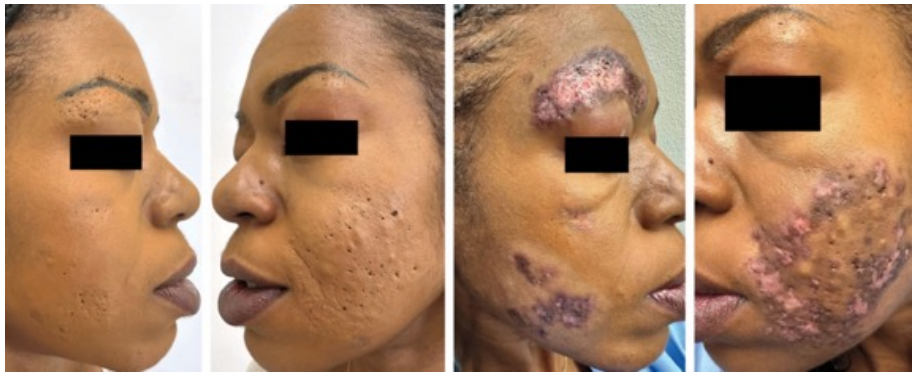
https://www.mdc-berlin.de/de/veroeffentlichungstypen/clinical-journal-club

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

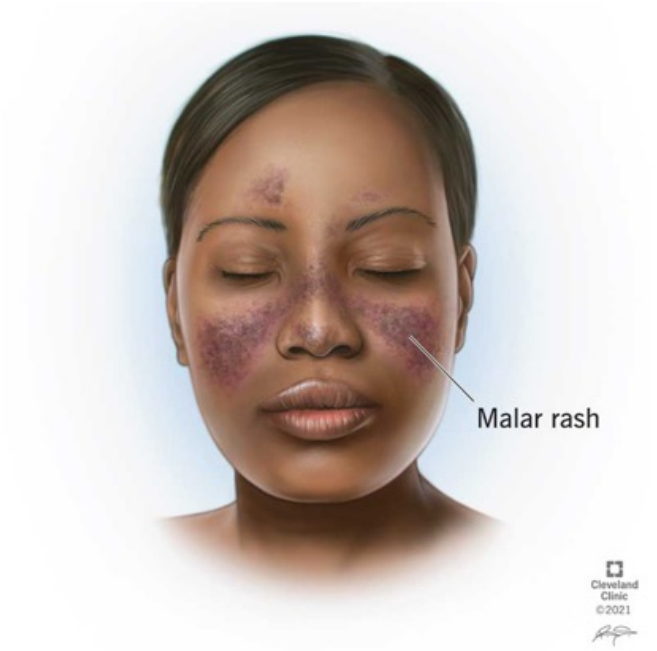


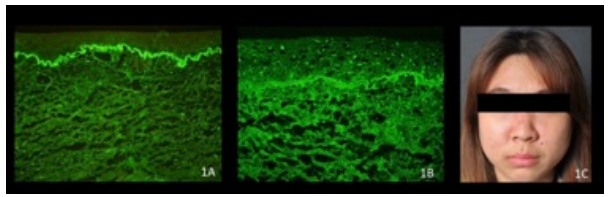
A 42-year-old woman with a 20-pack-year smoking history presented to the dermatology clinic with a 2-year history of a facial rash. One year before presentation, the patient's rash had been evaluated without a request for removal of her makeup, and treatment for possible acne had been recommended. At the current presentation, a skin examination was performed after removal of her makeup. An indurated plaque with central hypopigmentation, dilated follicular ostia, and alopecia over the right eyebrow were observed, along with a plaque with scattered areas of hyperpigmentation and hypopigmentation on the right cheek. On the left cheek, there were scattered nodules, open comedones, and areas of hyperpigmentation and hypopigmentation. What is the most likely diagnosis?

Cutaneous sarcoidosis
Discoid lupus erythematosus
Granuloma faciale
Lupus vulgaris
Rosacea

Examination of a biopsy specimen of the skin over the right eyebrow revealed a lichenoid infiltrate with involvement of the dermal–epidermal junction and follicular epithelium, along with dilated follicular ostia with superficial and deep dermal perifollicular and perivascular lymphocytic infiltrate. Thickening of the basement membrane and mucin deposits were also present. A direct immunofluorescence assay identified granular deposits of IgM and IgG at the dermal–epidermal junction. Laboratory studies to evaluate for systemic lupus erythematosus were notable only for an antinuclear antibody titer of 1:160. A diagnosis of discoid lupus erythematosus — a type of chronic cutaneous lupus erythematosus — was made.

Der diskoide Lupus erythematodes (DLE) ist die häufigste chronische Form des kutanen Lupus erythematodes; eine Autoimmunerkrankung der Haut. Häufigkeit: Selten, Prävalenz < 5/10.000 in Europa, jedoch 2- bis 3-mal häufiger als der systemische Lupus erythematodes. Typisches Erkrankungsalter zwischen 20 und 40 Jahren.





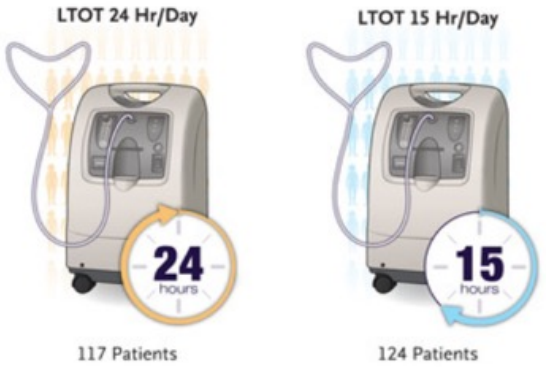
A. Direct immunofluorescence (DIF) findings of cutaneous lupus erythematosus showing positive homogenous deposits of immunoglobulin (Ig)M at the dermo-epidermal junction (DEJ) were recognized as lupus bands. (10x magnification). B. DIF findings of acute cutaneous lupus erythematosus showed positive epidermal nuclear staining of IgG. (20x magnification). C. Clinical presentation of acute cutaneous lupus erythematosus showed ill-defined erythematous plaque localized on both cheeks and nose.

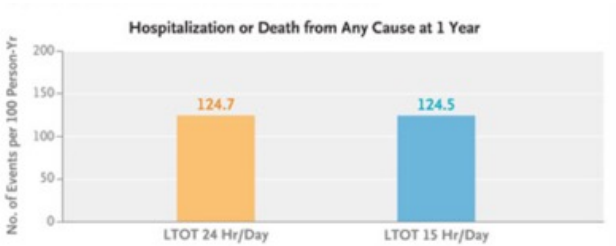
Die Langzeit-Sauerstoff-Therapie (LTOT) führt bei Patienten mit chronisch respiratorischer Insuffi- zienz nachweislich zur Prognoseverbesserung. Pathogenetisch sind eine Verbesserung der Oxy- genierung, eine Abnahme des pulmonal-arteriel- len Drucks sowie eine Abnahme der Atemarbeit von Bedeutung.
Eine Sauerstofflangzeittherapie ist angezeigt, wenn der Sauerstoffpartialdruck über einen längeren Zeitraum wiederholt den Wert von 55 mmHg unterschreitet (chronische Hypoxämie) und andere Therapiemethoden nicht zu einer Besserung geführt haben. Die Indikation ist außerdem auch bei einem Sauerstoffpartialdruck zwischen 55 und 60 mmHg gegeben, wenn zusätzlich eine Polyglobulie mit einem Hämatokrit ≥ 55 % bzw. ein Cor pulmonale besteht.
Für mobile Patienten eignet sich eine mobile Sauerstofftherapie mit transportablen Sauerstoffgeräten zum Erhalt der Mobilität und zur Unterstützung der Patientencompliance bezogen auf die tägliche Nutzungsdauer von mindestens 15 Stunden.

Long-Term Oxygen Therapy for 24 or 15 Hours per Day in Severe Hypoxemia

Long-term oxygen supplementation for at least 15 hours per day prolongs survival among patients with severe hypoxemia. On the basis of a nonrandomized comparison, long-term oxygen therapy has been recommended to be used for 24 hours per day, a more burdensome regimen.

To test the hypothesis that long-term oxygen therapy used for 24 hours per day does not result in a lower risk of hospitalization or death at 1 year than therapy for 15 hours per day, we conducted a multicenter, registry-based, randomized, controlled trial involving patients who were starting oxygen therapy for chronic, severe hypoxemia at rest. The patients were randomly assigned to receive long-term oxygen therapy for 24 or 15 hours per day. The primary outcome, assessed in a time-to-event analysis, was a composite of hospitalization or death from any cause within 1 year. Secondary outcomes included the individual components of the primary outcome assessed at 3 and 12 months.





The number of adverse events, including burn injuries, fall-related injuries, and nosebleeds, was similar in the two groups.

On the basis of two randomized clinical trials that were conducted in the 1970s and involved patients with chronic obstructive pulmonary disease (COPD), long-term oxygen therapy has become an established treatment to prolong survival among patients with chronic, severe resting hypoxemia. More than one million people receive long-term oxygen therapy in the United States alone, and this therapy constitutes the highest direct cost related to COPD after hospitalization.

Severe hypoxemia may be defined on the basis of the partial pressure of oxygen (Pao_2) or the oxyhemoglobin saturation as measured by pulse oximetry (Spo_2) and whether right heart failure or polycythemia is present. For example, severe hypoxemia may be defined as a resting Pao_2 lower than 55 mm Hg (7.4 kPa) or an Spo_2 lower than 88% or defined as a Pao_2 lower than 60 mm Hg (8.0 kPa) with the patient breathing ambient air along with signs of heart failure or a hematocrit higher than 54%. When severe hypoxemia is present, long-term oxygen therapy is recommended to be used for at least 15 hours per day, but use for 24 hours per day may prolong survival according to a nonrandomized comparison.

However, long-term oxygen therapy is associated with a high burden of adverse effects, restricted mobility, and increased social isolation. Being dependent on oxygen equipment often causes feelings of shame, stigma, and restricted autonomy. This burden may be especially high for patients receiving long-term oxygen therapy for 24 hours per day.

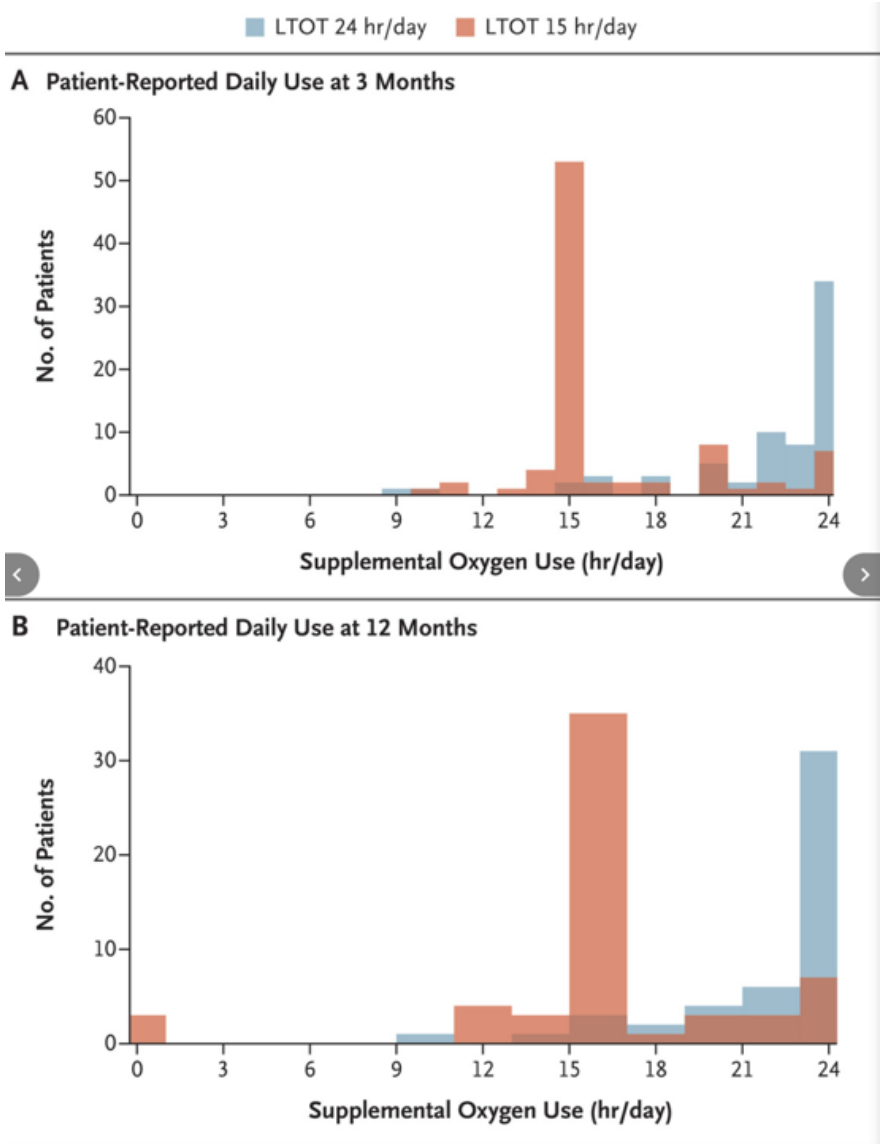
Methods

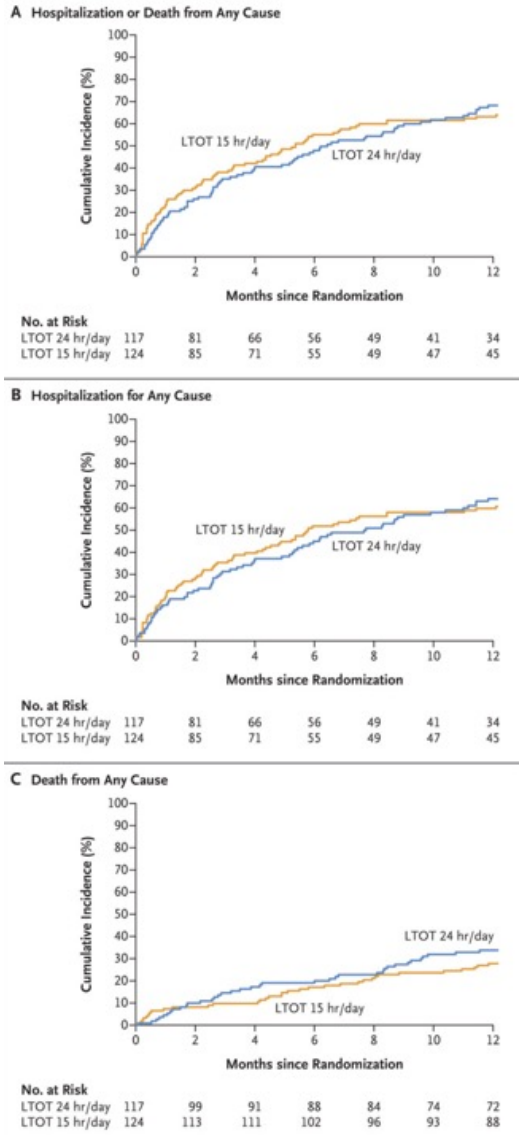
Trial Design and Patients

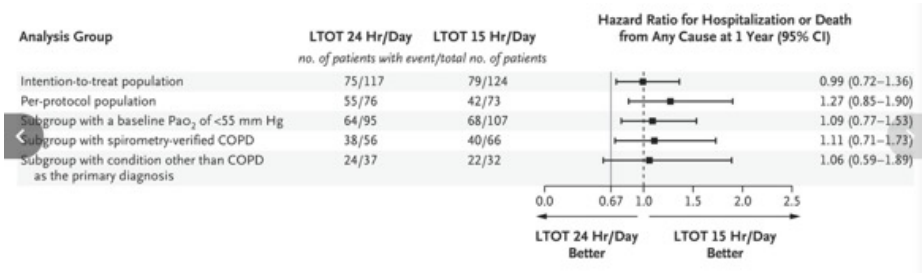
The Registry-Based Treatment Duration and Mortality in Long-Term Oxygen Therapy (REDOX) trial was a multicenter, phase 4, randomized, controlled trial evaluating whether long-term oxygen therapy used for 24 hours per day is not superior to therapy used for 15 hours per day. The trial was conducted with the use of the Swedish National Registry for Respiratory Failure (Swedevox), which includes approximately 85% of all the patients who have started long-term oxygen therapy in Sweden since 1987.

Patients underwent screening within 28 days after starting long-term oxygen therapy. We included patients 18 years of age or older who met established criteria for the receipt of long-term oxygen therapy for chronic severe hypoxemia. Patients were eligible for inclusion if they had a resting Pao_2 lower than 55 mm Hg or an Spo_2 lower than 88% while breathing ambient air or if they had a Pao_2 lower than 60 mm Hg while breathing ambient air along with signs of heart failure or polycythemia (hematocrit, >0.54).

Characteristic	LTOT 24 Hr/Day (N=117)	LTOT 15 Hr/Day (N=124)
Age — yr		
Mean	76.4±7.3	75.0±7.5
Median (IQR)	76.0 (73.0 to 82.0)	75.0 (72.0 to 79.0)
Sex — no. (%)		
Male	43 (36.8)	57 (46.0)
Female	74 (63.2)	67 (54.0)
Smoking status — no. (%)		
Never smoker	9 (7.7)	8 (6.5)
Ex-smoker	104 (88.9)	110 (88.7)
Current smoker	0	0
Missing data	4 (3.4)	6 (4.8)
Primary diagnosis — no. (%)		
COPD	80 (68.4)	92 (74.2)
Pulmonary fibrosis	20 (17.1)	14 (11.3)
Other†	15 (12.8)	18 (14.5)
Missing data	2 (1.7)	0
Secondary diagnosis — no. (%)		
Heart disease	8 (6.8)	8 (6.5)
Other pulmonary vascular disease	7 (6.0)	5 (4.0)
Pulmonary hypertension	2 (1.7)	2 (1.6)
COPD	2 (1.7)	0
Pulmonary fibrosis	1 (0.9)	1 (0.8)
Missing data	91 (77.8)	96 (77.4)
Pao_2 while breathing ambient air — mm Hg		
Mean	48.8±6.0	48.8±4.5
Median (IQR)	50.3 (46.5 to 53.3)	49.5 (45.8 to 52.5)
Spo_2 while breathing ambient air — %		
Mean	81.8±2.9	78.4±3.9
Median (IQR)	80.0 (80.0 to 84.0)	79.0 (75.0 to 81.0)
$Paco_2$ while breathing ambient air — mm Hg		
Mean	42.0±10.5	42.8±11.3
Median (IQR)	40.5 (35.3 to 49.5)	40.5 (35.3, to 48.8)
Pao_2 while breathing the prescribed oxygen — mm Hg		
Mean	64.5±9.8	63.0±8.3
Median (IQR)	63.8 (58.5 to 67.5)	62.3 (58.5 to 67.5)
Spo_2 while breathing the prescribed oxygen — %		
Mean	94.1±2.6	91.4±2.2
Median (IQR)	95.0 (92.0 to 96.0)	91.0 (90.0 to 94.0)
$Paco_2$ while breathing the prescribed oxygen — mm Hg		
Mean	43.5±12.0	43.5±9.8
Median (IQR)	41.3 (36.0 to 50.3)	42.0 (36.0 to 49.5)
FEV_1 — liters		
Mean	1.2±0.7	1.3±0.7
Median (IQR)	0.9 (0.6 to 1.6)	1.1 (0.7 to 1.7)
FVC — liters		
Mean	2.1±0.8	2.4±1.0
Median (IQR)	1.9 (1.6 to 2.5)	2.2 (1.6 to 3.0)
Prescribed oxygen therapy — no. (%)		
Stationary oxygen concentrator		
Yes	115 (98.3)	122 (98.4)
Missing data	2 (1.7)	0
Liquid oxygen		
Yes	2 (1.7)	2 (1.6)
Missing data	2 (1.7)	0
Portable oxygen equipment prescribed — no. (%)		
Yes	108 (92.3)	94 (75.8)
Missing data	2 (1.7)	2 (1.6)
Type of portable oxygen equipment — no. (%)		
Mobile concentrator	102 (87.2)	87 (70.2)
Oxygen cylinders	5 (4.3)	4 (3.2)
Liquid oxygen	1 (0.9)	2 (1.6)
Not known	0	1 (0.8)
Missing data	9 (7.7)	30 (24.2)
Oxygen flow rate		
Mean — liter/min	1.7±0.9	1.8±1.5
Median (IQR) — liter/min	1.5 (1.0 to 2.0)	1.5 (1.0 to 2.0)
Started LTOT after an exacerbation of underlying disease — no. (%)		
Yes	31 (26.5)	37 (29.8)
Missing data	20 (17.1)	22 (17.7)
Concurrent HMV treatment at baseline — no. (%)		
Yes	8 (6.8)	12 (9.7)
Missing data	0	0

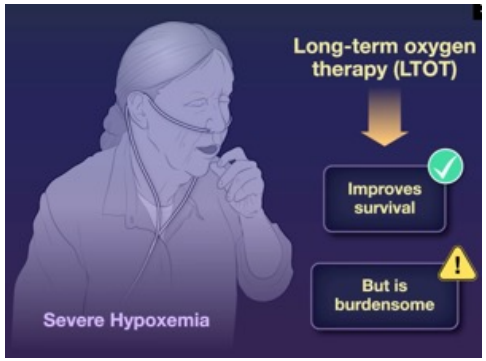

LTOT 24 hr/day
LTOT 15 hr/day
A Patient-Reported Daily Use at 3 Months
No. of Patients
Supplemental Oxygen Use (hr/day)
B Patient-Reported Daily Use at 12 Months
No. of Patients
Supplemental Oxygen Use (hr/day)

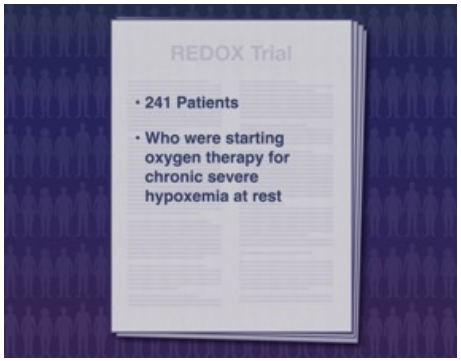

A Hospitalization or Death from Any Cause
Cumulative Incidence (%)
LTOT 15 hr/day
LTOT 24 hr/day
Months since Randomization
No. at Risk
LTOT 24 hr/day 117 81 66 56 49 41 34
LTOT 15 hr/day 124 85 71 55 49 47 45
B Hospitalization for Any Cause
Cumulative Incidence (%)
LTOT 15 hr/day
LTOT 24 hr/day
Months since Randomization
No. at Risk
LTOT 24 hr/day 117 81 66 56 49 41 34
LTOT 15 hr/day 124 85 71 55 49 47 45
C Death from Any Cause
Cumulative Incidence (%)
LTOT 24 hr/day
LTOT 15 hr/day
Months since Randomization
No. at Risk
LTOT 24 hr/day 117 99 91 88 84 74 72
LTOT 15 hr/day 124 113 111 102 96 93 88

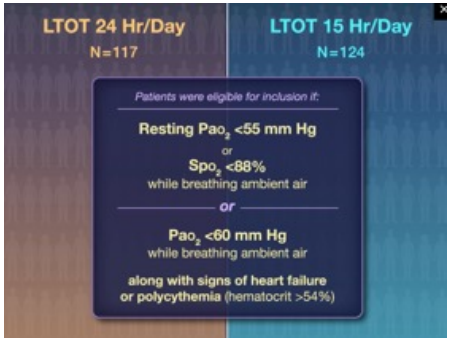


Trial Outcomes at 12 Months in the Intention-to-Treat Population.

Outcome	LTOT 24 Hr/Day (N=117)	LTOT 15 Hr/Day (N=124)	Estimated Effect (95% CI), 24 vs. 15 Hr/Day†
Primary outcome			
Hospitalization or death from any cause — no. (%)	75 (64.1)	79 (63.7)	0.99 (0.72 to 1.36)
Secondary outcomes			
Death from any cause — no. (%)	37 (31.6)	34 (27.4)	1.26 (0.79 to 2.01)
Hospitalization for any cause — no. (%)	67 (57.3)	71 (57.3)	1.00 (0.72 to 1.40)
MDP A1 scale score for overall unpleasantness‡			
No. of patients assessed	46	59	
Mean score	4.46±2.65	4.05±2.85	0.41 (−0.67 to 1.48)
Median score (IQR)	5.0 (2.0 to 6.0)	4.0 (2.0 to 7.0)	
FACIT scale score for fatigue§			
No. of patients assessed	37	55	
Mean score	22.51±11.23	22.20±9.78	0.31 (−4.07 to 4.70)
Median score (IQR)	22.0 (13.0 to 29.0)	23.0 (16.0 to 29.0)	
CAT score for health status¶			
No. of patients assessed	43	57	
Mean score	21.56±5.34	18.82±7.28	2.73 (0.12 to 5.35)
Median score (IQR)	21.0 (18.0 to 25.0)	19.0 (14.0 to 23.0)	
EQ-5D VAS score for perceived overall well-being‖			
No. of patients assessed	47	58	
Mean score	46.70±22.75	46.98±22.54	−0.28 (−9.09 to 8.53)
Median score (IQR)	50.0 (30.0 to 60.0)	45.0 (30.0 to 60.0)	
Preferred daily duration of therapy — no./total no. (%)			
15 hr/day	18/41 (43.9)	37/54 (68.5)	0.36 (0.15 to 0.84)
24 hr/day	23/41 (56.1)	17/54 (31.5)	—

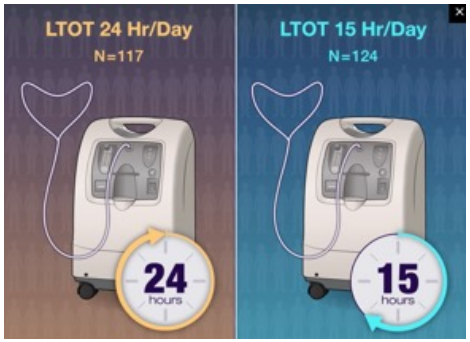

Long-term oxygen therapy (LTOT)
Improves survival
But is burdensome
Severe Hypoxemia


REDOX Trial
• 241 Patients
• Who were starting oxygen therapy for chronic severe hypoxemia at rest

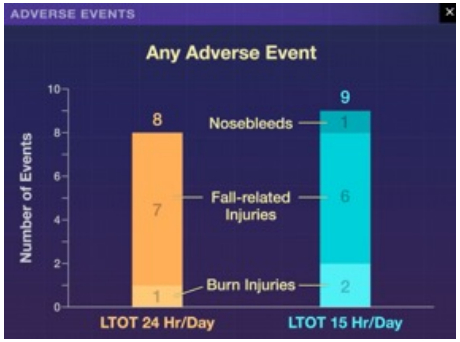

LTOT 24 Hr/Day
N=117
LTOT 15 Hr/Day
N=124
Patients were eligible for inclusion if:
Resting Pao2 <55 mm Hg
or
Spo2 <88%
while breathing ambient air
or
Pao2 <60 mm Hg
while breathing ambient air
along with signs of heart failure or polycythemia (hematocrit >54%)


SECONDARY OUTCOMES
Death from Any Cause
Estimated effect, 1.26 (95% CI, 0.79 to 2.01)
Hospitalization for Any Cause
Estimated effect, 1.00 (95% CI, 0.72 to 1.40)
Percentage of Patients
31.6%
27.4%
57.3%
57.3%
24 Hr
15 Hr
Overall Unpleasantness
(with breathing)
Estimated effect, 0.41 (95% CI, −0.67 to 1.48)
MDP A1 Scale Mean Score
4.46 ±2.65
4.05 ±2.85


Up to
24 hours
per day
is often considered
Some data have suggested additional bene

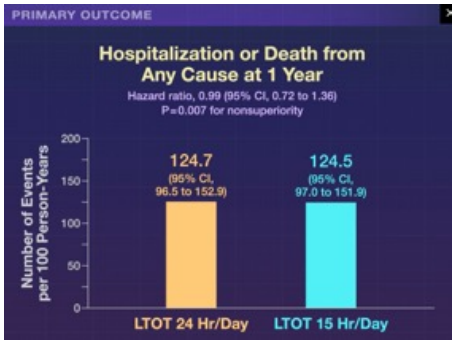

LTOT 24 Hr/Day
N=117
LTOT 15 Hr/Day
N=124
24 hours
15 hours


PRIMARY OUTCOME
Hospitalization or Death from Any Cause at 1 Year
24 hours
Not significantly lower
15 hours


ADVERSE EVENTS
Any Adverse Event
Number of Events
8
7
1
9
1
6
2
Nosebleeds
Fall-related Injuries
Burn Injuries
LTOT 24 Hr/Day
LTOT 15 Hr/Day

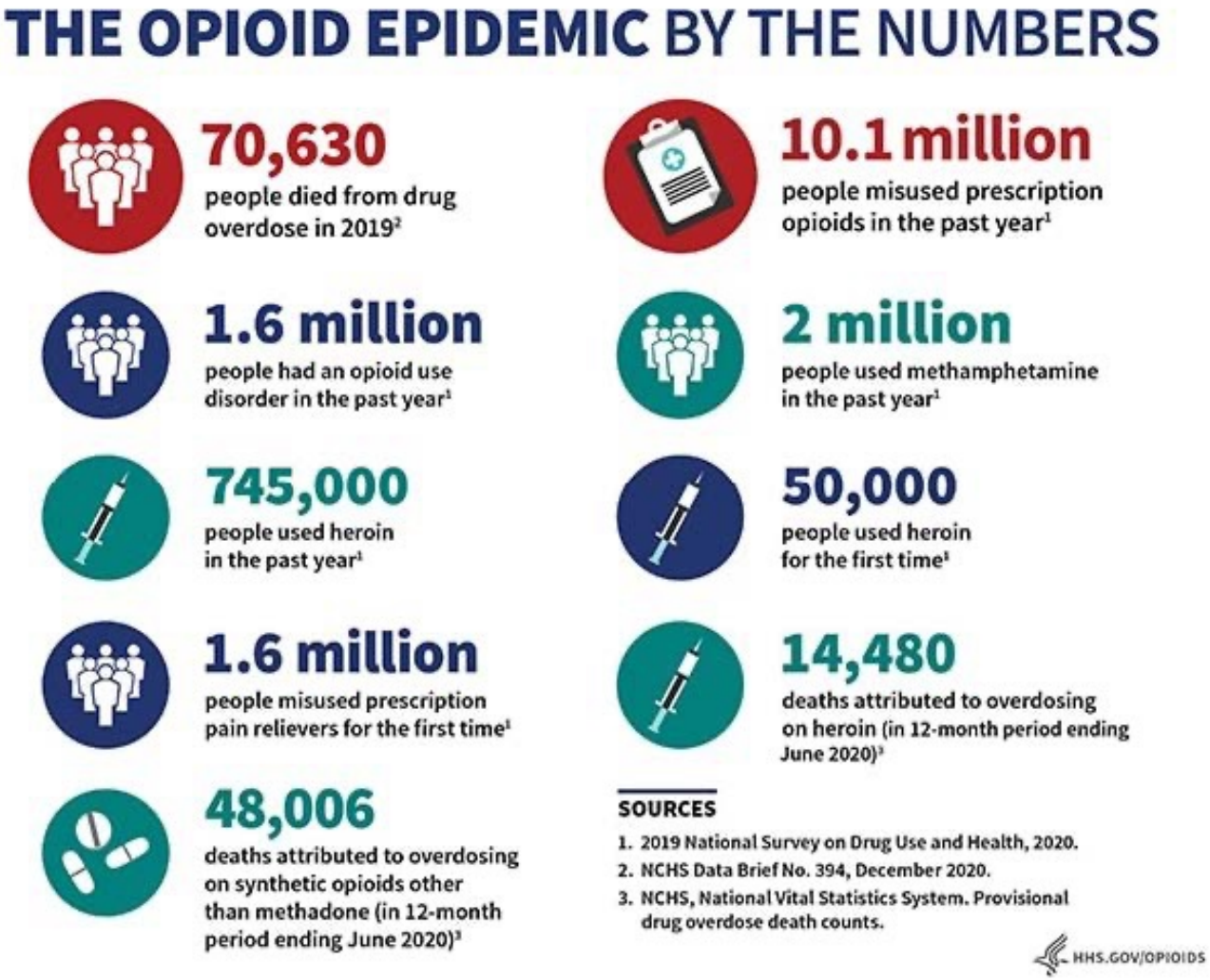

? Clinical Outcomes
15 hours
vs.
24 hours


LTOT 24 Hr/Day
N=117
LTOT 15 Hr/Day
N=124
Patients were eligible for inclusion if:
Resting Pao2 <55 mm Hg
or
Spo2 <88%
while breathing ambient air


PRIMARY OUTCOME
Hospitalization or Death from Any Cause at 1 Year
Hazard ratio, 0.99 (95% CI, 0.72 to 1.36)
P=0.007 for nonsuperiority
Number of Events per 100 Person-Years
124.7
(95% CI, 96.5 to 152.9)
124.5
(95% CI, 97.0 to 151.9)
LTOT 24 Hr/Day
LTOT 15 Hr/Day

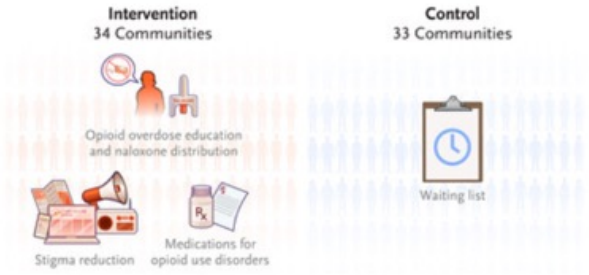

Long-term oxygen therapy
24 hours
was not superior to
15 hours
in reducing the risk of hospitalization or death within 1 year

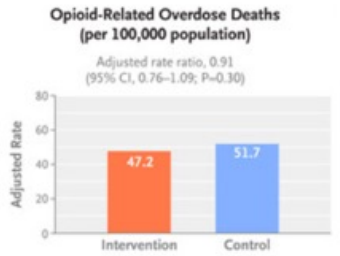
Opioid-involved overdose deaths rose from 49,860 in 2019 to 81,806 in 2022

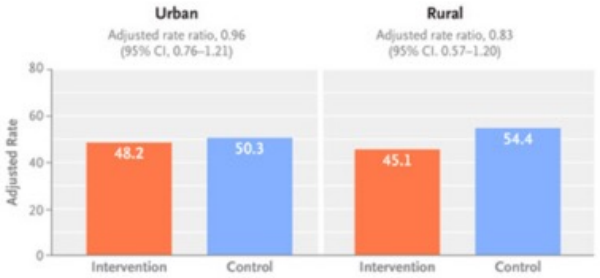


Community-Based Cluster-Randomized Trial to Reduce Opioid Overdose Deaths

Evidence-based practices for reducing opioid-related overdose deaths include overdose education and naloxone distribution, the use of medications for the treatment of opioid use disorder, and prescription opioid safety. Data are needed on the effectiveness of a community-engaged intervention to reduce opioid-related overdose deaths through enhanced uptake of these practices. In this community-level, cluster-randomized trial, we randomly assigned 67 communities in Kentucky, Massachusetts, New York, and Ohio to receive the intervention (34 communities) or a wait-list control (33 communities), stratified according to state. The trial was conducted within the context of both the coronavirus disease 2019 (Covid-19) pandemic and a national surge in the number of fentanyl-related overdose deaths. The trial groups were balanced within states according to urban or rural classification, previous overdose rate, and community population. The primary outcome was the number of opioid-related overdose deaths among community adults.



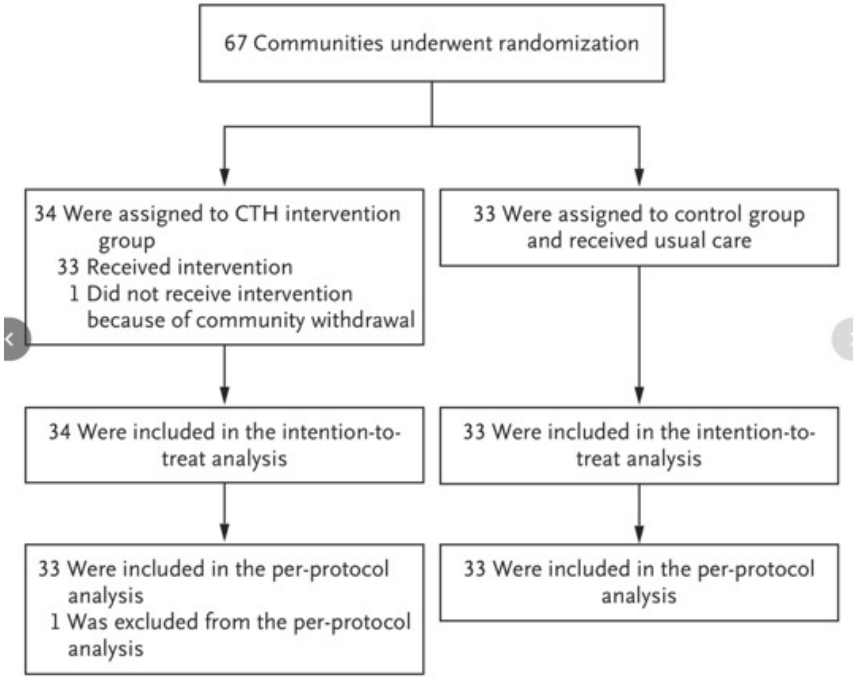




In 2016, the U.S. Surgeon General urged medical professionals to address the opioid crisis through advocacy, stigma reduction, uptake of treatment for opioid use disorder, and safer opioid prescribing. The National Academy of Medicine echoed this recommendation in 2017. Both reports highlighted the value of evidence-based practices to prevent or reverse opioid overdoses. These practices include education regarding overdose prevention and naloxone distribution, the use of medications (including methadone and buprenorphine) for the treatment of opioid use disorder, and safer opioid prescribing, dispensing, and disposal practices (i.e., prescription opioid safety).

To address these barriers, the National Institutes of Health launched the HEALing (Helping to End Addiction Long-term Initiative) Communities Study (HCS), a large, multistate implementation-science trial focused on substance use. The HCS research consortium designed the community-engaged, data-driven Communities That HEAL (CTH) intervention to rapidly scale up strategies to increase access to evidence-based practices and conduct communication campaigns in highly affected communities in Kentucky, Massachusetts, New York, and Ohio, with the primary goal of reducing the rate of opioid-related overdose deaths.

These practices include education regarding overdose prevention and naloxone distribution, the use of medications (including methadone and buprenorphine) for the treatment of opioid use disorder, and safer opioid prescribing, dispensing, and disposal practices (i.e., prescription opioid safety).



Variable	Intervention Communities				Control Communities				Rate Ratio
	Community (N=67)	Opioid-Related Overdose Deaths	Population†	Death Rate	Community (N=67)	Opioid-Related Overdose Deaths	Population†	Death Rate	
	no. (%)		*no.*	*no./100,000 population*	*no. (%)*		*no.*	*no./100,000 population*	
All communities	34 (50.7)	1771	4,439,170	39.9	33 (49.3)	1546	3,772,336	41.0	0.97
Opioid-related overdose deaths									
Mean no.	—	—	—	38.2±22.8	—	—	—	37.1±20.3	—
Median no. (IQR)	—	—	—	35.2 (21.6–49.3)	—	—	—	32.7 (23.6–48.6)	—
State									
Kentucky	8 (23.5)	260	617,841	42.1	8 (24.2)	361	815,764	44.3	0.95
Massachusetts	8 (23.5)	172	359,314	47.9	8 (24.2)	201	356,545	56.4	0.85
New York	8 (23.5)	256	1,101,497	23.2	8 (24.2)	318	976,069	32.6	0.71
Ohio	10 (29.4)	1083	2,360,518	45.9	9 (27.3)	666	1,623,958	41.0	1.12
Urban or rural category									
Urban	19 (55.9)	1538	3,793,353	40.5	19 (57.6)	1377	3,242,663	42.5	0.95
Rural	15 (44.1)	233	645,817	36.1	14 (42.4)	169	529,673	31.9	1.13
Age group — yr									
18 to 34	—	531	1,334,880	39.8	—	508	1,178,210	43.1	0.92
35 to 54	—	848	1,353,341	62.7	—	751	1,180,392	63.6	0.98
≥55	—	392	1,750,949	22.4	—	287	1,413,734	20.3	1.10
Sex									
Male	—	1235	2,133,827	57.9	—	1071	1,825,776	58.7	0.99
Female	—	536	2,305,343	23.3	—	475	1,946,560	24.4	0.95
Race or ethnic group‡									
Non-Hispanic White	—	1374	3,229,233	42.5	—	1119	2,750,369	40.7	1.05
Non-Hispanic Black	—	267	728,037	36.7	—	278	545,357	51.0	0.72
Hispanic	—	115	281,329	40.9	—	130	322,654	40.3	1.01
Non-Hispanic other	—	12	200,571	6.0	—	17	153,956	11.0	0.54
Missing data	—	3			—	2			

Unadjusted Rate Ratio of Opioid-Related Overdose Deaths

Variable	Intervention Communities		Control Communities		Unadjusted Rate Ratio
	Opioid-Related Overdose Deaths	Population	Opioid-Related Overdose Deaths	Population	
	number of persons				
All communities	65.3±98.1	130,563.8± 200,088.0	69.6±143.8	114,313.2± 201,417.3	0.94
State					
Kentucky	48.9±46.5	77,230.1± 80,938.9	76.1±168.7	101,970.5± 202,045.3	1.11
Massachusetts	25.1±22.2	44,914.3± 26,559.3	30.1±24.7	44,568.1± 33,628.8	0.74
New York	59.0±73.9	137,687.1± 140,779.9	67.9±74.6	122,008.6± 106,012.1	0.73
Ohio	115.6±156.3	236,051.8± 322,922.0	100.4±223.0	180,439.8± 325,173.2	1.24
Urban or rural category					
Urban	100.2±120.1	199,650.2± 248,385.2	106.8±182.1	170,666.5± 252,614.9	0.96
Rural	21.1±19.4	43,054.5± 19,075.4	19.1±14.8	37,833.8± 23,733.0	0.92
Age group — yr					
18 to 34	17.6±25.6	39,261.2± 60,440.2	19.5±42.1	35,703.3± 69,802.6	0.88
35 to 54	32.4±48.8	39,804.1± 60,321.8	33.7±70.3	35,769.5± 65,163.6	0.97
≥55	15.3±24.7	51,498.5± 79,908.4	16.4±32.3	42,840.4± 67,485.8	0.97
Sex					
Male	44.9±68.2	62,759.6± 94,370.9	48.5±98.4	55,326.5± 96,853.5	0.89
Female	20.4±30.1	67,804.2± 105,743.9	21.1±45.6	58,986.7± 104,579.4	1.08
Race or ethnic group					
Non-Hispanic White	46.6±61.6	94,977.4± 128,763.1	46.6±91.2	83,344.5± 135,601.7	0.97
Non-Hispanic Black	13.6±30.6	21,412.9± 55,089.6	16.2±46.9	16,526.0± 45,296.8	0.96
Hispanic	4.0±8.0	8,274.4± 13,482.1	5.4±10.8	9,777.4± 17,743.5	0.77
Non-Hispanic other	0.9±2.2	5,899.1± 9,757.0	1.2±2.9	4,665.3± 11,990.9	0.79
Missing data	0.3±0.8		0.4±0.9		

Adjusted Rate of Opioid-Related Overdose Deaths, According to Population.

Population	Adjusted Rate in Intervention Communities (95% CI)	Adjusted Rate in Control Communities (95% CI)	Adjusted Rate Ratio (95% CI)	P Value†
	no./100,000 population			
Intention-to-treat analysis	47.2 (41.8–53.2)	51.7 (44.9–59.6)	0.91 (0.76–1.09)	0.30
Per-protocol analysis	47.2 (41.8–53.3)	51.6 (44.8–59.4)	0.91 (0.77–1.09)	—

Adjusted Rate of Opioid-Related Overdose Deaths

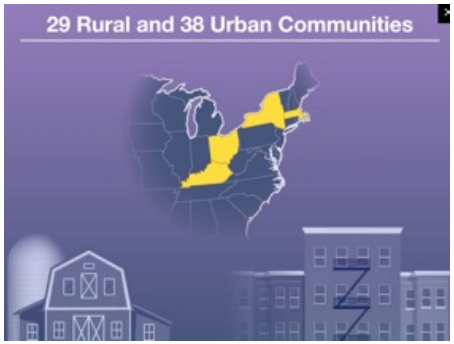
Variable	Adjusted Rate in Intervention Communities (95% CI)	Adjusted Rate in Control Communities (95% CI)	Adjusted Rate Ratio (95% CI)
	no./100,000 population		
State			
Kentucky	59.8 (44.5–80.4)	59.3 (35.5–99.2)	1.01 (0.56–1.81)
Massachusetts	45.0 (30.7–65.9)	52.2 (38.0–71.8)	0.86 (0.54–1.37)
New York	46.4 (32.1–67.0)	53.1 (41.7–67.7)	0.87 (0.56–1.35)
Ohio	39.3 (31.7–48.7)	43.0 (28.9–64.1)	0.91 (0.58–1.44)
Urban or rural category			
Urban	48.2 (41.5–55.9)	50.3 (41.6–60.9)	0.96 (0.76–1.21)
Rural	45.1 (35.3–57.7)	54.4 (41.4–71.5)	0.83 (0.57–1.20)
Age — yr			
18 to 34	46.2 (39.8–53.5)	51.3 (42.4–62.1)	0.90 (0.72–1.13)
35 to 54	69.9 (58.2–83.9)	76.6 (64.8–90.5)	0.91 (0.73–1.15)
≥55	33.6 (27.8–40.7)	39.3 (28.9–53.6)	0.86 (0.59–1.23)
Sex			
Male	60.6 (50.6–72.6)	69.2 (58.4–82.1)	0.88 (0.71–1.08)
Female	34.1 (29.0–40.0)	37.2 (30.2–45.8)	0.91 (0.71–1.18)
Race or ethnic group			
Non-Hispanic White	45.4 (36.6–56.3)	47.6 (38.0–59.5)	0.95 (0.72–1.26)
Non-Hispanic Black	70.3 (52.4–94.2)	77.1 (54.9–108.4)	0.91 (0.59–1.40)
Hispanic	39.3 (24.4–63.3)	46.4 (31.6–68.0)	0.85 (0.46–1.57)
Non-Hispanic other	16.5 (7.5–36.4)	28.2 (13.6–58.7)	0.59 (0.20–1.68)

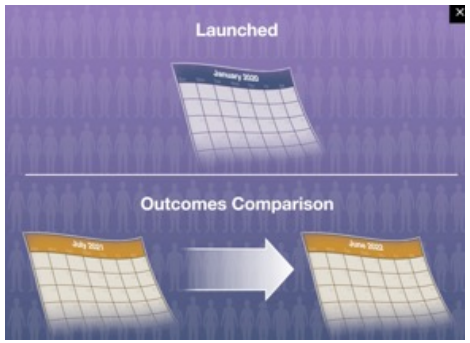
First, the evidence-based practices were addressed by a complex array of strategies for high-risk populations in health care, behavioral health, and criminal legal sectors. After the strategy selection process, only 10 months preceded the comparison period to establish agency partnerships and implement evidence-based practices.

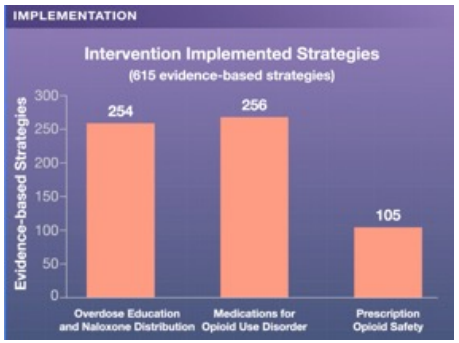
Second, the intervention launch (in January 2020) occurred 2 months before the Covid-19 shutdown, which severely disrupted systems targeted by the CTH intervention.

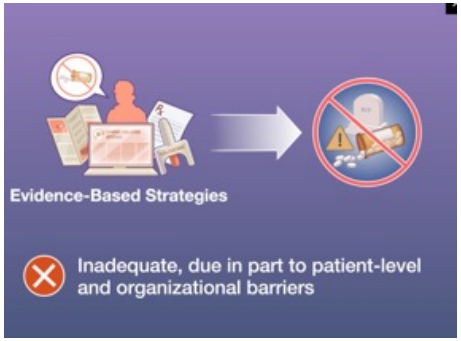
Third, the change in the illicit drug market may have reduced the effectiveness of the intervention, because fentanyl became a more prevalent opioid and a more commonly used adulterant in stimulants and counterfeit pills.

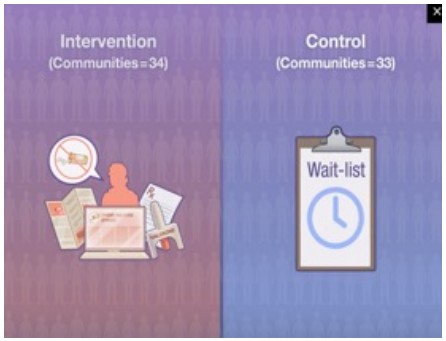

Opioid-Related Overdose Deaths
X 10

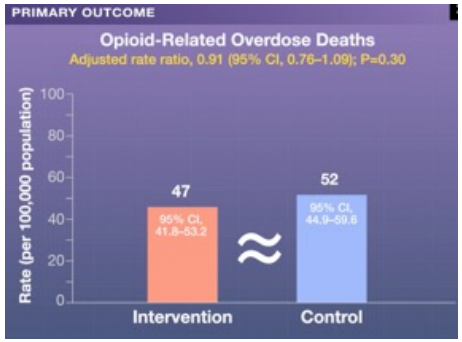

29 Rural and 38 Urban Communities


Launched
Outcomes Comparison

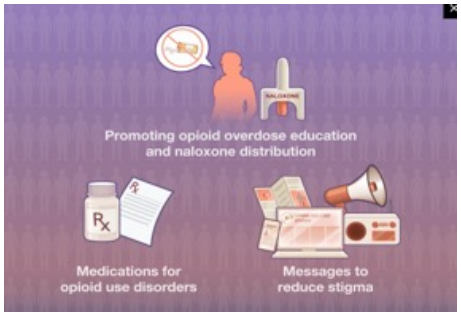

IMPLEMENTATION
Intervention Implemented Strategies
(615 evidence-based strategies)
Evidence-based Strategies
254
256
105
Overdose Education and Naloxone Distribution
Medications for Opioid Use Disorder
Prescription Opioid Safety

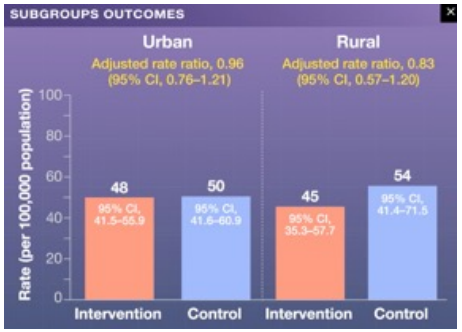

Evidence-Based Strategies
Inadequate, due in part to patient-level and organizational barriers


Intervention
(Communities=34)
Control
(Communities=33)
Wait-list


PRIMARY OUTCOME
Opioid-Related Overdose Deaths
Adjusted rate ratio, 0.91 (95% CI, 0.76–1.09); P=0.30
Rate (per 100,000 population)
47
95% CI, 41.8–53.2
52
95% CI, 44.9–59.6
Intervention
Control

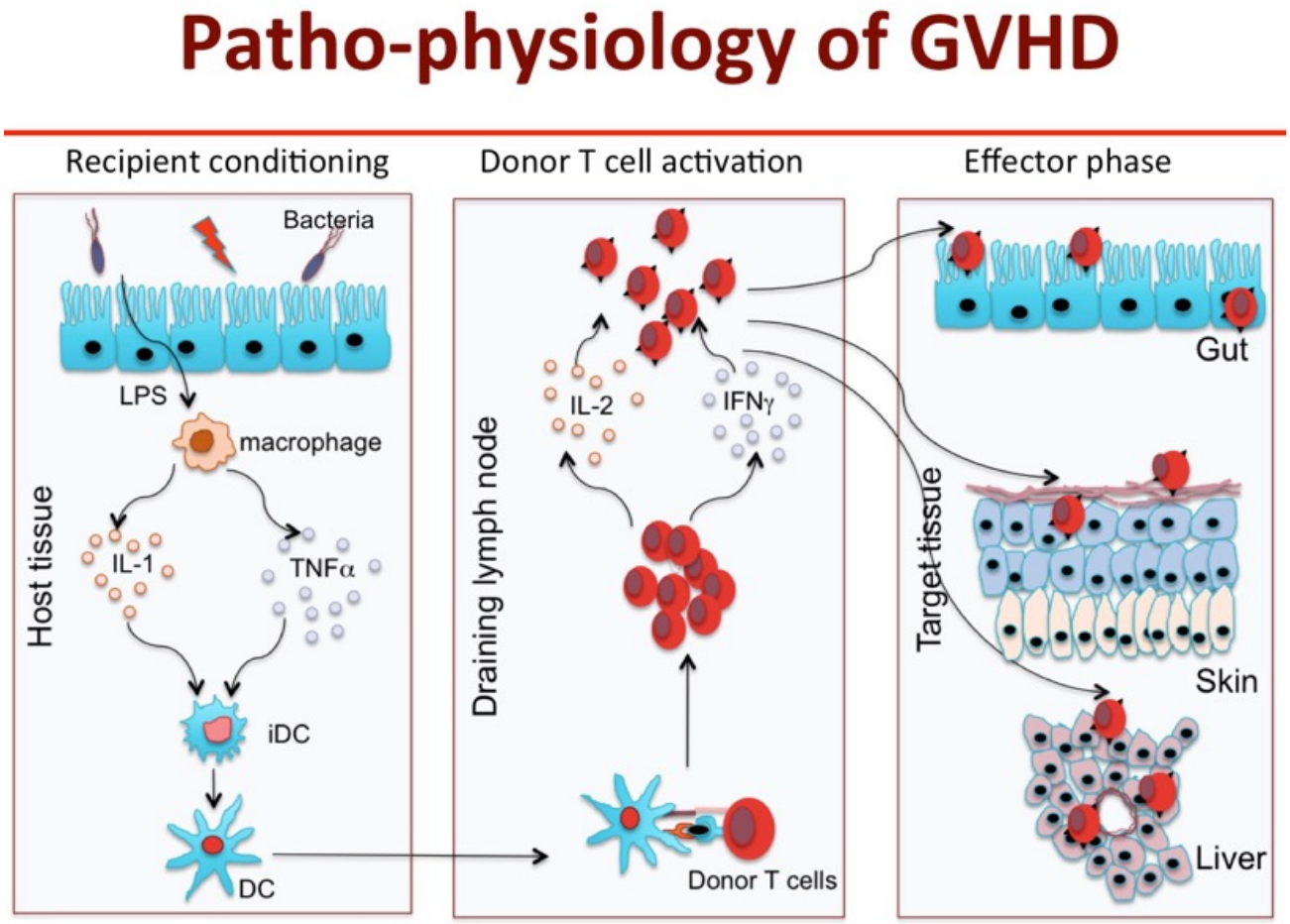

IMPLEMENTATION
Intervention Implemented Strategies
(615 evidence-based strategies)
Only about one third were implemented before the comparison period
Overdose Education and Naloxone Distribution
Medications for Opioid Use Disorder
Prescription Opioid Safety


Promoting opioid overdose education and naloxone distribution
Medications for opioid use disorders
Messages to reduce stigma


SUBGROUPS OUTCOMES
Urban
Adjusted rate ratio, 0.96 (95% CI, 0.76–1.21)
Rural
Adjusted rate ratio, 0.83 (95% CI, 0.57–1.20)
Rate (per 100,000 population)
48
95% CI, 41.5–55.9
50
95% CI, 41.6–60.9
45
95% CI, 35.3–57.7
54
95% CI, 41.4–71.5
Intervention
Control
Intervention
Control


Did not reduce the rate of such deaths across communities in four U.S. states

Die Graft-versus-Host-Reaktion entsteht durch die Übertragung immunkompetenter Zel len mit dem Transplantat, die ursprünglich aus dem Knochenmark, aus der Milz oder aus den Lymphknoten des Spenders stammen. Transplantierte T-Zellen erkennen das Gewebe des Empfängers als fremd, wodurch im Empfängerorganismus zelluläre Immunreaktionen ausgelöst werden. Zur Fremderkennung der Empfänger-Antigene kommt es, weil die allogenen T-Zellen nur für die MHC-präsentierbaren Peptide des Spenders, nicht aber des Empfängers eine Immuntoleranz ausgebildet haben.



Key Concepts

Conditioning

A term used to describe a course of treatment comprising one or more medications administered to patients before transplantation of allogeneic or autologous hematopoietic stem cells. Typically, radiation and alkylating agents such as busulfan that eliminate the recipient's hematopoietic cells are given to "make space" for the transplanted cells. For most allogeneic transplant recipients, additional agents are given to eliminate immune cells and prevent immunologic rejection of the graft.

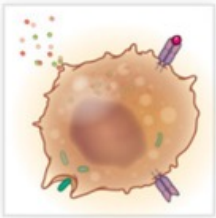
Hematopoietic stem cell

A type of stem cell that differentiates into the cellular components of the blood, including red cells, granulocytes, lymphocytes, monocytes, and platelets.

Chronic graft-versus-host disease (cGVHD) remains the major cause of late morbidity after allogeneic hematopoietic cell transplantation. Colony-stimulating factor 1 receptor (CSF-1R)–dependent macrophages promote cGVHD fibrosis, and their elimination in preclinical studies ameliorated cGVHD. Axatilimab is a humanized monoclonal antibody that inhibits CSF-1R signaling and restrains macrophage development.

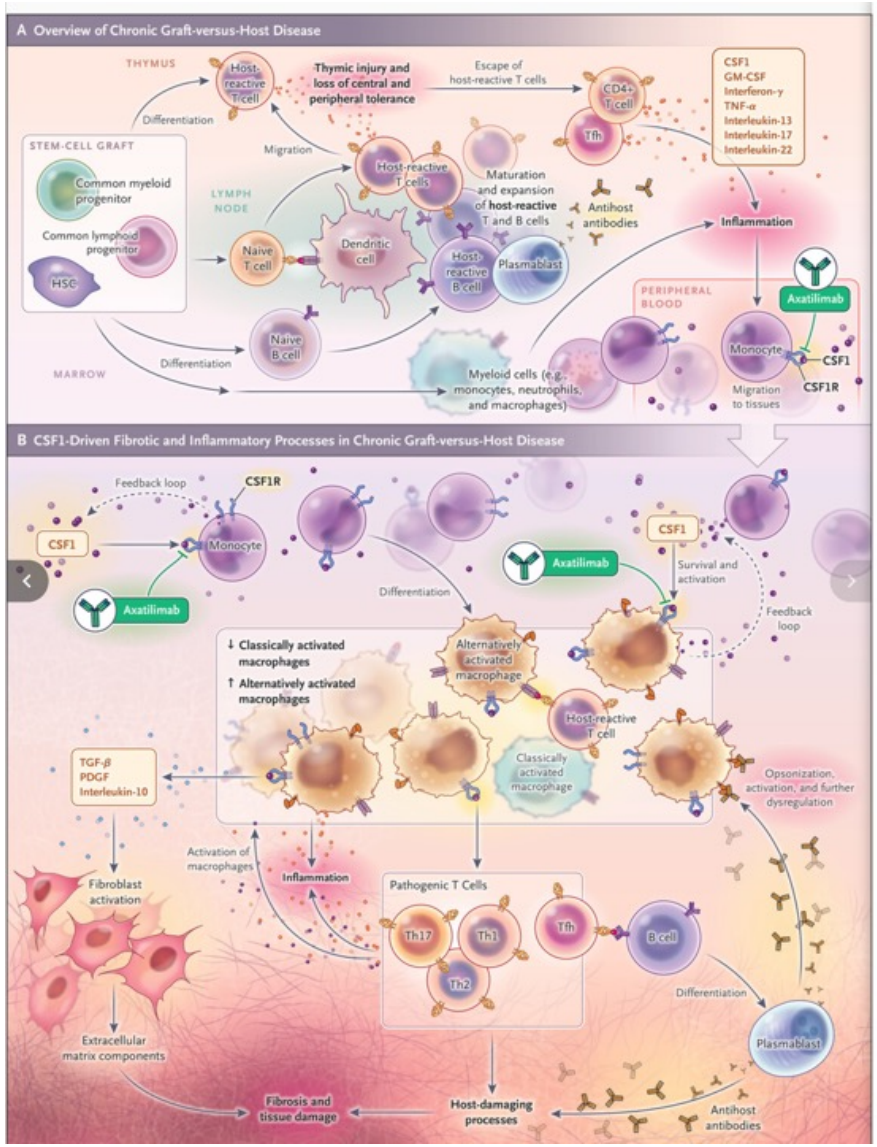
Hematopoietic stem-cell transplantation

A procedure in which a patient receives blood-forming stem cells (hematopoietic stem cells) to replace damaged or diseased bone marrow and provide the body with a means of producing healthy blood cells and a functional immune system. Hematopoietic stem-cell transplantation can be divided into separate phases. The first is a preparative or conditioning regimen (with the use of chemotherapy, radiation, or both), which eliminates the recipient's own hematopoietic cells to "make space" for the transplanted cells and reduce the risk of immunologic rejection of the graft. Subsequent phases include the infusion of the hematopoietic cells, aplasia, engraftment, and the recovery of hematopoietic functions. The cells may be sourced from the patient (autologous transplantation), a donor (allogeneic transplantation), or umbilical cord blood.



Macrophage

A type of immune cell that plays a crucial role in the immune system by digesting cellular debris and pathogens. Macrophages originate from monocytes in the blood and confer innate immunity, which is typically the body's first line of defense against foreign antigens. In addition, they help mediate wound healing and tissue repair by releasing growth factors and antiinflammatory cytokines. Macrophages can be found within many organs, including the liver, brain, bones, and lungs, as well as in the blood, particularly at sites of infection.



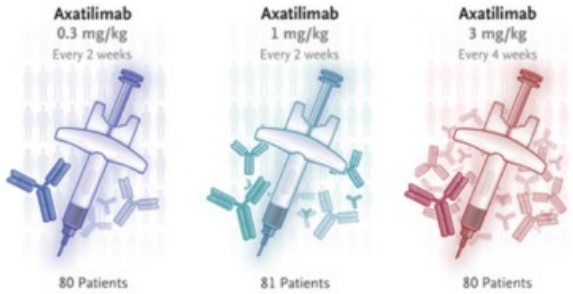
Pathophysiology of Chronic Graft-versus-Host Disease.

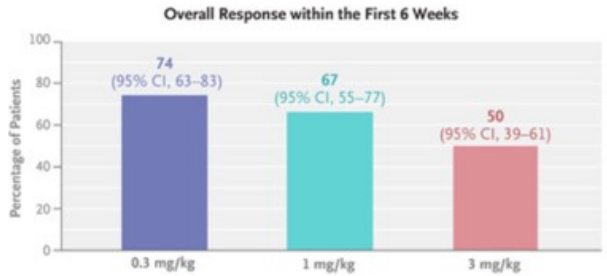
Immune mediators of graft-versus-host disease (GVHD), including T cells, B cells, and myeloid cells, are transferred directly in the graft or are derived from hematopoietic stem cells (HSCs) (Panel A). HSC-derived naïve T cells may escape thymic central and peripheral tolerance, leading to the maturation and expansion of host-reactive T cells. These immune cells contribute to inflammation through direct cell contact–mediated damage and the production of cytokines such as colony-stimulating factor 1 (CSF1), granulocyte–macrophage colony-stimulating factor (GM-CSF), interferon-γ, tumor necrosis factor α (TNF-α), and various interleukins. T- and B-cell homeostasis is disturbed, leading to activation of follicular helper T cells (Tfh), the differentiation of plasmablasts, and subsequent production of host-reactive immunoglobulins. In the periphery, monocytes migrate to tissues, further propagating the inflammatory response and leading to tissue damage. CSF1 drives fibrotic and some inflammatory processes (Panel B). Inflammation during GVHD induces the differentiation of monocytes into classically activated and alternatively activated macrophages, which interact with host-reactive T cells and antibodies and contribute to tissue fibrosis and damage. In addition, the activation of fibroblasts by transforming growth factor β (TGF-β), platelet-derived growth factor (PDGF), and interleukin-10 leads to the production of extracellular matrix components, further exacerbating fibrosis. The feedback loop between CSF1 and its receptor (CSF1R) perpetuates inflammation and tissue injury. Axatilimab, a CSF1R inhibitor, blocks the CSF1R–CSF1 pathway and thus monocyte-to-macrophage differentiation and the activation and survival of macrophages, thereby ameliorating deleterious effects observed in chronic GVHD target tissues. Th1 denotes type 1 helper T cell, Th2 type 2 helper T cell, and Th17 type 17 helper T cell.

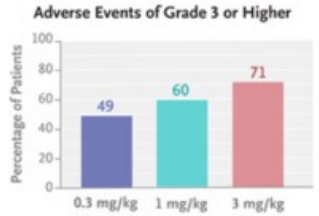
Axatilimab in Recurrent or Refractory Chronic Graft-versus-Host Disease

Colony-stimulating factor 1 receptor (CSF1R)–dependent monocytes and macrophages are key mediators of chronic graft-versus-host disease (GVHD), a major long-term complication of allogeneic hematopoietic stem-cell transplantation. The CSF1R-blocking antibody axatilimab has shown promising clinical activity in chronic GVHD.

In this phase 2, multinational, pivotal, randomized study, we evaluated axatilimab at three different doses in patients with recurrent or refractory chronic GVHD. Patients were randomly assigned to receive axatilimab, administered intravenously, at a dose of 0.3 mg per kilogram of body weight every 2 weeks (0.3-mg dose group), at a dose of 1 mg per kilogram every 2 weeks (1-mg dose group), or at a dose of 3 mg per kilogram every 4 weeks (3-mg dose group). The primary end point was overall response (complete or partial response) in the first six cycles; the key secondary end point was a patient-reported decrease in chronic GVHD symptom burden, as assessed by a reduction of more than 5 points on the modified Lee Symptom Scale (range, 0 to 100, with higher scores indicating worse symptoms). The primary end point would be met if the lower bound of the 95% confidence interval exceeded 30%.







Adverse events of grade 3 or higher occurred in all three dose groups. Events leading to discontinuation occurred in 5 patients in the 0.3-mg dose group (6%), 18 patients in the 1-mg dose group (22%), and 14 patients in the 3-mg dose group (18%).

Colony-stimulating factor 1 (CSF1) and interleukin-34–mediated signaling through the CSF1 receptor (CSF1R) play key roles in regulating the development and function of tissue macrophages in healthy persons and in persons with disease. In addition to their role in promoting tumor-driven immune evasion, CSF1R signaling–dependent monocytes and macrophages are essential mediators of inflammation and fibrosis in chronic GVHD and a range of autoimmune diseases. Consequently, blocking CSF1R offers a targeted approach to attenuating monocyte-driven and macrophage-driven disorders and may reduce the manifestations of chronic GVHD. Axatilimab, a high-affinity, humanized IgG4 monoclonal antibody, inhibits ligand-mediated CSF1R signaling and thereby affects the differentiation and function of CSF1R-expressing monocytes and macrophages. A study in mice showed that early post-transplantation administration of a CSF1R blocking antibody targeted donor-derived macrophages and ameliorated chronic GVHD; these findings may translate into new ways to treat patients with established chronic GVHD. In an early-phase clinical study involving patients with recurrent or refractory chronic GVHD, axatilimab showed promising preliminary efficacy and safety results accompanied by the preferential elimination of CSF1R-dependent nonclassical monocytes and tissue macrophages. Here we present the results of the primary analysis of AGAVE-201, a phase 2, multinational, pivotal, randomized study that evaluated the efficacy and safety of axatilimab at three different doses.

Patient Eligibility

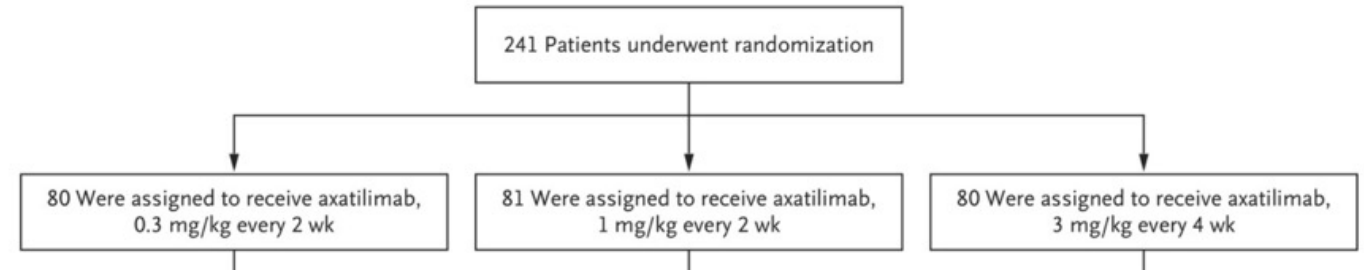
Patients with refractory or recurrent chronic GVHD were eligible for enrollment in the study if they were 2 years of age or older, had active signs and symptoms of chronic GVHD according to the 2014 National Institutes of Health (NIH) Consensus criteria, and had previously received at least two lines of systemic therapy.

Study Design

Patients were randomly assigned, in a 1:1:1 ratio, to receive axatilimab, administered intravenously, at a dose of 0.3 mg per kilogram of body weight every 2 weeks (0.3-mg dose group), 1 mg per kilogram every 2 weeks (1-mg dose group), or 3 mg per kilogram every 4 weeks (3-mg dose group). These doses were based on the safety and efficacy results observed in the earlier phase 1–2 study.

End Points

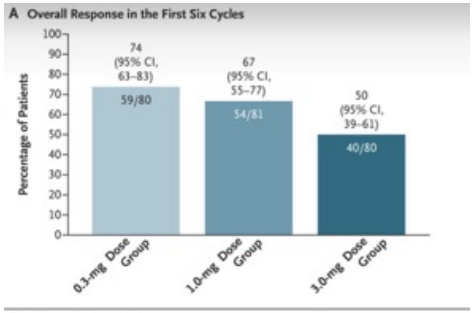
The primary end point was overall response, defined as a complete or partial response according to the NIH Consensus criteria, within the first six cycles after randomization (i.e., from randomization to day 169 or the beginning of cycle 7, whichever was later).

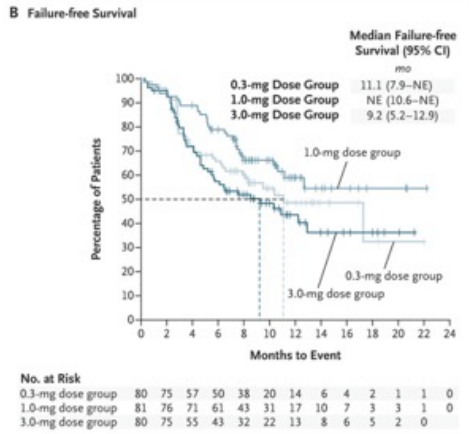


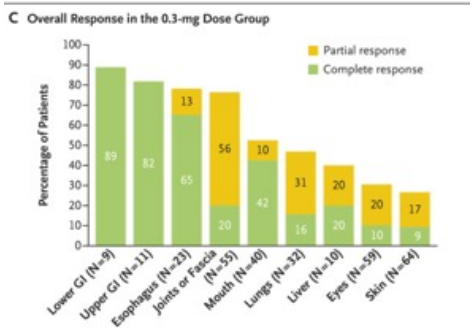
Characteristic	0.3-mg Dose Group (N=80)	1-mg Dose Group (N=81)	3-mg Dose Group (N=80)
Median age (range) — yr	50 (7–76)	56 (26–81)	53 (7–79)
Age group — no. (%)			
<17 yr	4 (5)	0	3 (4)
≥17 to <65 yr	55 (69)	62 (77)	61 (76)
≥65 yr	21 (26)	19 (23)	16 (20)
Male sex — no. (%)	47 (59)	51 (63)	53 (66)
Race or ethnic group — no. (%)†			
American Indian or Alaska Native	0	1 (1)	0
Asian	4 (5)	4 (5)	8 (10)
Black or African descent	2 (2)	2 (2)	1 (1)
Native Hawaiian or other Pacific Islander	0	0	1 (1)
White	68 (85)	70 (86)	62 (78)
Not reported	5 (6)	4 (5)	7 (9)
Other	1 (1)	0	1 (1)
Hispanic or Latino ethnic group — no. (%)†			
Yes	5 (6)	9 (11)	5 (6)
No	73 (91)	69 (85)	73 (91)
Not reported or unknown	2 (2)	3 (4)	2 (2)
Median time from chronic GVHD diagnosis to randomization (range) — yr	3.9 (0.4–17.6)	4.1 (0.6–17.1)	3.8 (0.4–15.4)
Global severity rating — no. (%)‡			
Mild or moderate	17 (21)	17 (21)	15 (19)
Severe	63 (79)	64 (79)	65 (81)
Median no. of organs involved (maximum no.)§	4 (8)	4 (7)	3 (7)
Organs involved — no. (%)			
Skin	64 (80)	63 (78)	66 (82)
Eyes	59 (74)	70 (86)	54 (68)
Mouth	40 (50)	40 (49)	32 (40)
Esophagus	23 (29)	18 (22)	20 (25)
Upper GI	11 (14)	8 (10)	9 (11)
Lower GI	9 (11)	5 (6)	4 (5)
Liver	10 (12)	13 (16)	17 (21)
Lungs	32 (40)	41 (51)	35 (44)
Joints and fascia	55 (69)	56 (69)	51 (64)
Median no. of previous systemic chronic GVHD therapy (range)	4 (2–12)	4 (2–14)	4 (2–15)
Previous use of ≥1 FDA-approved systemic chronic GVHD therapy — no. (%)	67 (84)	69 (85)	68 (85)
Ibrutinib	27 (34)	19 (23)	29 (36)
Ruxolitinib	57 (71)	64 (79)	58 (72)
Belumosudil	16 (20)	19 (23)	21 (26)
Best response to the most recent previous chronic GVHD treatment — no. (%)			
Complete response	4 (5)	2 (2)	2 (2)
Partial response	26 (32)	27 (33)	21 (26)
No change	32 (40)	39 (48)	45 (56)
Progression	6 (8)	7 (9)	3 (4)
Unknown	12 (15)	6 (7)	9 (11)
Concomitant systemic therapy for chronic GVHD — no./total no. (%)¶			
Glucocorticoids	56/79 (71)	45/81 (56)	55/79 (70)
Calcineurin inhibitor	18/79 (23)	26/81 (32)	22/79 (28)

Adverse Event	0.3-mg Dose Group (N=79)	1-mg Dose Group (N=81)	3-mg Dose Group (N=79)
	number of patients (percent)		
Any adverse event	76 (96)	80 (99)	78 (99)
Grade ≥3	39 (49)	49 (60)	56 (71)
Serious	30 (38)	33 (41)	38 (48)
Fatal	1 (1)	7 (9)	6 (8)
Any grade event in ≥20% of any dose group			
Aspartate aminotransferase level increased	11 (14)	31 (38)	43 (54)
Blood creatine kinase level increased	9 (11)	26 (32)	49 (62)
Lipase level increased	9 (11)	21 (26)	39 (49)
Amylase level increased	3 (4)	10 (12)	34 (43)
Blood lactate dehydrogenase level increased	11 (14)	22 (27)	32 (41)
Alanine aminotransferase level increased	10 (13)	18 (22)	31 (39)
Periorbital edema	2 (3)	19 (23)	23 (29)
Fatigue	18 (23)	16 (20)	21 (27)
γ-Glutamyltransferase level increased	8 (10)	16 (20)	21 (27)
Covid-19	13 (16)	18 (22)	11 (14)
Diarrhea	13 (16)	18 (22)	7 (9)
Blood alkaline phosphatase level increased	5 (6)	4 (5)	17 (22)
Headache	15 (19)	14 (17)	16 (20)
Any grade infection	58 (73)	59 (73)	55 (70)
Any grade key infection or reactivation			
Covid-19	15 (19)	19 (23)	14 (18)
Pneumonia	9 (11)	12 (15)	8 (10)
Aspergillus	0	3 (4)	0
Cytomegalovirus	0	1 (1)	2 (3)
Epstein–Barr virus	0	0	4 (5)
Any grade infusion-related reaction	6 (8)	4 (5)	1 (1)
Any grade ≥3 event in ≥5% of any dose group			
Pneumonia	8 (10)	7 (9)	5 (6)
Blood creatine kinase level increased	1 (1)	6 (7)	12 (15)
Covid-19	3 (4)	5 (6)	5 (6)
Hypertension	3 (4)	5 (6)	4 (5)
γ-Glutamyltransferase level increased	1 (1)	2 (2)	4 (5)
Lipase level increased	1 (1)	1 (1)	4 (5)
Periorbital edema	0	1 (1)	5 (6)
Any serious event in ≥5% of any dose group			
Covid-19	2 (3)	4 (5)	5 (6)
Pneumonia	7 (9)	8 (10)	4 (5)
Any adverse event leading to dose interruption	30 (38)	34 (42)	25 (32)
Any adverse event leading to dose reduction	5 (6)	6 (7)	13 (16)
Any adverse event leading to discontinuation of axatilimab	5 (6)	18 (22)	14 (18)†

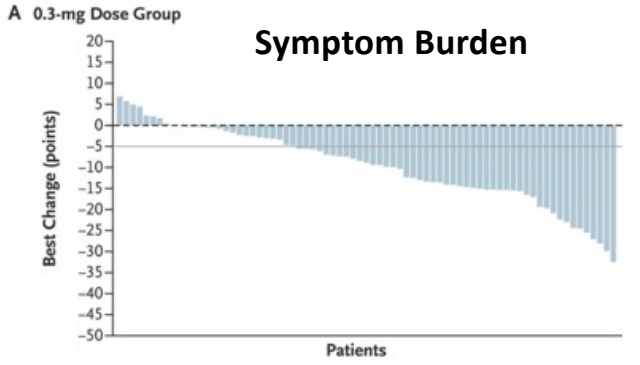
Responses

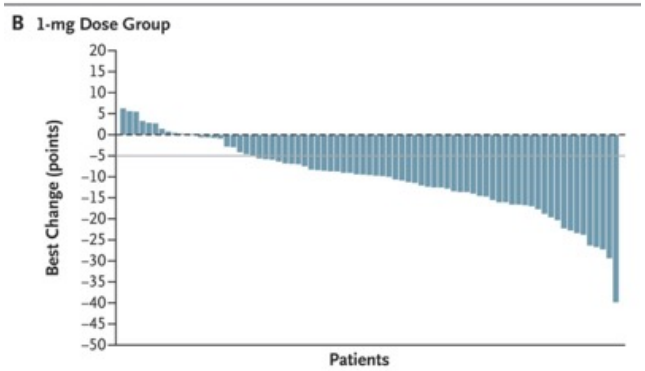


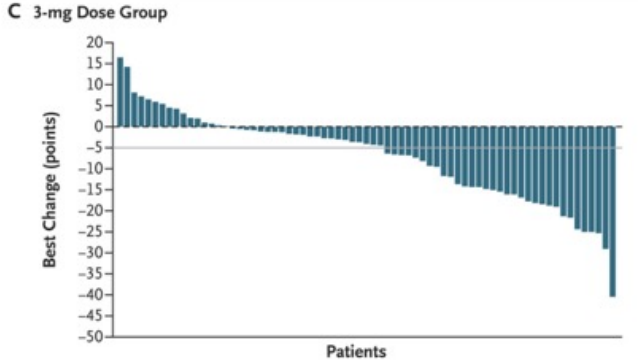




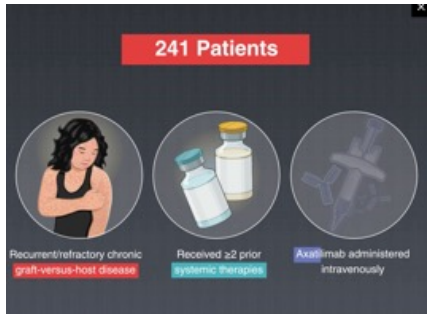
Symptom Burden

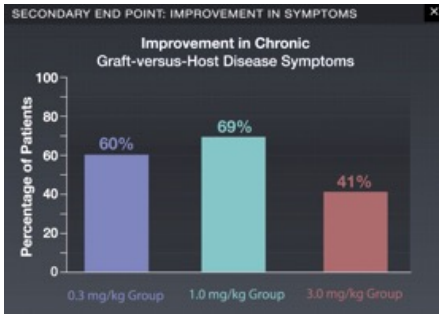


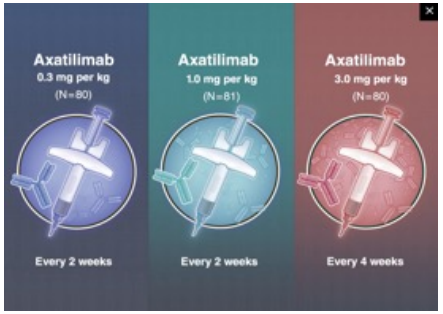


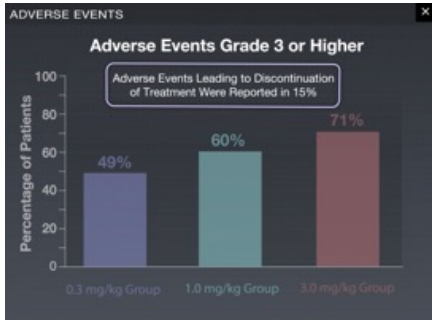


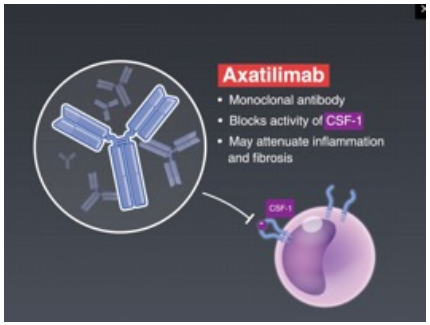

Allogeneic Hematopoietic
Stem-Cell Transplantation

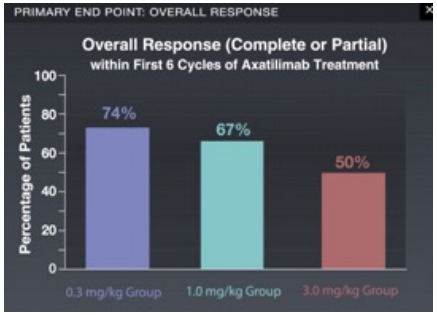

241 Patients
Recurrent/refractory chronic graft-versus-host disease
Received ≥2 prior systemic therapies
Axatilimab administered intravenously

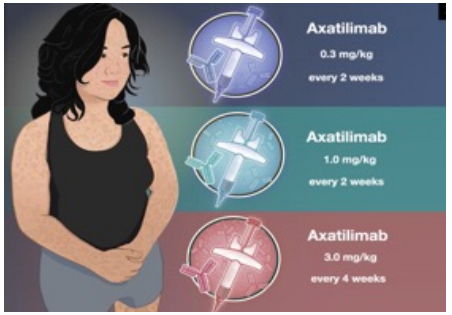

SECONDARY END POINT: IMPROVEMENT IN SYMPTOMS
Improvement in Chronic Graft-versus-Host Disease Symptoms
Percentage of Patients
100
80
60
40
20
0
60%
69%
41%
0.3 mg/kg Group
1.0 mg/kg Group
3.0 mg/kg Group


Axatilimab
0.3 mg per kg
(N=80)
Every 2 weeks
Axatilimab
1.0 mg per kg
(N=81)
Every 2 weeks
Axatilimab
3.0 mg per kg
(N=80)
Every 4 weeks

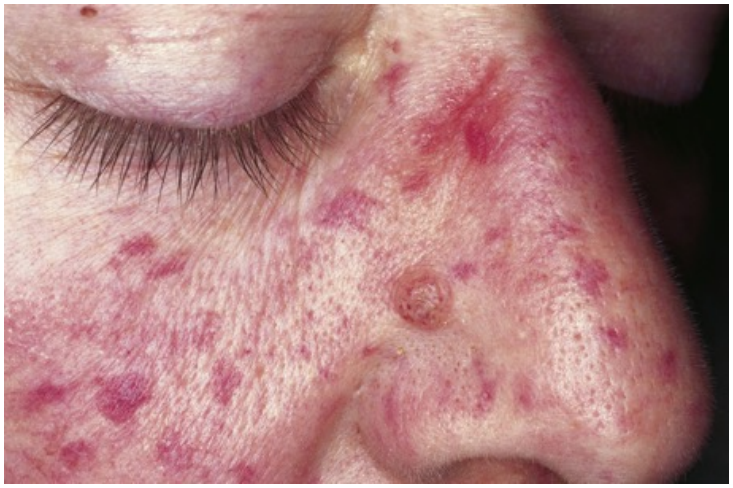

ADVERSE EVENTS
Adverse Events Grade 3 or Higher
Adverse Events Leading to Discontinuation of Treatment Were Reported in 15%
Percentage of Patients
100
80
60
40
20
0
49%
60%
71%
0.3 mg/kg Group
1.0 mg/kg Group
3.0 mg/kg Group

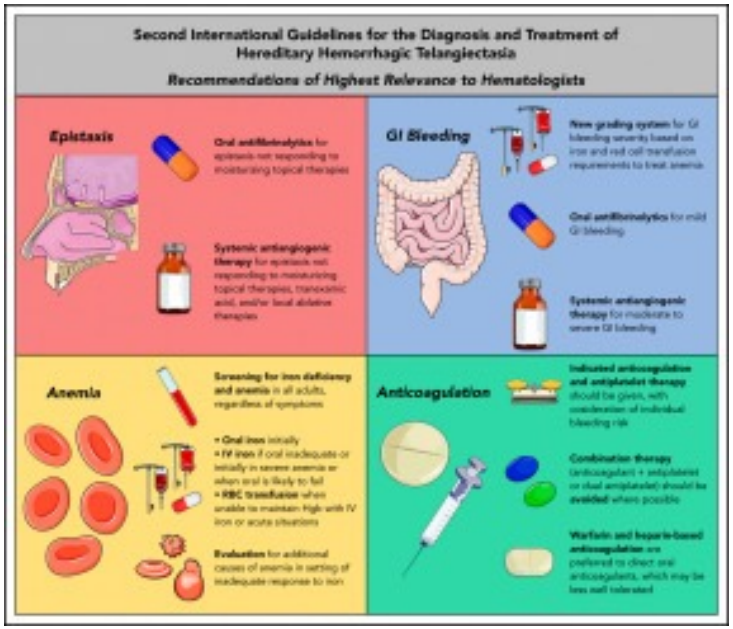

Axatilimab
• Monoclonal antibody
• Blocks activity of CSF-1
• May attenuate inflammation and fibrosis
CSF-1


PRIMARY END POINT: OVERALL RESPONSE
Overall Response (Complete or Partial)
within First 6 Cycles of Axatilimab Treatment
Percentage of Patients
100
80
60
40
20
0
74%
67%
50%
0.3 mg/kg Group
1.0 mg/kg Group
3.0 mg/kg Group


Axatilimab
0.3 mg/kg
every 2 weeks
Axatilimab
1.0 mg/kg
every 2 weeks
Axatilimab
3.0 mg/kg
every 4 weeks

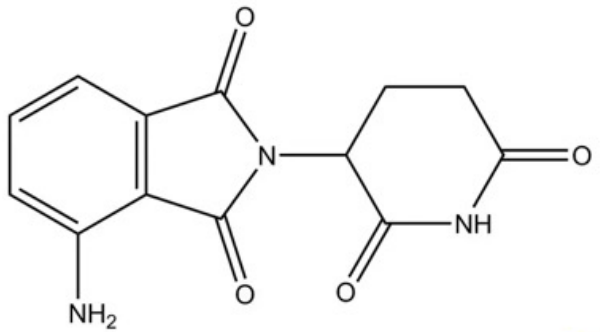
Morbus Osler oder Oslersche Krankheit, auch Morbus Osler-Weber-Rendu, ist eine angeborene Erkrankung, bei der es zu einer krankhaften Erweiterung von Blutgefäßen kommt. Unter anderem weiten sich kleinste Gefäße von Haut und Schleimhaut und sind anschließend als stecknadelkopf- bis reiskorngroße rote Flecken zu sehen. Besondere Bedeutung haben diese Teleangiektasien im Magen-Darm-Trakt, weil sie dort Ursache für häufig wiederkehrende (rezidivierende) Blutungen (hämorrhagische Diathesen) sein können. Es können jedoch auch bedeutend größere Gefäßerweiterungen auftreten. Diese entstehen besonders in der Lunge, dem Gehirn und der Leber. Die Veränderungen machen sich oft lange Zeit nicht bemerkbar, können jedoch z. B. durch Blutungen plötzlich sehr bedrohlich werden (s. u.). Die ersten Anzeichen der Erkrankung zeigen sich meist in der Pubertät mit Nasenbluten, bei wenigen Patienten jedoch auch ohne Nasenbluten und zum Teil viel später.





Pomalidomid

Pomalidomid ist ein Strukturanalogon von Thalidomid und wirkt sowohl immunmodulatorisch als auch tumorzid. Der Wirkstoff wird in Kombination mit Bortezomib und/oder Dexamethason als Zweitlinientherapie zur Behandlung des Multiplen Myeloms angewendet.



Wirkmechanismus

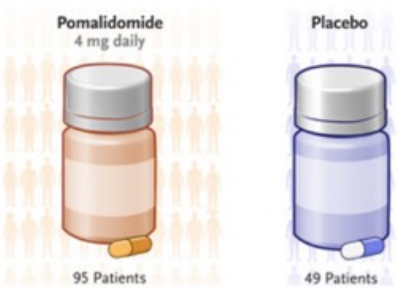
Pomalidomid ist ein Strukturanalogon von Thalidomid und hat sowohl immunmodulatorische als auch tumorzide Wirkungen (Immunmodulatory Imide drug, IMiD). Der Wirkstoff hemmt insbesondere die Proliferation und induziert die Apoptose hämatopoetischer Tumorzellen sowie gegen den dritten Vertreter der Gruppe, Lenalidomid, resisteter Zellinien.

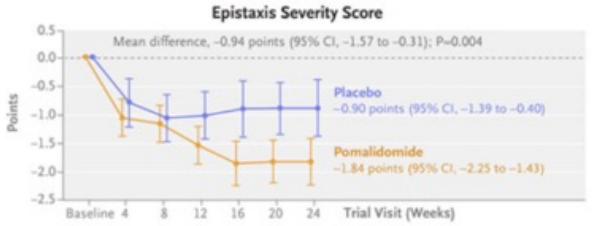
Pomalidomid verstärkt die durch T-Zellen und durch natürliche Killerzellen (NK) vermittelte Immunität und hemmt die Bildung von proinflammatorischen Zytokinen (wie z. B. TNF-α und IL-6) durch Monozyten.

Der Wirkstoff bindet direkt an das Protein Cereblon (CRBN). Dieses bildet mit dem DNA Damage-Binding Protein 1 (DDB1), Cullin 4 (CUL4) und dem Cullin 1 Regulator (ROC1) einen E3-Ubiquitin-Ligase-Komplex, der zahlreiche Proteine modifiziert und zum proteasomalen Abbau der Substrate führt. Pomalidomid kann die Auto-Ubiquitinylierung von CRBN innerhalb des Komplexes hemmen.

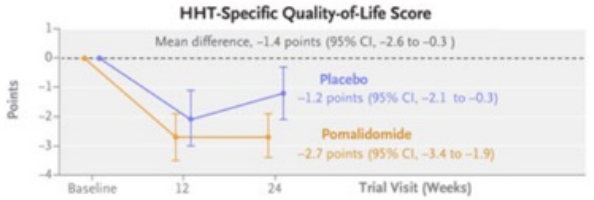
Pomalidomide for Epistaxis in Hereditary Hemorrhagic Telangiectasia

Hereditary hemorrhagic telangiectasia (HHT) is characterized by extensive telangiectasias and arteriovenous malformations. The primary clinical manifestation is epistaxis that results in iron-deficiency anemia and reduced health-related quality of life.
We conducted a randomized, placebo-controlled trial to evaluate the safety and efficacy of pomalidomide for the treatment of HHT. We randomly assigned patients, in a 2:1 ratio, to receive pomalidomide at a dose of 4 mg daily or matching placebo for 24 weeks. The primary outcome was the change from baseline through week 24 in the Epistaxis Severity Score (a validated bleeding score in HHT; range, 0 to 10, with higher scores indicating worse bleeding). A reduction of 0.71 points or more is considered clinically significant. A key secondary outcome was the HHT-specific quality-of-life score (range, 0 to 16, with higher scores indicating more limitations).





The HHT-specific quality-of-life score (a key secondary outcome) decreased by 2.7 points with pomalidomide as compared with 1.2 points with placebo (higher scores indicate more limitations).



Among adverse events of special interest, constipation, neutropenia, and rash were common and occurred more often with pomalidomide than with placebo.

Hereditary hemorrhagic telangiectasia (HHT) affects approximately 1 in 3800 persons and is the second most common inherited bleeding disorder. HHT is an autosomal dominant vasculopathy caused by pathogenic variants that affect transforming growth factor β–bone morphogenic protein signaling and result in fragile mucocutaneous telangiectasias and visceral arteriovenous malformations. Recurrent epistaxis develops in more than 95% of patients, and coexisting psychiatric disorders (especially depression and post-traumatic stress disorder) and reduced health-related quality of life are frequently reported. Gastrointestinal bleeding occurs in one third of patients, and iron-deficiency anemia develops in most patients.

No treatments for HHT are approved by the Food and Drug Administration (FDA) or the European Medicines Agency. Management of bleeding involves the temporizing measures of ablative procedures for telangiectasias in the nose and gastrointestinal tract, off-label use of antifibrinolytic drugs, and potentially more aggressive surgery (e.g., surgical closure of the nares). However, given the systemic angiogenic dysregulation inherent in HHT, repurposing systemic antiangiogenic agents for its treatment has been explored.

Methods

Patients and Trial Oversight

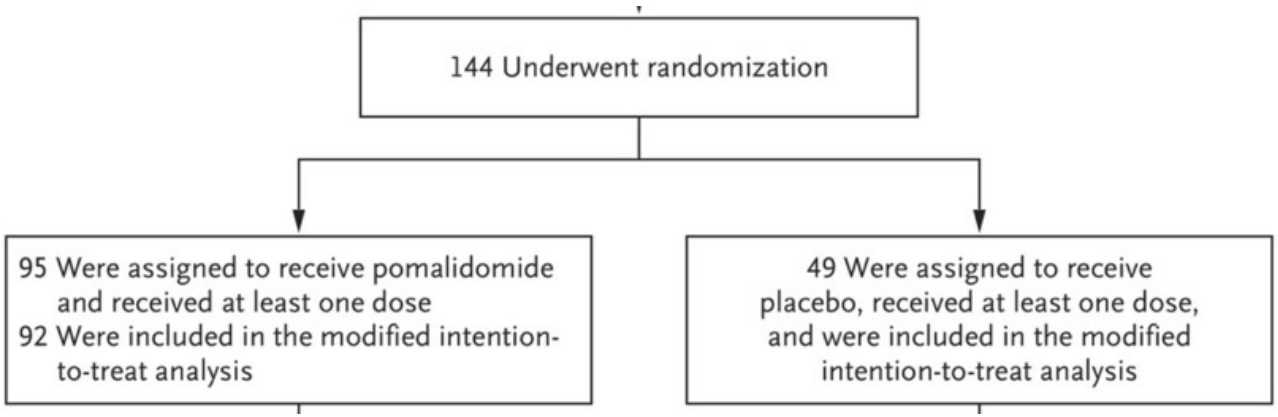
Adult patients were eligible for inclusion in the trial if they had received a definite diagnosis of HHT as defined by the Curaçao criteria, if they had an Epistaxis Severity Score of at least 3 within the 3 months before screening, and if they had anemia at screening or had received iron infusions or red-cell transfusions in the previous 6 months.

Trial Design, Randomization, and Treatment

In this double-blind, randomized trial conducted at 11 U.S. sites, we assessed epistaxis and health-related quality of life every 4 weeks during the 24 weeks in which patients received pomalidomide or placebo and at 4 weeks after the end of the treatment period. The patients were randomly assigned, in a 2:1 ratio, to receive pomalidomide at a dose of 4 mg daily or matching placebo.

Outcomes

The primary outcome was the change from baseline in the Epistaxis Severity Score through week 24. The Epistaxis Severity Score was assessed at baseline (for the 4 weeks before baseline), at each 4-week visit (for the preceding 4 weeks), and at the visit that occurred 4 weeks after the end of the treatment period.



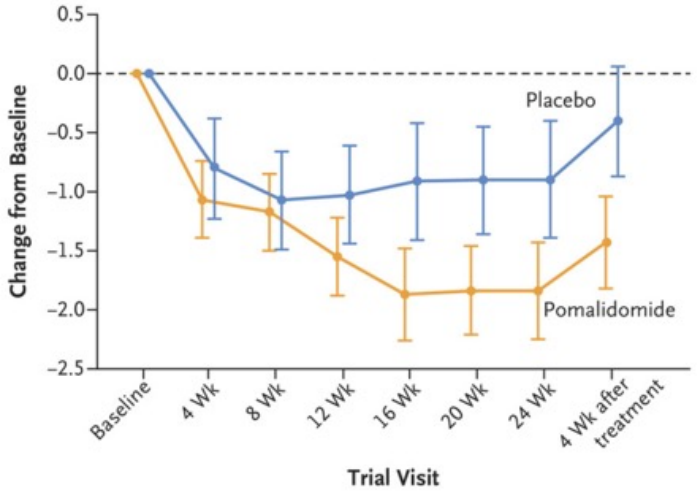
Characteristic	Total (N=144)	Pomalidomide (N=95)	Placebo (N=49)
Age — yr	58.8±12.2	58.8±13.0	58.7±10.7
Female sex — no. (%)	69 (48)	45 (47)	24 (49)
Non-White race — no./total no. (%)†	15/141 (11)	9/94 (10)	6/47 (13)
Hispanic or Latino ethnic group — no./total no. (%)†	5/141 (4)	2/94 (2)	3/47 (6)
Pathogenic variants — no.‡	134	88	46
ENG — no. (%)	50 (37)	37 (42)	13 (28)
ACVRL1 — no. (%)	69 (51)	38 (43)	31 (67)
SMAD4 — no. (%)	1 (1)	1 (1)	0 (0)
None identified — no. (%)	14 (10)	12 (14)	2 (4)
Any HHT involvement other than epistaxis — no. (%)	103 (72)	69 (73)	34 (69)
Gastrointestinal bleeding	53 (37)	34 (36)	19 (39)
Brain	15 (10)	9 (9)	6 (12)
Liver	35 (24)	25 (26)	10 (20)
Lungs	58 (40)	42 (44)	16 (33)
Pulmonary hypertension — no. (%)	9 (6)	4 (4)	5 (10)
High-output heart failure — no. (%)	3 (2)	2 (2)	1 (2)
Red-cell transfusion in previous 6 mo — no. (%)	28 (19)	20 (21)	8 (16)
Emergency department visit in previous 6 mo — no. (%)	25 (17)	16 (17)	9 (18)
Iron infusion in previous 6 mo — no. (%)	121 (84)	79 (83)	42 (86)
Median amount of iron infused (IQR) — mg/4-wk period§	170 (100–375)	170 (85–375)	170 (125–340)
Oral iron supplementation — no. (%)	63 (44)	42 (44)	21 (43)
Hemoglobin level — g/dl	11.5±2.3	11.4±2.4	11.8±2.1
Median ferritin level (IQR) — ng/ml	57 (24–147)	54 (23–165)	64 (28–127)
Anemia — no. (%)	99 (69)	66 (69)	33 (67)
Epistaxis Severity Score¶			
Mean score in previous 4 wk	5.0±1.5	4.9±1.5	5.2±1.4
Score ≥6 — no. (%)	29 (20)	17 (18)	12 (24)
HHT-specific quality-of-life score‖	6.3±3.1	5.8±2.9	7.1±3.4
Median daily epistaxis duration (IQR) — min/day**	11.7 (5.8–20.6)	11.1 (4.0–19.1)	12.4 (7.1–26.6)
Neuro-QoL Satisfaction with Social Roles and Activities T score††	45.2±6.2	45.4±6.3	44.7±6.0
PROMIS T score‡‡			
For emotional distress–depression	50.3±9.8	49.3±9.8	52.4±9.6
For fatigue	56.4±10.3	55.8±10.1	57.7±10.8

Efficacy Outcomes at the End of Week 24.

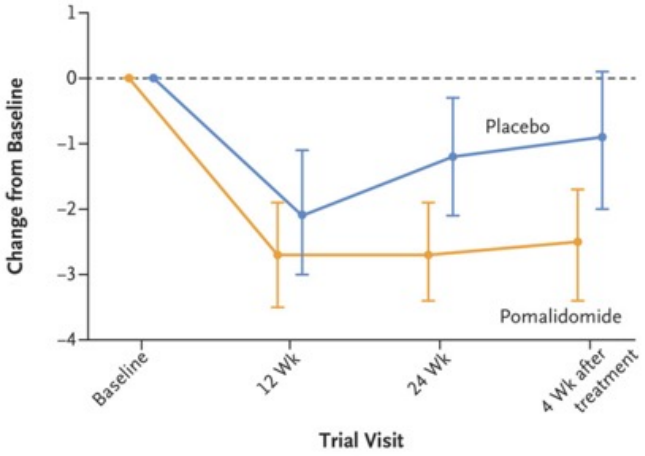
Outcome	Pomalidomide (N=92)	Placebo (N=49)	Estimated Difference
	model estimate (95% CI)		*difference (95% CI)*
Primary outcome			
Change in Epistaxis Severity Score†	−1.84 (−2.25 to −1.43)	−0.90 (−1.39 to −0.40)	−0.94 (−1.57 to −0.31)
Key secondary outcomes‡			
Change in HHT-specific quality-of-life score	−2.7 (−3.4 to −1.9)	−1.2 (−2.1 to −0.3)	−1.4 (−2.6 to −0.3)
Median amount of iron infused (IQR) — mg/4-wk period§			
Through 24 wk	170 (0 to 408)	204 (33 to 341)	−32 (−107 to 43)¶
Wk 12–24	0 (0 to 340)	333 (0 to 500)	−115 (−230 to 0)¶
Received any red-cell transfusions through 24 wk — no. (%)	15 (16)	11 (22)	0.73 (0.36 to 1.46)‖
Received any red-cell transfusions, 12–24 wk — no. (%)	7 (9)	8 (18)	0.53 (0.21 to 1.37)‖
Change in daily epistaxis duration — min/day**			
Mean duration	−6.1 (−10.7 to −1.6)	−3.7 (−9.4 to 2.0)	−2.4 (−9.6 to 4.7)
Intensity-weighted mean duration	−12.2 (−17.1 to −7.3)	−3.3 (−9.5 to 2.8)	−8.9 (−16.5 to −1.2)
Change in Neuro-QoL Satisfaction with Social Roles and Activities T score††	2.8 (1.2 to 4.5)	1.6 (−0.4 to 3.6)	1.3 (−1.2 to 3.8)
Other secondary outcomes			
Change in PROMIS T score			
For emotional distress–depression	−2.3 (−4.2 to −0.5)	−3.4 (−5.6 to −1.2)	1.1 (−1.7 to 3.8)
For fatigue‡‡	−1.5 (−3.7 to 0.6)	−1.0 (−3.5 to 1.6)	−0.6 (−3.8 to 2.7)
Receipt of any iron infusion or blood transfusion through 24 wk — no. (%)	68 (74)	37 (76)	0.96 (0.71 to 1.21)‖
Receipt of endoscopic intervention through 24 wk — no. (%)	8 (9)	5 (10)	0.85 (0.29 to 2.47)‖
Change in laboratory assessment results§§			
Median transferrin saturation (IQR) — %	2 (−5 to 13)	1 (−5 to 16)	0 (−7 to 7)¶
Median ferritin level (IQR) — ng/ml	5 (−30 to 67)	−1 (−42 to 51)	3 (−35 to 41)¶
Hemoglobin level — g/dl	0.32 (−0.10 to 0.75)	0.05 (−0.46 to 0.56)	0.27 (−0.37 to 0.92)
Hematocrit — %	0.40 (−0.81 to 1.60)	−0.23 (−1.69 to 1.24)	0.62 (−1.22 to 2.47)
Mean corpuscular volume — fl	3.21 (1.94 to 4.49)	1.08 (−0.46 to 2.62)	2.13 (0.17 to 4.09)
Mean cellular hemoglobin concentration — g/dl	0.55 (0.21 to 0.89)	0.12 (−0.29 to 0.53)	0.44 (−0.08 to 0.95)

Der Serin/Threonin-Proteinkinase-Rezeptor R3 ist ein Enzym, das beim Menschen vom ACVRL1-Gen kodiert wird. ACVRL1 ist ein Rezeptor im TGF-beta-Signalweg. Es ist auch als Activin-Rezeptor-ähnliche Kinase 1 oder ALK1 bekannt.

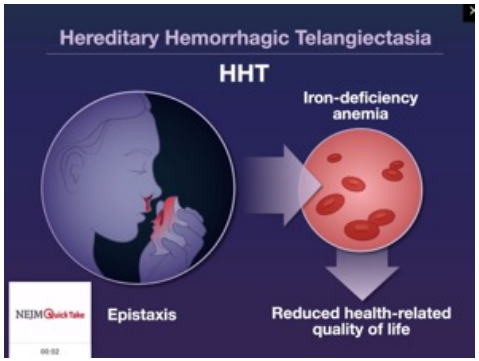
A Epistaxis Severity Score



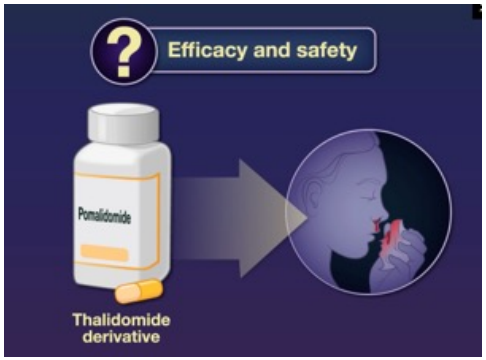
B HHT–Specific Quality-of-Life Score



Outcome	Pomalidomide (N=95)	Placebo (N=49)	P Value
Adverse events of special interest — no. of patients (%)			
Constipation	45 (47)	9 (18)	<0.001
Fatigue	42 (44)	17 (35)	0.27
Neutropenia	42 (44)	5 (10)	<0.001
Rash†	33 (35)	5 (10)	0.002
Tremor‡	8 (8)	0	0.04
Venous thromboembolism§	4 (4)	1 (2)	0.50
Thrombocytopenia	4 (4)	0	0.15
Peripheral neuropathy¶	3 (3)	0	0.21
Arterial thromboembolism	0	0	1.00
Other adverse events of at least moderate severity and at least possibly related to trial regimen — no. of patients (%)			
Dyspnea‖	4 (4)	0	0.15
Muscle spasms	2 (2)	1 (2)	0.98
Alanine aminotransferase level increased	1 (1)	0	0.47
Mouth ulceration	1 (1)	0	0.47
Tachycardia	1 (1)	0	0.47
Peripheral edema	0	0	1.00
Any serious adverse event — no. of patients (%)	22 (23)	8 (16)	0.34
Any bleeding serious adverse event — no. of patients (%)	6 (6)	5 (10)	0.50
Epistaxis	2 (2)	2 (4)	0.61
Gastrointestinal	1 (1)	3 (6)	0.11
Unspecified	3 (3)	0	0.55
Any grade ≥3 adverse event — no. of patients (%)**	45 (47)	12 (24)	0.01
Strongest action taken for an adverse event per patient — no. of patients (%)			
Regimen stopped	15 (16)	1 (2)	0.01
Regimen interrupted	38 (40)	7 (14)	0.002
Dose reduced	12 (13)	0	0.009
Median change in platelet count through 24 wk (IQR) — per μl††	−38,000 (−75,000 to 21,000)	9000 (−22,000 to 27,000)	0.07
Platelet count — no./total no. of patients (%)‡‡			0.26
≥150,000 per μl, normal range	83/92 (90)	44/49 (90)	
100,000 to <150,000 per μl	7/92 (8)	2/49 (4)	
50,000 to <100,000 per μl	1/92 (1)	3/49 (6)	
<50,000 per μl	1/92 (1)	0	
Mean change in neutrophil count per μl through 24 wk (95% CI) §§	−1710 (−2030 to −1390)	−20 (−420 to 380)	<0.001
Neutrophil count — no./total no. of patients (%)‡‡			<0.001
≥1450 per μl, normal range	33/92 (36)	44/49 (90)	
1000 to <1450 per μl	32/92 (35)	4/49 (8)	
500 to <1000 per μl	24/92 (26)	1/49 (2)	
<500 per μl	3/92 (3)	0	
Hemoglobin <6.5 mg/dl — no. of patients (%)	3 (3)	3 (6)	0.42

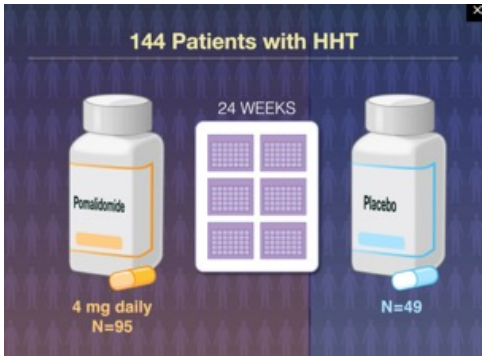

Hereditary Hemorrhagic Telangiectasia
HHT
Iron-deficiency anemia
NEJM Quick Take
Epistaxis
Reduced health-related quality of life

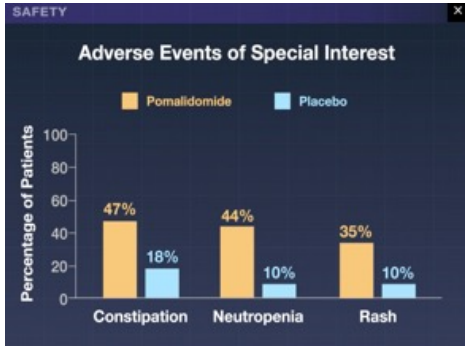

PRIMARY OUTCOME
Change from Baseline through Week 24
Epistaxis Severity Score
Change from Baseline
0.5
0.0
−0.5
−1.0
−1.5
−2.0
−2.5
Placebo
−0.90
Pomalidomide
−1.84
Baseline 4 8 12 16 20 24
Trial Visit (Weeks)


Efficacy and safety
Pomalidomide
Thalidomide derivative


SECONDARY OUTCOME
HHT–Specific Quality-of-Life Score
Range from 0 to 16
Mean difference, −1.4 points (95% CI, −2.6 to −0.3)
Change from Baseline
1
0
−1
−2
−3
−4
Placebo
−1.2 points
Pomalidomide
−2.7 points
Baseline 12 Wk 24 Wk
Trial Visit


HHT
Pomalidomide
Reduced epistaxis severity
Improve disease-specific quality of life
No unexpected safety signals


144 Patients with HHT
24 WEEKS
Pomalidomide
Placebo
4 mg daily
N=95
N=49


SAFETY
Adverse Events of Special Interest
Pomalidomide
Placebo
Percentage of Patients
100
80
60
40
20
0
47%
18%
44%
10%
35%
10%
Constipation
Neutropenia
Rash

Primary Central Nervous System Vasculitis

KEY POINTS

PRIMARY CENTRAL NERVOUS SYSTEM VASCULITIS

- Primary central nervous system (CNS) vasculitis is a rare, frequently misdiagnosed condition that affects the brain and spinal cord and is characterized by a variety of neurologic symptoms at presentation, such as focal neurologic deficits, headache, and cognitive decline.
- Cerebral angiography is often used for diagnosis; however, the specificity is low, and the results must be interpreted with consideration of the patient's medical history, as well as clinical and laboratory findings and the results of magnetic resonance imaging and magnetic resonance angiography. A CNS-tissue biopsy showing vasculitis can provide a definitive diagnosis.
- Small-vessel and medium-to-large-vessel inflammatory involvement characterize two subsets of primary CNS vasculitis with different diagnostic methods (biopsy vs. angiography) and distinct clinical characteristics and outcomes.
- The differential diagnosis includes reversible cerebral vasoconstriction syndrome, intracranial atherosclerosis, intravascular lymphoma, moyamoya disease and syndrome, secondary cerebral vasculitis (which can occur in connective-tissue diseases), systemic vasculitis, and infections.
- Early recognition is important because treatment with glucocorticoids with or without cytotoxic drugs, particularly cyclophosphamide, is effective in many patients and may prevent serious outcomes.

Primary central nervous system (CNS) vasculitis, also known as primary angiitis of the CNS, is a rare form of vasculitis that is limited to the brain and spinal cord and causes a variety of neurologic syndromes. Because of its rarity and the similarity of some of these syndromes to more common disorders, primary CNS vasculitis is often misidentified. Descriptions of this condition date back only to the mid-1950s. Primary CNS vasculitis may occur in children, although this is uncommon. In this review, we focus on the disorder in adults.

Epidemiology

Primary CNS vasculitis has had an estimated annual incidence of 2.4 cases per 1 million person-years in Olmsted County, Minnesota. The disorder affects persons of all ages, and its prevalence is similar among male and female patients. Mortality has been reported to range from 8 to 23%, with approximately a quarter of patients having severe disability despite treatment. Factors associated with higher mortality include advanced age, cognitive impairment at the initial presentation, and cerebral infarctions on imaging.

Clinical Manifestations

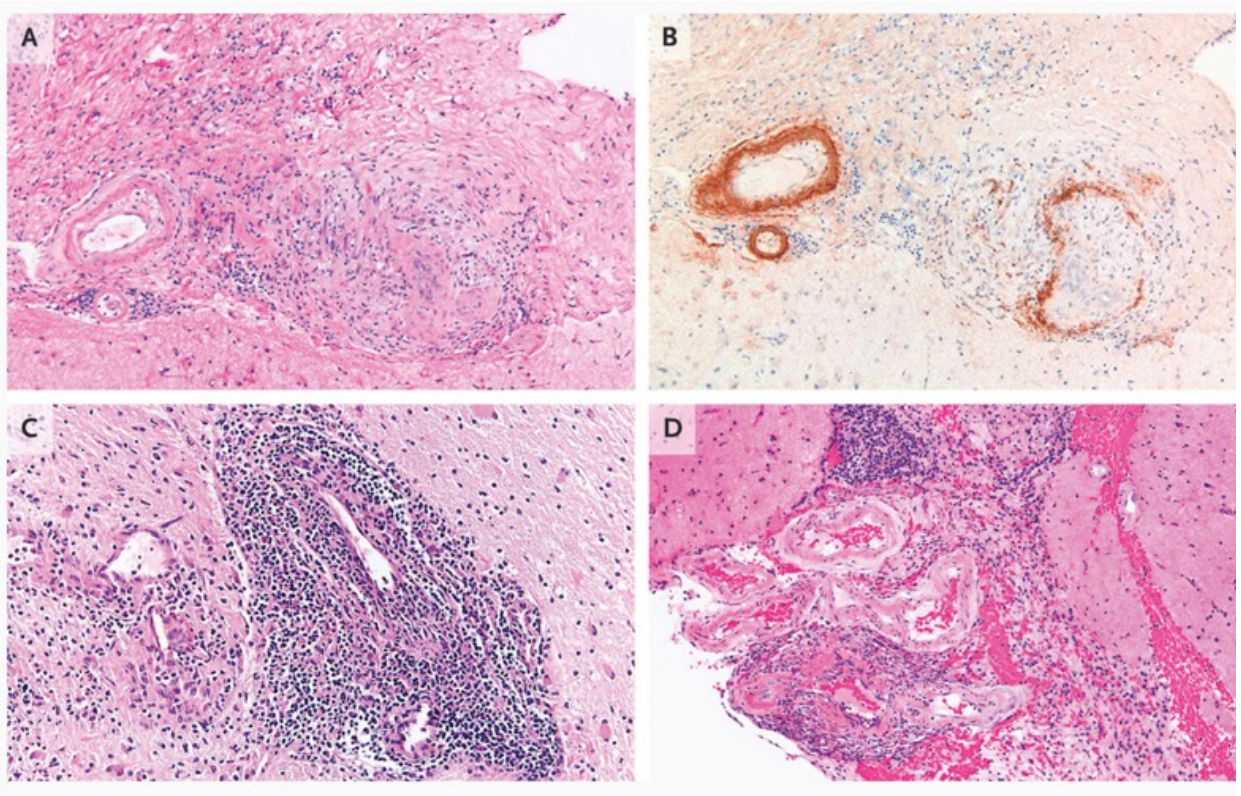
Clinical manifestations at the time of diagnosis vary and may suggest other, more common neurologic disorders. The most common manifestation at the initial presentation has been a sudden onset of focal neurologic deficits, which is suggestive of an ischemic event such as a stroke or transient ischemic attack that includes aphasia, ataxia, and visual-field defects. Other common features are headaches, progressive cognitive decline, and acute or subacute encephalopathy, which is often characterized by an acute confusional state that may progress to drowsiness and coma.

Main Clinical Manifestations of Primary CNS Vasculitis at Presentation in Two Cohorts.

Manifestation	Mayo Clinic Cohort (N=101)	French Cohort (N=52)
	number (percent)	
Focal neurologic deficits	68 (67)	43 (83)
Headaches	64 (63)	28 (54)
Cognitive impairment	50 (50)	18 (35)
Speech disorders (aphasia or dysarthria)	43 (43)	18 (35)
Visual symptoms†	32 (32)	8 (15)
Ataxia	19 (19)	6 (12)
Seizure	16 (16)	17 (33)
Vertigo or dizziness	9 (9)	15 (29)
Fever	9 (9)	7 (13)
Intracranial hemorrhage	8 (8)	10 (19)‡
Psychiatric disorders	NR	13 (25)
Amnestic syndrome	9 (9)	NR

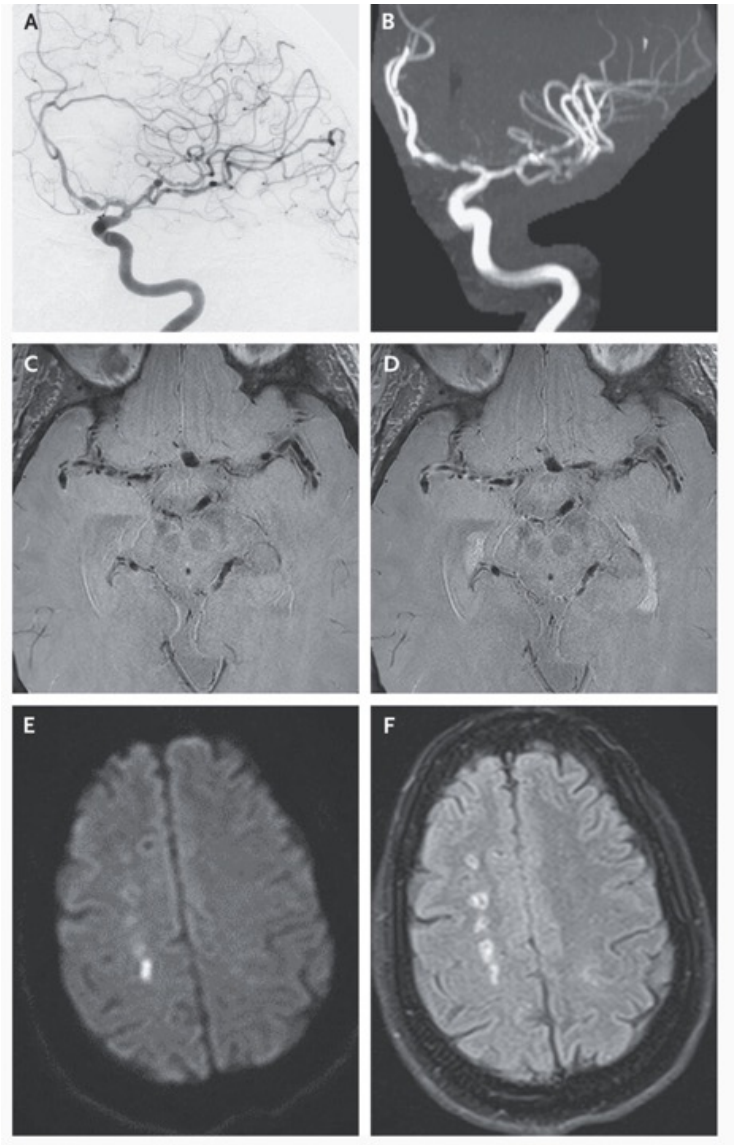
Clinical Manifestations of Primary CNS Vasculitis.

Manifestation	Prevalence	Characteristics	Treatment	Outcome
	%			
Tumorlike mass lesion[11,12]	4–12	Proved by biopsy Often normal findings on DSA and MRA Seizures, headache, and focal neurologic deficit at presentation Lesions with gadolinium enhancement on MRI Association with CAA	Glucocorticoids alone or in most cases combined with cyclophosphamide	Favorable response to treatment Good outcomes Poorer outcomes in the patients with CAA Better outcomes with glucocorticoids and cyclophosphamide than with glucocorticoids alone
Prominent leptomeningeal enhancement[13]	8	Prominent gadolinium leptomeningeal enhancement on MRI Sudden clinical onset Cognitive dysfunction at presentation Normal findings on DSA and MRA Proved by biopsy Association with CAA	Glucocorticoids alone or combined with cyclophosphamide	Rapid and favorable response to treatment Good outcomes
Intracranial hemorrhage[7,9,14]	9–13	Intracerebral more common than subarachnoid hemorrhage Infrequent cerebral infarcts Association with necrotizing vasculitis	Glucocorticoids alone or combined with cyclophosphamide	Favorable response to treatment and outcomes
Spinal cord involvement[15,16]	5	Rarely the only manifestation; usually, there is subsequent brain involvement Association with lymphoma (Hodgkin's disease) Multisegmental longitudinal lesions Cervical and thoracic spinal cord involvement	Glucocorticoids and cyclophosphamide	Therapeutic response Mortality of 20–25% among treated patients and 75% among untreated patients
Rapidly progressive and catastrophic course[17,18]	8–11	Granulomatous or necrotizing vasculitis (or both) Frequent paraparesis or quadriparesis at presentation Bilateral, progressive, large-vessel vasculitis with newly developing lesions Multiple and bilateral acute cerebral infarctions High CSF protein level	Glucocorticoids and cyclophosphamide	High mortality (27–73%), particularly in the first 2–3 weeks Poor therapeutic response
Lymphoma association[19]	6	Vasculitis and lymphoma diagnosed simultaneously in most cases (70%) More often Hodgkin's lymphoma Spinal cord involvement Gadolinium leptomeningeal enhancement on MRI Granulomatous vasculitis	Glucocorticoids alone or glucocorticoids and cyclophosphamide	Therapeutic response in two thirds of patients Poor response in one third of patients Mortality of 30% High incidence of neurologic disability
Unihemispheric relapsing vasculitis[20]	1.4	Negative on angiography and positive on biopsy Different neuropathologic patterns Multiple flares Seizures at diagnosis and during flares Unilateral lesions with gadolinium enhancement on MRI Normal CSF in most patients	Glucocorticoids, cyclophosphamide, azathioprine, mycophenolate mofetil, methotrexate, rituximab	Response to glucocorticoids Long-term therapy with glucocorticoids at high doses for maintenance of remission Resistance to traditional immunosuppressants Usually slight disability with mild cognitive impairment



Histopathological Findings of Primary Central Nervous System Vasculitis from Brain Biopsies.

Panel A shows granulomatous vasculitis with extensive amyloid deposits in the leptomeningeal vessels, where the vessel wall is thickened by an amorphous eosinophilic material indicative of amyloid, with Panel B showing confirmation by amyloid-beta immunostaining. Granulomatous inflammatory infiltrate is present in the vessel on the right, causing obliteration of the lumen and destruction of the vascular wall. Panel C shows dense perivascular and transmural lymphocytic infiltrate typical of the lymphocytic pattern of vasculitis. Panel D shows necrotizing vasculitis with transmural acute inflammation and segmental transmural fibrinoid necrosis involving a leptomeningeal small artery, without giant cells or granulomas. The image in Panel C is shown at twice the magnification of the images in Panels A, B, and D.



Imaging in a Patient with Primary Central Nervous System Vasculitis.

Magnetic resonance angiography (Panel A) and digital subtraction angiography (Panel B) show alternating stenosis and dilatation of the left anterior cerebral artery and left middle cerebral artery. Vessel-wall imaging before (Panel C) and after (Panel D) gadolinium administration shows enhancement in the wall that is consistent with inflammation in the right middle cerebral artery. Diffusion-weighted magnetic resonance imaging (MRI) shows a recent infarction (Panel E), and T2-weighted fluid-attenuated inversion recovery MRI shows chronic infarctions in the right middle cerebral artery distribution (Panel F).

Differential Diagnosis

The nonspecific nature of clinical features of primary CNS vasculitis makes it difficult to differentiate from conditions with overlapping features. The categories below present the greatest challenges.

Nonvasculitic Disorders

Nonvasculitic disorders are alternative diagnostic considerations, particularly when there are multiple strokes that occur over time. A history of thunderclap headaches and typical precipitating factors for reversible cerebral vasoconstriction syndrome, along with normal findings on MRI of the brain or the presence of convexity subarachnoid hemorrhage and minimal or no enhancement on high-resolution MRI of the vessel wall, aid in the differentiation of reversible cerebral vasoconstriction syndrome from primary CNS vasculitis.

Systemic Disorders That May Cause CNS Vasculitis

Secondary CNS vasculitic involvement, although uncommon, can occur in the context of systemic disorders. In these cases, there is typically evidence of active disease outside the nervous system, and an evaluation, especially for manifestations of organ involvement beyond the CNS, should generally be conducted to rule out these conditions before a diagnosis of primary CNS vasculitis is made. Cerebral infarctions, white-matter lesions, and a variety of clinical manifestations, including progressive cognitive decline, may be present in such cases.

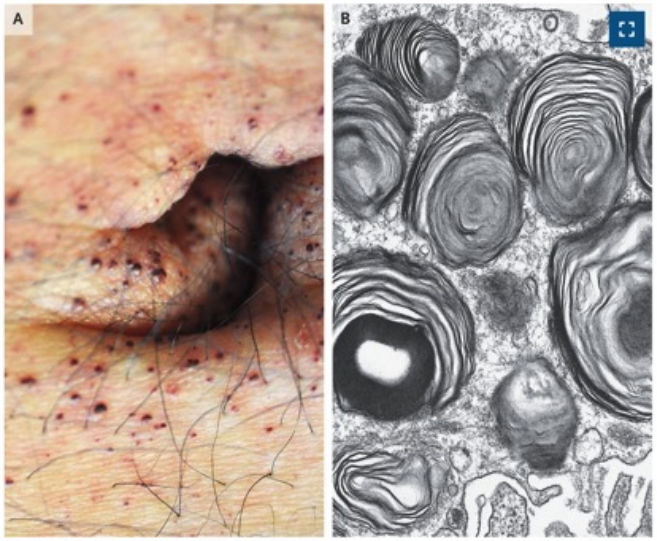
Treatment and Outcomes

Evidence-based recommendations for the treatment of primary CNS vasculitis from randomized, controlled clinical trials are lacking. Current treatment protocols have been based primarily on retrospective cohort studies, in which a limited number of patients is often enrolled, and on therapeutic approaches that are used in other forms of vasculitis. For decades, glucocorticoids, often in combination with a traditional immunosuppressant such as cyclophosphamide, have been used to treat primary CNS vasculitis.

Conclusions

Primary CNS vasculitis is a rare disease that affects the brain and spinal cord with a range of nonspecific neurologic symptoms. Diagnosis relies on findings from brain MRI, intracranial CTA or MRA, digital subtraction cerebral angiography, and cerebral biopsy and on the ruling out of alternative causes. The size of the predominantly affected arteries allows categorization of primary CNS vasculitis into small-vessel and medium-to-large vessel types that have distinct clinical characteristics and outcomes. The management of this condition involves balancing immunosuppressive therapies against their potential risks. Future research could define the underlying pathophysiology, discover biomarkers, and refine diagnostic criteria and treatment for this disorder.

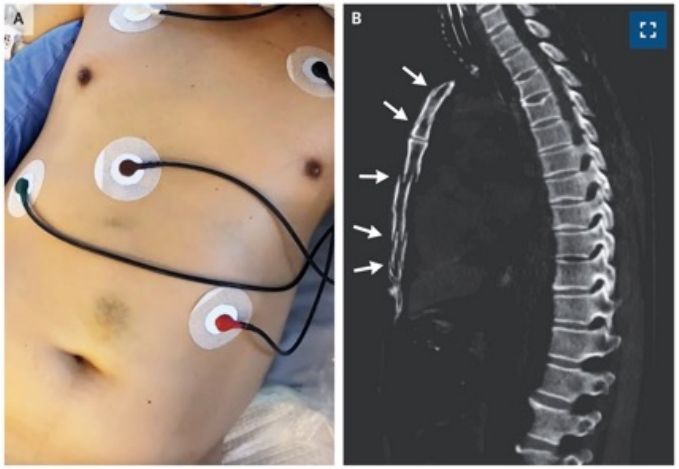
Fabry's Disease



A 44-year-old man presented to the rheumatology clinic with a 5-year history of heat intolerance and burning pain in his hands and feet. He also had exertional dyspnea, decreased perspiration, sinus tachycardia, and proteinuria of unclear cause. On physical examination, there were periumbilical vascular skin lesions that had been present for the previous 20 years (Panel A), a finding consistent with angiokeratomas. A sample from a 24-hour urine collection showed nonnephrotic proteinuria. Light microscopy of a sample of kidney tissue was notable for focally swollen podocytes with vacuolated cytoplasm. Electron microscopy showed lamellated deposits typical of globotriaosylceramide in podocytes, a finding known as zebra bodies that is characteristic of Fabry's disease (Panel B). A leukocyte assay showed that α-galactosidase A activity was less than 1.0 nmol per hour per milligram of protein (reference range, 45 to 85). Genetic testing identified a variant in *GLA*. A diagnosis of Fabry's disease was made. Fabry's disease is an X-linked lysosomal storage disease characterized by a deficiency in α-galactosidase A, a lysosomal hydrolase enzyme. The resulting accumulation of glycosphingolipids within cells leads to various symptoms, including neuropathy, autonomic dysfunction, hypohidrosis, skin lesions, and proteinuria (as seen in this patient). Genetic testing of the patient's family identified the *GLA* variant in his mother and brother. Treatment with enzyme-replacement therapy was started, and referral was made to neurology, nephrology, and cardiology specialists for cardiac evaluation and long-term management of the condition.

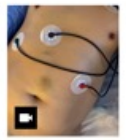
Flail Chest

Instabiler Thorax



A 59-year-old man with a history of chronic obstructive pulmonary disease was brought to the emergency department after a motor vehicle collision. The steering wheel of the patient's car had struck his chest after the airbag had not deployed. His heart rate was 99 beats per minute, blood pressure 123/84 mm Hg, respiratory rate 30 breaths per minute, and oxygen saturation 90% while he was receiving supplemental oxygen (fraction of inspired oxygen, 0.45). The physical examination was notable for ecchymoses on the chest and abdomen (Panel A). There was also inward collapse of the anterior and right chest wall during inspiration and outward expansion during expiration (see video). A diagnosis of flail chest — paradoxical movement of a segment of chest wall due to multiple rib fractures in multiple places — was made. Flail chest is associated with a high risk of pulmonary contusion and acute respiratory failure. Computed tomography of the chest showed fractures of multiple ribs on both sides, as well as several fractures in the sternal body and manubrium (Panel B, arrows). Endotracheal intubation was performed, followed by open reduction and internal fixation of the rib and sternal fractures. The patient's trachea was extubated on postoperative day 2, and he was discharged home on postoperative day 8. At the 1-month follow-up, the flail chest had fully resolved.

VIDEO



Paradoxical Chest Movement during Breathing 0m 8s

Case 29-2024: A 47-Year-Old Man with Confusion and Kidney Failure

The patient had been well until 6 days before the current admission, when fatigue and myalgias developed. During the subsequent 2 days, he continued to report to his job at a restaurant. Four days before this admission, the patient's coworkers noticed that he was mildly confused. On the day of this admission, the confusion markedly increased, and new word-finding difficulties and garbled speech developed. Emergency medical services were called, and the patient was brought to the emergency department of this hospital.

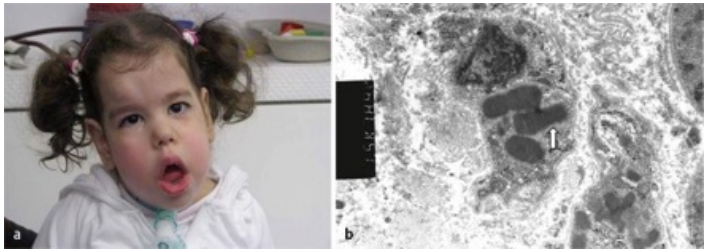
On evaluation in the emergency department, the patient was not able to participate fully in the interview or a review of systems because of confusion, but he described feeling hot and short of breath. He had not mentioned any recent cough, nausea, vomiting, diarrhea, or headache to his family or coworkers. He had no known recent falls, trauma, travel, or sick contacts.

The patient smoked marijuana occasionally and had smoked cigarettes as a teenager. He drank alcohol infrequently and did not use illicit drugs. His sister had Sjögren's syndrome, nemaline myopathy, cardiomyopathy, Fanconi's anemia, and renal tubular acidosis. His parents were healthy.

On examination, the temporal temperature was 35.8°C, the blood pressure 142/78 mm Hg, the pulse 114 beats per minute, the respiratory rate 30 breaths per minute, and the oxygen saturation 96% while the patient was breathing ambient air. The patient appeared anxious. He was alert and oriented; however, when he was asked a question, he often needed clarification and was slow to answer. He could not recite the days of the week backward and had difficulty following complex commands. His face was symmetric, and no dysarthria was noted. Cranial-nerve function, muscle tone and strength, sensation, proprioception, deep-tendon reflexes, and gait were normal. He did not have photophobia. The mucous membranes were moist, and the neck was supple. There was no jugular venous distention. The heart sounds were normal, and the lungs were clear on auscultation. The abdomen was nontender, and there was no hepatosplenomegaly. He had no leg swelling or rash.

Die Nemalin-Myopathie (NM) umfasst ein weites Spektrum kongenitaler Myopathien, die gekennzeichnet sind durch Hypotonie, Muskelschwäche und abgeschwächte oder fehlende tiefe Sehnenreflexe. In der Muskelbiopsie sind Nemalinkörper (Stäbchen) nachweisbar.

Name	Gen	Genlokus	Erbgang
NEM 1	TPM3	1q22-q23	autosomal-dominant
NEM 2	NEB	2q22	autosomal-rezessiv
NEM 3	ACTA1	1q42.1	hauptsächlich autosomal-dominant; selten autosomal-rezessiv
NEM 4	TPM2	9p13.2-p13.1	
NEM 5	TNNT1	19q13.2	
NEM 6	KBTBD13	15q22.31	autosomal-dominant
NEM 7	CFL2	14q12	

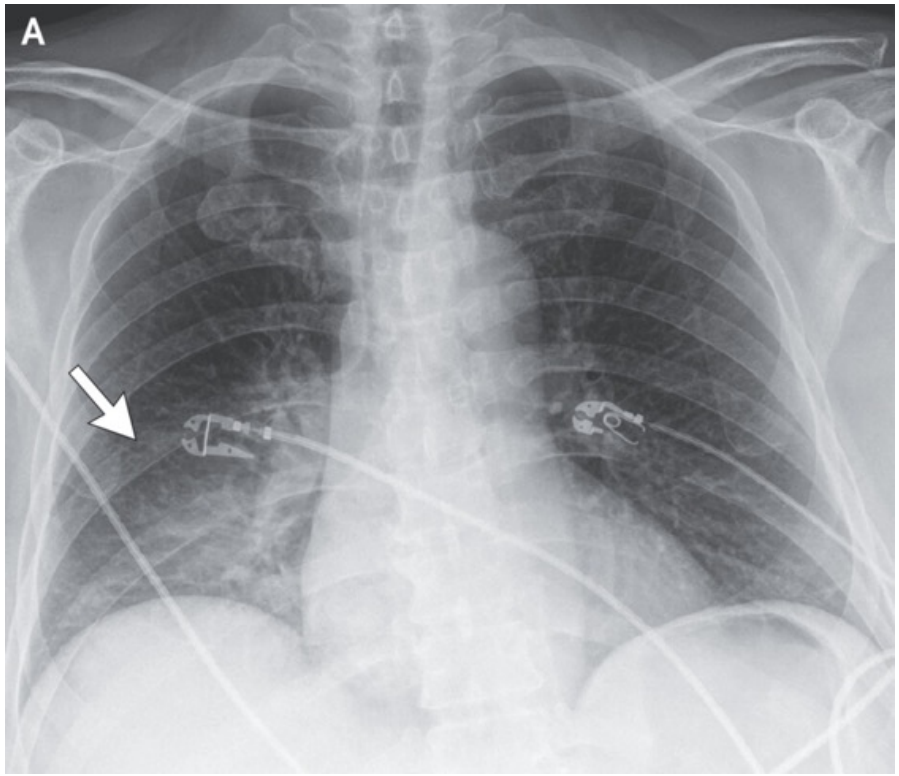


Die Klinik der Erkrankung ist außerordentlich variabel, was die Entwicklung einer sinnvollen klinischen Systematik erschwert. Stark generalisiert kann man "normale" und "schwere" Verläufe unterscheiden.
Schwere Verläufe gehen mit Fehlen von Spontan- oder Atembewegungen schon bei der Geburt einher und führen meist bereits in den ersten Lebensmonaten zum Tod.
Der normale Verlauf kann mit langsam fortschreitender, stagnierender, oder auch abnehmender Muskelschwäche einhergehen. Die muskuläre Hypotonie befällt typischerweise die Stamm-, Bulbär- und Gesichtsmuskulatur. Der Befall der Atemmuskulatur kann zu Hypoventilation und rezidivierenden Atemwegsinfektionen führen. Durch die Schwäche der Bulbärmuskulatur leiden die Patienten unter Sprechstörungen und Schluckstörungen, was eine Sondenernährung notwendig machen kann.

Ursächlich für die Fanconi-Anämie sind Mutationen in Genen, die für die DNA-Reparatur und genomische Stabilität verantwortlich sind. In erster Linie wird die Erkrankung autosomal-rezessiv, selten auch X-chromosomal-rezessiv vererbt. Die Erkrankung ist durch eine erhöhte Chromosomenbruchrate charakterisiert, welche die Entwicklung von malignen Tumoren begünstigt. Besonders häufig erkranken Patienten an einem myelodysplastischen Syndrom und an einer akuten myeloischen Leukämie (AML).

The patient had a white-cell count of 13,270 per microliter (reference range, 4500 to 11,000). The blood urea nitrogen level was 117 mg per deciliter (41.8 mmol per liter; reference range, 8 to 25 mg per deciliter [2.9 to 8.9 mmol per liter]), the creatinine level 13.0 mg per deciliter (1149 µmol per liter; reference range, 0.6 to 1.5 mg per deciliter [53 to 133 µmol per liter]), and the creatine kinase level 28,581 U per liter (reference range, 60 to 400). He had hyponatremia, hyperkalemia, and acidosis, as well as elevated blood levels of aspartate aminotransferase and alanine aminotransferase. Laboratory test results are shown. A comprehensive urine toxicology screen was negative, as was a serum toxicology screen for acetaminophen, salicylates, ethanol, and tricyclic antidepressants. Nucleic acid testing of a specimen obtained from the nasopharynx was negative for severe acute respiratory syndrome coronavirus 2, adenovirus, human metapneumovirus, influenza virus types A and B, parainfluenza virus types 1 through 4, and respiratory syncytial virus, as well as Bordetella pertussis, B. parapertussis, Chlamydia pneumoniae, and Mycoplasma pneumoniae.

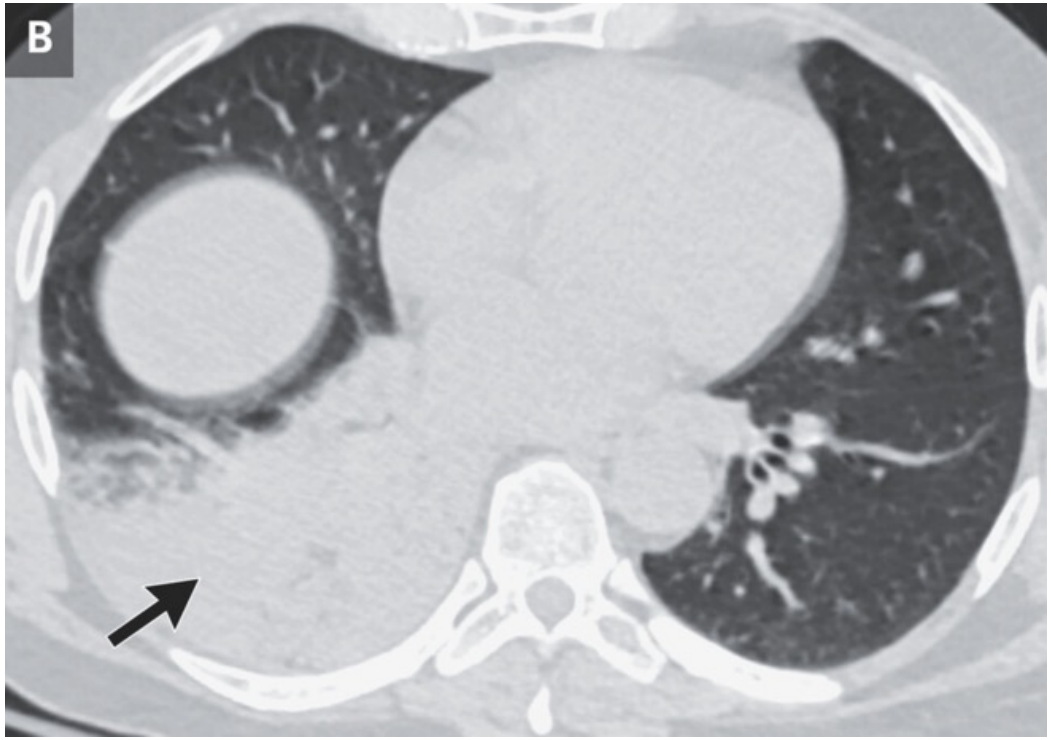
Variable	Reference Range, Adults†	On Admission
Blood		
White-cell count (per µl)	4500–13,000	13,270
Differential count (per µl)		
Neutrophils	1800–7700	12,560
Lymphocytes	1000–4800	240
Monocytes	200–1200	230
Eosinophils	0–900	10
Basophils	0–300	60
Immature granulocytes	0–100	170
Hematocrit (%)	36.0–46.0	46.7
Hemoglobin (g/dl)	12.0–16.0	16.5
Platelet count (per µl)	150,000–450,000	191,000
Sodium (mmol/liter)	135–145	125
Potassium (mmol/liter)	3.4–5.0	6.0
Chloride (mmol/liter)	98–108	75
Carbon dioxide (mmol/liter)	23–32	9
Urea nitrogen (mg/dl)	8–25	117
Creatinine (mg/dl)	0.6–1.5	13.0
Glucose (mg/dl)	70–110	184
Anion gap (mmol/liter)	3–17	41
Magnesium (mg/dl)	1.7–2.4	3.7
Calcium (mg/dl)	8.5–10.5	8.0
Albumin (g/dl)	3.3–5.0	3.7
Aspartate aminotransferase (U/liter)	9–32	418
Alanine aminotransferase (U/liter)	7–33	1272
Alkaline phosphatase (U/liter)	30–100	74
Total bilirubin (mg/dl)	0.0–1.0	0.7
Lactic acid (mmol/liter)	0.5–2.0	2.3



Creatine kinase (U/liter)	60–400	28,581
Lactate dehydrogenase (U/liter)	110–210	1334
C-reactive protein (mg/liter)	0.0–8.0	220.4
Erythrocyte sedimentation rate (mm/hr)	0–13	69
Ferritin (μg/liter)	20–300	5064
D-Dimer (ng/ml)	0–500	>10,000
Prothrombin time (sec)	11.5–14.5	16.2
Prothrombin-time international normalized ratio	0.9–1.1	1.3
Venous blood gases		
pH	7.30–7.40	7.26
Partial pressure of carbon dioxide (mm Hg)	38–50	27
Partial pressure of oxygen (mm Hg)	35–50	29
Urine		
Bilirubin	Negative	Negative
Urobilinogen	Negative	Negative
Blood	Negative	3+
Glucose	Negative	1+
Ketones	Negative	Negative
Leukocyte esterase	Negative	Negative
Nitrite	Negative	Negative
pH	5.0–9.0	5.5
Specific gravity	1.001–1.035	1.014
Protein	Negative	2+
Red cells (per high-power field)	0–2	10–20
White cells (per high-power field)	0–10	10–20

An anteroposterior chest radiograph (portable) shows an opacity in the right lower lobe (arrow). Where is the lateral view?!?

(I believe the metabolic acidosis is best explained by an eGFR of zero and suggest that dialysis was done.)

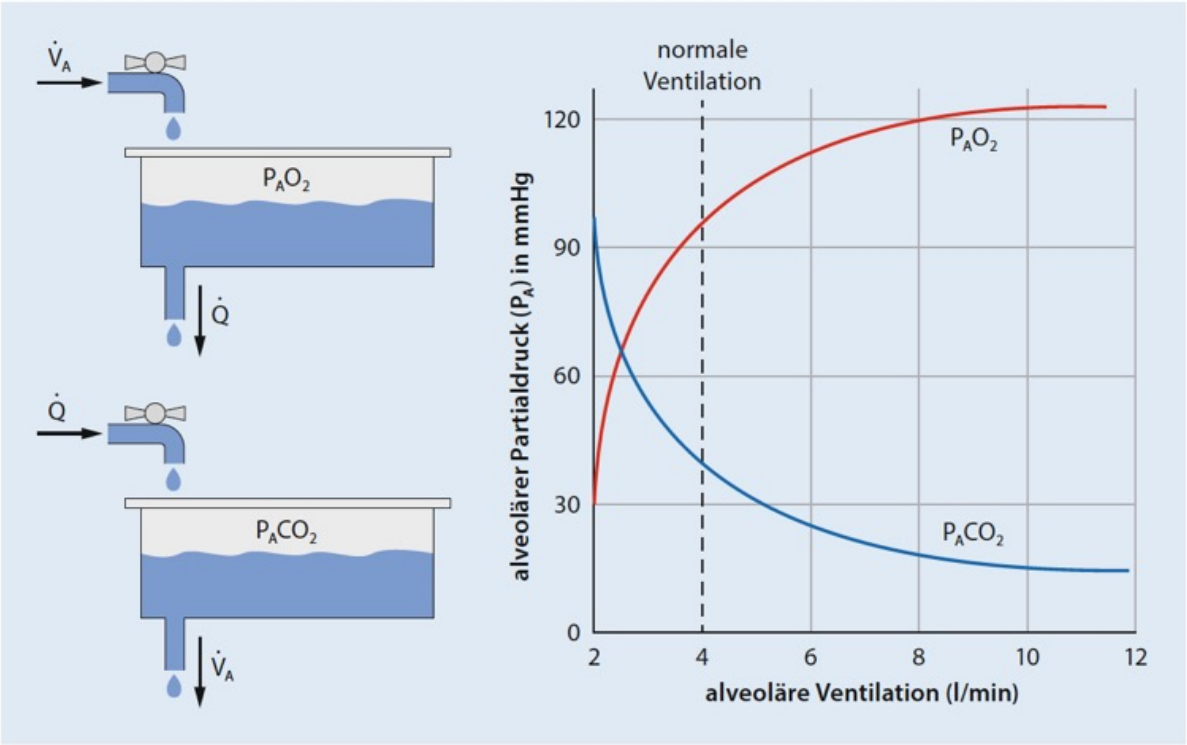


Lungs were clear to ascultation!

An axial image obtained on CT of the chest, abdomen, and pelvis (Panel B), performed without the administration of intravenous contrast material, shows consolidation in the right lower lobe with minimal adjacent ground-glass opacity (arrow). He had no lymphadenopathy.

Intravenous dextrose, insulin, calcium gluconate, and fluids were administered, and treatment with intravenous ceftriaxone and azithromycin was started. A Foley catheter was placed, and oliguria was noted. The patient was admitted to this hospital.

Three hours after the patient's arrival, the temporal temperature increased to 38.2°C. The respiratory rate increased to 45 breaths per minute, and the oxygen saturation decreased to 89% while the patient was breathing ambient air. Supplemental oxygen was delivered through a nasal cannula at a rate of 6 liters per minute, and the oxygen saturation increased to 98%.



Bei einer alveolären Ventilation von 4 l/min liegt der CO2-Partialdruck (pCO2) bei 40mmHg, der pO2 liegtbei>90mmHg.DieseWerte sind,wie alle Clearance-Formeln, vom Fick-Prinzip abgeleitet (VA alveoläre Ventilation, Q Perfusion)

Alveolar gas formula: $PAO_2 = 150 – PCO_2 \times 1.25 = 120$

This 47-year-old man presented with an acute illness that was characterized by nontraumatic, nonexertional rhabdomyolysis, oliguric kidney failure, lung consolidation with systemic inflammation, encephalopathy, and liver injury. It is notable that he had a family history of nemaline myopathy, and his exposures included the use of dietary supplements, residence in a converted factory, and smoking marijuana.

The presentation suggests two possible prime movers: nontraumatic, nonexertional rhabdomyolysis and lung consolidation with systemic inflammation. The other conditions that were noted on presentation — oliguric kidney failure, anion-gap and non–anion-gap metabolic acidosis, liver injury, and encephalopathy — can all be reasonably classified as end-organ injuries resulting from the primary process.

Of the two possible prime movers, nontraumatic, nonexertional rhabdomyolysis will be the focus of my differential diagnosis. I purposely used a noncommittal description for the second possible prime mover: lung consolidation with systemic inflammation. I am reluctant to use the more specific label of pneumonia because the case presentation does not fit my theoretical illness script for pneumonia. In cases of classic community-acquired pneumonia, I would expect the patient to be an older adult with coexisting conditions who presents with some combination of fever, dyspnea, cough, and chest pain. In this case, the patient is a younger adult whose primary symptoms include fatigue, myalgias, and confusion. As a result, I will build my differential diagnosis around nontraumatic, nonexertional rhabdomyolysis, while keeping in mind that the ultimate diagnosis must link the two prime movers and the secondary conditions.

Nemaline Myopathy

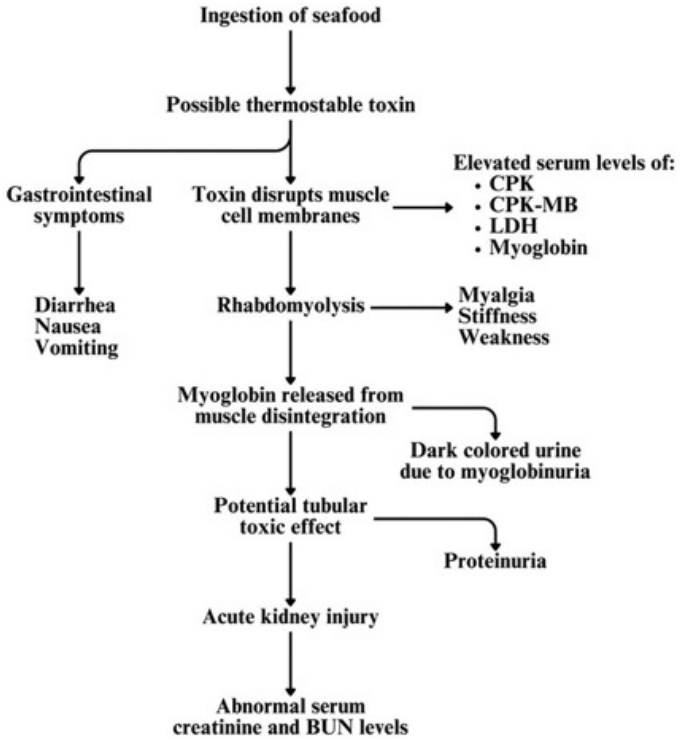
Nemaline myopathy is a rare genetic disorder caused by genetic variants that affect the proteins of the thin filament of the skeletal muscle sarcomere. Most patients have congenital disease and present at birth with normal to mildly elevated creatine kinase levels and symmetric generalized weakness that is disproportionately bulbar and axial. In a case series involving 76 patients with late-onset nemaline myopathy, half the patients had monoclonal gammopathy of unknown significance. The mismatching case features and time course make nemaline myopathy unlikely to be the diagnosis in this case.

Toxins, Poisons, and Drugs

Exposure to toxins and poisons can cause rhabdomyolysis. Heavy metals and venom have been reported to cause rhabdomyolysis, as has Haff disease, which is associated with the consumption of fish. Use of supplements, such as creatine, ephedra, and caffeine, has been described in cases of rhabdomyolysis and is relevant in this case. Patients with rhabdomyolysis who took these supplements often had other factors to consider, such as exertion, heat exposure, or the use of prescription medications. This patient reported taking ginseng and burdock root supplements, which have not been associated with rhabdomyolysis. However, because of limited regulatory oversight, it is often hard to discern the ingredients in many supplements.

Die Haff-Krankheit ist ein Syndrom unerklärlicher Rhabdomyolyse, das innerhalb von 24 Stunden nach dem Verzehr von Fisch auftritt. Es wird vermutet, dass es durch ein nicht identifiziertes Toxin verursacht wird. Rhabdomyolyse tritt auf, wenn beschädigtes Muskelgewebe seine Proteine und Elektrolyte ins Blut abgibt.

Na = 125
Cl = 75
HCO_3 = 9
AG = 41 (up 29)
H = 54
pCO_2 = 27
Lactate = 2.3
Urine Ketones = 0



Inflammatory Myopathy

Inflammatory myopathy warrants consideration, given this patient's family history of Sjögren's syndrome, which is characterized by lacrimal and salivary gland inflammation. Pulmonary manifestations include bronchiolitis, cystic lung disease, and fibrotic disease; lung consolidation is not a typical radiographic finding. Muscular manifestations of Sjögren's syndrome are rare and usually progress over a subacute time course.

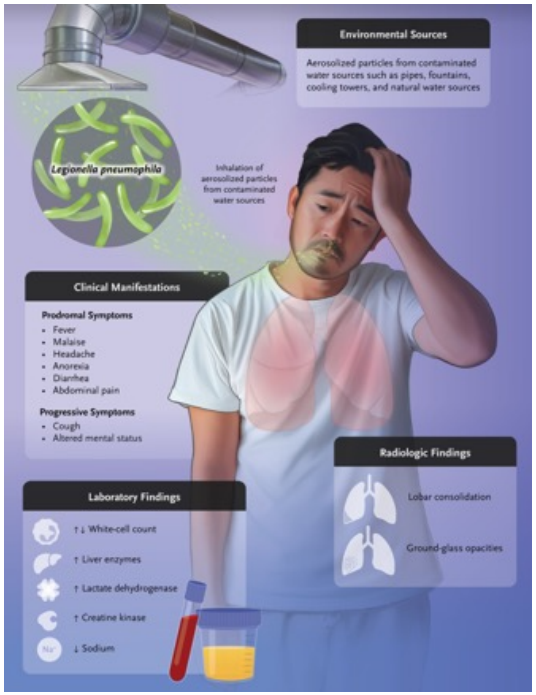
Infection

Multiple viral, fungal, and bacterial infections can cause rhabdomyolysis. The combined presence of rhabdomyolysis and lung consolidation, along with the acute onset and severity of this patient's presentation, is compatible with a diagnosis of influenza. Influenza is unlikely, given the negative nucleic acid amplification test (NAAT); however, when the pretest probability is high, it is prudent to consider a false negative test. False negative nasopharyngeal NAATs have been observed with some influenza subtypes that have a predilection for the lower respiratory tract, such as H1N1 and H5N1.

Distinguishing Legionella from Streptococcal Infection

Either legionella or streptococcal infection could be the cause of this patient's illness. The findings on presentation and results of laboratory tests alone cannot reliably distinguish one from the other. In more than half of pneumonia cases, no causative pathogen is identified. In this case, it was prudent to treat both causes empirically. As I try to distinguish one cause from the other, I will review the case details that may inform the final diagnosis.

Nonspecific laboratory findings in this patient also fit with a diagnosis of legionella. These include hyponatremia, leukocytosis with lymphopenia, an erythrocyte sedimentation rate greater than 90 mm per hour, a blood level of C-reactive protein greater than 180 mg per liter, microscopic hematuria, elevated levels of aspartate aminotransferase and alanine aminotransferase, a ferritin level of more than twice the upper limit of the normal range, and an elevated level of lactate dehydrogenase. The absence of gastrointestinal symptoms is notable, since such symptoms are a common feature of legionella infection.



Environmental Sources, Clinical Manifestations, Laboratory Findings, and Radiologic Findings of Legionella Pneumonia.

Transmission typically occurs through aerosolization from an environmental source. Inhalation and inoculation result in prodromal symptoms, including fever, malaise, and headache. Over the course of several days, a cough develops that may or may not be productive of purulent sputum. Altered mental status is frequently described with severe cases. Nonpulmonary symptoms, such as headache and gastrointestinal symptoms, may be severe and lead to misdiagnosis. Laboratory findings are consistent with severe community-acquired pneumonia and may show leukocytosis or leukopenia, elevated levels of liver enzymes, lactate dehydrogenase, and creatine kinase, and hyponatremia; however, these findings lack specificity. Radiologic findings nearly always include a consolidating pneumonia at the time of presentation. Extrapulmonary infection is rare and occurs almost exclusively in immunocompromised patients.

Given the patient's metabolic derangement and oliguric kidney failure, the nephrology service was consulted, and an emergency hemodialysis catheter was placed immediately after admission. A transthoracic echocardiogram (TTE) obtained on hospital day 2 showed a diffusely hypokinetic left ventricle with no regional wall-motion abnormalities and with an ejection fraction of 37%. Treatment was started with isosorbide dinitrate, hydralazine, and metoprolol for the management of heart failure. His kidney function recovered over the next 2 weeks, and the temporary dialysis catheter was removed on hospital day 10. No kidney biopsy was performed, and the acute kidney injury was attributed to rhabdomyolysis and severe infection. A repeat TTE obtained 9 days after the first showed full recovery of the left ventricular ejection fraction; therefore, the previous cardiomyopathy was determined to be stress-related.

Characteristics of Common Diagnostic Tests for Legionella Pneumonia.

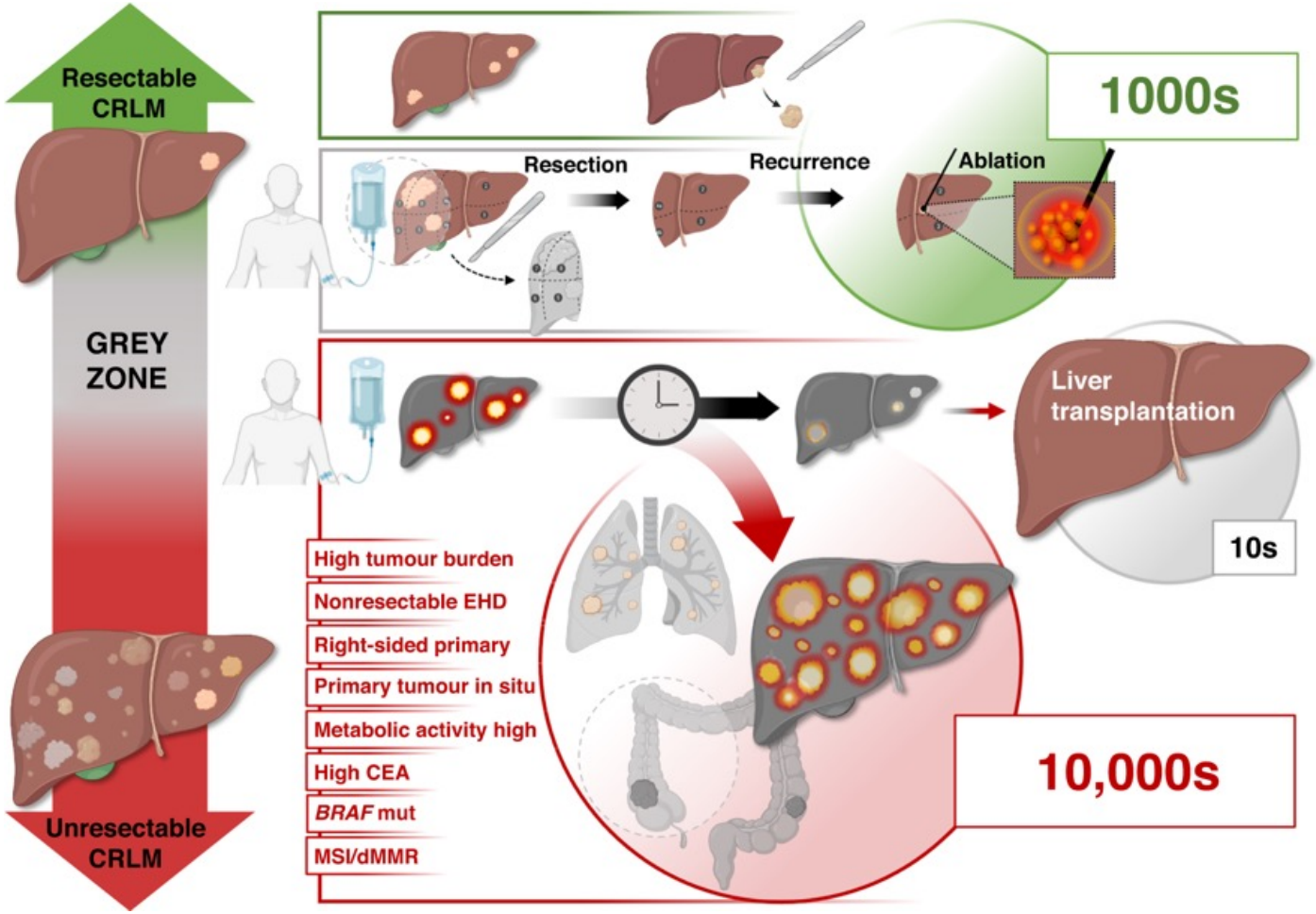
Test	Specimen Type	Sensitivity	Specificity
		percent	
Culture	Sputum, bronchoalveolar lavage, tissue, and blood	20–95	100
Antigen	Urine	60–95	>99
PCR	Sputum and bronchoalveolar lavage	70–95	95–99
Antibody	Serum	20–70	95–99
Immunofluorescence	Sputum, bronchoalveolar lavage, tissue, and blood	20–50	99

The diagnostic test in this case was a legionella urinary antigen test, which was positive and confirmed the diagnosis of legionella infection.

Discussion of Management

The patient initially received treatment with ceftriaxone and azithromycin, in accordance with guidelines from the American Thoracic Society for the treatment of severe community-acquired pneumonia that results in hospitalization. The antimicrobial regimen was narrowed to azithromycin after the diagnosis of legionella infection was made, and his fevers, mental status, and supplemental oxygen requirement gradually improved over the next 4 days. Treatment was briefly transitioned to doxycycline on hospital day 5 owing to concern for QT prolongation; however, after his hypoxemia notably worsened and fevers returned, the decision was made to discontinue doxycycline and restart macrolide therapy. Repeat chest imaging showed worsening ground-glass opacities, but sputum cultures remained negative. The patient's treatment regimen was transitioned to levofloxacin monotherapy on hospital day 9. He had a rapid resolution of his supplemental oxygen requirement and fever, as well as a return to his baseline mental status. In total, he completed 10 days of pathogen-directed therapy.

Metastatic colon cancer is an advanced-stage malignancy that originated in the colon and has traveled to other areas of the body. While colon cancer can spread anywhere in the body, it most often affects the liver or lungs.



Liver transplantation plus chemotherapy versus chemotherapy alone in patients with permanently unresectable colorectal liver metastases (TransMet): results from a multicentre, open-label, prospective, randomised controlled trial

Summary

Background Despite the increasing efficacy of chemotherapy, permanently unresectable colorectal liver metastases are associated with poor long-term survival. We aimed to assess whether liver transplantation plus chemotherapy could improve overall survival.

Methods TransMet was a multicentre, open-label, prospective, randomised controlled trial done in 20 tertiary centres in Europe. Patients aged 18–65 years, with Eastern Cooperative Oncology Group performance score 0–1, permanently unresectable colorectal liver metastases from resected *BRAF*-non-mutated colorectal cancer responsive to systemic chemotherapy (≥3 months, ≤3 lines), and no extrahepatic disease, were eligible for enrolment. Patients were randomised (1:1) to liver transplantation plus chemotherapy or chemotherapy alone, using block randomisation. The liver transplantation plus chemotherapy group underwent liver transplantation for 2 months or less after the last chemotherapy cycle. At randomisation, the liver transplantation plus chemotherapy group received a median of 21·0 chemotherapy cycles (IQR 18·0–29·0) versus 17·0 cycles (12·0–24·0) in the chemotherapy alone group, in up to three lines of chemotherapy. During first-line chemotherapy, 64 (68%) of 94 patients had received doublet chemotherapy and 30 (32%) of 94 patients had received triplet regimens; 76 (80%) of 94 patients had targeted therapy. Transplanted patients received tailored immunosuppression (methylprednisolone 10 mg/kg intravenously on day 0; tacrolimus 0·1 mg/kg via gastric tube on day 0, 6–10 ng/mL days 1–14; mycophenolate mofetil 10 mg/kg intravenously day 0 to <2 months and switch to everolimus 5–8 ng/mL), and postoperative chemotherapy, and the chemotherapy group had continued chemotherapy. The primary endpoint was 5-year overall survival analysed in the intention to treat and per-protocol population. Safety events were assessed in the as-treated population. The study is registered with ClinicalTrials.gov (NCT02597348), and accrual is complete.

Findings Between Feb 18, 2016, and July 5, 2021, 94 patients were randomly assigned and included in the intention-to-treat population, with 47 in the liver transplantation plus chemotherapy group and 47 in the chemotherapy alone group. 11 patients in the liver transplantation plus chemotherapy group and nine patients in the chemotherapy alone group did not receive the assigned treatment; 36 patients and 38 patients in each group, respectively, were included in the per-protocol analysis. Patients had a median age of 54·0 years (IQR 47·0–59·0), and 55 (59%) of 94 patients were male and 39 (41%) were female. Median follow-up was 59·3 months (IQR 42·4–60·2). In the intention-to-treat population, 5-year overall survival was 56·6% (95% CI 43·2–74·1) for liver transplantation plus chemotherapy and 12·6% (5·2–30·1) for chemotherapy alone (HR 0·37 [95% CI 0·21–0·65]; p=0·0003) and 73·3% (95% CI 59·6–90·0) and 9·3% (3·2–26·8), respectively, for the per-protocol population. Serious adverse events occurred in 32 (80%) of 40 patients who underwent liver transplantation (from either group), and 69 serious adverse events were observed in 45 (83%) of 54 patients treated with chemotherapy alone. Three patients in the liver transplantation plus chemotherapy group were retransplanted, one of whom died postoperatively of multi-organ failure.

Interpretation In selected patients with permanently unresectable colorectal liver metastases, liver transplantation plus chemotherapy with organ allocation priority significantly improved survival versus chemotherapy alone. These results support the validation of liver transplantation as a new standard option for patients with permanently unresectable liver-only metastases.

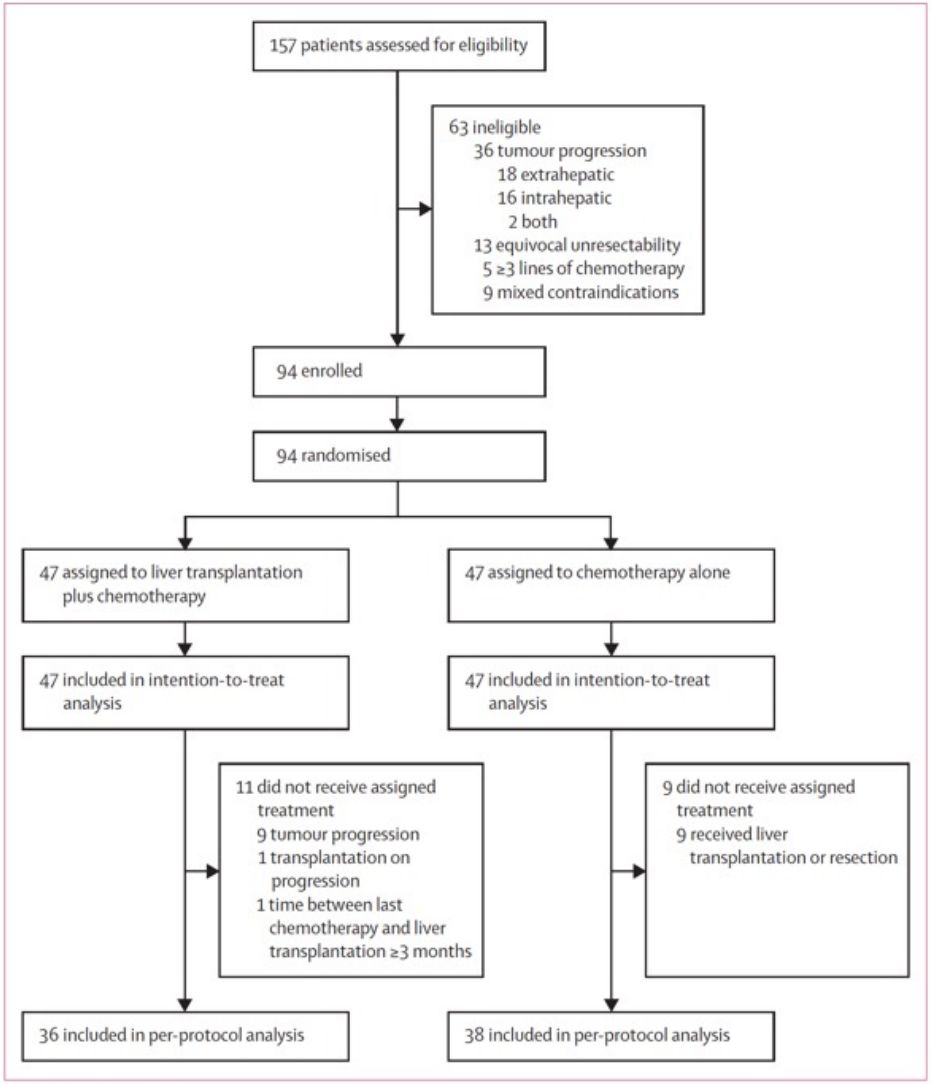


Figure 1: **Trial profile**

	Liver transplantation plus chemotherapy (n=47)	Chemotherapy alone (n=47)
Primary tumour		
Primary tumour site*		
Right	7 (15%)	7 (15%)
Left	25 (53%)	29 (62%)
Rectum	15 (32%)	11 (23%)
(y)pT3-T4		
Yes	37 (79%)	38 (81%)
No	9 (19%)	9 (19%)
Missing	1 (2%)	0
(y)pN status		
N0	21 (45%)	16 (34%)
N+	26 (55%)	31 (66%)
RAS mutation status		
Yes	17 (36%)	13 (28%)
No	29 (62%)	32 (69%)
Missing	1 (2%)	2 (4%)
Mismatch repair status		
Proficient mismatch repair	47 (100%)	46 (98%)
Deficient mismatch repair	0	1 (2%)
Liver metastases at diagnosis		
Timing of metastases		
Synchronous†	47 (100%)	45 (96%)
Metachronous	0	2 (4%)
Number of colorectal liver metastases	20·0 (14·0–25·0)	20·0 (12·0–25·0)
<10	5 (11%)	7 (15%)
10–20	19 (40%)	18 (38%)
>20	23 (49%)	22 (47%)
Diameter of largest colorectal liver metastases, mm	55·0 (43·0–76·0)	50·0 (27·0–83·0)
CEA level, ng/mL	305·0 (32·9–762·0)	81·0 (20·0, 530·0)
CA19–9 level, UI/mL	96·0 (19·7–800·0)	193·0 (20·9–1949·0)
Systemic chemotherapy after diagnosis		
Type of chemotherapy (first line)		
Fluorouracil alone	0	0
Oxaliplatin based	22 (47%)	22 (47%)
Irinotecan based	9 (19%)	11 (23%)
Triplet chemotherapy	16 (34%)	14 (30%)
Targeted therapy (first line)		
None	8 (17%)	10 (21%)
Anti-VEGF only	21 (45%)	16 (34%)
Anti-EGFR only	18 (38%)	21 (45%)
Tumour response (first line)‡		
Complete response	1 (2%)	0
Partial response	27 (57%)	27 (57%)
Stable disease	14 (30%)	14 (30%)
Progression	5 (11%)	5 (11%)
Missing	0	1 (2%)

CA19–9=carbohydrate antigen 19–9. CEA=carcinoembryonic antigen. EGFR=epidermal growth factor receptor. VEGF=vascular endothelial growth factor. Data are n (%) or median (IQR). *Right=primary tumour located proximally to the colic flexure. Left=primary tumour located distally to the colic flexure. Rectum=primary tumour located within 15 cm of the anal verge. †Synchronous is defined as metastases diagnosed within 1 month of diagnosis of the primary tumour. ‡Tumour response was evaluated according to the Response Evaluation Criteria in Solid Tumours criteria version 1.1.

Table 1: **Baseline characteristics at diagnosis of colorectal liver metastases in the intention-to-treat population**

	Liver transplantation plus chemotherapy (n=47)	Chemotherapy alone (n=47)
Primary tumour		
Primary tumour site*		
Right	7 (15%)	7 (15%)
Left	25 (53%)	29 (62%)
Rectum	15 (32%)	11 (23%)
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Table 1: **Baseline characteristics at diagnosis of colorectal liver metastases in the intention-to-treat population**

	Liver transplantation plus chemotherapy (n=47)	Chemotherapy alone (n=47)
Age, years	52·0 (47·0–59·0)	55·0 (47·0–59·0)
Sex		
Male	27 (57%)	28 (60%)
Female	20 (43%)	19 (40%)
ECOG performance status		
0	38 (81%)	37 (79%)
1	9 (19%)	10 (21%)
Number of colorectal liver metastases	14·0 (8·0–25·0)	15·0 (5·0–25·0)
<10	12 (26%)	16 (34%)
10–20	20 (43%)	17 (36%)
>20	15 (32%)	14 (30%)
Diameter of largest colorectal liver metastases, mm	27·0 (18·0–42·0)	27·0 (16·0–45·0)
CEA, ng/mL	3·6 (2·2–12·4)	3·6 (2·0–22·1)
CA19–9, IU/mL	11·4 (5·9–30·0)	15·0 (6·5–28·7)
Fong's clinical risk score*		
Low (0–2)	20 (43%)	13 (28%)
High (3–5)	27 (57%)	34 (72%)
Time between diagnosis and randomisation, months	15·9 (11·8–25·7)	13·5 (9·0–19·4)
Ongoing chemotherapy		
Type of chemotherapy		
Fluorouracil alone	7 (15%)	1 (2%)
Oxaliplatin based	12 (26%)	11 (23%)
Irinotecan based	20 (43%)	27 (57%)
Triplet	8 (17%)	8 (17%)
Targeted therapy agent		
None	2 (4%)	4 (9%)
Anti-VEGF	17 (36%)	16 (34%)
Anti-EGFR	28 (60%)	27 (57%)
Number of chemotherapy cycles (last line)	14·0 (8·0–20·0)	11·0 (7·0–14·0)
Tumour response†		
Partial response	26 (55%)	21 (45%)
Stable disease	21 (45%)	26 (55%)

(Table 2 continues in next column)

(Continued from previous column)

	Liver transplantation plus chemotherapy (n=47)	Chemotherapy alone (n=47)
Grade ≥3 toxicity (CTCAE)		
Yes	6 (13%)	8 (17%)
No	39 (83%)	34 (72%)
Missing	2 (4%)	5 (11%)
Cumulative chemotherapy		
Total number of chemotherapy lines		
1	18 (38%)	23 (49%)
2	21 (45%)	17 (36%)
3	8 (17%)	7 (15%)
Cumulative number of chemotherapy cycles (total lines)	21·0 (18·0–29·0)	17·0 (12·0–24·0)
≤12	3 (6%)	14 (30%)
13–23	25 (53%)	21 (45%)
≥24	19 (40%)	12 (26%)
Previous curative intent surgery		
None	43 (91%)	37 (79%)
Minor hepatectomy	2 (4%)	5 (11%)
Major hepatectomy	2 (4%)	5 (11%)
Delay between primary resection and randomisation >24 months		
Yes	5 (11%)	7 (15%)
No	42 (89%)	40 (85%)

CA19–9=carbohydrate antigen 19–9. CEA=carcinoembryonic antigen. CTCAE=Common Terminology Criteria for Adverse Events. ECOG=Eastern Cooperative Oncology Group. EGFR=epidermal growth factor receptor. IU=international units. VEGF=vascular endothelial growth factor. Data are n (%) or median (IQR). *Despite the decrease in size and tumour markers levels, patients remained with multiple metastases impossible to resect completely. †Tumour response was evaluated according to the Response Evaluation Criteria in Solid Tumors criteria, version 1.1.

Table 2: **Baseline characteristics at randomisation in the intention-to-treat population**

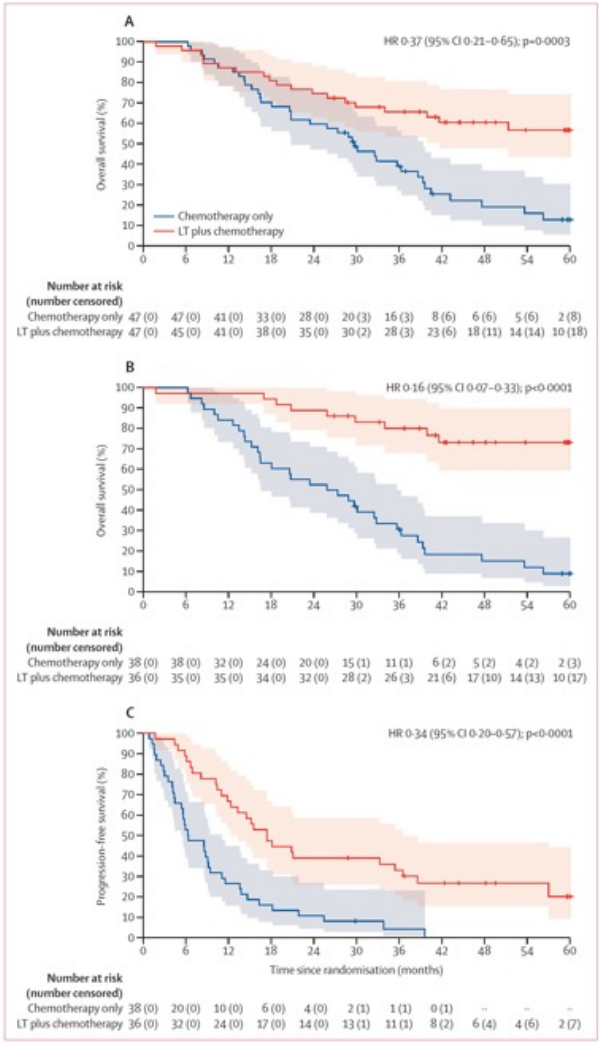


Figure 2: **Survival outcomes in chemotherapy alone and chemotherapy plus liver transplantation**
Overall survival in the intention-to-treat population (A) and per-protocol population (B), and progression-free survival in the per-protocol population (C). Shaded areas represent 95% CIs. Tick marks represent censored patients. LT=liver transplantation. HR=hazard ratio.

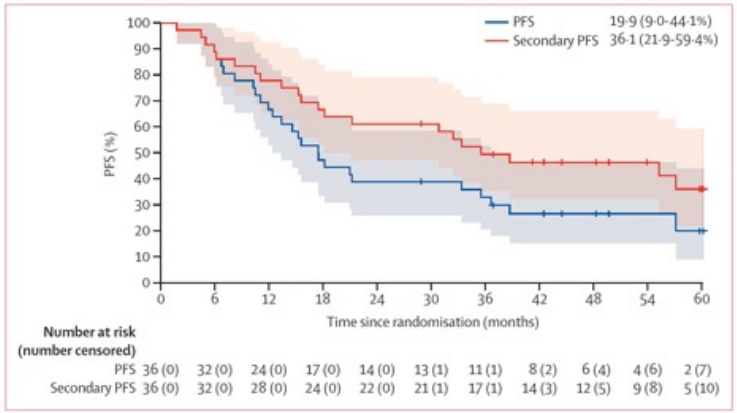


Figure 3: **Secondary PFS in liver transplantation plus chemotherapy group who had a liver transplantation in the per-protocol population**
A significant proportion of the 28 patients who presented with recurrence after liver transplantation were considered eligible for potentially curative treatment of the recurrent disease. These patients were therefore censored from the PFS curve at the time of recurrence. As they become free from disease after resection or ablation of their recurrence, they were no longer considered to be censored in the corrected secondary PFS. Secondary PFS shows the effect of the treatment of recurrence when compared with primary PFS. Shaded areas represent 95% CIs. Tick marks represent censored patients. PFS is defined as the time to first recurrence after liver transplantation. Secondary PFS is the time to first recurrence without secondary remission occurring after liver transplantation. PFS=progression-free survival.

	Any grade (n=36)	Grade ≥3b (n=36)
Hepatic		
Biliary	5/36 (14%)	4/36 (11%)
Arterial	6/36 (17%)	1/36 (3%)
Early graft dysfunction*	4/36 (11%)	3/36 (8%)
Collection	3/36 (8%)	1/36 (3%)
Primary non-function†	2/36 (6%)	2/36 (6%)
Haemorrhage	2/36 (6%)	2/36 (6%)
Hepatic or caval	1/36 (3%)	1/36 (3%)
Ascites	2/35 (6%)	0
Portal	1/36 (3%)	0
Rejection	3/35 (8%)	0
Digestive		
Ileus	3/36 (8%)	1/36 (3%)
Malnutrition	1/36 (3%)	0
Other	7/33 (19%)	1/35 (3%)
General condition	2/34 (6%)	0
Haematological		
Anaemia	1/36 (3%)	0
Other or not defined	3/34 (8%)	0
Pulmonary		
Pleural effusion	6/36 (17%)	1/36 (3%)
Other	4/36 (11%)	3/36 (8%)
Cardiovascular		
DVT	2/35 (6%)	0
Other	7/34 (19%)	1/34 (3%)
Renal	8/36 (22%)	1/36 (3%)
Superficial site infection	3/36 (8%)	2/36 (6%)
Infection		
CMV	3/36 (8%)	0
Other	7/33 (19%)	1/35 (3%)
Diabetes	6/36 (17%)	0

Data are n/N (%). CMV=cytomegalovirus. DVT=deep vein thrombosis. *Early graft dysfunction was defined according to Olthoff and colleagues.[33] †PNF was defined according to Makowka and colleagues.[34]

Table 3: **Postoperative complications in the liver transplantation plus chemotherapy group according to the per-protocol population**

	Liver transplantation plus chemotherapy (n=24)		Chemotherapy alone (n=38)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any toxicity	23/24 (96%)	8/22 (36%)	35/36 (97%)	17/36 (47%)
Haematological disorders	10/24 (42%)	4/23 (17%)	16/29 (55%)	6/25 (24%)
Gastrointestinal disorders	15/23 (65%)	3/21 (14)	26/29 (90%)	3/27 (11%)
Nervous system disorders	4/23 (17%)	1/22 (5%)	21/31 (68%)	3/27 (11%)
General disorders	15 (63%)	0	29/34 (85%)	2/24 (8%)
Renal disorders	0	0	1/23 (4%)	0
Infectious disorders	0	0	2/28 (7%)	0
Immune system disorders	0	0	3/29 (10%)	0
Other disorders	15/24 (63%)	3/22 (14%)	31/33 (94%)	10/27 (37%)

Data are n/N (%).

Table 4: **Toxicity related to systemic chemotherapy after randomisation in the per-protocol population**

Research in context

Evidence before this study

Complete resection of liver metastases is the best option for long-term survival in patients with liver metastases from colorectal cancer. However, this surgical treatment is only suitable for a small proportion of patients, and systemic chemotherapy remains the standard of care for patients with unresectable liver metastases. Recent advances in liver transplantation, including living-donor transplantation and use of partial grafts, as well as positive findings from pilot, non-controlled studies (NCT01311453 and NCT01479608), have reignited interest in liver transplantation for patients with permanently unresectable colorectal liver metastases.

We searched PubMed from database inception to April 17, 2024, with the search terms "colorectal cancer", "colorectal carcinoma", "rectal cancer", "rectal carcinoma", "colon cancer", "colon carcinoma", "liver metastasis", and "transplant" for randomised trials comparing liver transplantation plus chemotherapy with chemotherapy alone in patients with metastatic colorectal cancer. No randomised controlled trials comparing systemic chemotherapy plus liver transplantation versus chemotherapy alone were identified.

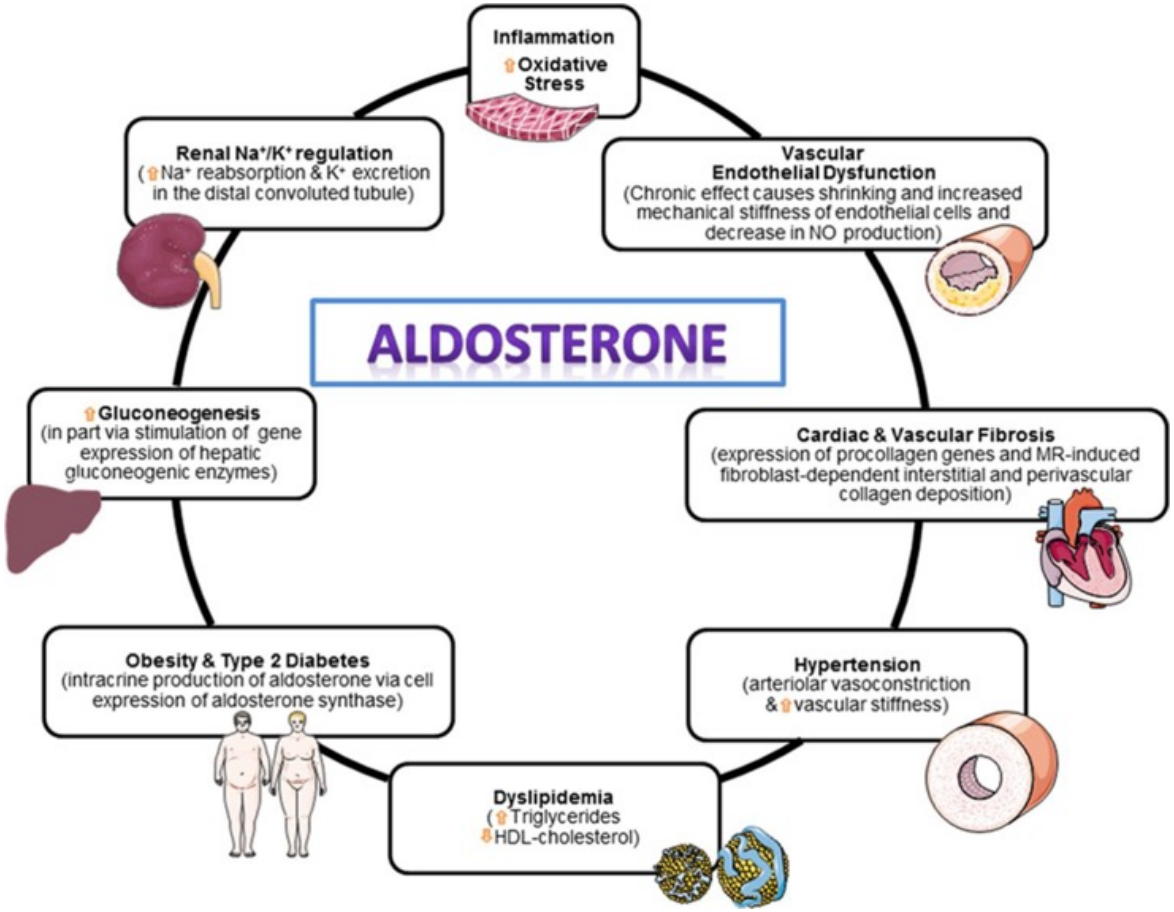
Added value of this study

To our knowledge, the TransMet trial is the first randomised study to prospectively compare liver transplantation plus chemotherapy versus chemotherapy alone as the current standard of care in patients with permanently unresectable colorectal cancer and liver metastases. Our findings show that patients with permanently unresectable liver metastases from colorectal cancer have better overall survival after liver transplantation following chemotherapy than patients receiving chemotherapy alone. This is the first comparative study demonstrating a notable benefit of transplantation in liver metastases from an aggressive digestive cancer, expanding the concept of transplant oncology. In the absence of evidence from randomised controlled trials, the role of liver transplantation in addition to systemic chemotherapy in patients with permanently unresectable liver metastases from colorectal cancer has not been scientifically shown. Strong evidence of clinical benefit is especially important in this setting, given the demand for, and scarcity of organs as well as the competition with standard indications.

Implications of all the available evidence

The TransMet trial shows that liver transplantation plus chemotherapy considerably improves outcomes, achieving a potential of cure in patients with permanently unresectable colorectal cancer liver metastases compared with chemotherapy alone. These findings support liver transplantation plus chemotherapy as a new standard option for carefully selected patients with permanently unresectable liver metastases from colorectal cancer.

Mineralocorticoid receptor antagonists (MRAs) reduce hospitalisations and death in patients with heart failure and reduced ejection fraction (HFrEF), but the benefit in patients with heart failure and mildly reduced ejection fraction (HFmrEF) or heart failure and preserved ejection fraction (HFpEF) is unclear.



Mineralocorticoid receptor antagonists in heart failure: an individual patient level meta-analysis

Summary

Background Mineralocorticoid receptor antagonists (MRAs) reduce hospitalisations and death in patients with heart failure and reduced ejection fraction (HFrEF), but the benefit in patients with heart failure and mildly reduced ejection fraction (HFmrEF) or heart failure and preserved ejection fraction (HFpEF) is unclear. We evaluated the effect of MRAs in four trials that enrolled patients with heart failure across the range of ejection fraction.

Methods This is a prespecified, individual patient level meta-analysis of the RALES (spironolactone) and EMPHASIS-HF (eplerenone) trials, which enrolled patients with HFrEF, and of the TOPCAT (spironolactone) and FINEARTS-HF (finerenone) trials, which enrolled patients with HFmrEF or HFpEF. The primary outcome of this meta-analysis was a composite of time to first hospitalisation for heart failure or cardiovascular death. We also estimated the effect of MRAs on components of this composite, total (first or repeat) heart failure hospitalisations (with and without cardiovascular deaths), and all-cause death. Safety outcomes were also assessed, including serum creatinine, estimated glomerular filtration rate, serum potassium, and systolic blood pressure. An interaction between trials and treatment was tested to examine the heterogeneity of effect in these populations. This study is registered with PROSPERO, CRD42024541487.

Findings 13 846 patients were included in the four trials. MRAs reduced the risk of cardiovascular death or heart failure hospitalisation (hazard ratio 0·77 [95% CI 0·72–0·83]). There was a statistically significant interaction by trials and treatment (p for interaction=0·0012) due to the greater efficacy in HFrEF (0·66 [0·59–0·73]) compared with HFmrEF or HFpEF (0·87 [0·79–0·95]). We observed significant reductions in heart failure hospitalisation in the HFrEF trials (0·63 [0·55–0·72]) and the HFmrEF or HFpEF trials (0·82 [0·74–0·91]). The same pattern was observed for total heart failure hospitalisations with or without cardiovascular death. Cardiovascular death was reduced in the HFrEF trials (0·72 [0·63–0·82]) but not in the HFmrEF or HFpEF trials (0·92 [0·80–1·05]). All-cause death was also reduced in the HFrEF trials (0·73 [0·65–0·83]) but not in the HFmrEF or HFpEF trials (0·94 [0·85–1·03]). With an MRA, the risk of hyperkalaemia was doubled compared with placebo (odds ratio 2·27 [95% CI 2·02–2·56]), but the incidence of serious hyperkalaemia (serum potassium >6·0 mmol/L) was low (2·9% *vs* 1·4%); the risk of hypokalaemia (potassium <3·5 mmol/L) was halved (0·51 [0·45–0·57]; 7% *vs* 14%).

Interpretation Steroidal MRAs reduce the risk of cardiovascular death or heart failure hospitalisation in patients with HFrEF and non-steroidal MRAs reduce this risk in patients with HFmrEF or HFpEF.

	RALES (n=1663)	EMPHASIS-HF (n=2737)	TOPCAT (n=3445)	FINEARTS-HF (n=6001)	Total (n=13 846)
Age, years	65 (11)	68 (7)	68 (9)	72 (9)	69 (9)
Sex					
Female	446 (27%)	610 (22%)	1775 (52%)	2732 (46%)	5563 (40%)
Male	1217 (73%)	2127 (78%)	1670 (48%)	3269 (54%)	8283 (60%)
Race or ethnicity					
White	1440 (87%)	2268 (83%)	3062 (89%)	4735 (79%)	11 505 (83%)
Black	120 (7%)	67 (2%)	302 (9%)	88 (1%)	577 (4%)
Asian	32 (2%)	316 (12%)	19 (1%)	996 (17%)	1363 (10%)
Other	71 (4%)	86 (3%)	62 (2%)	182 (3%)	401 (3%)
Region					
North America	114 (7%)	248 (9%)	1477 (43%)	471 (8%)	2310 (17%)
Latin America	433 (26%)	98 (4%)	290 (8%)	641 (11%)	1462 (11%)
Western Europe	1066 (64%)	1005 (37%)	0	1204 (20%)	3275 (24%)
Central and eastern Europe	0	988 (36%)	1678 (49%)	2630 (44%)	5296 (38%)
Asia-Pacific	50 (3%)	398 (15%)	0	1055 (18%)	1503 (11%)
BMI, kg/m²	NR	27·5 (4·9)	32·1 (7·1)	29·9 (6·1)	30·0 (6·4)
BMI category, kg/m²					
<30	NR	1983 (72%)	1533 (44%)	3296 (55%)	6812/12 145 (56%)
≥30	NR	739 (27%)	1902 (55%)	2692 (45%)	5333/12 145 (44%)
Missing	1663	15	10	13	1701
Systolic blood pressure, mm Hg	122 (20)	124 (17)	129 (14)	129 (15)	127 (16)
Heart rate, beats per min	81 (14)	72 (13)	69 (10)	71 (11)	72 (12)
LVEF, %	25% (7)	26% (5)	57% (7)	53% (8)	45% (15)
NYHA class					
I or II	7 (<1%)	2730 (100%)	2303 (67%)	4146 (69%)	9186/13 835 (66%)
III or IV	1656 (100%)	3 (<1%)	1136 (33%)	1854 (31%)	4649/13 835 (34%)
Missing	0	4	6	1	11
Previous heart failure hospitalisation	NR	1438 (53%)	2489 (72%)	3619 (60%)	7546/12 177 (62%)
Missing	1663	3	3	0	1669

Previous heart failure hospitalisation	NR	1438 (53%)	2489 (72%)	3619 (60%)	7546/12 177 (62%)
Missing	1663	3	3	0	1669
NT-proBNP, pg/mL	NR	NR	843·0 (463·0–1720·0)	1041·4 (448·5–1945·9)	1013·5 (449·6–1929·8)
eGFR, mL/min per 1·73 m²	63 (22)	65 (18)	65 (19)	63 (20)	64 (19)
eGFR category, mL/min per 1·73 m²					
<60	841 (51%)	1092 (40%)	1463 (42%)	2844 (47%)	6240/13 827 (45%)
≥60	817 (49%)	1633 (60%)	1980 (57%)	3157 (53%)	7587/13 827 (55%)
Missing	5	12	2	0	19
Potassium, mmol/L	4·2 (0·4)	4·3 (0·4)	4·3 (0·4)	4·4 (0·5)	4·3 (0·5)
Diabetes	369 (22%)	859 (31%)	1118 (32%)	2454 (41%)	4800 (35%)
Hypertension	391 (24%)	1819 (66%)	3147 (91%)	5325 (89%)	10 682 (77%)
Atrial fibrillation	183 (11%)	844 (31%)	1214 (35%)	3273 (55%)	5514 (40%)
Myocardial infarction	472 (28%)	1380 (50%)	893 (26%)	1541 (26%)	4286 (31%)
Stroke	NR	262 (10%)	265 (8%)	708 (12%)	1235/12 183 (10%)
ACE inhibitor or ARB	1589 (96%)	2558 (93%)	2900 (84%)	4246 (71%)	11 293 (82%)
ARN inhibitor	NR	NR	NR	513 (9%)	513 (4%)
SGLT2 inhibitor	NR	NR	NR	817 (14%)	817 (6%)
β blocker	171 (10%)	2374 (87%)	2676 (78%)	5095 (85%)	10 316 (75%)
Diuretic	1502 (90%)	2326 (85%)	2817 (82%)	5930 (99%)	12 575 (91%)
Digitalis glycosides	1216 (73%)	740 (27%)	342 (10%)	471 (8%)	2769 (20%)

Data are reported as mean (SD), n (%), or median (IQR). NR=not reported. LVEF=left ventricular ejection fraction. NYHA=New York Heart Association. NT-proBNP=N-terminal pro B-type natriuretic peptide. eGFR=estimated glomerular filtration rate. ACE=angiotensin-converting enzyme. ARB=angiotensin receptor blocker. ARN=angiotensin receptor neprilysin.

Table 1: **Baseline characteristics of patients in each mineralocorticoid receptor antagonist trial and in the total population studied**

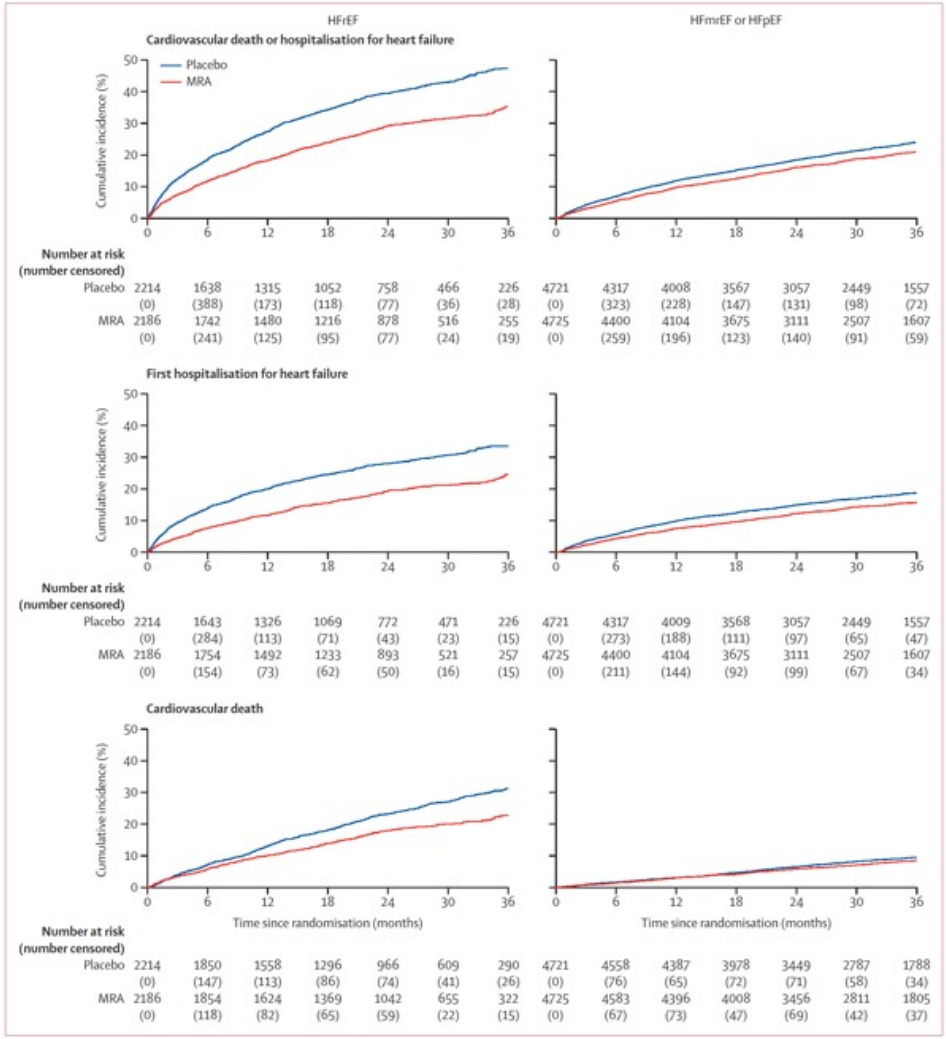


Figure 1: **Kaplan–Meier curves illustrating the cumulative incidence of prespecified efficacy outcomes**
The outcomes shown are cardiovascular death or hospitalisation for heart failure, hospitalisation for heart failure, and cardiovascular death. Panels on the left show patients with HFrEF and panels on the right show patients with HFmrEF or HFpEF. HFmrEF=heart failure and mildly reduced ejection fraction. HFpEF=heart failure and preserved ejection fraction. HFrEF=heart failure and reduced ejection fraction. MRA=mineralocorticoid receptor antagonist.

	RALES (n=1663)		EMPHASIS-HF (n=2737)		EMPHASIS-HF and RALES (n=4400)		TOPCAT (n=3445)		FINEARTS-HF (n=6001)		TOPCAT and FINEARTS-HF (n=9446)		All trials (n=13 846)	
	HR or RR (95% CI)	p value	HR or RR (95% CI)	p value	HR or RR (95% CI)	Interaction p value	HR or RR (95% CI)	p value	HR or RR (95% CI)	p value	HR or RR (95% CI)	Interaction p value	HR or RR (95% CI)	Interaction p value
Cardiovascular death or heart failure hospitalisation*	0·66 (0·57 to 0·75)	<0·0001	0·66 (0·56 to 0·78)	<0·0001	0·66 (0·59 to 0·73)	0·97	0·90 (0·78 to 1·05)	0·20	0·85 (0·76 to 0·94)	0·0025	0·87 (0·79 to 0·95)	0·49	0·77 (0·72 to 0·83)	0·0012
ARR	16·1 (11·2 to 20·9)	..	5·7 (3·5 to 7·8)	..	6·0 (4·5 to 7·4)	..	0·6 (–0·3 to 1·6)	..	1·7 (0·6 to 2·8)	..	1·5 (0·6 to 2·4)	..	2·7 (2 to 3·4)	..
Heart failure hospitalisation*	0·65 (0·54 to 0·77)	<0·0001	0·61 (0·50 to 0·75)	<0·0001	0·63 (0·55 to 0·72)	0·67	0·83 (0·69 to 0·99)	0·043	0·82 (0·72 to 0·92)	0·0011	0·82 (0·74 to 0·91)	0·92	0·74 (0·69 to 0·80)	0·022
ARR	10·3 (6·6 to 14·1)	..	4·6 (2·8 to 6·4)	..	4·5 (3·3 to 5·8)	..	0·8 (0 to 1·6)	..	1·6 (0·7 to 2·6)	..	1·6 (0·8 to 2·4)	..	2·5 (1·8 to 3·1)	..
Cardiovascular death†	0·69 (0·58 to 0·82)	<0·0001	0·77 (0·62 to 0·96)	0·018	0·72 (0·63 to 0·82)	0·45	0·90 (0·73 to 1·12)	0·35	0·93 (0·78 to 1·10)	0·40	0·92 (0·80 to 1·05)	0·85	0·81 (0·74 to 0·89)	0·082
ARR	6·8 (3·7 to 9·8)	..	1·8 (0·3 to 3·2)	..	2·2 (1·3 to 3·2)	..	0·3 (–0·3 to 0·9)	..	0·3 (–0·3 to 0·9)	..	0·3 (–0·2 to 0·8)	..	0·7 (0·4 to 1·1)	..
Total heart failure hospitalisations*‡	0·65 (0·54 to 0·78)	<0·0001	0·53 (0·42 to 0·67)	<0·0001	0·60 (0·52 to 0·69)	0·58	0·79 (0·66 to 0·96)	0·019	0·83 (0·74 to 0·93)	0·0015	0·82 (0·74 to 0·90)	0·79	0·74 (0·68 to 0·80)	0·0044
ARR	15·2 (8 to 22·4)	..	7·4 (3·9 to 10·9)	..	8·0 (5·3 to 10·8)	..	1·5 (–0·2 to 3·2)	..	2·6 (0·7 to 4·4)	..	2·5 (0·9 to 4·2)	..	4·0 (2·7 to 5·3)	..
Cardiovascular death and total heart failure hospitalisations*‡	0·68 (0·59 to 0·79)	<0·0001	0·58 (0·48 to 0·70)	<0·0001	0·64 (0·57 to 0·72)	0·62	0·82 (0·70 to 0·98)	0·025	0·85 (0·76 to 0·95)	0·0032	0·84 (0·77 to 0·92)	0·82	0·76 (0·71 to 0·82)	0·0015
ARR	20·0 (12·1 to 27·8)	..	8·4 (4·7 to 12·2)	..	9·1 (6·4 to 11·8)	..	1·8 (–0·2 to 3·7)	..	2·8 (0·7 to 4·9)	..	2·8 (1·1 to 4·5)	..	4·5 (3·2 to 5·9)	..
All-cause death	0·71 (0·61 to 0·82)	<0·0001	0·78 (0·64 to 0·95)	0·014	0·73 (0·65 to 0·83)	0·46	0·93 (0·79 to 1·11)	0·43	0·94 (0·83 to 1·06)	0·29	0·94 (0·85 to 1·03)	0·99	0·85 (0·78 to 0·92)	0·021
ARR	7·9 (4·5 to 11·3)	..	2 (0·4 to 3·5)	..	2·5 (1·5 to 3·5)	..	0·3 (–0·5 to 1·1)	..	0·5 (–0·4 to 1·3)	..	0·5 (–0·2 to 1·2)	..	1·2 (0·6 to 1·7)	..

Interaction p value is the p value for test of interaction between trial and treatment effect. HR=hazard ratio. RR=rate ratio. ARR=absolute rate reduction per 100 patient-years. *Includes urgent visits for worsening heart failure as a hospitalisation equivalent. †The definition of cardiovascular death was that used in the original trials. ‡RR estimated using a negative binomial model due to missing data on time to recurrent hospitalisations in RALES.

Table 2: **Effect of mineralocorticoid receptor antagonist treatment on the prespecified efficacy outcomes in each of the trials**

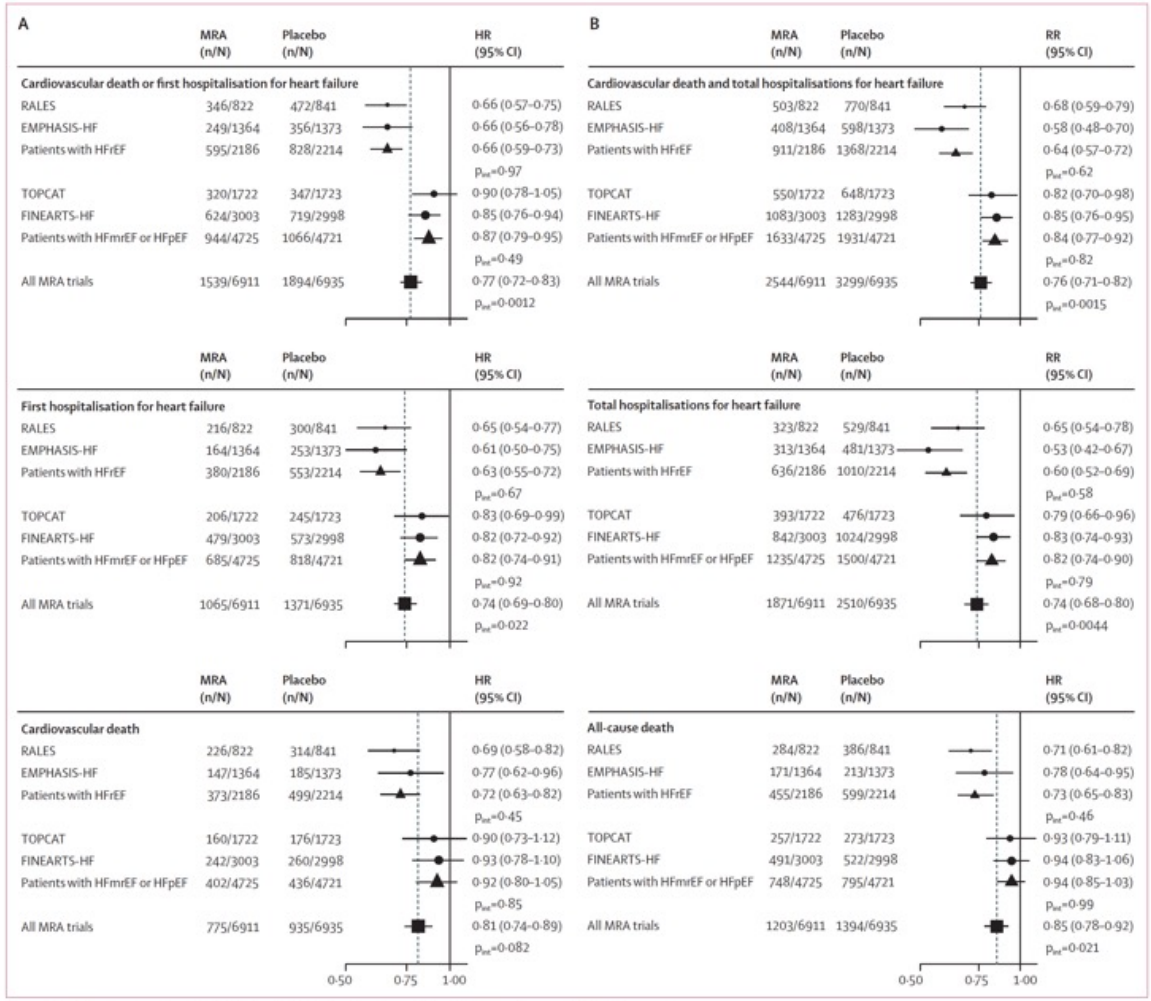
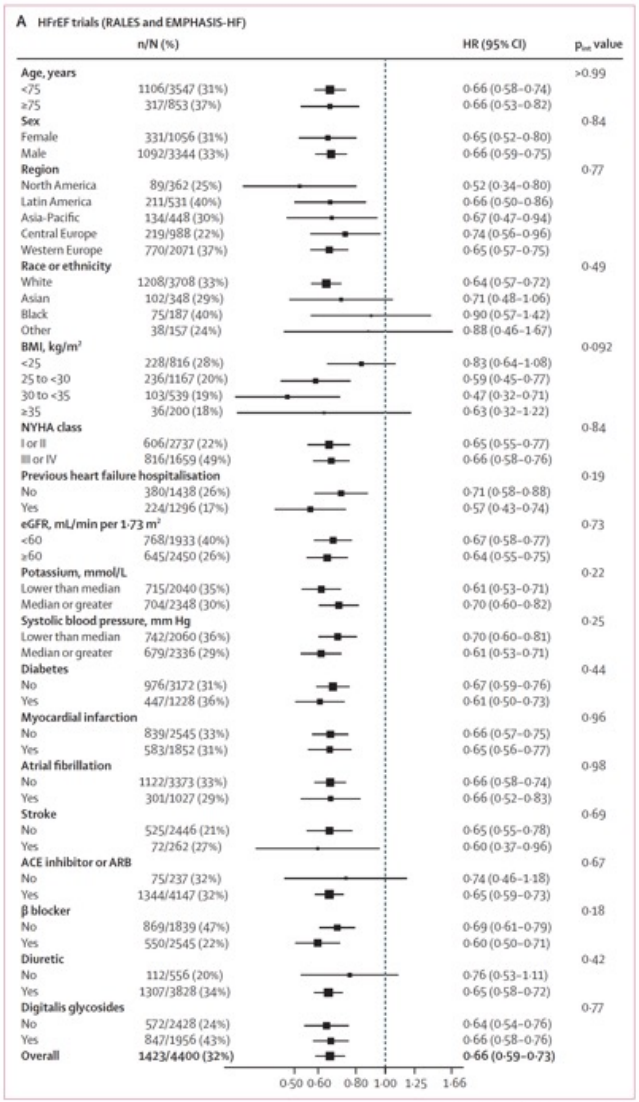


Figure 2: **Effect estimates from the individual patient level meta-analysis of MRAs and prespecified efficacy outcomes**

(A) Forest plots show cardiovascular death or hospitalisation for heart failure, heart failure hospitalisation, and cardiovascular death. (B) Forest plots show a composite of total heart failure hospitalisations and cardiovascular death, total (first and repeat) heart failure hospitalisations, and all-cause death. FINEARTS-HF included urgent visits for worsening heart failure as a hospitalisation equivalent. Estimates from the models in all four trials and split by HFrEF and HFmrEF or HFpEF trials, with p_{int} displayed. HFmrEF=heart failure and mildly reduced ejection fraction. HFpEF=heart failure and preserved ejection fraction. HFrEF=heart failure and reduced ejection fraction. HR=hazard ratio. MRA=mineralocorticoid receptor antagonist. p_{int}=p value for treatment-by-trial interaction. RR=rate ratio.



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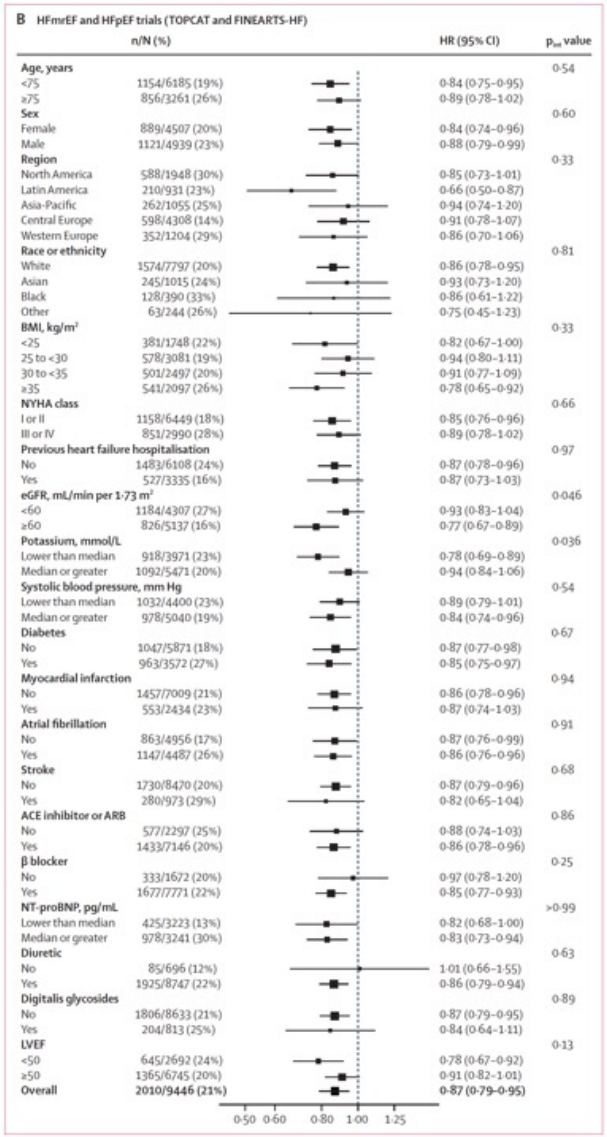


Figure 3: **Effect of mineralocorticoid receptor antagonist treatment on the composite of cardiovascular death or hospitalisation for heart failure (time-to-first-event analysis) in key subgroups**

(A) Combined RALES and EMPHASIS-HF trials. (B) Combined TOPCAT and FINEARTS-HF trials. FINEARTS-HF included urgent visits for worsening heart failure as a hospitalisation equivalent. ACE=angiotensin-converting enzyme. ARB=angiotensin receptor blocker. eGFR=estimated glomerular filtration rate. HFmrEF=heart failure and mildly reduced ejection fraction. HFpEF=heart failure and preserved ejection fraction. HFrEF=heart failure and reduced ejection fraction. HR=hazard ratio. LVEF=left ventricular ejection fraction. NT-proBNP=N-terminal pro B-type natriuretic peptide. NYHA=New York Heart Association. p_{int}=p value for treatment-by-trial interaction.

	RALES			EMPHASIS-HF			TOPCAT			FINEARTS-HF		
	Spirono-lactone group (n=822)	Placebo group (n=841)	OR (95% CI)	Eplerenone group (n=1360)	Placebo group (n=1369)	OR (95% CI)	Spirono-lactone group (n=1699)	Placebo group (n=1691)	OR (95% CI)	Finerenone group (n=2993)	Placebo group (n=2993)	OR (95% CI)
Hypotension												
Systolic blood pressure <90 mm Hg	79/776 (10%)	61/797 (8%)	1·24 (0·93–1·64)	71/1337 (5%)	53/1341 (4%)	1·36 (0·95–1·96)	65/1699 (4%)	33/1691 (2%)	2·00 (1·31–3·06)	146/2934 (5%)	95/2935 (3%)	1·57 (1·20–2·04)
Systolic blood pressure <100 mm Hg	215/776 (28%)	210/797 (26%)	1·07 (0·87–1·31)	261/1337 (20%)	209/1341 (16%)	1·31 (1·08–1·60)	267/1699 (16%)	188/1691 (11%)	1·49 (1·22–1·82)	556/2934 (19%)	374/2935 (13%)	1·60 (1·39–1·85)
Elevated serum creatinine												
≥2·5 mg/dL	70/779 (9%)	43/797 (5%)	1·73 (1·17–2·57)	28/1171 (2%)	22/1170 (2%)	1·28 (0·73–2·25)	101/1691 (6%)	55/1685 (3%)	1·88 (1·35–2·63)	167/2928 (6%)	110/2921 (4%)	1·55 (1·21–1·98)
≥3·0 mg/dL	30/779 (4%)	17/797 (2%)	1·84 (1·01–3·36)	9/1171 (1%)	11/1170 (1%)	0·82 (0·34–1·98)	42/1691 (2%)	24/1685 (1%)	1·76 (1·06–2·92)	77/2928 (3%)	45/2921 (2%)	1·73 (1·19–2·50)
Reduction in eGFR												
>20%	433/821 (53%)	330/840 (39%)	1·72 (1·42–2·10)	259/899 (29%)	222/922 (24%)	1·28 (1·04–1·57)	869/1652 (53%)	750/1650 (45%)	1·33 (1·16–1·53)	1676/2928 (57%)	1220/2921 (42%)	1·87 (1·68–2·07)
>30%	288/821 (35%)	189/840 (23%)	1·86 (1·50–2·31)	155/899 (17%)	99/922 (11%)	1·73 (1·32–2·27)	516/1652 (31%)	402/1650 (24%)	1·41 (1·21–1·64)	1033/2928 (35%)	642/2921 (22%)	1·94 (1·72–2·17)
Elevated serum potassium												
>5·5 mmol/L	127/779 (16%)	38/797 (5%)	3·89 (2·67–5·67)	158/1336 (12%)	96/1340 (7%)	1·74 (1·33–2·27)	198/1691 (12%)	92/1685 (5%)	2·30 (1·78–2·97)	426/2921 (15%)	207/2915 (7%)	2·23 (1·88–2·66)
>6·0 mmol/L	32/779 (4%)	9/797 (1%)	3·75 (1·78–7·91)	34/1336 (3%)	25/1340 (2%)	1·37 (0·81–2·32)	40/1691 (2%)	16/1685 (1%)	2·53 (1·41–4·53)	90/2921 (3%)	44/2915 (2%)	2·07 (1·44–2·99)
Reduced serum potassium												
<3·5 mmol/L	54/779 (7%)	149/797 (19%)	0·32 (0·23–0·45)	100/1336 (7%)	150/1340 (11%)	0·64 (0·49–0·84)	205/1691 (12%)	331/1685 (20%)	0·56 (0·47–0·68)	145/2921 (5%)	299/2915 (10%)	0·46 (0·37–0·56)

Data are n/N (%) unless otherwise specified. OR=odds ratio. eGFR=estimated glomerular filtration rate.

Table 3: **Effect of mineralocorticoid receptor antagonist treatment on the prespecified safety outcomes in each trial**

Research in context

Evidence before this study

Clinical practice guidelines give a strong recommendation (class I) for the use of mineralocorticoid receptor antagonists (MRAs) in heart failure and reduced ejection fraction (HFrEF) based on two large randomised trials. By contrast, guidelines give either a weak recommendation or no recommendation for MRAs in heart failure and mildly reduced ejection fraction (HFmrEF) or heart failure and preserved ejection fraction (HFpEF) because the steroidal MRA spironolactone did not show significant benefit in this population.

Added value of this study

We performed an individual patient level meta-analysis of four large, prospective placebo-controlled trials of MRAs in heart failure. This analysis included almost 14 000 patients and confirms the large benefit in patients with HFrEF. It also shows that MRAs reduce the risk of the composite of cardiovascular death or hospitalisation for heart failure in patients with heart failure and an ejection fraction of 40% or greater. The benefits were consistent across a broad range of subgroups.

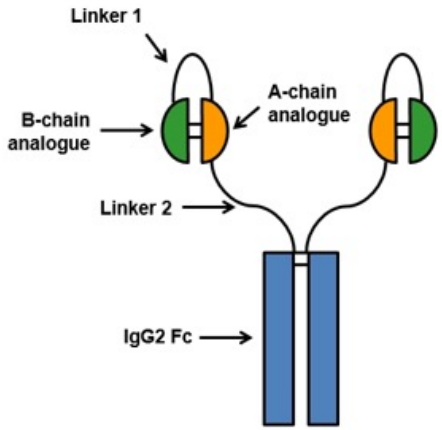
Implications of all the available evidence

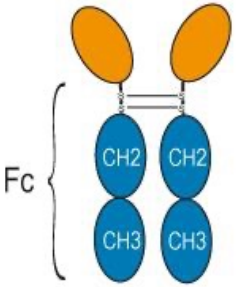
This individual patient level meta-analysis shows that steroidal MRAs reduce the risk of cardiovascular death or heart failure hospitalisation in patients with HFrEF and non-steroidal MRAs reduce this risk in HFmrEF or HFpEF, and it supports their use in patients without a contraindication to treatment.

Insulin efsitora alfa ist ein neuartiges Insulinanalogon, das von Eli Lilly zur Behandlung von Diabetes entwickelt wurde. In einer Phase-II-Studie wurde festgestellt, dass seine glykämische Kontrolle und Sicherheit mit Insulin degludec vergleichbar sind.

Background

- Weekly insulin efsitora alfa (basal insulin Fc, efsitora alfa [efsitora]) is an insulin receptor agonist that combines a novel single-chain insulin variant with a human immunoglobulin G2 fragment crystallisable domain
- Studies were designed to evaluate once-weekly efsitora vs. once-daily insulin degludec (iDeg) in randomised, parallel, open-label studies for 26 or 32 weeks





Fc=fragment crystallisable; Ig=immunoglobulin.

Once-weekly insulin efsitora alfa versus once-daily insulin degludec in adults with type 1 diabetes (QWINT-5): a phase 3 randomised non-inferiority trial

Summary

Background Insulin efsitora alfa (efsitora) is a once-weekly basal insulin. This phase 3 study aimed to assess the efficacy and safety of efsitora compared with insulin degludec (degludec) in adults with type 1 diabetes.

Methods This randomised, 52-week, parallel-design, open-label, treat-to-target non-inferiority study conducted at 82 global health-care centres, randomly assigned (1:1) adults (ie, those aged ≥18 years) with type 1 diabetes glycated haemoglobin A_{1c} (HbA_{1c}) 7·0–10·0% (53·0–85·8 mmol/mol) to efsitora (n=343) or, degludec (n=349), both in combination with insulin lispro. The primary endpoint was the change in HbA_{1c} from baseline to week-26 (non-inferiority margin=0·4%). The trial was registered at ClinicalTrials.gov (NCT05463744) and is completed.

Findings Between Aug 12, 2022, and May 7, 2024, of 893 participants enrolled, 692 (77%) participants were randomly assigned to once-weekly efsitora or once-daily degludec, and 623 (90%) participants completed the study. Mean HbA_{1c} decreased from 7·88% (62·66 mmol/mol) at baseline to 7·41% (57·5 mmol/mol) at week 26 with efsitora and from 7·94% (63·3 mmol/mol) at baseline to 7·36% (56·9 mmol/mol) at week 26 with degludec. Mean HbA_{1c} change from baseline to week 26 was –0·51% with efsitora and –0·56% with degludec (estimated treatment difference 0·052%, 95% CI –0·077 to 0·181; p=0·43), confirming a non-inferiority margin of 0·4% for efsitora compared with degludec. Rates of combined level 2 (<54 mg/dL [3·0 mmol/L]) or level 3 severe hypoglycaemia were higher with efsitora compared with degludec (14·03 *vs* 11·59 events per patient year of exposure; estimated rate ratio 1·21, 95% CI 1·04 to 1·41; p=0·016) during weeks 0–52, with the highest rates during weeks 0–12. Severe hypoglycaemia incidence was higher with efsitora (35 [10%] of 343) versus degludec (11 [3%] of 349) during weeks 0–52. Overall incidence of treatment-emergent adverse events was similar across treatment groups. One death not related to the study treatment occurred in the degludec group.

Interpretation In adults with type 1 diabetes, once-weekly efsitora showed non-inferior HbA_{1c} reduction compared with daily insulin degludec. Higher rates of combined level 2 or level 3 hypoglycaemia and greater incidence of severe hypoglycaemia in participants treated with efsitora compared with participants treated with degludec might suggest the need for additional evaluation of efsitora dose initiation and optimisation in people with type 1 diabetes.

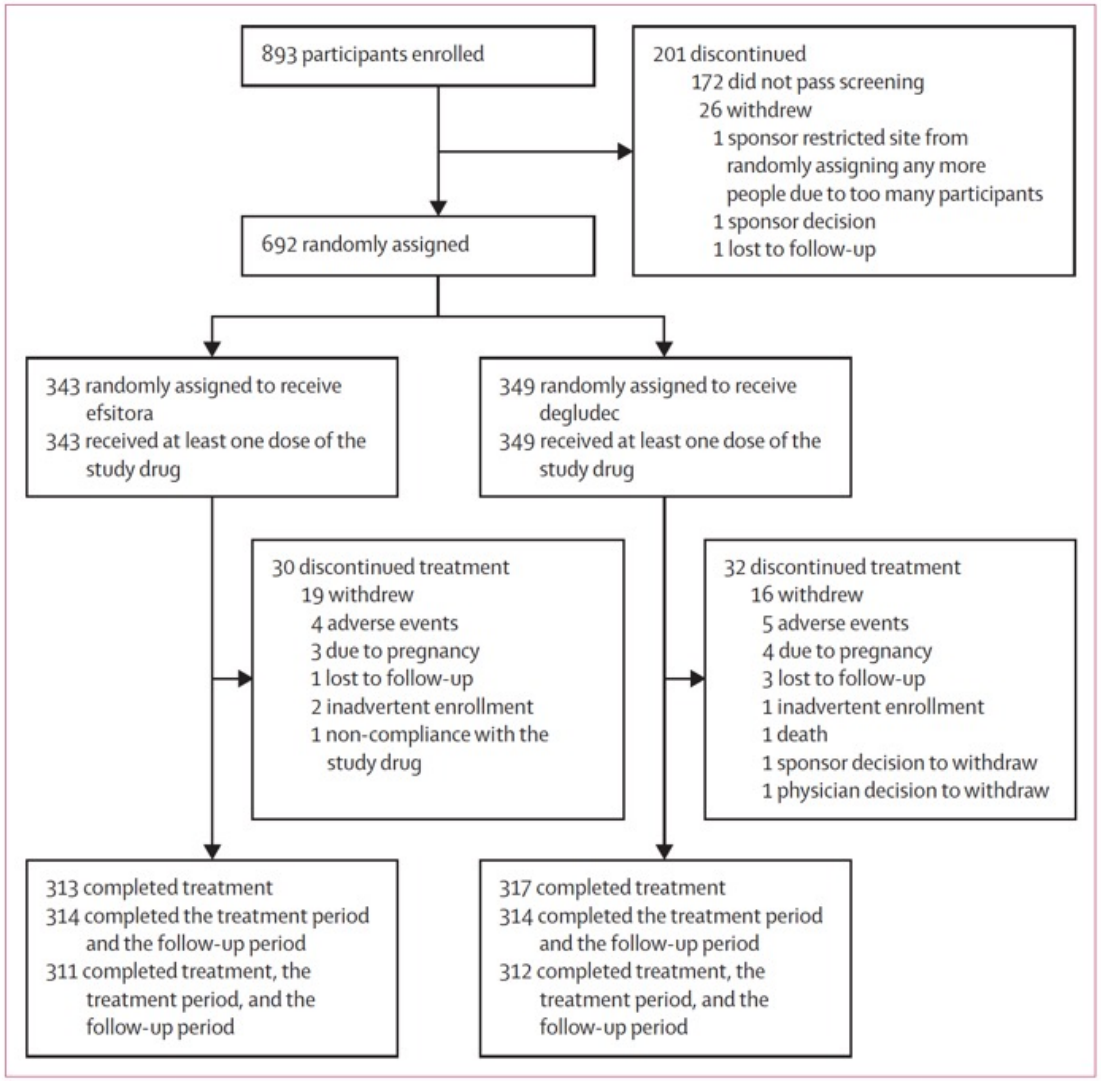


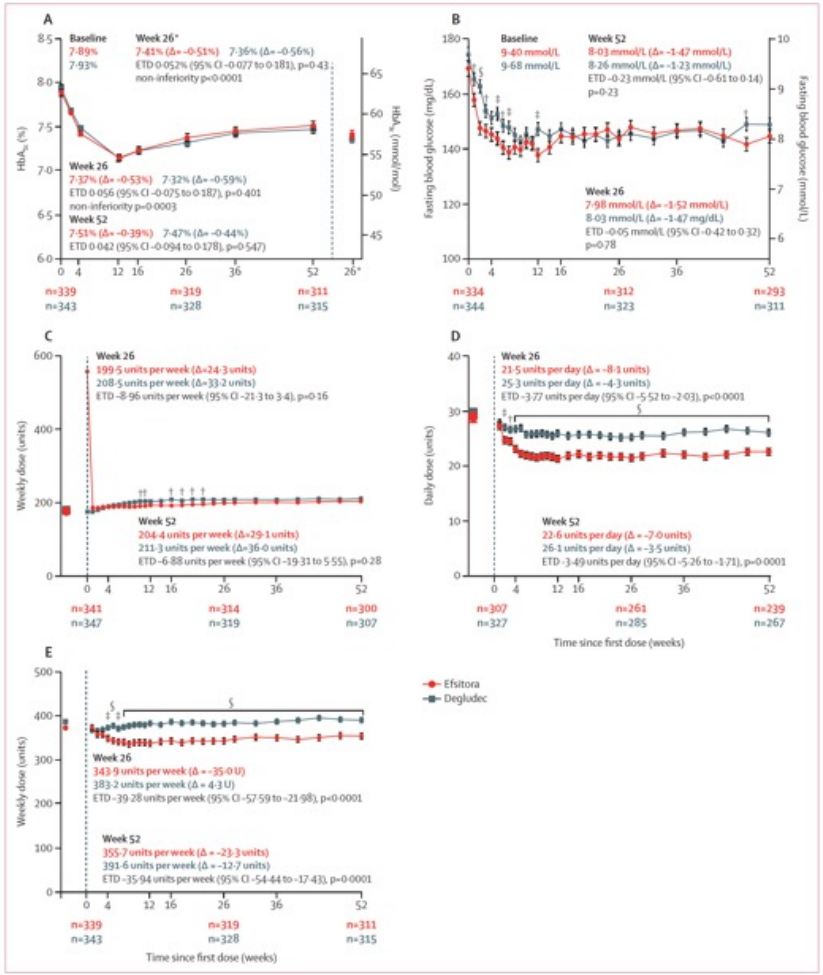
Figure 1: **Trial profile**

	Efsitora (n=343)	Degludec (n=349)	Overall (N=692)
Sex			
Female	150 (44%)	158 (45%)	308 (45%)
Male	193 (56%)	191 (55%)	384 (55%)
Age, years	44·4 (14·2)	43·6 (14·0)	44·0 (14·1)
Race			
American Indian or Alaska native	1 (<1%)	0	1 (<1%)
Asian	69 (20%)	73 (21%)	142 (21%)
Black or African American	11 (3%)	13 (4%)	24 (3%)
Native Hawaiian or other Pacific Islander	1 (<1%)	0	1 (<1%)
White	259 (76%)	262 (75%)	521 (75%)
Multiple	2 (1%)	1 (<1%)	3 (<1%)
Ethnicity			
Hispanic or Latin American	121 (35%)	116 (33%)	237 (34%)
Not Hispanic or Latin American	221 (64%)	230 (66%)	451 (65%)
Not reported	1 (<1%)	3 (1%)	4 (1%)
Weight, kg	76·2 (15·6)	74·8 (15·9)	75·5 (15·8)
BMI, kg/m²	26·5 (4·0)	25·9 (4·1)	26·2 (4·0)
Screening HbA_{1c}, %	8·18 (0·75)	8·20 (0·77)	8·19 (0·76)
Screening HbA_{1c}, mmol/mol	65·9 (8·2)	66·1 (8·5)	66·0 (8·4)
Baseline HbA_{1c}, %	7·88 (0·75)	7·94 (0·72)	7·91 (0·73)
Baseline HbA_{1c}, mmol/mol	62·7 (8·2)	63·3 (7·9)	63·0 (8·0)
Baseline fasting self-monitored blood glucose, mg/dL	163·8 (138·1–195·5)	165·4 (135·2–202·8)	164·5 (137·1–198·3)
Baseline fasting self-monitored blood glucose, mmol/L	9·1 (7·7–10·9)	9·2 (7·5–11·3)	9·1 (7·6–11·0)
Baseline fasting serum glucose, mg/dL	153·6 (113·0–205·0)	160·0 (118·0–214·0)	158·5 (115·0–208·0)
Baseline fasting serum glucose, mmol/L	8·5 (6·3–11·4)	8·9 (6·6–11·9)	8·8 (6·4–11·6)
Duration of diabetes, years	17·1 (10·1–26·9)	17·9 (11·1–26·9)	17·4 (10·9–26·9)
Pre-study basal insulin			
Insulin degludec	163 (48%)	157 (45%)	320 (46%)
Insulin glargine U100	127 (37%)	114 (33%)	241 (35%)
Insulin glargine U300	41 (12%)	61 (17%)	102 (15%)
Insulin detemir	12 (3%)	17 (5%)	29 (4%)
Previous continuous glucose monitoring use	118 (34%)	123 (35%)	241 (35%)
Carbohydrate counting for bolus insulin dosing	160 (47%)	165 (47%)	325 (47%)

Data are n (%), mean (SD), or median (IQR). HbA1c=glycated haemoglobin A1c.

Table 1: **Participant demographic and baseline characteristics**

Total insulin dose over time



Weekly bolus insulin dose over time

***Figure 2*: Key efficacy outcomes among participants who received once-weekly efsitora and once-daily degludec**

Analysis for efficacy estimand by mixed model for repeated measures. (A) Shows the HbA_{1c} level over time, least squares mean (SE) efficacy estimand. The dashed line separates the efficacy estimand data, from the week 26-only treatment regimen estimand results. (B) Shows the least squares mean (SE) fasting glucose as measured by self-monitored blood glucose over time (efficacy estimand). (C) Shows the least squares mean (SE) weekly basal insulin dose over time. The dashed line separates the mean baseline insulin dose from the study period. (D) Shows the least squares mean (SE) weekly bolus insulin dose over time. The dashed line separates the mean baseline insulin dose from the study period. (E) Shows the least squares mean (SE) weekly total insulin dose over time. The dashed line separates the mean baseline insulin dose from the study period. ETD=estimated treatment difference. HbA_{1c}=glycated haemoglobin A_{1c}. *Data represent the estimated least squares mean values from the treatment regimen estimand at week 26. †p<0·05, ‡p<0·01, and §p<0·001 versus degludec and the solid line with the footnote above it indicate the data points below the solid line all have that level of significance.

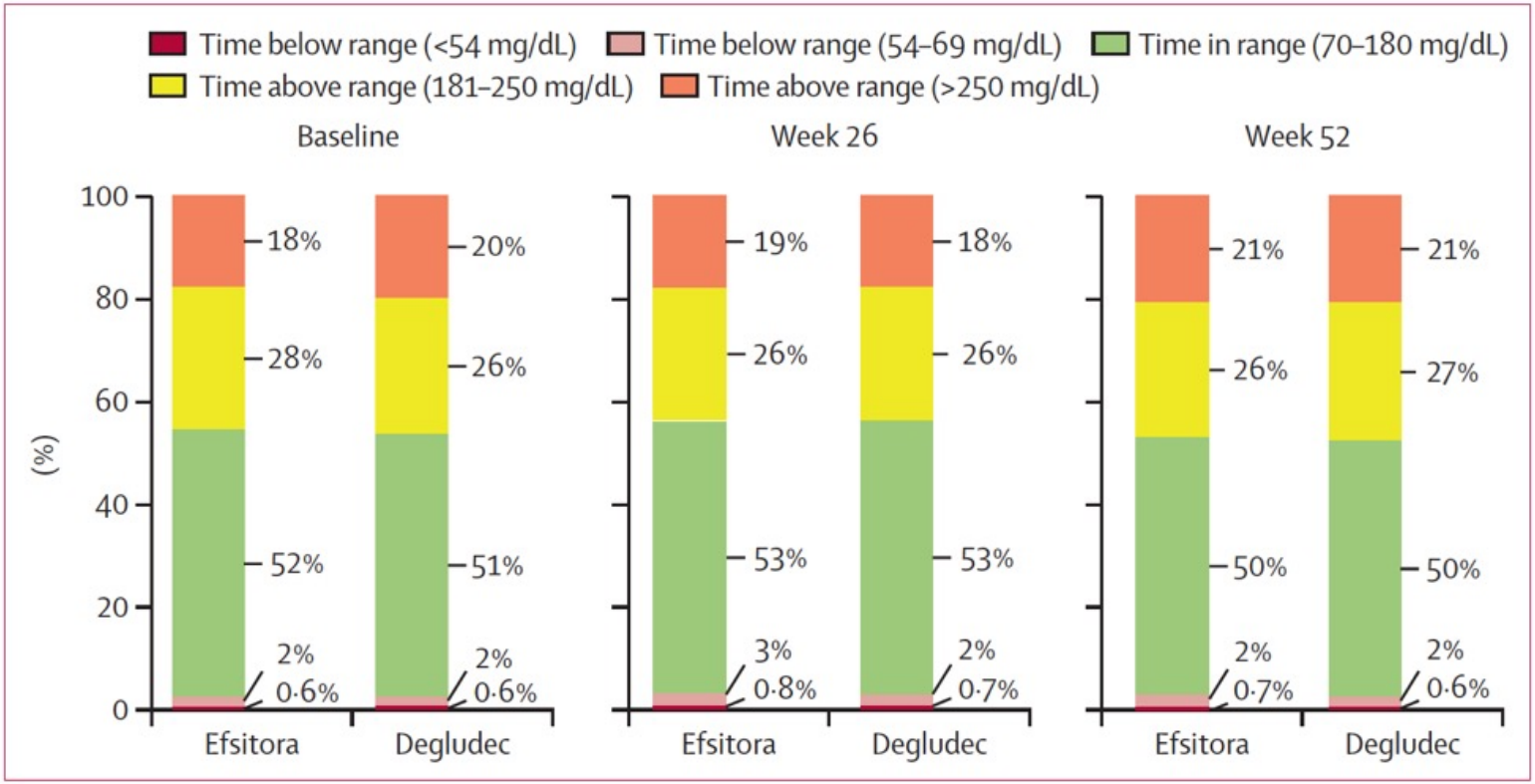


Figure 3: **Continuous glucose monitoring metrics**

Figure shows continuous glucose monitoring metrics at baseline, week 26, and week 52 for efsitora and degludec (efficacy estimand).

	Efsitora (n=343)		Degludec (n=349)		Efsitora *vs* Degludec
	Participants, n (%)	Episodes (rate per patient-year exposure)	Participants, n (%)	Episodes (rate per patient-year exposure)	Estimated relative rate (95% CI); p value
Hypoglycaemic episodes (overall)					
Level 1 hypoglycaemia					
Week 0–26	339 (99%)	7474 (46·04)	333 (95%)	6586 (39·13)	1·18 (1·05–1·32); p=0·0055
Week 0–52	340 (99%)	12 299 (39·19)	337 (97%)	11 122 (33·99)	1·15 (1·03–1·29); p=0·016
Combined level 2 or level 3 severe hypoglycaemia					
Week 0–26	293 (85%)	2662 (17·19)	289 (83%)	2319 (14·06)	1·22 (1·04–1·43); p=0·013
Week 0–52	305 (89%)	4175 (14·03)	306 (88%)	3740 (11·59)	1·21 (1·04–1·41); p=0·016
Level 3 severe hypoglycaemia					
Week 0–26	28 (8%)	35 (0·21)	9 (3%)	11 (0·06)	3·23 (1·42–7·38); p=0·0052
Week 0–52	35 (10%)	44 (0·14)	11 (3%)	13 (0·04)	3·44 (1·64–7·19); p=0·0011
Hypoglycaemic episodes (nocturnal)					
Level 1 hypoglycaemia					
Week 0–26	233 (68%)	844 (5·23)	219 (63%)	881 (5·13)	1·02 (0·83–1·25); p=0·86
Week 0–52	262 (76%)	1468 (4·68)	246 (70%)	1495 (4·48)	1·04 (0·85–1·28); p=0·68
Combined level 2 or level 3 severe hypoglycaemia					
Week 0–26	149 (43%)	388 (2·38)	147 (42%)	404 (2·39)	1·00 (0·76–1·30); p=0·97
Week 0–52	182 (53%)	630 (1·99)	181 (52%)	647 (1·96)	1·02 (0·79–1·31); p=0·90
Hypoglycaemic episodes (non-nocturnal)					
Level 1 hypoglycaemia					
Week 0–26	337 (98%)	6630 (40·66)	331 (95%)	5705 (34·16)	1·19 (1·06–1·34); p=0·0038
Week 0–52	339 (99%)	10 831 (34·36)	336 (96%)	9627 (29·71)	1·16 (1·03–1·30); p=0·016
Combined level 2 or level 3 severe hypoglycaemia					
Week 0–26	284 (83%)	2274 (14·59)	282 (81%)	1915 (11·35)	1·28 (1·09–1·52); 0·0030
Week 0–52	299 (87%)	3545 (11·81)	296 (85%)	3093 (9·43)	1·26 (1·08–1·49); 0·0044

Level 1 hypoglycaemia was defined as a glucose reading of ≥54 mg/dL and <70 mg/dL (3·0–3·9 mmol/L) from a blood glucose meter. Level 2 hypoglycaemia was defined as a glucose reading of <54 mg/dL (3·0 mmol/L) from a blood glucose meter. Level 3 hypoglycaemia was characterised by altered mental or physical status requiring assistance from another person for the treatment of hypoglycaemia. Nocturnal hypoglycaemia was between 0000 h and 0600 h and non-nocturnal hypoglycaemia was between 06:00 and midnight.

Table 2: **Hypoglycaemia**

Research in context

Evidence before this study

On May 9, 2024, we searched PubMed using the search terms "once-weekly basal insulin" OR "insulin efsitora alfa" AND "type 1 diabetes" for any articles published between Jan 1, 2000, and June 25, 2024. The search results included research articles detailing the pharmacokinetic and pharmacodynamic properties of insulin efsitora alfa (efsitora) and insulin icodec (icodec), the design of the phase 3 clinical development programme for efsitora, and the results from three phase 2 studies investigating the efficacy and safety of efsitora in adults with type 1 or type 2 diabetes. The search results included one phase 3 study investigating the efficacy and safety of icodec in adults with type 1 diabetes. A preclinical study and a phase 1 trial reported that the half-life of efsitora is 17 days with a 1·14 peak-to-trough insulin ratio over the course of the week. The phase 2 trials in people with type 1 diabetes or people with type 2 diabetes (insulin naive and those previously treated with basal insulin) showed comparable glycaemic control, as measured by glycated haemoglobin A_{1c} (HbA_{1c}), between efsitora and insulin degludec. In people who were insulin naive with type 2 diabetes or type 1 diabetes, the rate of hypoglycaemia was similar for efsitora and degludec. A lower rate of hypoglycaemia was shown in people with type 2 diabetes previously treated with basal insulin with efsitora compared with degludec. The phase 3 clinical development programme for efsitora, once-weekly insulin therapy (QWINT), was designed to evaluate efsitora treatment in people with diabetes across a diverse population.

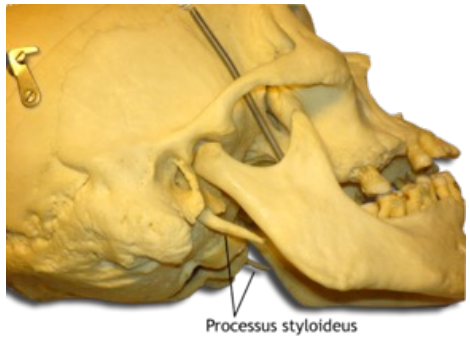
Added value of this study

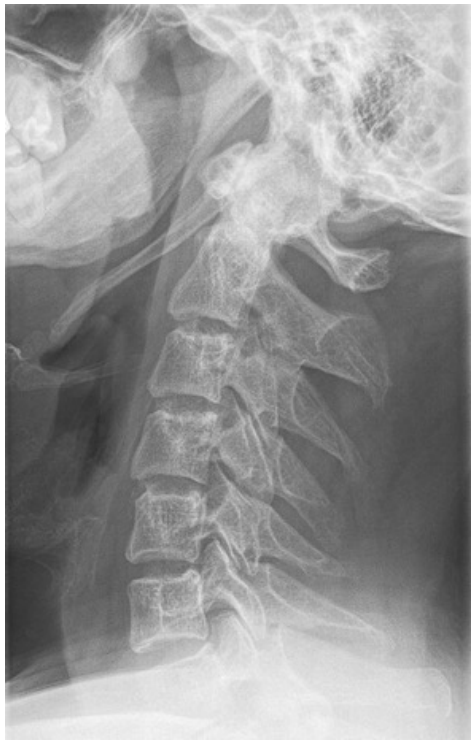
QWINT-5 is the only phase 3 clinical trial of the QWINT programme to evaluate the efficacy and safety of once weekly efsitora in combination with a bolus insulin (insulin lispro) in adults (ie, those aged 18 years and older) with type 1 diabetes. The phase 2 study of insulin efsitora in people with type 1 diabetes showed non-inferior HbA_{1c} reduction compared with insulin degludec without increased combined level 2 (<54 mg/dl [3·0 mmol/l) or level 3 hypoglycaemia over 26 weeks of treatment, but with statistically significantly higher HbA_{1c} and fasting glucose than degludec. Thus, a new dosing approach was implemented in the QWINT-5 study based on the phase 2 results to balance glycaemic efficacy with hypoglycaemia risk. In QWINT-5, efsitora compared with degludec treatment showed comparable improvement in HbA_{1c} and fasting glucose, with a higher rate of combined level 2 (<54 mg/dL [3·0 mmol/L]) or level 3 severe hypoglycaemia during the 52-week treatment period.

Implications of all the available evidence

ONWARDS 6 is the only published phase 3 study of a weekly insulin in people with type 1 diabetes. It showed that icodec was non-inferior to degludec in glycaemic control with an increased rate of combined level 2 or level 3 hypoglycaemia in participants receiving icodec. This randomised controlled trial in adults with type 1 diabetes showed non-inferior glycaemic control of efsitora compared with degludec. The rate of combined level 2 or level 3 hypoglycaemia was higher with efsitora versus degludec. There are inherent challenges in managing glucose levels while mitigating hypoglycaemia with weekly basal insulin, particularly in people with type 1 diabetes. Further evaluation of efsitora dose initiation and optimisation of basal-bolus insulin in type 1 diabetes might be needed, using this data together with the phase 2 trial data. This study highlights the possibility of a once-weekly basal insulin that could reduce patient burden and improve treatment adherence.

Das Eagle Syndrom kann entstehen wenn der Griffelfortsatz, der sogenannte Processus styloideus des Schläfenbeins (Os temporale) verlängert ist oder das Verbindungsband (Ligamentum stylohyoideum) zwischen dem Fortsatz und dem Zungenbein (Os hyoideum) verknöchert ist.



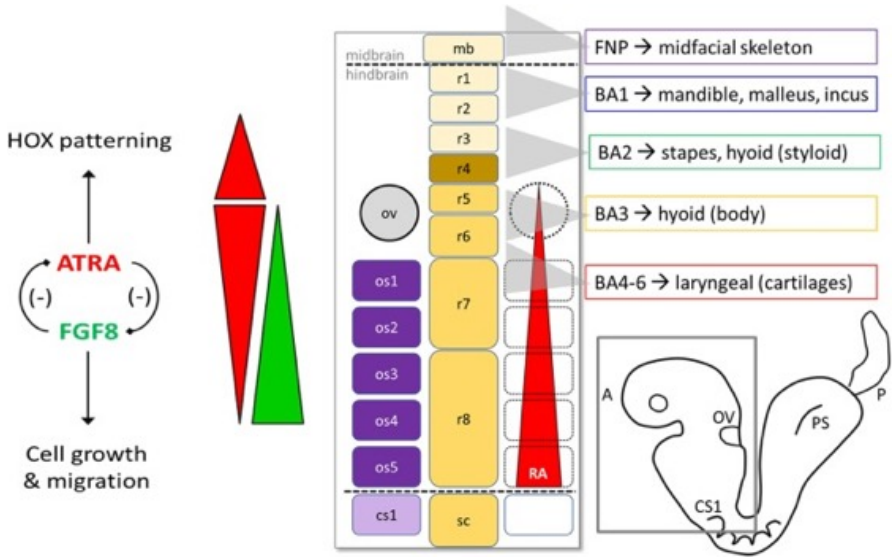


- unklare Halsschmerzen (41 %)
- Fremdkörpergefühl (Globussyndrom)
- Schmerzen im Rachen
- Benommenheit
- Tinnitus
- Palpationsschmerz in der Fossa tonsillaris
- Schwindel
- Beschwerden mit oder ohne Schmerzen beim Schlucken (Dysphagie/Odynophagie)
- Schmerzen bei Bewegung des Kopfes/Halses.
- Atypischer Gesichtsschmerz

Therapeutisch werden konservative Maßnahmen mit Kortikoidinjektionen in die Tonsillenloge, Neuroleptika oder bei therapierefraktären Beschwerden die Reduktionsplastik des Processus styloideus eingesetzt. Die einfache Schmerztherapie versagt meist.

The main skeletal adverse reaction of retinoids is hyperostosis. It mainly occurs with protracted treatments and high dosages, and its incidence may exceed 80% after a few years of administration.

All-trans retinoic acid (ATRA), the biologically active form of vitamin A, is instrumental in regulating the patterning and specification of the vertebrate embryo. Various animal models demonstrate adverse developmental phenotypes following experimental retinoid depletion or excess during pregnancy. Windows of vulnerability for altered skeletal patterning coincide with early specification of the body plan (gastrulation) and regional specification of precursor cell populations forming the facial skeleton (cranial neural crest), vertebral column (somites), and limbs (lateral plate mesoderm) during organogenesis. A common theme in physiological roles of ATRA signaling is mutual antagonism with FGF signaling. Consequences of genetic errors or environmental disruption of retinoid signaling include stage- and region-specific homeotic transformations to severe deficiencies for various skeletal elements.



Progressive cervical osteophytosis and dysphagia associated with isotretinoin treatment for rosacea

A 52-year-old builder with a 6-year history of neck pain and dysphagia was referred to our rheumatology unit by a spinal neurosurgeon who was concerned the patient might have axial spondyloarthritis.

A review of the patient's history found that at age 45 years, he had been referred to the spinal surgeons; an x-ray and CT scan of the cervical spine showed osteophytosis at C5-C7 (figure). The radiologist had noted elongation of the styloid processes and calcification of the stylohyoid ligaments, suggestive of Eagle's syndrome.

Aged 47 years, new osteophytosis within mid and lower cervical spine were noted after the patient had a work-related injury.

Aged 50 years, the patient had been referred to both the neurosurgeons due to persistent neck symptoms, and to the Ear, Nose, and Throat (ENT) department because of ongoing dysphagia. The conclusion at that time was that the main reason for his dysphagia was laryngospasm and that his cervical osteophytosis was unlikely to be a contributing factor.

Additionally, the patient had a history of long-standing rosacea and folliculitis, a metallic heart valve, hypertension, a stroke, and gout; he was prescribed medication which included warfarin, atorvastatin, bisoprolol, allopurinol, and isotretinoin. The prescription of isotretinoin, which had been started 13 years earlier to treat the rosacea, necessitated the patient remaining under the care of the dermatology department. He was an ex-smoker.

On examination, we found the patient to be well; his BMI was 29·0 kg/m² (typical range 18·5–24·9), his blood pressure was 142/82 mm Hg, and he had limited movement in his cervical spine, brisk reflexes, and some paraesthesia, which we considered to be related to his previous stroke. The patient had reduced movement in his left hip—consistent with advanced osteoarthritis. He had no skin rashes or peripheral synovitis.

Laboratory investigations found a typical C-reactive protein concentration (<0·5 mg/dL; normal range 0·3–1·0), total vitamin D concentration of 85 nmol/L (typical range 50–100), alkaline phosphatase concentration of 79 IU/L (typical range 30–130), parathyroid hormone concentration of 7·2 pmol/L (typical range 1·5–7·6), HbA_{1c} concentration of 35 mmol/mol (typical range 20–41), estimated glomerular filtration rate of 82 mL/min/1·73 m², and triglycerides concentration of 1·2 mmol/L (typical range <2·3). Testing for HLA-B27 was negative.

A review of previous x-rays showed progressive ossification of the patient's cervical spine, which impinged on adjacent soft-tissue structures—including the oesophagus (figure). An MRI confirmed multi-level spinal ossification consistent with a degenerative, rather than an inflammatory process; no evidence of axial spondyloarthritis or radiographic axial spondyloarthritis—which is also termed ankylosing spondylitis—was seen.

Furthermore, even though our patient had features of the metabolic syndrome—associated with diffuse idiopathic skeletal hyperostosis—the relatively young age at which his symptoms began, and the speed of progression of the symptoms indicated an alternative diagnosis. Considering the x-ray and MRI findings together with the absence of any markers of inflammation—ruling out diagnoses of axial spondyloarthritis or any other inflammatory arthropathies—and the history of isotretinoin treatment, we concluded the patient had retinoid-induced diffuse skeletal hyperostosis. We recommended that the isotretinoin was stopped, and the patient was again referred to the spinal surgeons for consideration of surgery to improve his dysphagia. At follow-up aged 53 years the patient was seen again by the ENT and spinal neurosurgeons and was listed for excision of his cervical osteophytosis.

Arthralgia and new bone formation have been recognised as side-effects of isotretinoin since it was first licensed for treatment of disorders of keratinisation—including severe cystic acne. Osteophytes involving the anterior margin of the cervical vertebrae may cause dysphonia, dyspnoea, or dysphagia. Clinicians need to be aware that the effects of retinoid-associated skeletal toxicity can be seen within 6 months of initiating treatment—although prompt withdrawal of the drug can prevent irreversible ossification.

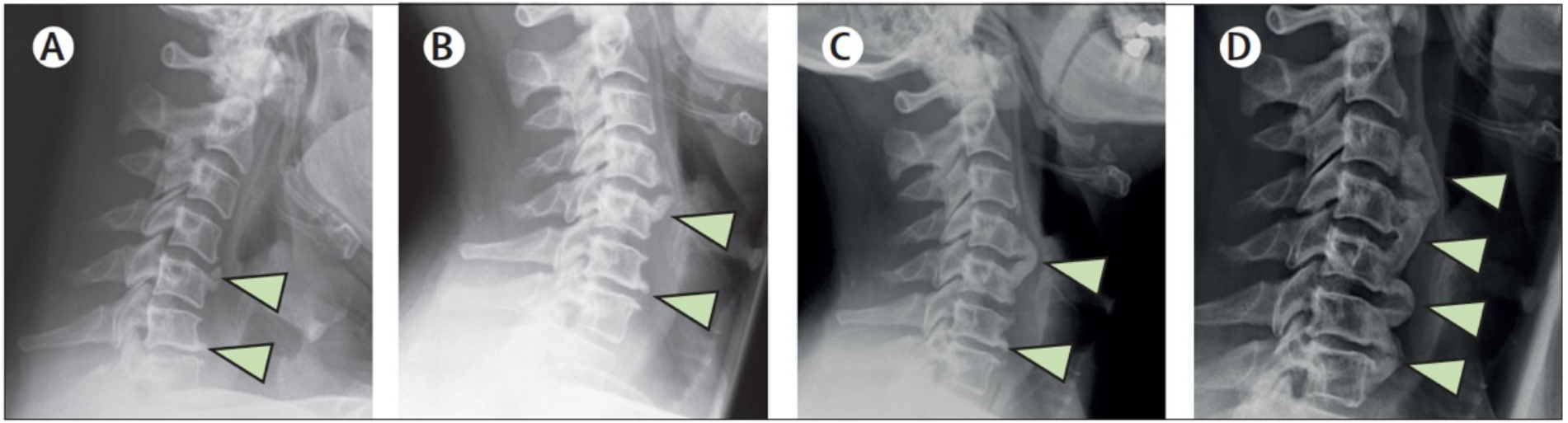
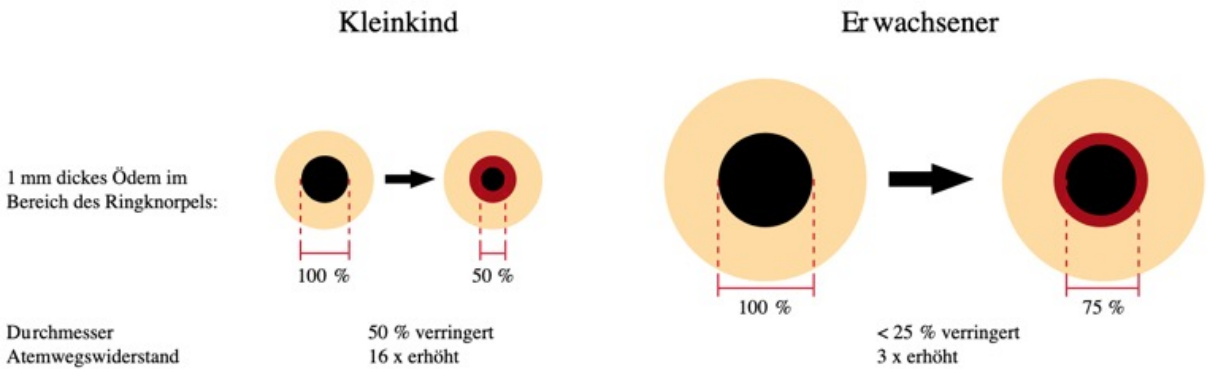


Figure: **Progressive cervical osteophytosis and dysphagia associated with isotretinoin treatment for rosacea**
Serial x-rays of the lateral view of the patient's cervical spine show progressive anterior vertebral bodies bridging new bone formation (arrows) progressing over time from ages 45 years (A), 47 years (B), 49 years (C), and 52 years (D) before presentation at our clinic.

Als Pseudokrupp oder Pseudocroup wird eine unspezifische Entzündung der oberen Atemwege im Bereich des Kehlkopfes unterhalb der Stimmritze bezeichnet, die durch einen charakteristischen bellenden Husten, Heiserkeit und bei schweren Verläufen auch Atemnot geprägt ist. Pseudokrupp tritt meist infolge viraler Infektionen auf. Die häufigsten Erreger sind Parainfluenza-(meist Typ 1), Influenza-(Typ A oder B), RS-, Rhino-, Adeno- und Metapneumoviren, gelegentlich auch Masern-, Windpocken-, Herpes-simplex und Epstein-Barr-Viren. Eine Studie aus dem Jahr 2022 aus den USA ergab, dass auch die Omikron-Variante des SARS-CoV-2-Virus insbesondere bei Kindern Pseudokrupp auslösen könnte. Negativ können sich starke Luftverschmutzung, Witterungseinflüsse und passives Rauchen auswirken, wobei dies keine ursächlichen Faktoren sind.

Gesetz von Hagen-Poiseuille ist hier gültig



Respiratory Syncytial Virus 2024 1

Severe respiratory syncytial virus infection in children: burden, management, and emerging therapies

The global burden of respiratory syncytial virus (RSV) lower respiratory tract infection (LRTI) in young children is high. The RSV prevention strategies approved in 2023 will be essential to lowering the global disease burden. In this Series paper, we describe clinical presentation, burden of disease, hospital management, emerging therapies, and targeted prevention focusing on developments and groundbreaking publications for RSV. We conducted a systematic search for literature published in the past 15 years and used a non-systematic approach to analyse the results, prioritising important papers and the most recent reviews per subtopic. Annually, 33 million episodes of RSV LRTI occur in children younger than 5 years, resulting in 3·6 million hospitalisations and 118 200 deaths. RSV LRTI is a clinical diagnosis but a clinical case definition and universal clinical tool to predict severe disease are non-existent. The advent of molecular point-of-care testing allows rapid and accurate confirmation of RSV infection and could reduce antibiotic use. There is no evidence-based treatment of RSV, only supportive care. Despite widespread use, evidence for high-flow nasal cannula (HFNC) therapy is insufficient and increased paediatric intensive care admissions and intubation indicate the need to remove HFNC therapy from standard care. RSV is now a vaccine-preventable disease in young children with a market-approved long-acting monoclonal antibody and a maternal vaccine targeting the RSV prefusion protein. To have a high impact on life-threatening RSV infection, infants at high risk, especially in low-income and middle-income countries, should be prioritised as an interim strategy towards universal immunisation. The implementation of RSV preventive strategies will clarify the full burden of RSV infection. Vaccine probe studies can address existing knowledge gaps including the effect of RSV prevention on transmission dynamics, antibiotic misuse, the respiratory microbiome composition, and long-term sequalae.

Key messages

- Severe respiratory syncytial virus (RSV) disease presents as three age-related clinical syndromes (sepsis in neonates, bronchiolitis in infants, and pneumonia in young children) but cannot be clinically distinguished from other respiratory illnesses without viral testing
- The worldwide burden of RSV is inequitably distributed, with the majority of life-threatening disease occurring in low-income and middle-income countries (LMICs; figure 1). All children are infected with RSV; approximately 5% develop RSV lower respiratory tract infection, 0·4% are hospitalised, and 0·02% die (figure 2)
- A substantial proportion (16%) of infants with life-threatening RSV infection have severe comorbidities, even if the majority of infants with severe RSV are term and previously healthy
- There is no treatment for RSV and hospital management consists of supportive care; high-flow nasal cannula therapy has been widely implemented for respiratory support despite insufficient evidence of efficacy against life-threatening disease
- Prevention is key for RSV as antivirals are not yet available; RSV should be considered a vaccine-preventable disease for all infants globally; high-risk groups, especially in LMICs, should be prioritised as an interim strategy on the road to universal immunisation
- The effect of RSV prevention on RSV transmission dynamics, antibiotic misuse, the respiratory microbiome composition, and long-term respiratory sequalae are crucial knowledge gaps (panel)

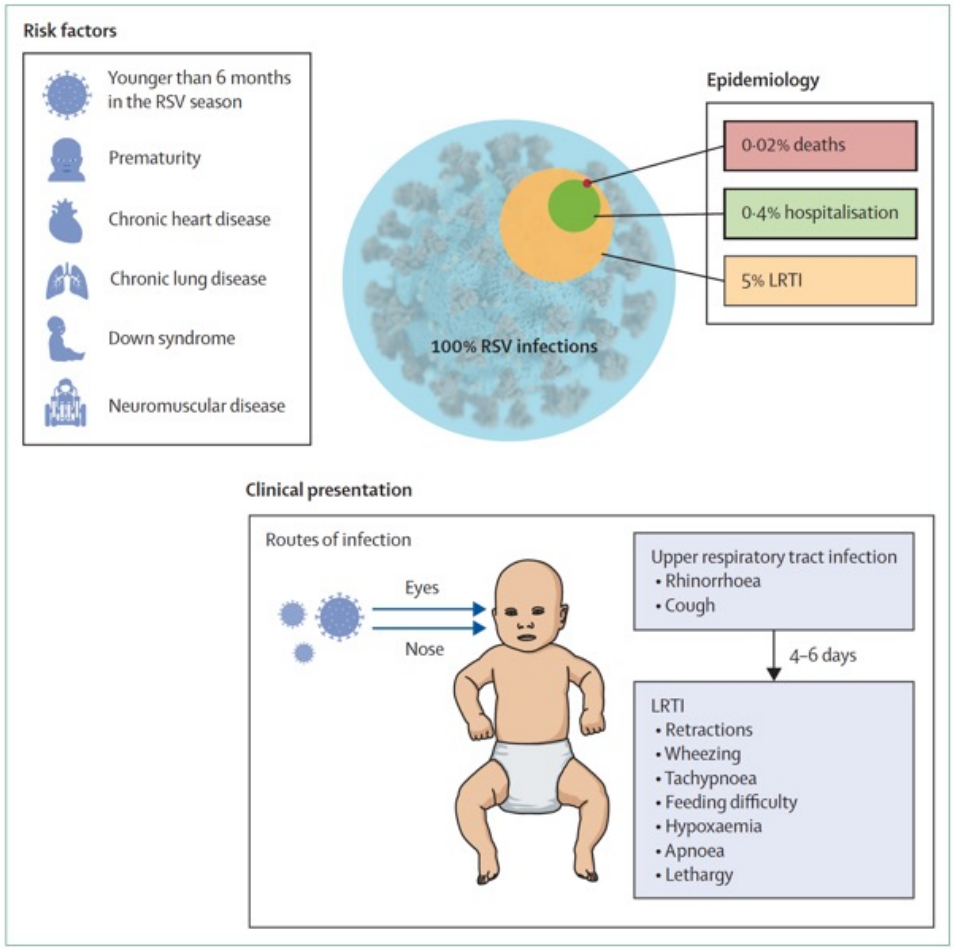


Figure 2: **Global epidemiology of severe RSV infection among children younger than 5 years**
Global epidemiology of severe RSV according to global burden estimates in 2019: all children are infected with RSV,[21] 33 million (5%) of 690 million children younger than 5 years have RSV LRTI,[27] 3 million (0·4%) are hospitalised, and 118 200 (0·02%) children die from RSV LRTI.[1] RSV infects primarily through the nose, but also through the eyes.[28] There are well defined risk factors for severe RSV disease. Figure was created using Piktochart. LTRI=lower respiratory tract infection. RSV=respiratory syncytial virus.

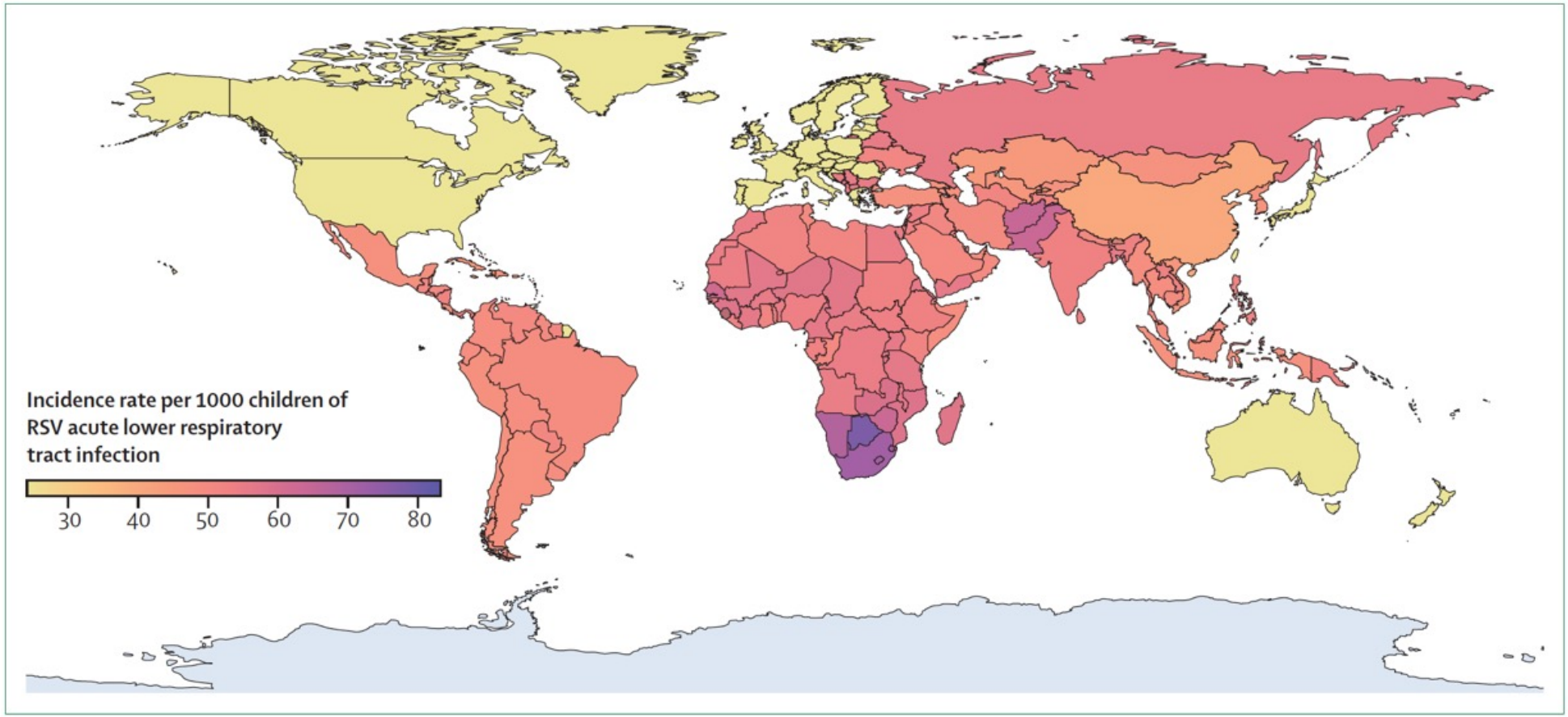


Figure 1: **Heat map of incidence rate estimates of RSV acute lower respiratory infection per 1000 children for children younger than 5 years in 2019**
Data from the latest global burden estimates for RSV was used to make a heat map of global incidence of RSV acute lower respiratory tract infection (data for 137 LMICs were available).[1] A scale of colours was used to show higher (purple) and lower (yellow) incidence. Country-specific incidence rates estimates were used if available. If country-specific data were not available, incidence for countries classified by World Bank income regions was used (ie, low income, lower-middle income, upper-middle income, and high income) and the aggregate value for the region was used. Ploty.js software was used to make the world map. RSV=respiratory syncytial virus.

	Parameters	Designed for RSV	Target population	Outcome used to test the score	Study done to test or create the score	Model building method reported	Model performance and validation	User	Setting	Tested in LMICs	Comments
Wang Bronchiolitis Severity Score[39-41]	RR, retractions, wheezing, general condition	No	Younger than 24 months	Pulse oximetry	Cross-sectional study	No	Observer agreement	Physicians	Outpatient	Yes, Türkiye	Low performance and reliability
Modified Tal Score[42,43]	SpO2, RR, wheeze, accessory respiratory muscle use	No	Younger than 12 months	Supplementary oxygen	Randomised clinical trial	No	Reliability, ROC	Physicians	Outpatient	No	No prediction oxygen therapy
ReSVinet Score[38]	Feeding tolerance, medical intervention, respiratory difficulty, RR, apnoea, general condition, fever	No	Healthy, younger than 24 months	Wood-Downes Score, length of stay, PICU, treatments	Retrospective and prospective study	No	Cronbach's coefficient, reliability, ROC, external validation	Physicians and parents	Outpatient and inpatient	Yes, datasets from Colombia and Rwanda	Externally validated for RSV
Modified respiratory index score[44,45]	RR, retractions, wheezing, mental status	No	Younger than 24 months, less than four wheezing episodes	>2 days hospital stays, oxygen therapy, intravenous hydration	Prospective observational study	No	ROC, sensitivity analysis, positive and negative predictive values, external validation	Physicians	Inpatient	No	Low performance and reliability
Bronchiolitis Score of Sant Joan de Deu[42,46]	SpO2, heart rate, RR, wheeze, indrawing, air entry	No	Healthy, younger than 24 months	PICU, length of stay, mortality	Prospective observational study	No	Cronbach's coefficient, intraclass correlation coefficient reliability, ROC	Physicians	Inpatients	No	Evaluation of both validity and reliability
Global Respiratory Severity Score[41,42,47]	Appearance, wheezing, rales, retractions, cyanosis, lethargy, poor air movement, RR, SpO2 movement	Yes	Healthy, term, younger than 10 months	Length of stay	Prospective cohort study	Missing values imputation, factor analysis, likelihood ratio, logistic regression	ROC, correlation with length of stay, external validation	Physicians	Outpatient and inpatient	No	Internal consistency
Bronchiolitis Severity Score[48,49]	RR, retractions, dyspnoea, auscultation	No	Children with asthma, bronchiolitis or wheezing	Not specified	Retrospective and prospective study	No	Reliability, ROC	Physicians	Outpatient	Yes, India	Low performance and reliability
Escala de Severidad de la Bronquiolitis Aguda[42,50,51]	Wheezing, crackles, breathing effort, inspiratory to expiratory ratio, RR, heart rate	No	Healthy, term, younger than 12 months	Bronchiolitis severity (home, ward, PICU)	Cross-sectional study	No	Cronbach's coefficient, factor analysis, reliability	Physicians	Outpatient and inpatient	No	Internal consistency

Scores used or developed for asthma were excluded. The most frequently studied clinical severity scores according to a 2024 review[39] were all included in the table. LMICs=low-income and middle-income countries. PICU=paediatric intensive care unit. ROC=receiver operating characteristic curve. RR=respiratory rate. RSV=respiratory syncytial virus. SpO2=pulse oxygen saturation.

Table: **Overview and evidence summary for severity scoring in lower respiratory tract illnesses**

Panel: Respiratory syncytial virus major new insights and remaining knowledge gaps

Major new insights in the past 15 years

- The majority of life-threatening respiratory syncytial virus (RSV) infection occurs in low-income and middle-income countries (LMICs) and more than 70% of RSV deaths occur out of the hospital
- Infants younger than 6 months at the start of the RSV season are at the highest risk of death
- Insights into the structure of the surface RSV fusion protein have allowed an understanding of neutralising antibodies and have been the key to successful RSV vaccine development
- RSV is now a vaccine-preventable disease as new preventive interventions have been approved and implemented in several countries
- Initial real-world effectiveness data of RSV preventive monoclonal antibodies show high coverage and efficacy

Remaining knowledge gaps

- Burden: the global burden of RSV-associated paediatric intensive care unit admissions, community deaths, and severe disease in LMICs need to be further quantified to facilitate implementation of RSV vaccines; little is known about the burden of RSV during the neonatal period
- Management: further validation of a clinical severity score is needed to guide global uniformity in assessment of the severity of RSV infection; efficacy of widely implemented high-flow nasal cannula against clinical outcomes of RSV infection needs to be studied
- Vaccine impact: vaccine probe studies can allow assessment of the effect of new RSV prevention on secondary outcomes such as community mortality, all-cause lower respiratory tract infection, RSV transmission, antibiotic misuse, long-term respiratory sequelae, and the respiratory microbiome

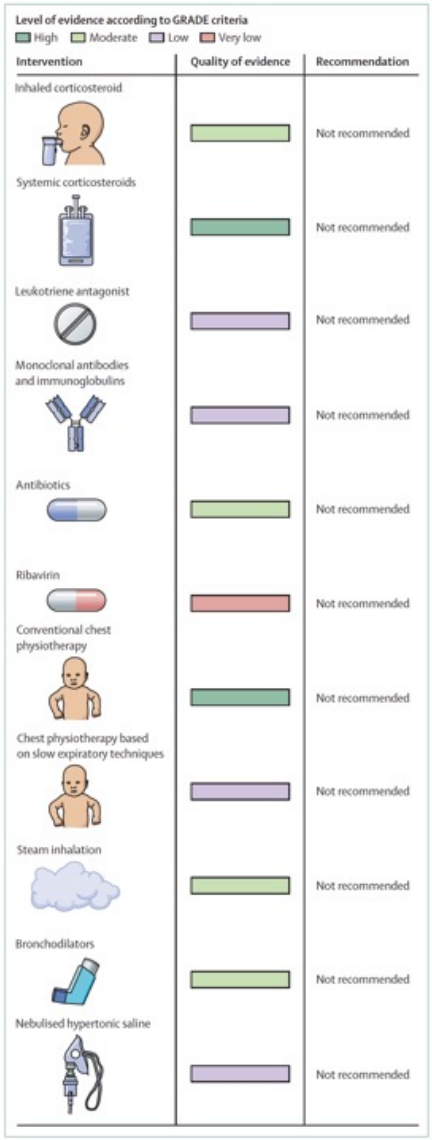


Figure 3: **Evidence-based treatment of severe RSV infection**
The intervention and recommendation for use in hospital management (recommended or not recommended) are listed, and the quality of evidence for this recommendation is presented (ie, high, moderate, low, or very low). Quality of evidence was assessed based on GRADE-criteria and if possible, taken from Cochrane review of the literature.[67-75] GRADE= Grading of Recommendations, Assessment, Development, and Evaluations. RSV=respiratory syncytial virus.

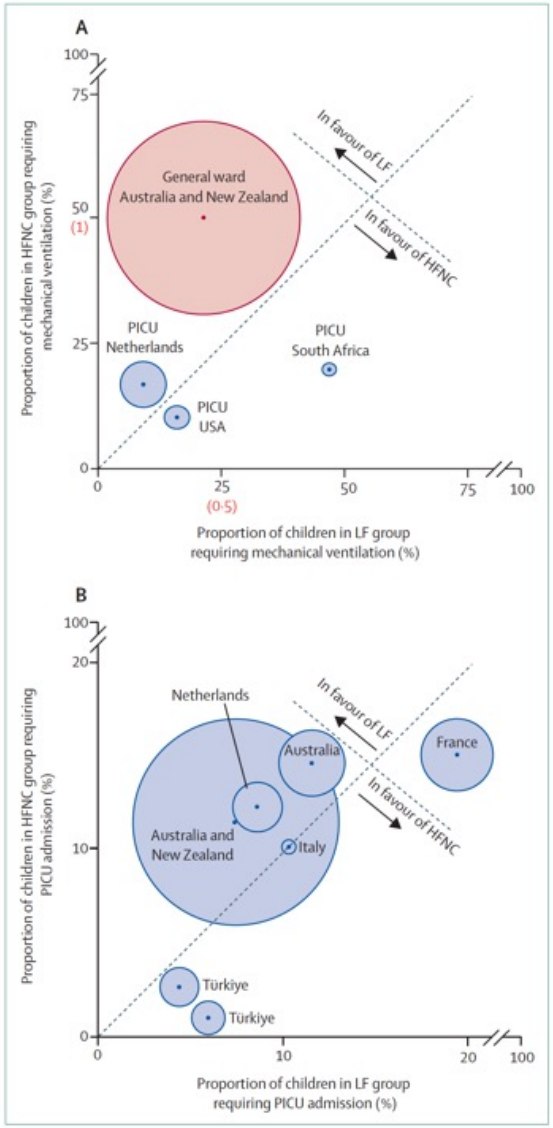


Figure 4: **Proportion of life-threatening RSV disease in children receiving HFNC compared with LF**

(A) Data on proportion of life-threatening RSV disease in children, defined as requiring mechanical ventilation, was extracted from all RCTs comparing HFNC and LF;[87-100] if the data on life-threatening disease were available, the RCT was included. A dual axis (red and black) is shown for interpretability, as trial size varied too much to fit in one figure. All studies in blue circles use the standard black axis. The Franklin trial, indicated in a red circle (comparatively large and percentages low [<1·5%]), uses the x axis indicated in red. The circle sizes are proportional to the sample size in the trial, with the center of the circle at the point estimate. Country and site of trial setting are written in the circles. The dotted line represents equal percentage of the outcome in both trial groups. (B) Data on proportion of life-threatening RSV disease in children, defined as PICU admission, was extracted from all RCTs comparing HFNC and LF; if the data were available, the RCT was included in the figure. The circle sizes are proportional to the sample sizes in the trial, where the centre of the circle at the point estimate. Country where the RCT was conducted is written in the circle. The dotted line represents equal percentage of the outcome in both trial groups. HFNC=high-flow nasal canula. LF=low-flow nasal canula. PICU=paediatric intensive care unit. RCT=randomised clinical trial.

Conclusions and future directions

We have entered a new era of paediatrics in which RSV has become a vaccine-preventable disease in all children. Although universal immunisation should be the target, high-risk groups could be prioritised in the process of vaccine implementation, including LMIC populations carrying the highest burden of life-threatening RSV. Treatment of RSV shows little promise and supportive care is the foundation of management. The advent and widespread implementation of HFNC does not have an evidence base and this therapy should be removed from standard practice. Implementation of RSV preventive strategies as a vaccine probe study will help to address existing knowledge gaps (panel). Vaccine implementation will have real-world impact including effectiveness against all-cause LRTI and impact on the respiratory microbiome. Gaps in knowledge remain, including the effect of RSV prevention on long-term RSV sequalae (eg, wheezing and asthma), and vaccine implementation could elucidate the (causal) relationship between RSV infection and asthma. This knowledge can be discovered by investigating vaccine probe type approaches using real-world data in which the difference in the outcome of interest between immunised and non-immunised individuals or populations can be ascribed to the vaccine-specific pathogen, and as such outcomes that were not assessed in the licensure trials can be evaluated.[159] A vaccine probe study approach allows examination of associations between RSV infection (prevented by immunisation) and outcomes that might require large numbers of participants. Other gaps in knowledge include the potential of future paediatric vaccination to interrupt transmission of RSV to vulnerable populations and patterns of transmission between different populations (young children, older children, adults, and older adults). Furthermore, the effect of RSV vaccination against antibiotic misuse remains to be found out.

Respiratory Syncytial Virus 2024 4

Respiratory syncytial virus vaccination and immunoprophylaxis: realising the potential for protection of young children

The search for safe and efficacious products to prevent severe respiratory syncytial virus (RSV) disease in young infants has lasted more than 60 years. In high-income and middle-income countries, two new products have been authorised: an RSV monoclonal antibody for administration to infants (nirsevimab) and an RSV prefusion F maternal vaccine (RSVpreF [Pfizer, Puurs, Belgium]) for administration to pregnant people. These products are not yet available in low-income and lower-middle-income countries, where most RSV deaths occur. Other papers in this Series describe the acute burden of RSV disease in young children, the effects of RSV infection in early childhood on long-term lung health, and the burden of RSV disease and disease prevention products in older adults. In this Series paper, we briefly review the efficacy, effectiveness, and safety of nirsevimab and RSVpreF maternal vaccine for protection of infants. We then explore potential regulatory, policy, and implementation pathways and provide case studies of intervention uptake in Spain and Argentina, and considerations for use in Kenya. We also explore the health economic evidence to inform product introduction decisions. With sufficient political will and affordable pricing, RSV disease prevention in infants can become a global reality.

Key messages

- Respiratory syncytial virus (RSV) is the leading worldwide cause of acute respiratory illness in children younger than 5 years, with more than 6 million RSV wheezing or pneumonia cases and more than 100 000 RSV deaths occurring each year. Most of these deaths occur in children younger than 6 months, and more than 90% occur in low-income and lower-middle-income countries.
- We have seen remarkable progress in the development of products to prevent RSV disease in infants. This progress includes the approval of two highly effective products: RSVpreF, a vaccine given to pregnant people to boost RSV antibody concentrations and protect infants through transplacental antibody transfer, and nirsevimab, a long-acting monoclonal antibody (mAb) given to infants at birth or in the first few months of life.
- As of July, 2024, the RSVpreF maternal vaccine, nirsevimab, or both products have been approved in more than 50 high-income or upper-middle-income countries and in India (a lower-middle-income country), but not yet in any other lower-middle-income or low-income countries, or in any African countries.
- Galicia (Spain) and Argentina have achieved remarkable success with the introduction of nirsevimab (in the case of Galicia) or the RSVpreF vaccine (in Argentina) through coordinated efforts by policy makers, professional societies, and other stakeholders; lessons from Galicia, Argentina, and other settings can inform countries that have yet to approve or implement nirsevimab or RSVpreF.
- Every country should have the opportunity to select the type of RSV intervention (maternal immunisation or long-acting mAb) that best fits the needs of its population and its health system.
- Efforts are underway to ensure that the RSVpreF maternal vaccine is available, affordable, and acceptable worldwide, including in low-income and lower-middle-income countries, but additional attention is needed to ensure global availability of an RSV infant mAb at affordable prices.

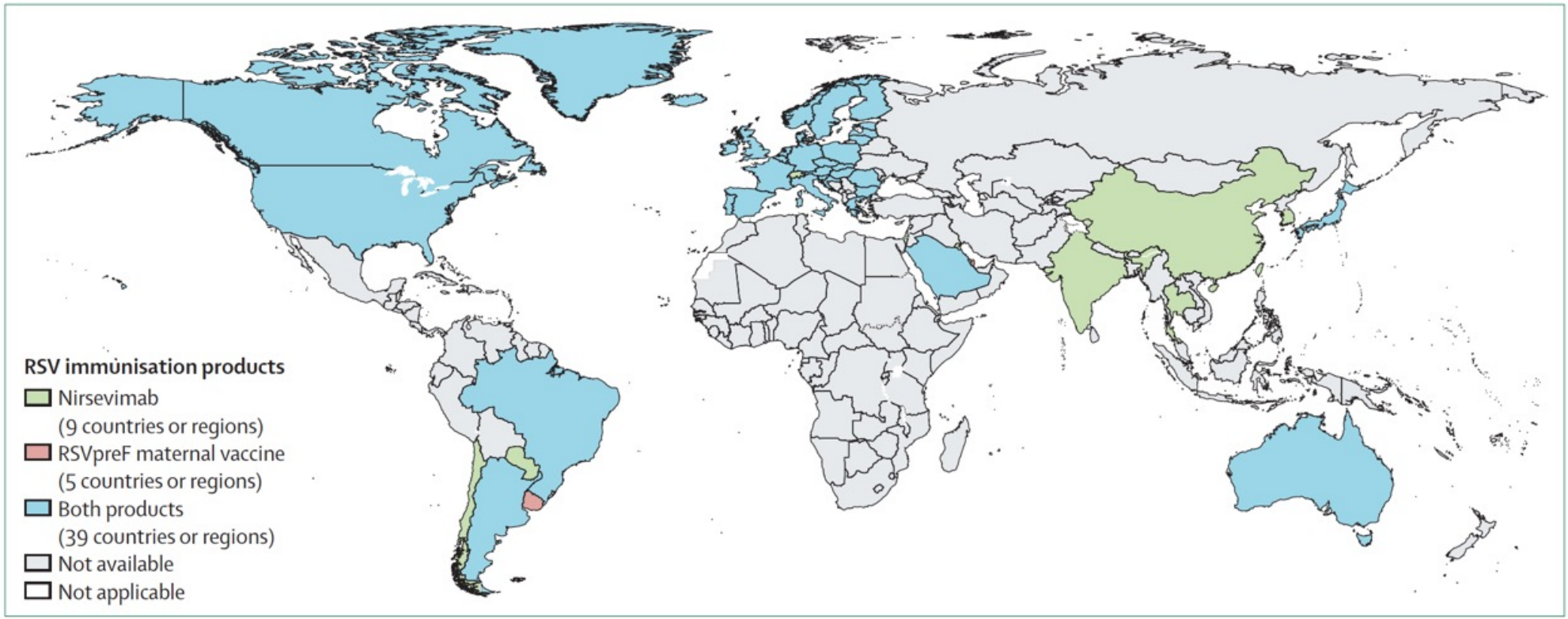


Figure 1: **Global market authorisations of RSV immunisation products to protect infants**

Information is accurate as of July 19, 2024 (Snow V, Pfizer, personal communication; Villafana T, AstraZeneca, personal communication). RSV=respiratory syncytial virus. RSVpreF=respiratory syncytial virus prefusion F.

	Regulatory approval	NITAG recommendations
Australia	24–36 weeks	Yes (28–36 weeks and beyond)
Argentina	32–36 weeks	Yes (32–36 weeks)
Bahrain	24–36 weeks	Unknown or not yet available
Brazil	24–36 weeks	Unknown or not yet available
Canada	32–36 weeks	Yes (32–36 weeks)
EU*	24–36 weeks	Austria (24–26 weeks), Belgium (28–36 weeks), France (32–36 weeks), Luxembourg (32–36 weeks)
Hong Kong	32–36 weeks	Unknown or not yet available
Japan	24–36 weeks	Unknown or not yet available
Macau	32–36 weeks	Unknown or not yet available
Qatar	24–36 weeks	Unknown or not yet available
Saudi Arabia	24–36 weeks	Unknown or not yet available
United Arab Emirates	24–36 weeks	Unknown or not yet available
UK	28–36 weeks	Yes (28–36 weeks)
USA	32–36 weeks	Yes (32–36 weeks)
Uruguay	32–36 weeks	Yes (32–36 weeks)

Information is accurate as of July 19, 2024 (Snow V, Pfizer, personal communication). NITAG=National Immunization Technical Advisory Group. RSVpreF=respiratory syncytial virus prefusion F. *European Medicines Agency authorisation applies to all EU countries and to Iceland, Norway, and Lichtenstein.

Table 1: **Gestational age windows for RSVpreF maternal vaccine**

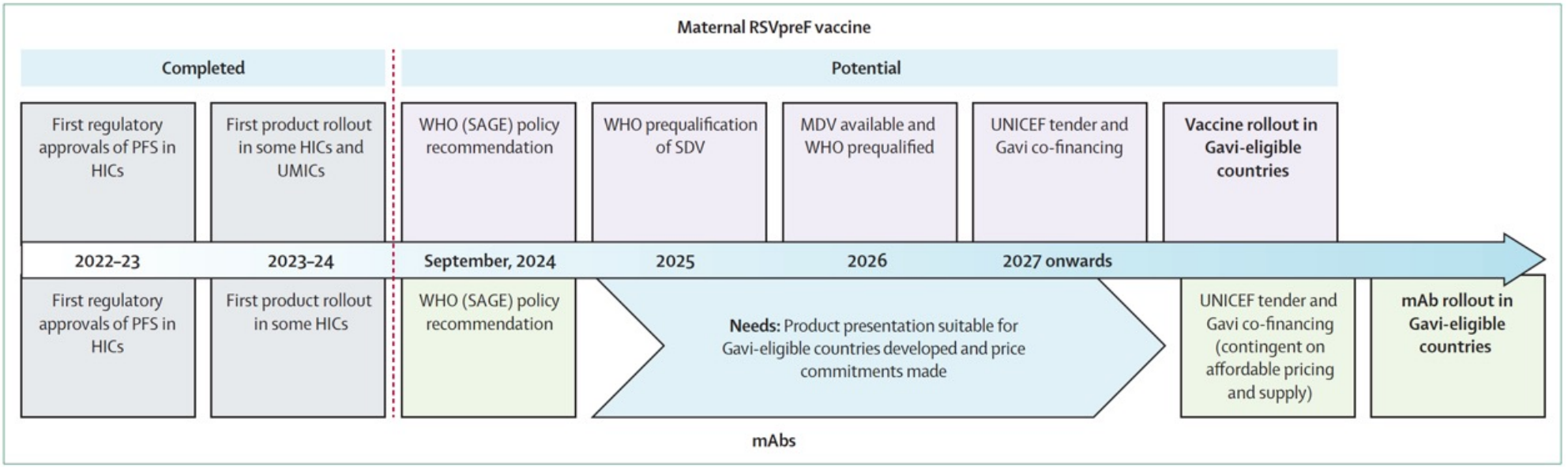


Figure 2: **Pathway toward RSV immunisation product availability for Gavi-eligible countries**

HICs=high-income countries. mAb=monoclonal antibody. MDV=multidose vial. PFS=pre-filled syringe. RSV=respiratory syncytial virus. RSVpreF=respiratory syncytial virus prefusion F. SAGE=Strategic Advisory Group of Experts. SDV=single dose vial. UMICs=upper middle income countries.

	Opportunities	Challenges	Actions	Results
Awareness and interest	High public health priority; well documented burden of disease; RSV surveillance in place; ample media attention on RSV bronchiolitis; upcoming elections	Ensuring sufficient priority and securing the necessary funds	Galician public health authorities anticipated the necessary budget before the official approval of nirsevimab	Early adoption; pragmatic public health decision; cascade effect in Spain that led to official inclusion in the national immunisation programme
Acceptance	Traditionally high coverage rates with all routine paediatric vaccines; 1 dose *vs* 5 doses compared with palivizumab in risk groups; strong and impactful previous RSV season in the mind of the public; great media attention on RSV bronchiolitis, which increases general awareness and interest; commitment of paediatric HCPs with RSV and the campaign	Potential fear of novelty related to new products; a monoclonal antibody *vs* a vaccine, with uncertainty over how this could be perceived, potentially causing confusion or reluctance	Information and education campaign for the population and HCPs, with informative meetings for HCPs, webinars and informative short videos, question and answer sessions, a media and press campaign, and a dedicated website	High immunisation uptake (>92%), with the majority of catch-up and infants who are at high-risk immunised before RSV circulation started (>90%)
Implementation and logistics	Traditionally strong commitment from paediatricians and parents with any immunisation programme; paediatrician-based primary care network; lessons learnt from paediatric influenza vaccination in previous years; flexible hospital access, including on weekends, to successfully increase immunisation uptake	Achieving not only high, but also timely, immunisation uptake before and during the RSV season; ensuring supply of sufficient doses for the whole season and target population	Early negotiation with the manufacturer to ensure supply; simple logistics to facilitate parental access; hospital-centred strategy for immunisation, including fewer sites and fewer people to train to administer it (simplifying immediate logistics given the short preparation time), parents being given flexible appointments (continual access including weekends, e-appointments), and being followed up with the opportunity to rebook if they miss appointment	No logistical issues encountered; rapid immunisation (in 2 weeks) of most eligible infants born out of season (ie, the catch-up and high-risk cohorts) was achieved before the start of RSV circulation
Surveillance and assessment	Electronic and centralised health registries in Galicia, including for primary care, hospitalisation, pharmacy, and microbiology; RSV testing that is routinely performed in paediatric hospital settings; strong genotyping capacity of the region that leveraged the COVID-19 pandemic upgrade in technology	Increased interest in RSV following the campaign could change clinical practice and increase case detection; assessment of the short-term and mid-term effects of nirsevimab on morbidity (eg, wheezing and asthma) and effect in health-care use (eg, primary and emergency care and drug prescription); potential bias in observational study	Predefined procedures for case identification, data extraction, and curation to be performed by Galician Health Information Systems experts; consensus on the case definitions, including breakthrough case definition; pre-agreed and validated protocol and strategy to assess mid-term effect of the campaign on morbidity, emergency departments, primary care, and prescription practice; academic and public health collaboration for data analysis and exploitation, ensuring transparent and rapid communication to the scientific community (NIRSE-GAL study protocol, NCT06180993)	Weekly update on epidemiological data related to the campaign made available in different languages at dedicated websites and on social media; fast-track communication of the most relevant data in reference to scientific congresses and peer-reviewed publications; RSV strains banked; all breakthrough case strains genotyped; information shared with GISAID
Associated costs	Savings from discontinuation of palivizumab use to be removed from the total budget; early adoption and public health use might help negotiate a lower price than that officially established with the Spanish medicine agency	Novel drug, no formal cost-effectiveness studies available at the time of the negotiation	Pragmatic decision to start RSV immunisation campaign was taken; immunisation cost negotiated at a lower price than that officially established for the 2023–24 campaign; future investment and continuity of the strategy conditional upon impact and cost-effectiveness analysis on the basis of the collected data of 2023–24 season	Given the overall results achieved with the 2023–24 campaign, decision made to continue with the same strategy for the 2024–25 season

GISAID=Global Initiative on Sharing All Influenza Data. HCP=health-care providers. RSV=respiratory syncytial virus.

Table 2: **Opportunities, challenges, actions, and results in the implementation of nirsevimab in Galicia (Spain)[47–55]**

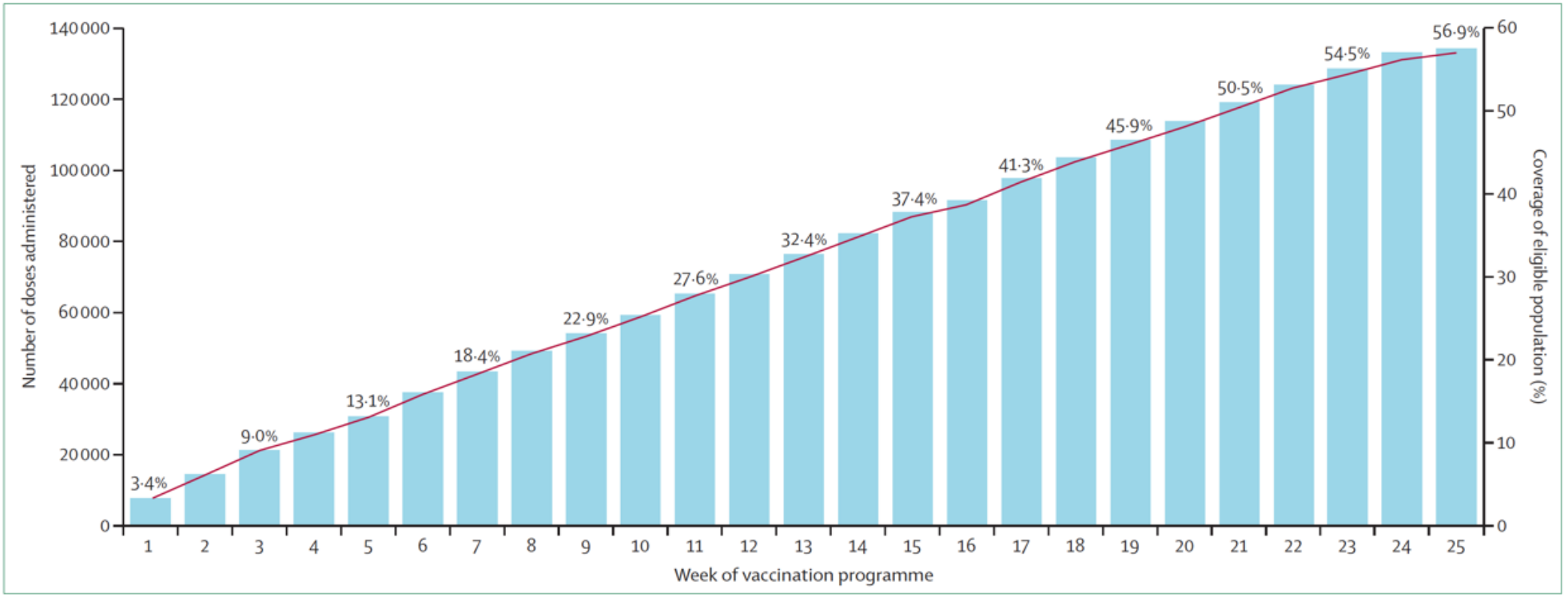


Figure 3: **Doses and coverage of the RSVpreF maternal vaccine administered to pregnant people in Argentina in 2024**

RSVpreF=respiratory syncytial virus prefusion F.

	Opportunities	Challenges	Actions	Results
Awareness and interest	High public health priority; well documented burden of disease; large outbreak in the 2023 season with a notable impact on the health-care system in Argentina and the region; high media attention to RSV bronchiolitis	Ensuring sufficient priority and securing the necessary funds; little time to complete the decision-making process before RSV season starts; upcoming elections	National Ministry of Health authorities anticipating the necessary budget before the official approval of the RSVpreF maternal vaccine; early contact with the National Regulatory Agency and the producer to accelerate product evaluation and approval; strong support from the 24 provincial health ministers in Argentina for the strategy, based on their experience with maternal vaccination and the impact of the 2023 RSV outbreak on health services that required the suspension of elective surgeries and contracting for additional human resources, among other issues	Early adoption; pragmatic public health decision; approval, purchase, receipt, and distribution of the vaccine before the onset of viral circulation enabled timely initiation of vaccination nationwide
Acceptance	Traditionally high confidence in vaccination programme; strong maternal immunisation experience (eg, for influenza, Tdap, and COVID-19); strong and impactful previous RSV season in the mind of the public; great media attention on RSV bronchiolitis increased general awareness and interest	Potential fear of novelty related to new products; short interval for recruiting pregnant individuals (between weeks 32 and 36 of gestation)	Information and education campaign for the target population, obstetricians, and HCPs; intense and timely collaborative work with the 24 jurisdictions, technical guidelines, vaccinator manual, and social media dissemination materials	Inclusion of the vaccine in the national vaccination schedule (managed by the national government), distribution to all 24 provinces, and free availability at all vaccination centres without the need for a prescription; substantial progress towards the vaccination coverage goal as Argentina nears the end of the RSV season
Implementation and logistics	Traditionally strong commitment from vaccinators, health-care teams, and pregnant people for maternal vaccination; lessons learnt from maternal vaccination against influenza, Tdap, and COVID-19 in previous years, which involved obstetricians and scientific societies offering the vaccine during any health-care contact	Achieving not only high, but also timely, immunisation uptake before and during the RSV season; ensuring supply of sufficient doses for the whole season and target population	Early negotiation with the manufacturer to ensure adequate supply; actions are based on an extensive network of vaccination centres in general hospitals, paediatric hospitals, and maternity hospitals, as well as intensive outreach activities and provincial coordination with the private sector and social security	No logistical issues encountered; vaccine distribution completed to provinces and vaccination centres before the onset of viral circulation; rapid progress occurred in the initial months of the vaccination programme
Surveillance and assessment	Integrated vaccination registry, whether through the national system or each jurisdiction's interoperable system, including primary care, hospitalisation, and other health-care subsystems; routine RSV testing conducted in paediatric hospital settings; Latin America's strong genotyping capabilities that leverage technological upgrades from the COVID-19 pandemic; Argentina being part of the international genomic surveillance network	NA	Strengthening the dissemination of clinical surveillance guidelines and laboratory guidelines for respiratory diseases; weekly updates on the epidemiological situation; strengthening the vaccine safety surveillance system to maintain public and health-care team confidence and to evaluate the extension of the vaccination interval	The RSV season is ongoing in the southern hemisphere, but to date, the hospitalisation rate is below previous years; a study will be done to evaluate vaccine effectiveness

The information provided herein is based on author experience (unpublished). HCPs=health-care providers. RSV=respiratory syncytial virus. RSVpreF=respiratory syncytial virus prefusion F. NA=not applicable.

Table 3: **Opportunities, challenges, actions, and results in the implementation of RSVpreF maternal vaccine in Argentina**

Conclusion

The RSVpreF maternal vaccine and nirsevimab are highly effective interventions that each have the potential to reduce the substantial burden of acute RSV disease and death in young infants. These products might also provide important secondary benefits to children, the community, and the health system, including prevention of secondary bacterial pneumonia, decreases in all-cause infant mortality, improvements in lung health,[8] reduced inappropriate antibiotic use, and amelioration of the burden on health systems.[91] Both products have now been authorised in many HICs and some upper-middle-income countries. To date, only nirsevimab has been authorised in a low-income or lower-middle-income country[6] and implementation has yet to occur for either product in these settings, which bear a highly disproportionate burden of RSV-associated morbidity and mortality. As seen from the examples of nirsevimab in Spain and the RSVpreF maternal vaccine in Argentina, the political will to make RSV immunisation a priority drove coordinated and sustained collaboration between regulatory and policy-making bodies, education of health-care providers and parents, and sustained health-system support of implementation efforts. Each country capitalised on the particular strengths of its health system, which led to hospital-based administration of nirsevimab in Spain and use of immunisation clinics for delivery of the RSVpreF maternal vaccine in Argentina. Additionally, RSV was perceived as a substantial threat to infant health because of the previous severe RSV seasons in each country.

Kirsten rat sarcoma viral oncogene homolog (KRAS)

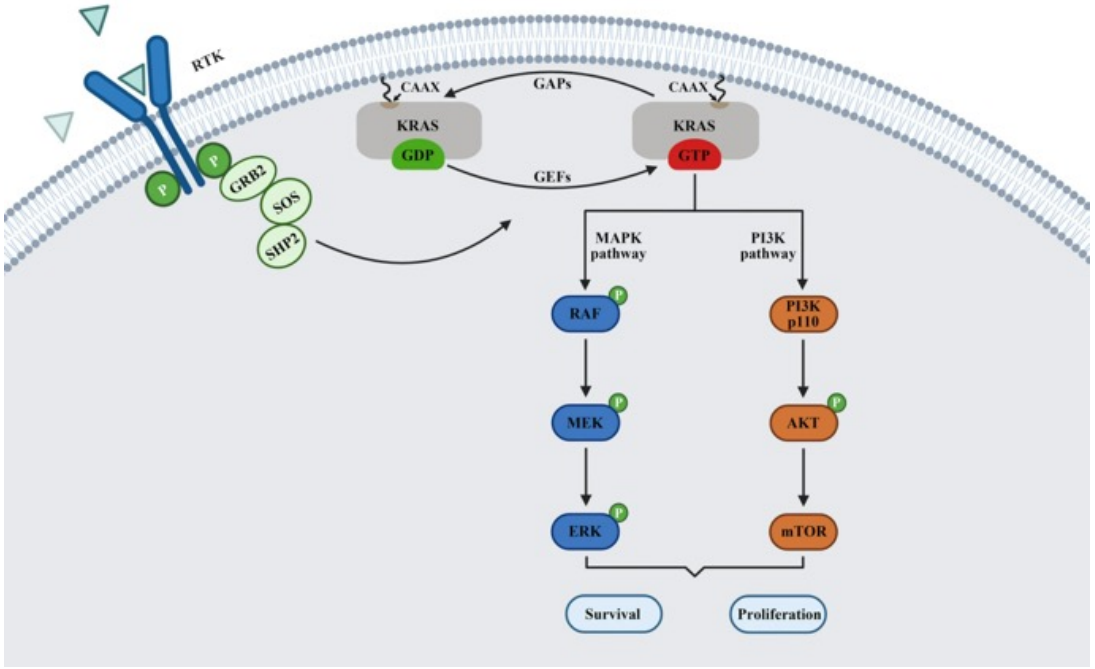
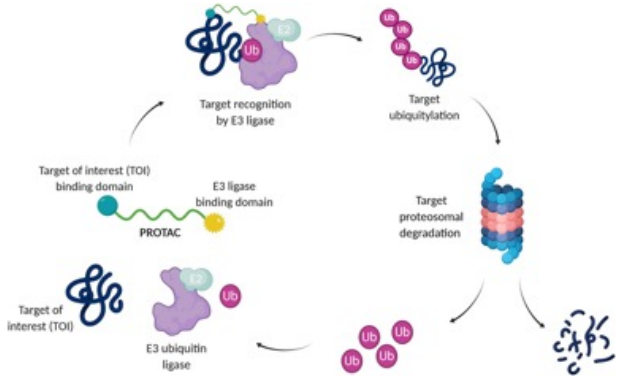
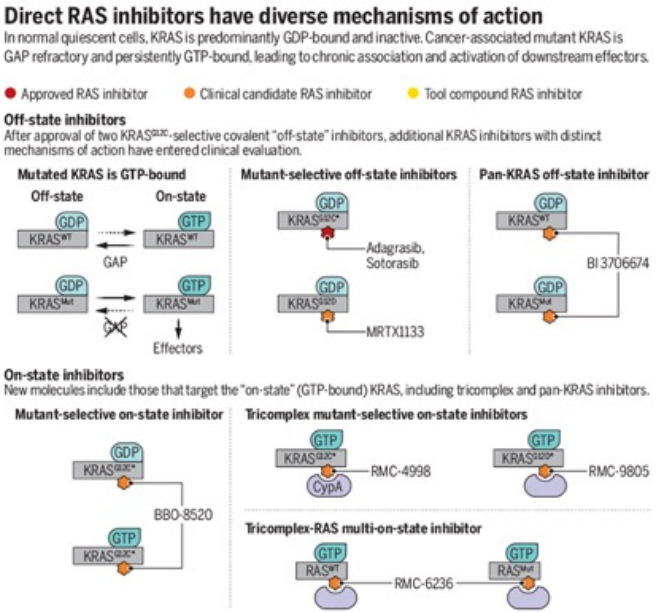


Figure showing how tyrosine kinase receptor signaling is modulated by KRAS. One can interrogate various KRAS mutants using cell lines that express specific KRAS mutations.

In the 20 years since the concept of a proteolysis-targeting chimera (PROTAC) molecule harnessing the ubiquitin–proteasome system to degrade a target protein was reported, TPD has moved from academia to industry, where numerous companies have disclosed programmes in preclinical and early clinical development.

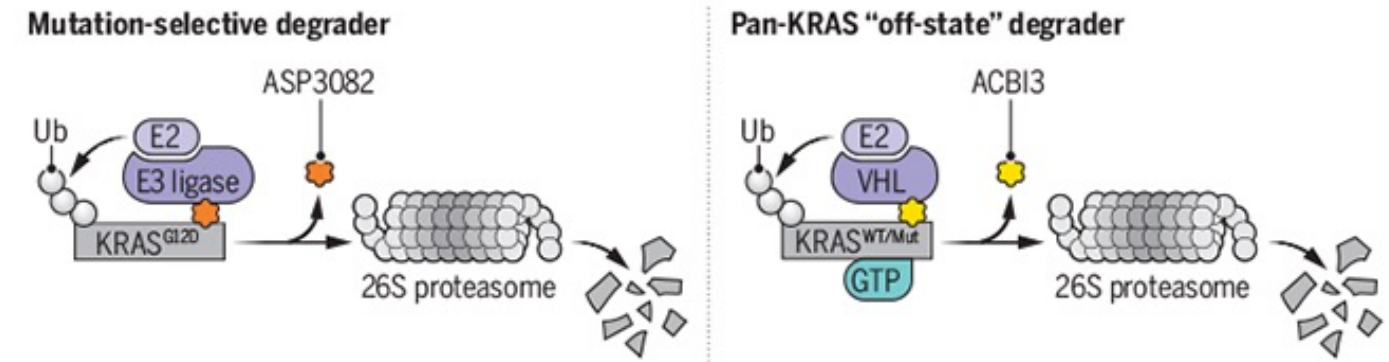


RMC-9805 acts as a covalent allosteric inhibitor that recognizes the on state of KRASG12D, functioning as a tricomplex inhibitor that forms an initial binary complex with cyclophilin A, which then recognizes KRAS. ASP3082 is a PROTAC comprising a $KRAS^{G12D}$-selective binding ligand joined by a linker to an E3 ubiquitin ligase-binding element, which recruits an undisclosed E3 ligase to cause ubiquitylation and proteasomemediated degradation of $KRAS^{G12D}$.



PROTAC-based degraders

New inhibitors also include proteolysis-targeting chimera (PROTAC)–based molecules, which can target single or multiple mutant KRAS versions.



Asterisk (*) denotes covalent modification of G12X substitution. CypA, cyclophilin A; GAP, GTPase activating protein; GDP, guanosine diphosphate; GTP, guanosine triphosphate; Mut, mutated (G12X, G13X, Q61X, etc.); Ub, ubiquitin; VHL, von Hippel–Lindau protein; WT, wild type.

The foundation of the PROTAC-based strategy of Popow *et al*. to target different KRAS mutant proteins was their recently described pan-KRAS off-state inhibitor BI-2865, which blocked multiple KRAS mutations. The SIIP binding motif of BI-2865 was used together with a linker coupled to an established binding motif for the Von Hippel– Lindau (VHL) E3 ligase. Structure-based design identified an initial compound 4, which showed high activity against 13 of the 17 most prevalent KRAS mutations, including $KRAS^{G12D}$. A comparison of the KRAS degrading compound 4 with a chemically related compound that also binds and inhibits KRAS but lacks degrading activity showed that degradation resulted in 10-fold greater potency to inhibit KRAS and longer durability. And a compound designed to enhance the in vivo properties of compound 4, designated ACBI3, potently suppressed tumor growth in mouse xenograft models based on $KRAS^{G12D}$mutant colorectal carcinoma and $KRAS^{G12V}$mutant (V, valine) ovarian leiomyosarcoma cell lines. However, ACBI3 was not compared directly in vivo with a control inhibitor unable to degrade KRAS, so how much of its tumor-regressing capability was due specifically to its degrader properties is unknown.

Targeting cancer with small-molecule pan-KRAS degraders

Guided by biophysical and structural studies of ternary complexes, we designed a heterobifunctional small molecule that potently degrades 13 out of 17 of the most prevalent oncogenic KRAS alleles. Compared with inhibition, KRAS degradation results in more profound and sustained pathway modulation across a broad range of KRAS mutant cell lines, killing cancer cells while sparing models without genetic KRAS aberrations. Pharmacological degradation of oncogenic KRAS was tolerated and led to tumor regression in vivo. Together, these findings unveil a new path toward addressing KRAS-driven cancers with small-molecule degraders.

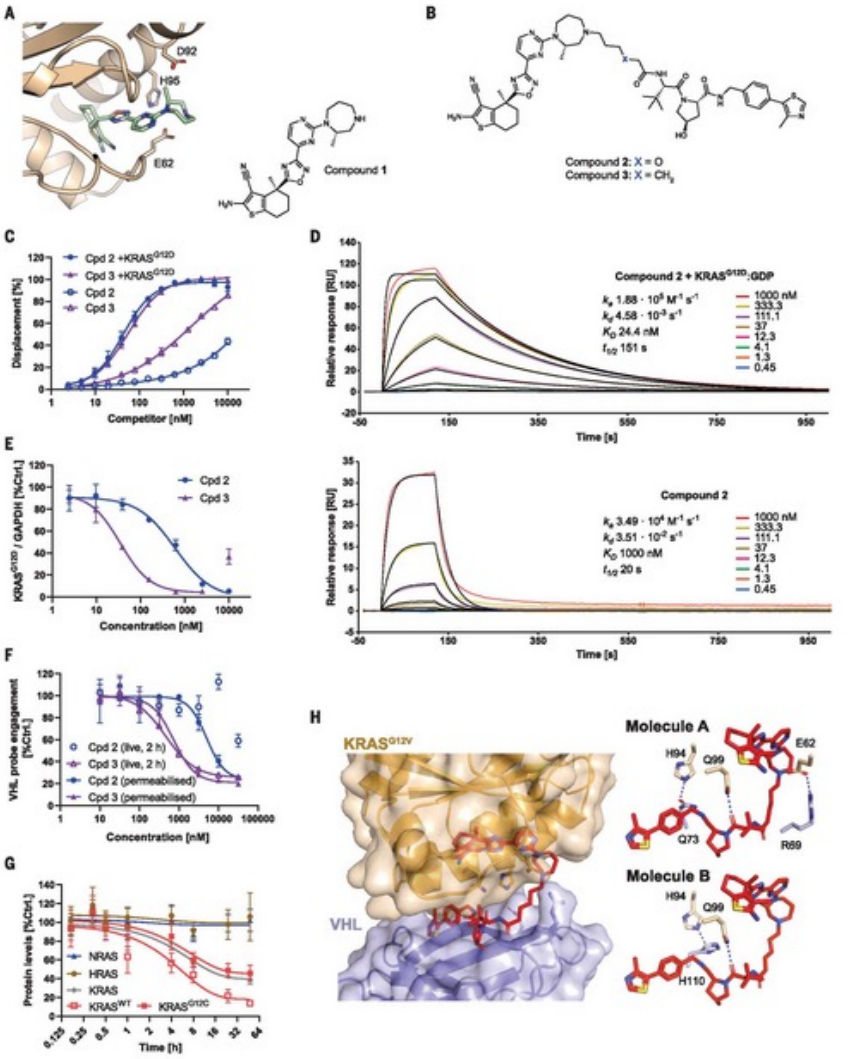
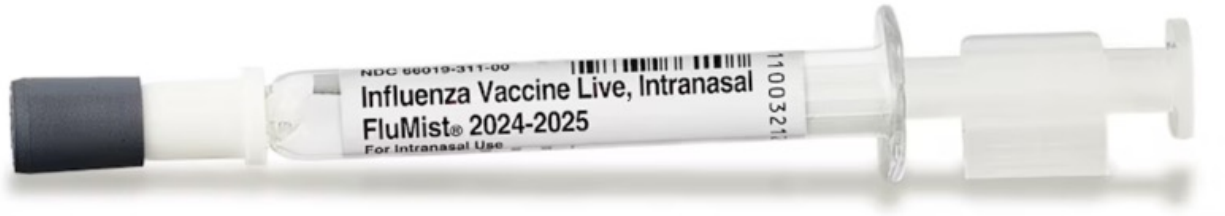


Fig. 1. Identification of reversible, KRAS-selective degraders. (**A**) Exit vector explored to derivatize KRAS binders. Three-dimensional crystal structure of KRAS displayed is in brown, and compound **1** is in green (PDB ID 8QUG). (**B**) Chemical structures of compounds **2** and **3**. (**C**) VCB FP displacement for compounds **2** and **3** in presence or absence of saturating $KRAS^{G12D}$ concentrations ($n = 3$ independent experiments, SD). (**D**) SPR characterization of ternary complex

FDA approves first nasal spray flu vaccine for use at home

Consumers with a prescription will be able to order online starting next year.



The Food and Drug Administration on Friday approved the first at-home flu vaccine, a nasal spray that consumers with a prescription will be able to order online starting next year.

Health experts say the convenience of the spray — FluMist — could lead to increased flu vaccination rates.

The maker of the vaccine, AstraZeneca, said it will supply the vaccine to a third-party online pharmacy where people can complete a screening assessment to determine if they are candidates. The pharmacy will then evaluate patients' eligibility and decide if they are able to administer the vaccine.

Seasonal flu is highly contagious, and the Centers for Disease Control and Prevention estimates 4,900 to 51,000 people died of the flu annually between 2010 and 2023. The past couple of years, flu vaccination rates remained relatively similar but were lower than during the 2020-2021 flu season — the first full season amid the coronavirus pandemic.

FluMist contains attenuated live viruses, which are weakened forms of the flu virus that cannot cause illness. This is why people with weakened immune systems, those who are pregnant and people with certain medical conditions are not eligible for the vaccine, as they may be at risk of adverse side effects.

The current out-of-pocket cost for FluMist can range from $35 to $45, but for many people with insurance, the vaccine is free.