. “And if they could straighten themselves out, you know, if they could save themselves.”