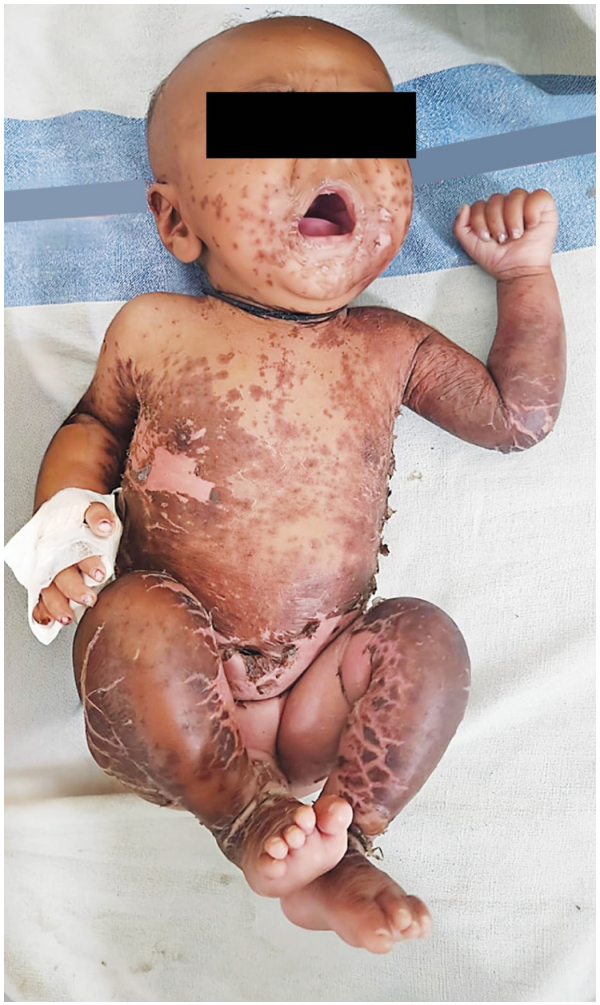
https://www.mdc-berlin.de/de/veroeffentlichungstypen/clinical-journal-club

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!



On physical examination, the baby was irritable, with sparse, wispy, hypopigmented hair and pitting edema of the arms and legs. Desquamation of hyperpigmented patches was seen on the legs, arms, and trunk; the underlying skin was hypopigmented. A diagnosis of kwashiorkor — also known as edematous malnutrition or severe acute malnutrition with pitting edema of the arms and legs — was made. Kwashiorkor may be diagnosed in malnourished children on the basis of the presence of pitting edema, regardless of height and weight values. The typical dermatosis, as seen in this baby, resembles flaking paint.

A 5-month-old full-term baby boy was brought to the outpatient clinic with a 3-week history of a rash. Physical examination is shown. His weight-for-age z score was −3.4, and his length-for-age z score was −5.6. Labs revealed a serum albumin level of 1.9 g per deciliter (reference range, 3.5 to 5.0). What is the most likely diagnosis?

Celiac disease

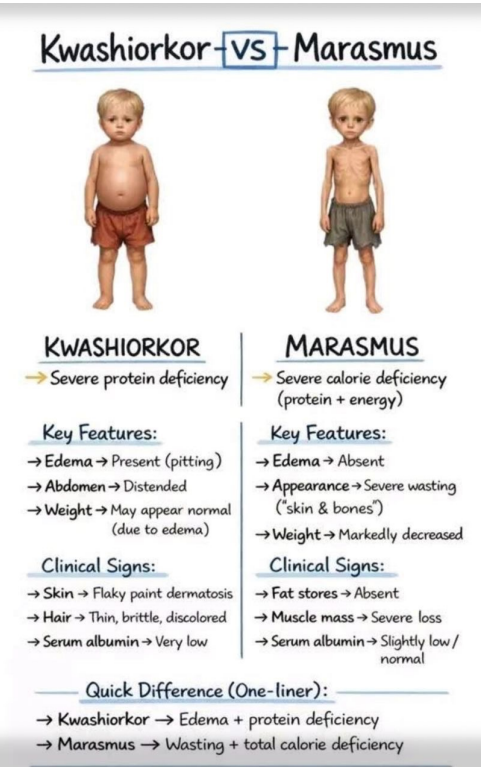
Kwashiorkor

Marasmus

Nephrotic syndrome

Staphylococcal scalded skin syndrome

Kwashiorkor (auch bekannt als Hungerödem) ist eine **lebensbedrohliche Form der schweren Protein-Energie-Mangelernährung**, die durch einen **extremen Mangel an Eiweiß** bei oft scheinbar ausreichender Zufuhr von Kohlenhydraten (Kalorien) ausgelöst wird. Die Erkrankung betrifft vorwiegend **Säuglinge und Kleinkinder in Entwicklungsländern**. Der Name stammt aus einer westafrikanischen Sprache (Ga) und bedeutet übersetzt „die Krankheit, die das ältere Kind bekommt, wenn das nächste geboren wird“. Dies beschreibt den typischen Fall, bei dem ein Kind abrupt abgestillt und auf eine proteinarme, rein kohlenhydratbasierte Kost (wie Brei aus Maniok oder Mais) umgestellt wird.



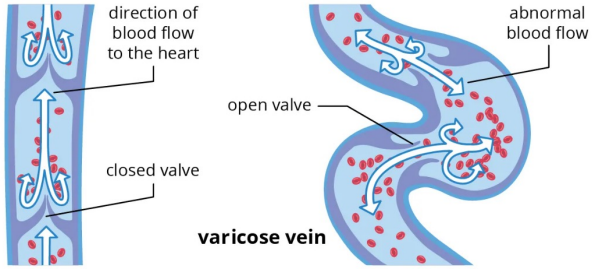
Symptome und klinisches Bild
Das auffälligste Merkmal von Kwashiorkor steht im Gegensatz zur extremen Abmagerung des Marasmus:

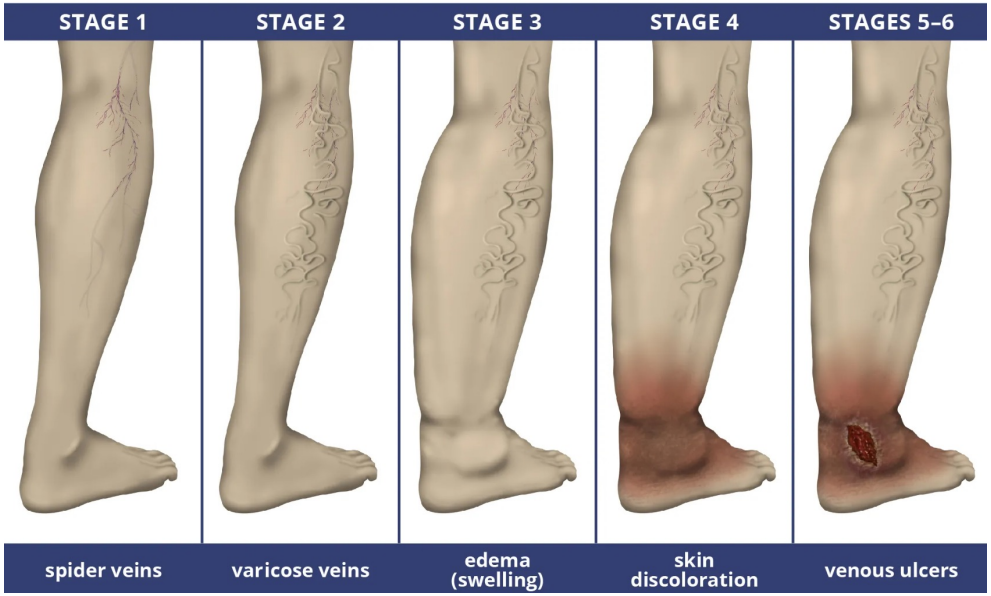
- **Aufgeblähter Bauch („Hungerbauch“)**: Ausgelöst durch Flüssigkeitsansammlungen in der Bauchhöhle (Aszites) und eine stark vergrößerte Fettleber (Hepatomegalie).

- **Ödeme**: Starke Wassereinlagerungen, besonders in den Füßen, Beinen und im Gesicht (sogenanntes „Mondgesicht“).
- **Hautveränderungen**: Schuppige, entzündete Flecken, Pigmentverlust und Wunden, die leicht bluten.
- **Haarveränderungen**: Das Haar verfärbt sich rötlich-gelb oder verblasst, wird brüchig und fällt leicht aus.
- **Muskelschwund und Lethargie**: Trotz des scheinbar „pummeligen“ Aussehens durch die Ödeme bauen Muskeln massiv ab. Die Kinder sind meist teilnahmslos und reizbar.

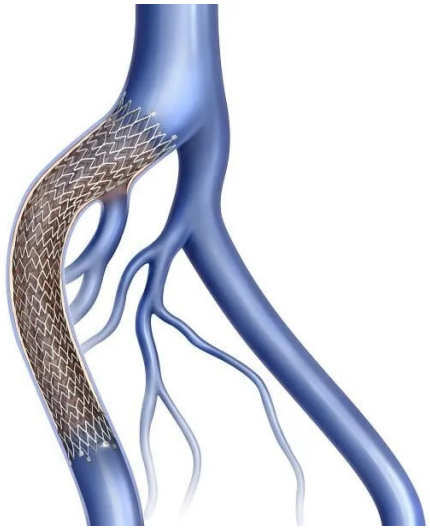
CHRONIC VENOUS INSUFFICIENCY

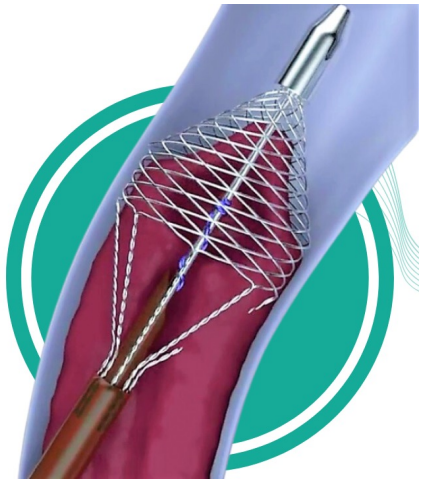
Chronic venous insufficiency occurs when one-way valves in veins that lie deep beneath the surface of the skin become damaged or weakened or when blood flow between the limbs and the heart is obstructed.





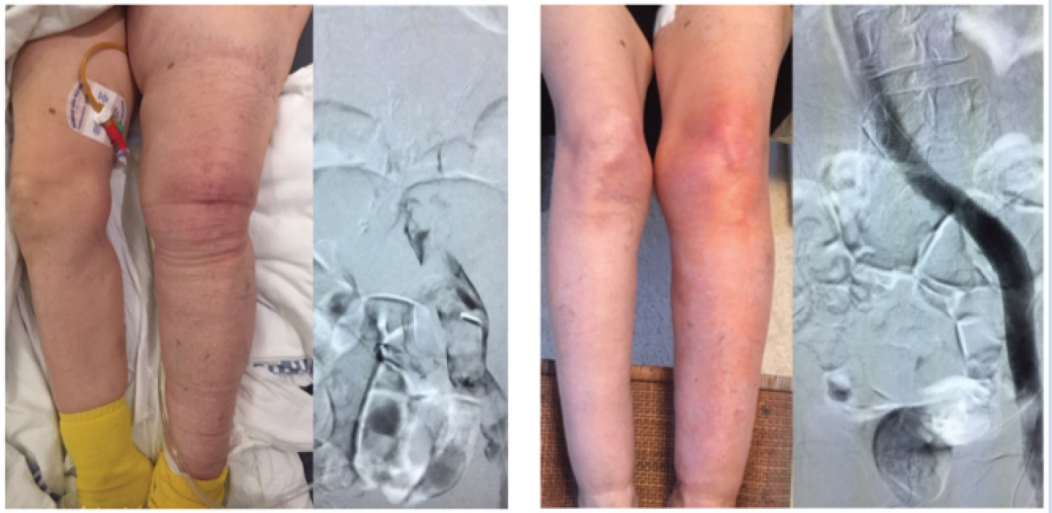
Venous Clinical Severity Score	
Skin pigmentation	Diffuse limited
Inflammation	None
Induration	None
Ulcers	0
Ulceration	< 3
Ulcer diameter	< 2 cm
Compressive therapy	Not used
Score: 5	
Link to reference publication	





DVT MANAGEMENT AND VENOUS STENTING

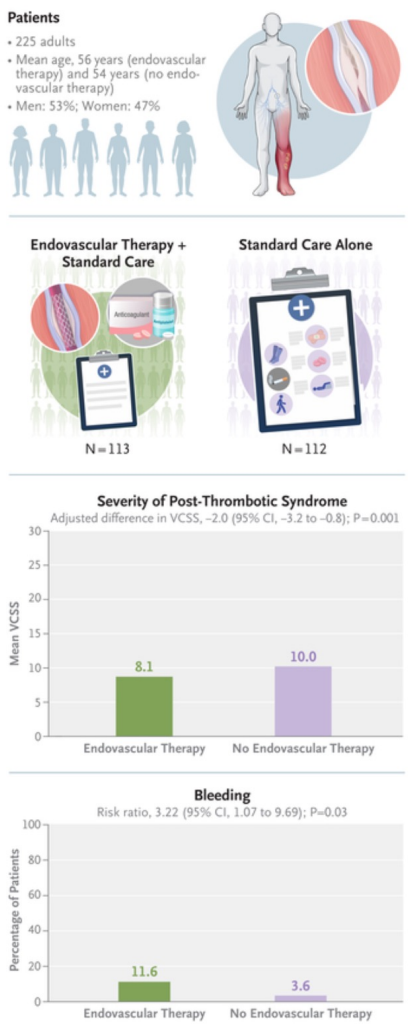
Before and After Venous Stenting



Endovascular Therapy for Post-Thrombotic Syndrome — A Randomized Trial

Post-thrombotic syndrome is common after deep-vein thrombosis and can cause severe symptoms involving the limbs that impair patients' activity and quality of life. Endovascular therapy can eliminate chronic venous obstruction and is hypothesized to reduce the severity of post-thrombotic syndrome.

We randomly assigned 225 patients with moderate or severe post-thrombotic syndrome and imaging-confirmed iliac-vein obstruction to receive endovascular therapy (iliac-vein stent placement and enhanced antithrombotic therapy) plus standard post-thrombotic syndrome care or standard post-thrombotic syndrome care alone. The severity of post-thrombotic syndrome at 6 months (the primary outcome) was assessed with the validated Venous Clinical Severity Score (VCSS) tool (scores range from 0 to 30, with higher scores indicating more severe post-thrombotic syndrome) by evaluators who were unaware of the group assignments. Key secondary outcomes included venous disease–specific and overall quality of life.



Post-thrombotic syndrome frequently develops after acute proximal deep-vein thrombosis (DVT). Relatively few affected patients receive focused treatment for post-thrombotic syndrome owing to a lack of awareness among the medical community with regard to available therapies and a lack of evidence of clinical benefit for such therapies. Venous hypertension plays a central role in post-thrombotic syndrome and stems from chronic venous obstruction, valvular reflux, elevation in central venous pressure, impairment of calf pump function, and lymphatic dysfunction. Post-thrombotic syndrome manifests across a broad severity spectrum; patients with post-thrombotic syndrome and iliac-vein obstruction often have chronic limb pain, swelling, skin changes, venous leg ulcers, or a combination of these symptoms, which impair function and quality of life.

Previous studies have suggested that imaging-guided endovascular placement of metallic stents may reduce iliofemoral venous obstruction and thereby improve venous function, decrease the severity of post-thrombotic syndrome, and improve quality of life. However, the benefits and risks of such therapy are unclear. We conducted the C-TRACT (Chronic Venous Thrombosis: Relief with Adjunctive Catheter-Directed Therapy) trial to determine whether endovascular therapy would reduce the severity of post-thrombotic syndrome.

Patient Population

Patients with moderate or severe post-thrombotic syndrome and iliac-vein obstruction were enrolled at 29 clinical centers in the United States. Post-thrombotic syndrome was defined as the presence of chronic venous disease in the ipsilateral leg of a patient who had had DVT at least 3 months before enrollment. Post-thrombotic syndrome was considered to be moderate or severe if the patient had substantial limitations in daily activities or work capacity owing to venous symptoms that resulted in a score of 8 or higher on the Venous Clinical Severity Score (VCSS) assessment tool, a score of 10 or higher on the Villalta post-thrombotic syndrome scale, or an open venous ulcer.

Stratification and Randomization

Patients were randomly assigned to receive either endovascular therapy (iliac-vein stent placement and enhanced antithrombotic therapy) or no endovascular therapy, with the use of a Web-based central randomization system.

Treatments

This included individualized compression therapy (starting with sized-to-fit, knee-high elastic compression stockings with a pressure of 20 to 30 mm Hg [Medi USA] for patients who had not previously used compression stockings) that was adjusted as needed to encourage adherence to their use; appropriate anticoagulant therapy; guidance on smoking cessation, leg elevation, exercise, and avoidance of limb trauma; and, for patients with an open venous ulcer, encouragement to take oral pentoxifylline and to use multilayer compression, along with referral to a wound and ulcer care clinic for comprehensive evidence-based care.

Characteristics of the Patients at Baseline.

Characteristics	Endovascular Therapy (N=112)	No Endovascular Therapy (N=112)
Age — yr	56.1±12.7	54.4±14.2
Female sex — no. (%)	52 (46.4)	54 (48.2)
Race — no. (%)†		
White	73 (65.2)	78 (69.6)
Black	31 (27.7)	23 (20.5)
Other	2 (1.8)	3 (2.7)
Data missing	6 (5.4)	8 (7.1)
Hispanic or Latino ethnic group — no. (%)†	12 (10.7)	15 (13.4)
Body-mass index‡	35.0±8.3	35.3±8.3
Index post-thrombotic syndrome in left leg — no. (%)	75 (67.0)	81 (72.3)
CEAP clinical class — no. (%)§		
C2 or C3	25 (22.3)¶	22 (19.6)
C4	51 (45.5)‖	58 (51.8)
C5	19 (17.0)	16 (14.3)
C6	17 (15.2)	16 (14.3)
Normal common femoral vein — no. (%)	40 (35.7)	45 (40.2)
VCSS**	12.5±4.3	12.3±4.3
VEINES-QOL score††	38.9±20.9	39.6±24.1
Calf circumference — cm	43.9±8.3	43.3±6.0
Receipt of any anticoagulant medication — no. (%)	90 (80.4)	94 (83.9)
Receipt of any antiplatelet medication — no. (%)	29 (25.9)	20 (17.9)
Use of any compression therapy — no. (%)	94 (83.9)	83 (74.1)
Valvular reflux, any vein — no. (%)	88 (78.6)	92 (82.1)

Treatments after Randomization.

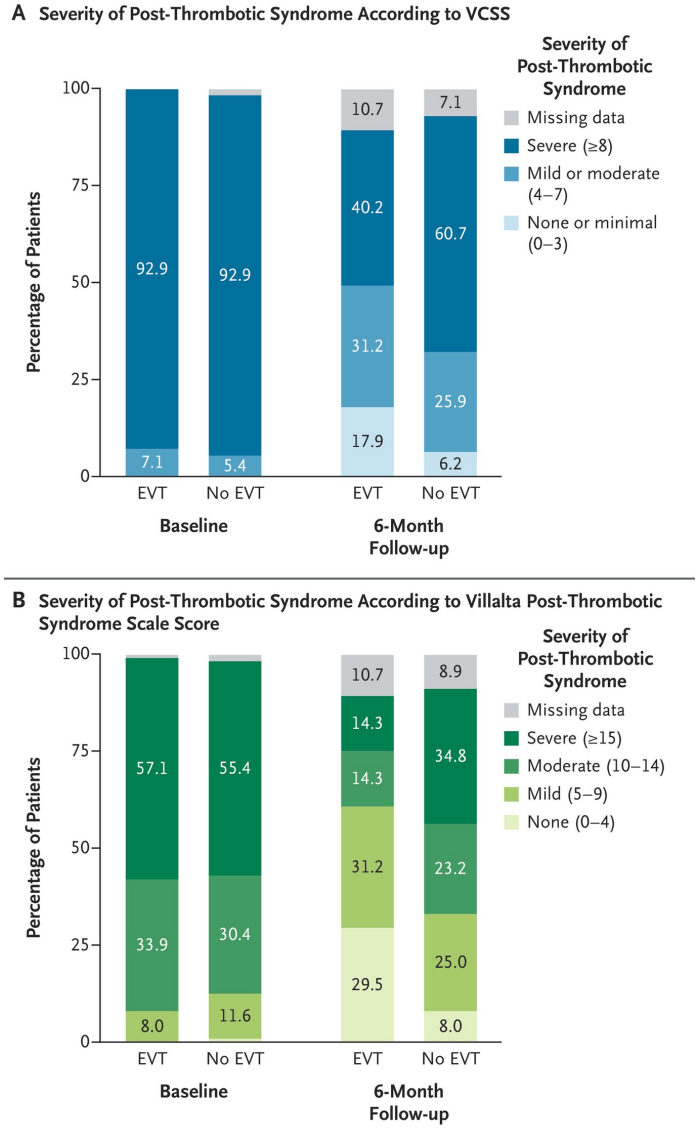
Treatment	Endovascular Therapy (N=112)	No Endovascular Therapy (N=112)
Current treatments at 6 mo — no./total no. (%)		
Any anticoagulant medication	95/101 (94.1)	87/105 (82.9)
Any antiplatelet medication	72/101 (71.3)	22/105 (21.0)
Any compression therapy	93/99 (93.9)	97/103 (94.2)
Pentoxifylline	1/101 (1.0)	5/105 (4.8)
Any other venoactive medication	5/101 (5.0)	10/105 (9.5)
Any analgesic medication	26/101 (25.7)	28/105 (26.7)
Any superficial vein treatment in previous 6 months — no./total no. (%)	6/112 (5.4)	0/112 (0.0)
Index endovascular therapy procedure		
Index endovascular therapy procedure started — no./total no. (%)*	102/112 (91.1)	—
Index endovascular therapy procedure with successful stent placement — no./total no. (%)†	98/102 (96.1)	—
Mean no. of stents per patient (range)	2.1 (1.0–7.0)	—
Maximum stent diameter — mm	15.4±2.0	—
Minimum stent diameter — mm	14.0±2.0	—
Inferior vena cava stented — no./total no. (%)†	19/102 (18.6)	—
Common iliac vein stented — no./total no. (%)†	84/102 (82.4)	—
External iliac vein stented — no./total no. (%)†	78/102 (76.5)	—
Common femoral vein stented — no./total no. (%)†	51/102 (50.0)	—
Femoral vein stented — no./total no. (%)†	1/102 (1.0)	—
Additional thrombolysis or thrombectomy — no./total no. (%)†	3/102 (2.9)	—
Type of stent placed — no.‡		
Abre (Medtronic)	81	—
S.M.A.R.T. (Cordis)	13	—
Venovo (Becton Dickinson)	53	—
Vici (Boston Scientific)	12	—
Wallstent (Boston Scientific)	28	—
Zilver Vena (Cook Medical)	22	—
Unknown	3	—

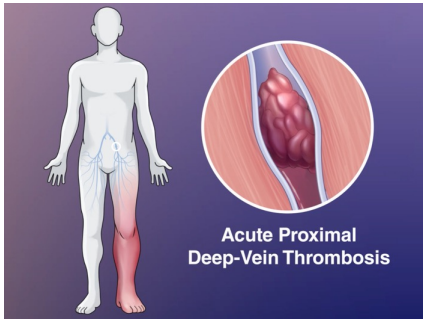
Outcomes.

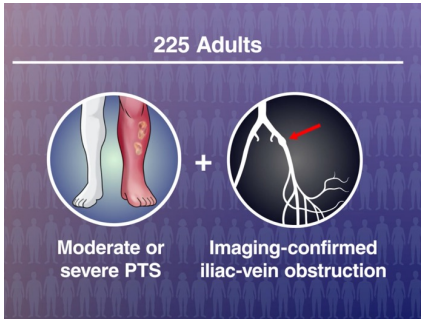
Outcome	Endovascular Therapy (N=112)	No Endovascular Therapy (N=112)	Adjusted Difference or Risk Ratio (95% CI)†	P Value
Continuous‡				
Primary outcome				
VCSS§	8.1±5.1	10.0±4.9	−2.0 (−3.2 to −0.8)	0.001
Secondary outcomes				
VEINES-QOL score¶	62.8±24.6	48.6±26.7	14.5 (9.5 to 19.4)	<0.001
SF-36 physical component summary score‖	56.0±16.4	49.9±17.1	6.1 (2.8 to 9.3)	<0.001
Villalta score**	8.2±5.7	12.3±6.4	−4.1 (−5.5 to −2.7)	—
Calf volume — cm^3††	2442.1±907.0	2392.2±849.6	−21.6 (−152.0 to 108.7)	—
Binary				
Secondary outcome				
Open venous ulcer — no. (%)	10 (8.9)	11 (9.8)	0.84 (0.42 to 1.71)	—
New ulcer	4 (3.6)	1 (0.9)	—	—
Persistent ulcer	6 (5.4)	10 (8.9)	—	—
Safety outcomes				
Symptomatic recurrent VTE — no. (%)	3 (2.7)	4 (3.6)	0.76 (0.17 to 3.28)	—
Stent thrombosis and other proximal DVT	3 (2.7)	0	—	—
Stent thrombosis only	1 (0.9)	0	—	—
Other proximal DVT only	0	4 (3.6)	—	—
Symptomatic pulmonary embolism	0	1 (0.9)	—	—
All bleeding — no. (%)	13 (11.6)	4 (3.6)	3.22 (1.07 to 9.69)	0.03
Major bleeding	4 (3.6)	1 (0.9)	4.01 (0.46 to 34.97)	—
Nonmajor bleeding	11 (9.8)	3 (2.7)	3.64 (1.02 to 12.93)	—
Death — no. (%)	1 (0.9)	0	—	—

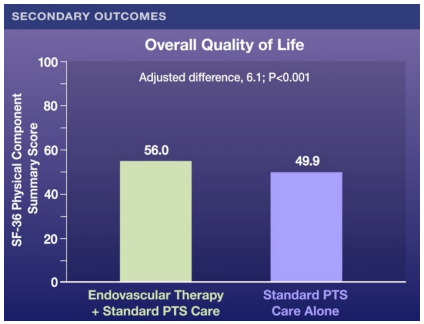
Categorical Distribution of VCSS and Villalta Scores.

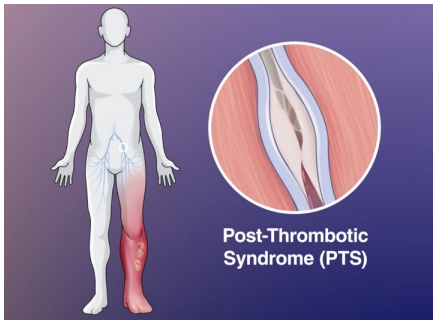
Panel A shows the distribution of patients at baseline and at the 6-month follow-up according to the three established severity categories for post-thrombotic syndrome scores on the Venous Clinical Severity Score (VCSS) assessment tool: no or minimal post-thrombotic syndrome (0 to 3), mild or moderate post-thrombotic syndrome (4 to 7),[4-7] and severe post-thrombotic syndrome (≥8).[14] The VCSS total score ranges from 0 to 30, with higher scores indicating more severe post-thrombotic syndrome. Baseline VCSS values were missing for 2 patients (1.8%) in the no-endovascular-therapy group. Panel B shows the distribution of patients at baseline and at the 6-month follow-up according to the four established severity categories on the Villalta post-thrombotic syndrome scale: no post-thrombotic syndrome (0 to 4), mild post-thrombotic syndrome (5 to 9),[5-9] moderate post-thrombotic syndrome (10 to 14),[10-14] and severe post-thrombotic syndrome (≥15).[12,16] The Villalta scale is an assessment of five patient-reported symptoms and six venous-disease signs, which were reported by clinicians who were unaware of the trial-group assignments; a leg with an ulcer was assigned a minimum score of 15 points. Total scores on the Villalta scale range from 0 to 33, with higher scores indicating more severe post-thrombotic syndrome. Baseline Villalta scores were missing for 1 patient (0.9%) in the endovascular-therapy group and for 2 patients (1.8%) in the no-endovascular-therapy group. Patients entered the trial with moderate or severe post-thrombotic syndrome, but over a period of 6 months, many of the patients' scores shifted to less severe categories, especially in the endovascular-therapy (EVT) group.



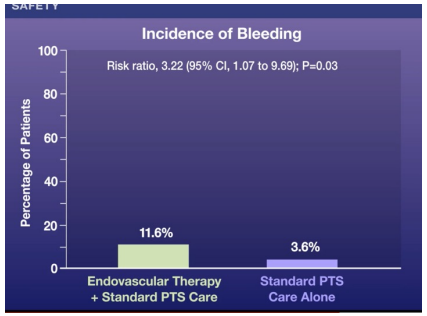

Acute Proximal
Deep-Vein Thrombosis

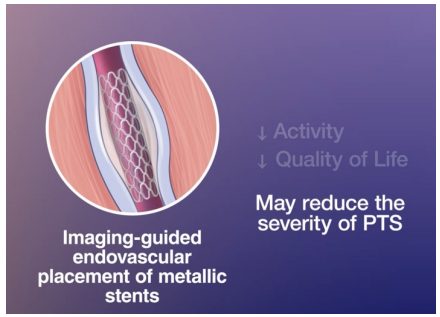

225 Adults
Moderate or
severe PTS
+
Imaging-confirmed
iliac-vein obstruction

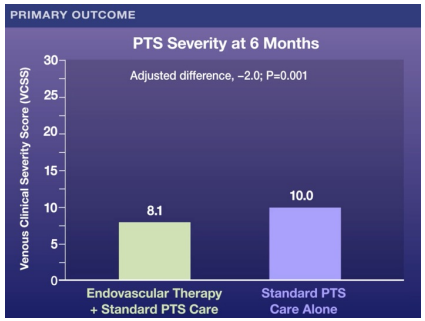

SECONDARY OUTCOMES
Overall Quality of Life
Adjusted difference, 6.1; P<0.001
SF-36 Physical Component Summary Score
100
80
60
40
20
0
56.0
49.9
Endovascular Therapy
+ Standard PTS Care
Standard PTS
Care Alone


Post-Thrombotic
Syndrome (PTS)


Endovascular Therapy
N=113
Standard PTS Care Alone
N=112
Iliac-vein stent
placement
+
Enhanced
antithrombotic
therapy
+ Standard PTS Care


SAFETY
Incidence of Bleeding
Risk ratio, 3.22 (95% CI, 1.07 to 9.69); P=0.03
Percentage of Patients
100
80
60
40
20
0
11.6%
3.6%
Endovascular Therapy
+ Standard PTS Care
Standard PTS
Care Alone


↓ Activity
↓ Quality of Life
May reduce the
severity of PTS
Imaging-guided
endovascular
placement of metallic
stents


PRIMARY OUTCOME
PTS Severity at 6 Months
Adjusted difference, −2.0; P=0.001
Venous Clinical Severity Score (VCSS)
30
25
20
15
10
5
0
8.1
10.0
Endovascular Therapy
+ Standard PTS Care
Standard PTS
Care Alone


Anticoagulant
Tablets
Antiplatelet
Tablets
+
↓ PTS severity
↑ Health-related quality of life over 6 months

Ist Vollbluttransfusion wirklich besser?

Der englische Begriff **whole blood** bedeutet auf Deutsch **Vollblut**. Es bezeichnet das unbehandelte, flüssige Blut aus dem Organismus, das sämtliche zelluläre Bestandteile (rote und weiße Blutkörperchen, Blutplättchen) sowie das Plasma und die Gerinnungsfaktoren enthält.

Im medizinischen Kontext wird es folgendermaßen unterschieden:

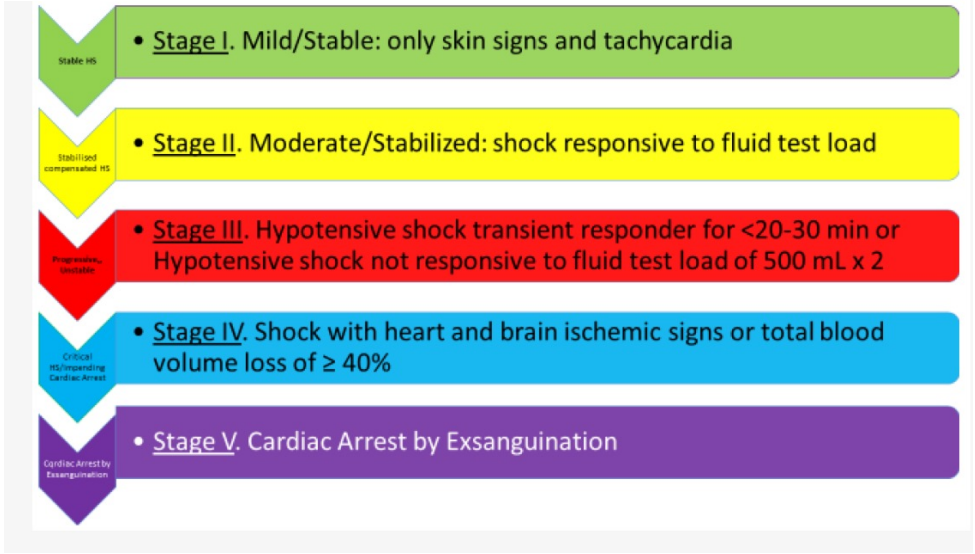
•**Vollblutspende (whole blood donation):** Die klassische Blutspende, bei der das Blut als Ganzes abgenommen und im Labor meist in verschiedene Komponenten aufgeteilt wird.

•**Vollbluttransfusion:** Die direkte Gabe von ungetrenntem, frischem Vollblut, was insbesondere in der Notfall- und Militärmedizin wieder an Bedeutung gewonnen hat.

•**Labordiagnostik:** Die Untersuchung von Blutproben (oft mit Zusätzen wie EDTA), bei der das gesamte Material inklusive aller Zellen analysiert wird – im Gegensatz zu abzentrifugiertem Serum oder Plasma.

Should We Be Switching to Whole Blood Instead of Component Therapy in Hemorrhagic Shock?

REBELEM

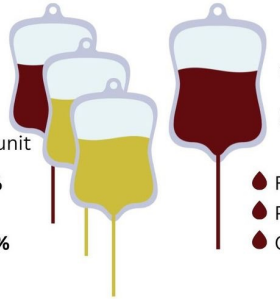


Difference between Component Therapy and Whole Blood

Component Therapy

680 mL RBC unit +
PLT unit + FFP unit + Cryo unit

- RBC concentration: **29%**
- Platelets: **80,000**
- Coagulation factors: **65%**



Whole Blood

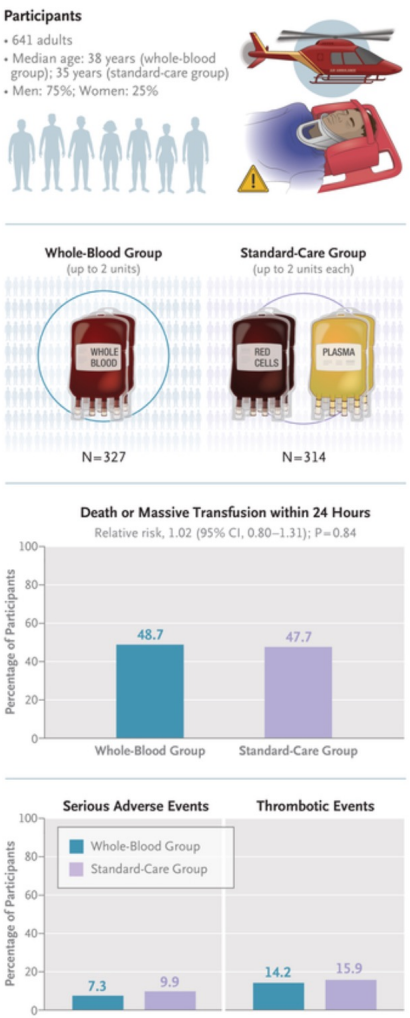
500 mL, single WB unit

- RBC concentration: **38-50 %**
- Platelets: **15,000-400,000**
- Coagulation factors: **100%**

Prehospital Whole Blood in Traumatic Hemorrhage — A Randomized Controlled Trial

Whole-blood transfusion has recently gained favor in the management of severe hemorrhage; however, data from large clinical trials evaluating its clinical effectiveness and safety are lacking.

We conducted a pragmatic, phase 3, multicenter, unblinded, randomized, superiority trial across 10 air ambulance services in England. Patients with major traumatic hemorrhage who were attended by a participating air ambulance service were randomly assigned to receive either whole-blood transfusion (up to 2 units) or standard care with blood components (up to 2 units each of red cells and plasma) before arrival at the hospital. The primary outcome was a composite of death from any cause or massive transfusion (≥10 units of blood components or products) within 24 hours after randomization.



Blood transfusion is a lifesaving treatment in the management of severe traumatic hemorrhage. The debate surrounding the relative benefits of transfusing individual blood components (red cells, plasma, or platelets) as compared with whole blood is ongoing, with a growing emphasis on early prehospital transfusion, which is performed as close to the time of injury as possible before arrival at the hospital.

Whole blood combines red cells, plasma, and platelets, although its composition and specifications vary between countries. Several countries have implemented whole-blood transfusion into clinical practice, and international randomized trials are ongoing; however, robust evidence comparing the clinical effectiveness and safety of whole-blood transfusion with blood-component therapy is limited.

In the United Kingdom, prehospital transfusion by air ambulance teams usually involves the administration of red cells alone, or red cells and plasma as separate components. Recently, leukocyte-depleted platelet-rich whole blood, containing red cells, plasma, and platelets, has become available and can be stored at 4°C (±2°C) for up to 21 days. The use of a single bag streamlines logistics, shortens administration time, aids limited circulatory access, and decreases the risk of transfusion errors.

Patient Population

Given the pragmatic nature of the trial, administration of whole blood and standard care was based on clinician judgment and the standard criteria for initiation of blood transfusion for each air ambulance service. Patients of any age with a traumatic injury leading to prehospital transfusion for the treatment of major hemorrhage were eligible to participate. Patients were excluded if intravenous or intraosseous access could not be established, if they had a known objection to blood transfusion, or if they had received blood components or products before the arrival of the air ambulance service.

Randomization and Treatment

We randomly assigned blood boxes in a 1:1 ratio to be packed with either whole blood or standard blood components. Randomization was performed with the use of a centralized, Web-based service (Sealed Envelope).

Outcomes

The primary outcome was a composite of death from any cause or massive transfusion (defined as ≥10 units of any blood components in adults, and ≥40 ml per kilogram of body weight in pediatric participants [<16 years of age with a body weight of <50 kg]) within 24 hours after randomization.

Methods

Trial Design

The SWiFT trial was a pragmatic, phase 3, multicenter, unblinded, randomized, controlled, superiority trial involving trauma patients with life-threatening bleeding across 10 air ambulance services (comprising physician–paramedic clinical teams), who were received by 19 hospitals. We compared the outcomes in participants who were randomly assigned to receive leukocyte-depleted whole blood (group O, with low levels of anti-A and anti-B antibodies) with outcomes in participants who received red cells and plasma (the standard-care group) in the prehospital setting. No other aspects of patient care during transport or after hospital arrival were altered.

Safety Outcomes.

Outcome	Whole-Blood Group (N=327)	Standard-Care Group (N=314)	Total (N=641)
Serious adverse events*			
Total no. of events	31	37	68
Participants with ≥1 serious adverse event — no. (%)	24 (7.3)	31 (9.9)	55 (8.6)
Transfusion-associated adverse events reported to National Hemovigilance scheme up to 14 days after randomization			
Participants with ≥1 event — no. (%)	0	2 (0.6)	2 (0.3)
Thrombotic events within 30 days after randomization			
Pulmonary embolus — no./total no. (%)	17/268 (6.3)	17/252 (6.7)	34/520 (6.5)
Deep venous thrombosis — no./total no. (%)	13/268 (4.9)	11/252 (4.4)	24/520 (4.6)
Myocardial infarction — no./total no. (%)	0/268 (0.0)	1/252 (0.4)	1/520 (0.2)
Stroke — no./total no. (%)	6/268 (2.2)	7/252 (2.8)	13/520 (2.5)
Peripheral ischemia causing tissue loss — no./total no. (%)	1/268 (0.4)	2/252 (0.8)	3/520 (0.6)
Other — no./total no. (%)	11/268 (4.1)	9/252 (3.6)	20/520 (3.8)
Participants with ≥1 event — no./total no. (%)†	38/268 (14.2)	40/252 (15.9)	78/520 (15.0)

Demographic and Clinical Characteristics of the Participants at Baseline and Treatment Characteristics.

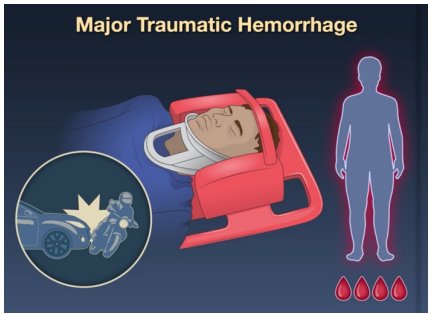
Characteristic	Whole-Blood Group (N=327)	Standard-Care Group (N=314)
Patient characteristics		
Median age (IQR) — yr†	38 (25–58)	35 (24–57)
Age <16 yr — no./total no. (%)	12/325 (3.7)	9/314 (2.9)
Male sex — no./total no. (%)‡	228/306 (74.5)	221/289 (76.5)
Median estimated weight on arrival of air ambulance service (IQR) — kg§	80 (70–90)	80 (70–90)
Injury characteristics		
Injury type — no./total no. (%)		
Blunt	238/325 (73.2)	214/309 (69.3)
Penetrating	87/325 (26.8)	95/309 (30.7)
Abbreviated Injury Scale score for the head — no./total no. (%)¶		
<3	127/219 (58.0)	104/196 (53.1)
≥3	92/219 (42.0)	92/196 (46.9)
Median Injury Severity Score (IQR)‖	33 (18–48)	34 (18–45)
Prehospital measurements**		
Median systolic blood pressure (IQR) — mm Hg	95 (75–121)	96 (79–120)
Median heart rate (IQR) — beats/min	110 (85–129)	110 (83–130)
Median respiratory rate (IQR) — breaths/min	22 (16–29)	23 (17–30)
Median oxygen saturation (IQR) — %††	95 (85–99)	94 (85–99)
Glasgow Coma Scale score — no./total no. (%)‡‡		
≤8	126/317 (39.7)	116/310 (37.4)
9–12	38/317 (12.0)	40/310 (12.9)
≥13	153/317 (48.3)	154/310 (49.7)
Median Glasgow Coma Scale score (IQR)	12 (5–15)	12 (6–15)
Prehospital treatment characteristics		
Intervention — no./total no. (%)§§		
Airway support	142/289 (49.1)	133/266 (50.0)
Breathing support	139/289 (48.1)	141/266 (53.0)
Thoracostomy	80/289 (27.7)	68/266 (25.6)
Spinal immobilization	118/289 (40.8)	116/266 (43.6)
Chest drain	8/289 (2.8)	10/266 (3.8)
Other	132/289 (45.7)	120/266 (45.1)
Median age of blood transfused (IQR) — days¶¶	13.5 (10–17)	18 (13–22.3)

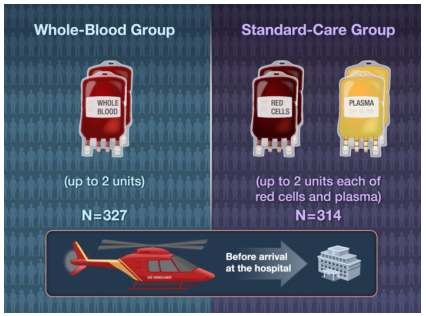
Outcomes

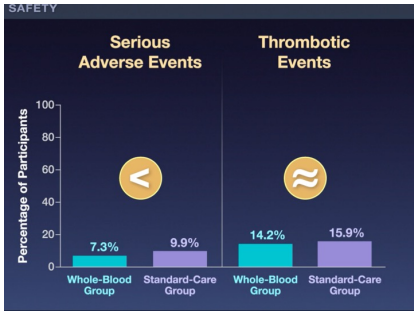
Outcome	Whole-Blood Group (N=327)	Standard-Care Group (N=314)	Relative Risk (95% CI)*	P Value†
Death or massive transfusion within 24 hours after randomization — no./total no. (%)				
Modified intention-to-treat population	153/314 (48.7)	144/302 (47.7)	1.02 (0.80–1.31)	0.84
Per-protocol population	145/291 (49.8)	130/273 (47.6)	1.05 (0.83–1.32)	

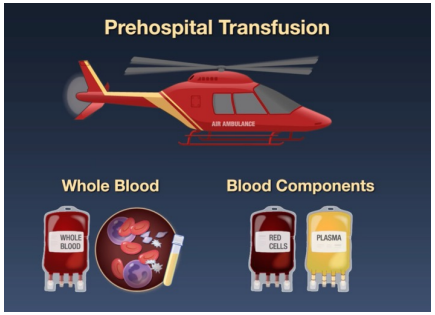
Secondary outcomes

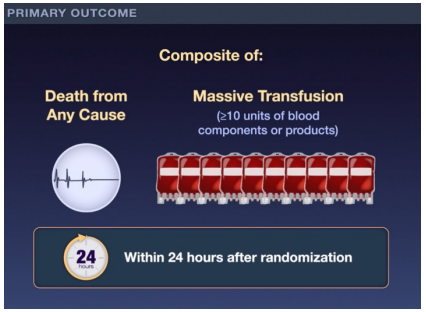
Population and Outcome	Whole-Blood Group (N=327)	Standard-Care Group (N=314)	Treatment Difference (95% CI)†
mITT			
Death from any cause — no./total no. (%)‡			
6 hr after randomization	27/318 (8.5)	22/301 (7.3)	RR, 1.16 (0.38–3.55)
24 hr after randomization	32/317 (10.1)	30/301 (10.0)	RR, 1.02 (0.39–2.66)
30 days after randomization	82/298 (27.5)	73/281 (26.0)	RR, 1.06 (0.70–1.61); HR, 1.08 (0.79–1.48)
90 days after randomization	87/286 (30.4)	74/272 (27.2)	RR, 1.12 (0.74–1.70); HR, 1.13 (0.83–1.55)
Massive transfusion — no./total no. (%)‡	136/303 (44.9)	123/290 (42.4)	RR, 1.07 (0.80–1.41)
Units of blood component received in the 24 hr after randomization, including prehospital transfusions — median (IQR); no. of participants with data¶			
Whole blood	4 (2–4); 314	4 (2–4); 7	RRa, NA
Red cells	4 (2–7); 220	4 (2–7); 294	RRa, 1.02 (0.85–1.22)
Fresh-frozen plasma	4 (2–7); 191	3 (2–6); 289	RRa, 1.14 (0.94–1.38)
Lyophilized plasma	2 (1–4); 11	2 (2–4); 18	RRa, NA
Platelets	1 (1–2); 94	1 (1–2); 89	RRa, 0.95 (0.58–1.54)
Cryoprecipitate	2 (2–3); 85	2 (2–4); 82	RRa, 0.91 (0.67–1.22)
Octaplas	4 (2–4); 4	4 (3–6); 3	RRa, NA
mITT minus those who died before arrival at acute care hospital‖			
Prothrombin time above normal range on hospital arrival — no./total no. (%)	94/231 (40.7)	71/233 (30.5)	RR, 1.31 (1.10–1.56)
mITT minus those who died before arrival at acute care hospital or withdrew within 30 days after randomization††**			
Overall days free from organ failure within 30 days after randomization — median (IQR); no. of participants with data	22 (0–29); 285	21 (0–29); 266	
Days free from advanced cardiovascular support — median (IQR); no. of participants with data	27 (12–30); 285	27 (10–30); 266	
Days free from advanced respiratory support — median (IQR); no. of participants with data	23 (1–29); 285	22 (0–29); 266	
Days free from advanced renal support — median (IQR); no. of participants with data	30 (18–30); 285	30 (24–30); 266	
mITT minus those who died before arrival at acute care hospital or withdrew within 90 days after randomization††‡‡			
Time in critical care up to 90 days — median (IQR); no. of participants with data	8 (4–19.5); 184	8 (3–19); 180	
Time in acute care hospital up to 90 days — median (IQR); no. of participants with data	17.5 (6–41); 300	20 (6–48); 284	

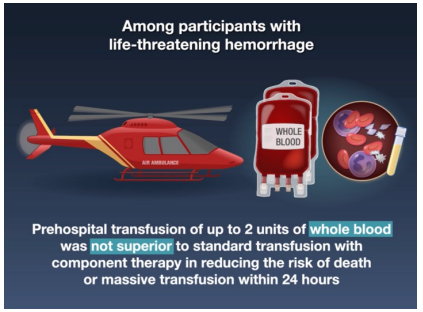

Major Traumatic Hemorrhage

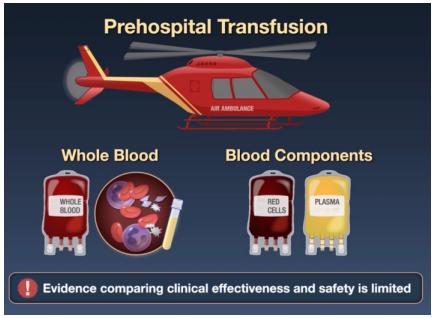

Whole-Blood Group
Standard-Care Group
WHOLE BLOOD
RED CELLS
PLASMA
(up to 2 units)
(up to 2 units each of red cells and plasma)
N=327
N=314
Before arrival at the hospital

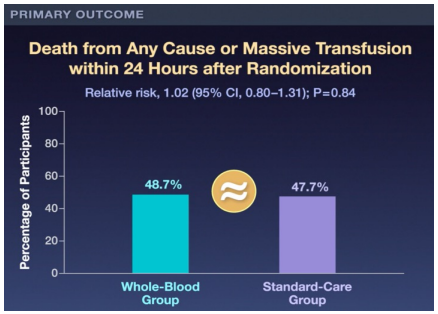

SAFETY
Serious Adverse Events
Thrombotic Events
Percentage of Participants
100
80
60
40
20
0
7.3%
9.9%
14.2%
15.9%
Whole-Blood Group
Standard-Care Group
Whole-Blood Group
Standard-Care Group


Prehospital Transfusion
AIR AMBULANCE
Whole Blood
Blood Components
WHOLE BLOOD
RED CELLS
PLASMA


PRIMARY OUTCOME
Composite of:
Death from Any Cause
Massive Transfusion
(≥10 units of blood components or products)
24 HOURS
Within 24 hours after randomization

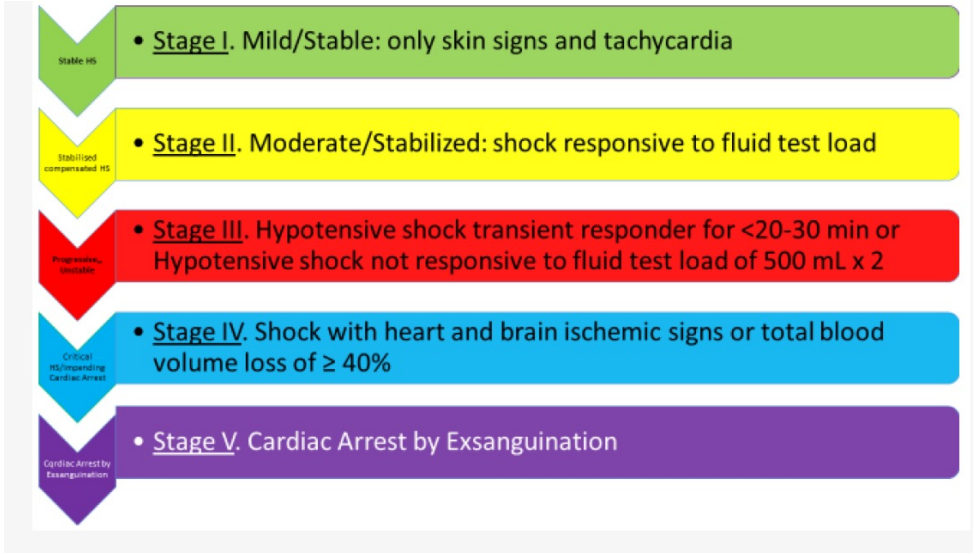

Among participants with life-threatening hemorrhage
AIR AMBULANCE
WHOLE BLOOD
Prehospital transfusion of up to 2 units of whole blood was not superior to standard transfusion with component therapy in reducing the risk of death or massive transfusion within 24 hours

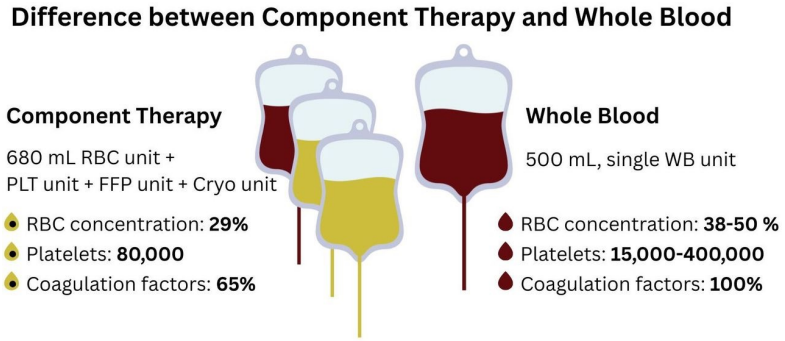

Prehospital Transfusion
AIR AMBULANCE
Whole Blood
Blood Components
WHOLE BLOOD
RED CELLS
PLASMA
Evidence comparing clinical effectiveness and safety is limited


PRIMARY OUTCOME
Death from Any Cause or Massive Transfusion within 24 Hours after Randomization
Relative risk, 1.02 (95% CI, 0.80–1.31); P=0.84
Percentage of Participants
100
80
60
40
20
0
48.7%
47.7%
Whole-Blood Group
Standard-Care Group

Should We Be Switching to Whole Blood Instead of Component Therapy in Hemorrhagic Shock?

REBELEM



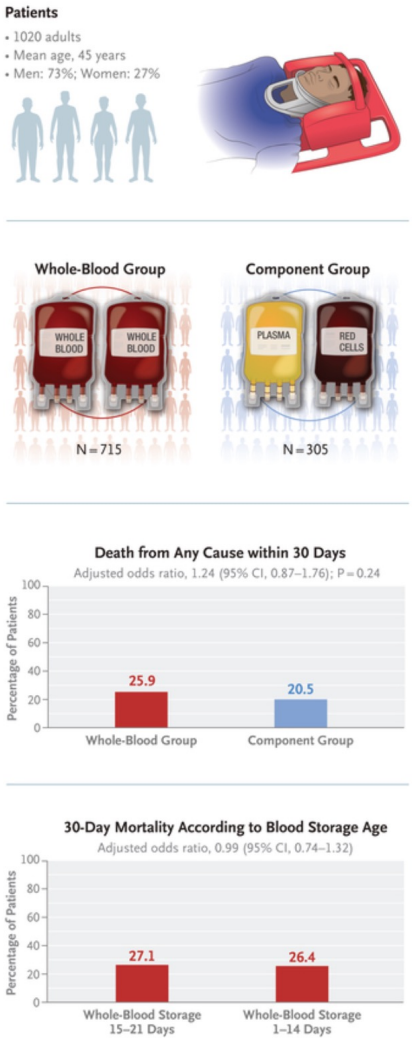


Whole blood transfusions are generally cheaper and more cost-effective than component transfusions for massive hemorrhage and trauma. While individual acquisition costs of whole blood units can sometimes be comparable to a single component (like packed red blood cells), whole blood use dramatically lowers total transfusion charges, overall volume wasted, and ancillary supply costs per patient.

Prehospital Resuscitation with Type O Whole Blood for Trauma and Hemorrhage

Blood transfusion before arrival at a hospital reduces mortality from traumatic hemorrhage and shock. Whether transfusion with whole blood is more beneficial than transfusion with blood components is uncertain, as are the effects of the length of time that blood products are in storage between donation and transfusion.

In this pragmatic, multicenter, phase 3, cluster-randomized trial, we assigned 44 air medical bases in a 2:1 ratio to the use of up to 2 units of whole blood or as-indicated blood components (plasma, red cells, or both) for prehospital transfusion in trauma patients during 1-month blocks. The primary outcome was death from any cause within 30 days after randomization. An observational substudy assessed outcomes according to the storage age of whole blood.



Treatment with low-titer group O whole blood (which has low anti-A and anti-B antibody titers) is increasingly used in both military and civilian settings because the logistics of transfusion are simpler than those with blood components and the blood is widely available from donors. Whole blood can provide rapid, balanced volume resuscitation and concomitant reversal of coagulopathy. Multiple observational studies have shown that resuscitation with whole blood is safe and is associated with better outcomes than resuscitation with blood components. Despite benefits in the early hospital setting, high-level evidence is limited with regard to the efficacy and safety of transfusion with whole blood in the prehospital phase of care. In addition, knowledge of whether any diminution of hemostatic potential occurs during storage of whole blood remains limited.

The Type O Whole Blood and Assessment of Age during Prehospital Resuscitation (TOWAR) trial was designed to evaluate the safety and efficacy of prehospital transfusion with low-titer group O whole blood as compared with blood components, as well as to characterize differences in outcome associated with the storage age of whole blood, in patients with severe injuries that warranted transfusion owing to risk of hemorrhagic shock. We hypothesized that prehospital transfusion with low-titer group O whole blood would lead to lower 30-day mortality than transfusion with blood components.

Patient Population

Patients transferred from the scene of injury or a referring emergency department to a participating trauma center were eligible for enrollment in the trial if they had had at least one episode of hypotension (defined as a systolic blood pressure of ≤90 mm Hg) and tachycardia (defined as a heart rate of ≥108 beats per minute) or if they had had severe hypotension (defined as a systolic blood pressure of ≤70 mm Hg) without tachycardia. Eligible patients were enrolled and underwent randomization during transport to the participating trauma center regardless of whether transfer originated at the scene of trauma or a referring emergency department.

Assignment of Intervention

Blood products were collected according to site blood-banking protocols and stored at air medical bases according to established procedures. Air medical bases assigned to use whole blood for a given month were stocked with 2 units of group O blood with anti-A and anti-B titers of less than 256 and a shelf life of up to 21 days.

Trial Outcomes

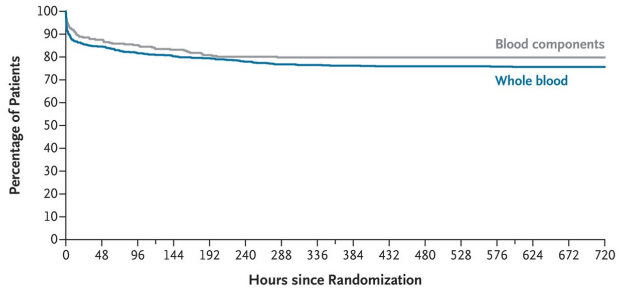
The primary outcome was death from any cause within 30 days after randomization.

Characteristic	Whole Blood (N=715)	Blood Components (N=305)
Mean age — yr	44.8±18.9	45.5±19.3
Female sex — no./total no. (%)	193/706 (27.3)	77/304 (25.3)
Race or ethnic group — no./total no. (%)†		
Non-White	168/631 (26.6)	80/289 (27.7)
Hispanic	65/613 (10.6)	31/263 (11.8)
Type of injury — no./total no. (%)		
Blunt	564/707 (79.8)	233/305 (76.4)
Penetrating	143/707 (20.2)	72/305 (23.6)
Mechanism of injury — no./total no. (%)‡		
Fall	53/707 (7.5)	28/305 (9.2)
Machinery	6/707 (0.8)	3/305 (1.0)
Motor vehicle collision	478/707 (67.6)	190/305 (62.3)
Struck by or against object	16/707 (2.3)	5/305 (1.6)
Firearm	107/707 (15.1)	51/305 (16.7)
Impalement	2/707 (0.3)	1/305 (0.3)
Stabbing	27/707 (3.8)	16/305 (5.2)
Other	45/707 (6.4)	19/305 (6.2)
Abbreviated Injury Scale score >2 — no./total no. (%)§		
Head and neck	260/661 (39.3)	106/290 (36.6)
Face	26/661 (3.9)	16/290 (5.5)
Chest	386/661 (58.4)	155/290 (53.4)
Abdomen	222/661 (33.6)	112/290 (38.6)
Limbs	268/661 (40.5)	120/290 (41.4)
External	11/661 (1.7)	3/290 (1.0)
Injury Severity Score — median (IQR)¶	25.0 (16.0–34.0)	23.0 (14.0–34.0)
Glasgow Coma Scale score — median (IQR)‖	11.0 (3.0–15.0)	13.0 (3.0–15.0)
Traumatic brain injury — no. (%)	296 (41.4)	109 (35.7)
Transfer site — no. (%)		
Scene of injury	507 (70.9)	215 (70.5)
Other hospital	208 (29.1)	90 (29.5)
Prehospital intervention — no./total no. (%)		
Intubation	389/715 (54.4)	147/304 (48.4)
Cardiopulmonary resuscitation	74/714 (10.4)	22/303 (7.3)
Defibrillation	12/714 (1.7)	3/302 (1.0)
Use of a tourniquet	94/715 (13.1)	49/305 (16.1)
Use of a pelvic binder	155/715 (21.7)	67/305 (22.0)
Treatment with tranexamic acid	298/713 (41.8)	114/304 (37.5)
Treatment with crystalloids or colloids	446/713 (62.6)	192/303 (63.4)

Outcomes

Outcome	Whole Blood (N=695)	Blood Components (N=298)	Effect Estimate (95% CI)†
Primary outcome			
Death within 30 days — no. (%)	180 (25.9)	61 (20.5)	1.24 (0.87 to 1.76)‡
Secondary outcomes			
Death within 3 hr — no./total no. (%)	64/679 (9.4)	16/298 (5.4)	1.72 (0.96 to 3.08)
Death within 6 hr — no./total no. (%)	76/679 (11.2)	21/298 (7.0)	1.55 (0.92 to 2.62)
Death within 24 hr — no./total no. (%)	98/679 (14.4)	33/298 (11.1)	1.25 (0.81 to 1.93)
In-hospital death — no./total no. (%)	171/689 (24.8)	58/298 (19.5)	1.25 (0.87 to 1.78)
Death from hemorrhage or exsanguination — no./total no. (%)§	61/677 (9.0)	23/295 (7.8)	1.08 (0.65 to 1.81)
Death from traumatic brain injury or herniation — no./total no. (%)§	61/677 (9.0)	23/295 (7.8)	0.98 (0.56 to 1.71)
Units transfused within 24 hr after arrival — median (IQR)			
Whole blood	0.0 (0.0 to 1.0)	0.0 (0.0 to 1.0)	0.91 (0.69 to 1.21)
Plasma	1.0 (0.0 to 4.0)	1.0 (0.0 to 5.0)	0.85 (0.66 to 1.11)
Platelets	0.0 (0.0 to 1.0)	0.0 (0.0 to 1.0)	0.86 (0.63 to 1.17)
Red cells	1.0 (0.0 to 4.0)	2.0 (0.0 to 5.0)	0.86 (0.67 to 1.09)
Cryoprecipitate	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.81 (0.49 to 1.32)
Hemostasis¶			
No. of patients/total no. (%)	619/694 (89.2)	277/296 (93.6)	0.61 (0.35 to 1.04)
Median time to hemostasis — min (IQR)	60.0 (60.0 to 78.0)	60.0 (60.0 to 80.0)	0.98 (0.88 to 1.09)
Multiple organ failure — no. (%)‖	98 (14.1)	37 (12.4)	1.12 (0.74 to 1.69)
Nosocomial infection — no. (%)	57 (8.2)	26 (8.7)	0.92 (0.55 to 1.54)
Acute respiratory distress syndrome — no. (%)‖	273 (39.3)	121 (40.6)	0.87 (0.66 to 1.17)
Coagulation measurements			
INR >1.5 within 1 hr after arrival — no./total no. (%)**	109/538 (20.3)	57/216 (26.4)	0.69 (0.46 to 1.02)
Median prothrombin time within 1 hr after arrival — sec (IQR)	14.2 (12.3 to 16.4)	14.5 (12.2 to 16.5)	0.05 (−0.68 to 0.78)

A Overall Survival According to Treatment Group



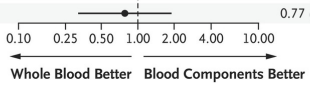
Log-rank test: χ^2=2.18; P=0.13

No. at Risk

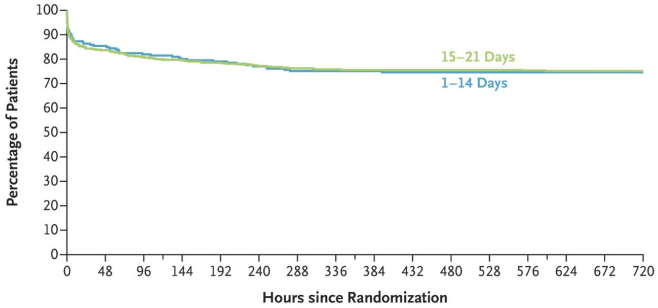
Blood components	297	249	239	238	237	237	237
Whole blood	681	552	532	520	518	516	516

B Subgroup Analysis of 30-Day Mortality

Subgroup	No. of Patients	Whole Blood	Blood Components	Odds Ratio (95% CI)
		no. of deaths/no. of patients (%)		
Overall	992	180/695 (25.9)	61/297 (20.5)	1.24 (0.87–1.76)
Head or neck AIS score >2				
Yes	359	81/254 (31.9)	35/105 (33.3)	0.92 (0.55–1.54)
No	566	70/388 (18.0)	25/178 (14.0)	1.20 (0.71–2.04)
Transfer site				
Scene of injury	703	133/491 (27.1)	47/212 (22.2)	1.26 (0.84–1.89)
Other hospital	290	47/204 (23.0)	14/86 (16.3)	1.21 (0.60–2.46)
Severe hypotension (≤70 mm Hg)				
Yes	543	130/377 (34.5)	40/166 (24.1)	1.59 (1.02–2.47)
No	450	50/318 (15.7)	21/132 (15.9)	0.84 (0.47–1.51)
Age				
18–55 yr	679	90/481 (18.7)	25/198 (12.6)	1.50 (0.86–2.61)
≥56 yr	307	85/209 (40.7)	35/98 (35.7)	1.31 (0.78–2.17)
Sex				
Male	720	130/498 (26.1)	46/222 (20.7)	1.23 (0.82–1.86)
Female	263	46/188 (24.5)	15/75 (20.0)	1.11 (0.54–2.26)
Race or ethnic group				
White	654	117/450 (26.0)	43/204 (21.1)	1.28 (0.84–1.95)
Non-White	244	29/165 (17.6)	13/79 (16.5)	0.79 (0.37–1.68)
Trauma center				
A	150	27/107 (25.2)	6/43 (14.0)	1.91 (0.68–5.31)
B	248	35/155 (22.6)	17/93 (18.3)	1.05 (0.52–2.10)
C	68	16/44 (36.4)	7/24 (29.2)	1.22 (0.38–3.95)
D, E, or K	64	11/54 (20.4)	4/10 (40.0)	0.40 (0.09–1.89)
F	39	7/30 (23.3)	3/9 (33.3)	1.04 (0.18–5.96)
G	116	19/88 (21.6)	4/28 (14.3)	1.50 (0.45–5.00)
H	62	14/42 (33.3)	4/20 (20.0)	2.15 (0.55–8.37)
I	113	32/85 (37.6)	6/28 (21.4)	2.33 (0.78–6.91)
J	133	19/90 (21.1)	10/43 (23.3)	0.77 (0.31–1.91)



A Overall Survival According to Blood Storage Age



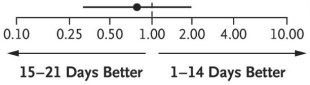
Log-rank test: χ^2=0.01; P=0.93

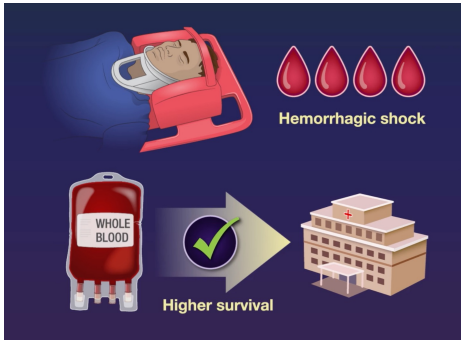
No. at Risk

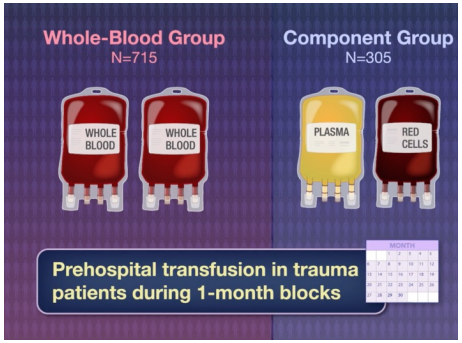
15–21 Days	205	168	159	155	153	153	153
1–14 Days	434	347	336	329	329	327	327

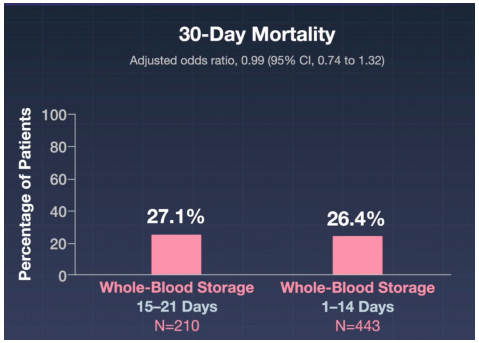
B Subgroup Analysis of 30-Day Mortality According to Blood Storage Age

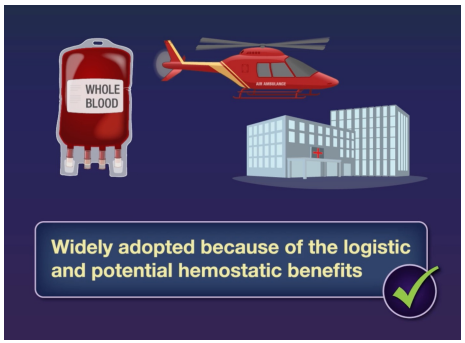
Subgroup	No. of Patients	15–21 Days	1–14 Days	Odds Ratio (95% CI)
		no. of deaths/no. of patients (%)		
Overall	653	57/210 (27.1)	117/443 (26.4)	0.99 (0.74–1.32)
Head or neck AIS score >2				
Yes	241	25/81 (30.9)	52/160 (32.5)	0.98 (0.50–1.94)
No	365	24/118 (20.3)	44/247 (17.8)	1.43 (0.78–2.61)
Transfer site				
Scene of injury	471	39/149 (26.2)	90/322 (28.0)	1.18 (0.69–2.02)
Other hospital	182	18/61 (29.5)	27/121 (22.3)	1.32 (0.57–3.08)
Severe hypotension (≤70 mm Hg)				
Yes	354	42/114 (36.8)	84/240 (35.0)	1.31 (0.75–2.30)
No	299	15/96 (15.6)	33/203 (16.3)	1.14 (0.52–2.49)
Age				
18–55 yr	452	26/140 (18.6)	61/312 (19.6)	1.41 (0.70–2.84)
≥56 yr	196	31/70 (44.3)	51/126 (40.5)	1.08 (0.56–2.08)
Sex				
Male	468	41/157 (26.1)	84/311 (27.0)	1.11 (0.65–1.91)
Female	176	15/50 (30.0)	30/126 (23.8)	1.63 (0.71–3.76)
Race or ethnic group				
White	425	38/127 (29.9)	75/298 (25.2)	1.29 (0.77–2.17)
Non-White	154	11/61 (18.0)	18/93 (19.4)	1.01 (0.39–2.63)
Trauma center				
A	98	13/37 (35.1)	14/61 (23.0)	1.18 (0.37–3.74)
B	153	5/37 (13.5)	30/116 (25.9)	0.90 (0.26–3.11)
C or H	75	6/15 (40.0)	20/60 (33.3)	0.67 (0.15–3.06)
D, E, F, or K	76	6/33 (18.2)	11/43 (25.6)	1.95 (0.50–7.57)
G or J	167	11/41 (26.8)	27/126 (21.4)	1.72 (0.64–4.62)
I	84	16/47 (34.0)	15/37 (40.5)	0.78 (0.31–1.96)

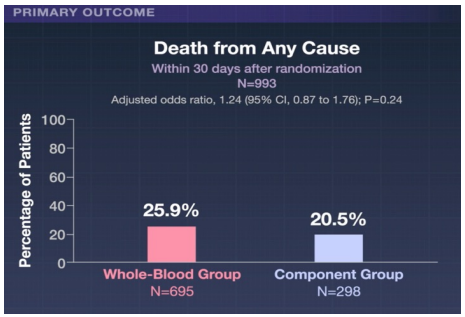


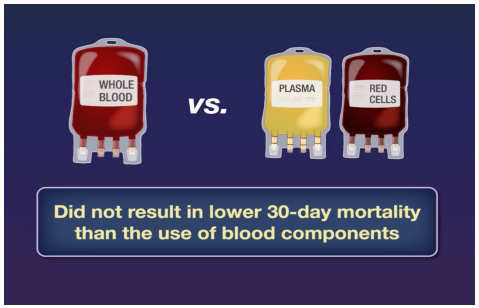

Hemorrhagic shock
WHOLE BLOOD
Higher survival

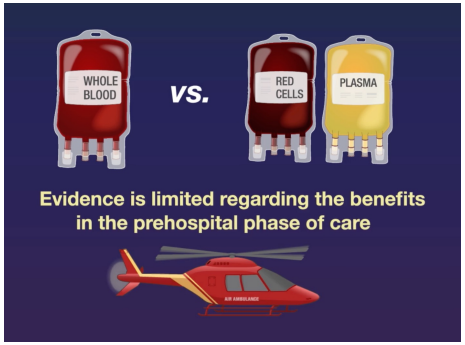

Whole-Blood Group
N=715
Component Group
N=305
WHOLE BLOOD
WHOLE BLOOD
PLASMA
RED CELLS
Prehospital transfusion in trauma patients during 1-month blocks

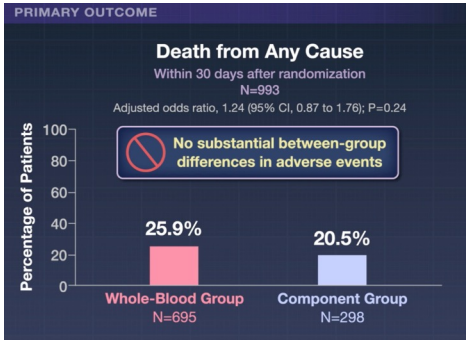

30-Day Mortality
Adjusted odds ratio, 0.99 (95% CI, 0.74 to 1.32)
Percentage of Patients
100
80
60
40
20
0
27.1%
26.4%
Whole-Blood Storage
15–21 Days
N=210
Whole-Blood Storage
1–14 Days
N=443


WHOLE BLOOD
Widely adopted because of the logistic and potential hemostatic benefits

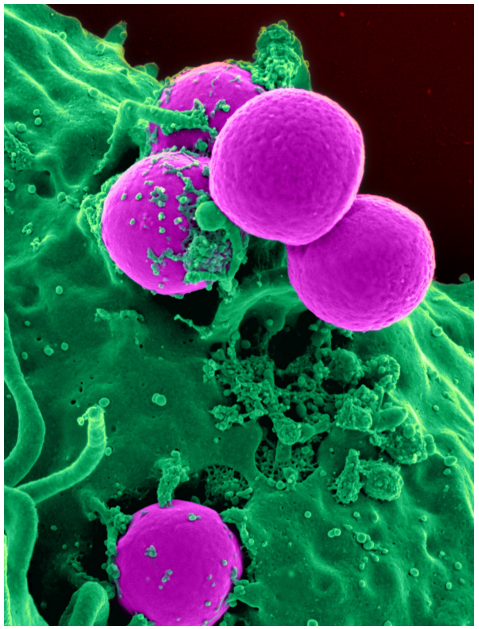

PRIMARY OUTCOME
Death from Any Cause
Within 30 days after randomization
N=993
Adjusted odds ratio, 1.24 (95% CI, 0.87 to 1.76); P=0.24
Percentage of Patients
100
80
60
40
20
0
25.9%
20.5%
Whole-Blood Group
N=695
Component Group
N=298

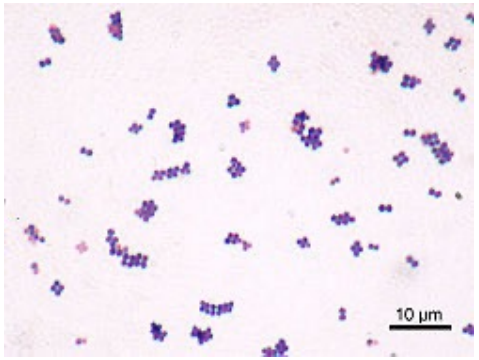

WHOLE BLOOD
vs.
PLASMA
RED CELLS
Did not result in lower 30-day mortality than the use of blood components


WHOLE BLOOD
vs.
RED CELLS
PLASMA
Evidence is limited regarding the benefits in the prehospital phase of care


PRIMARY OUTCOME
Death from Any Cause
Within 30 days after randomization
N=993
Adjusted odds ratio, 1.24 (95% CI, 0.87 to 1.76); P=0.24
No substantial between-group differences in adverse events
Percentage of Patients
100
80
60
40
20
0
25.9%
20.5%
Whole-Blood Group
N=695
Component Group
N=298

Methicillin-sensibler Staphylococcus aureus (MSSA) bezeichnet Bakterienstämme der Art *Staphylococcus aureus*, die im Gegensatz zu MRSA **empfindlich (sensibel) gegenüber dem Beta-Laktam-Antibiotikum Methicillin** und verwandten Wirkstoffen sind. Es handelt sich dabei um den bakteriellen Wildtyp.





Mikrobiologische Grundlagen

•**Keine mecA-Resistenz**: MSSA-Stämmen fehlt das *mecA*-Gen. Dieses Gen verändert bei MRSA die Penicillin-Bindeproteine (PBP2a), wodurch Beta-Laktam-Antibiotika nicht mehr binden können.

•**Penicillinase-Bildung**: Obwohl MSSA gegen Methicillin wirkt, sind über 80 % dieser Stämme resistent gegen einfaches Penicillin. Sie bilden Enzyme (Penicillinasen), die einfaches Penicillin spalten. Daher sind modifizierte Beta-Laktame notwendig.

•**Natürliches Vorkommen**: Das Bakterium besiedelt als normaler Kommensale bei etwa 20 bis 30 % aller gesunden Menschen dauerhaft die Haut und die Schleimhäute, insbesondere den Nasenvorhof.

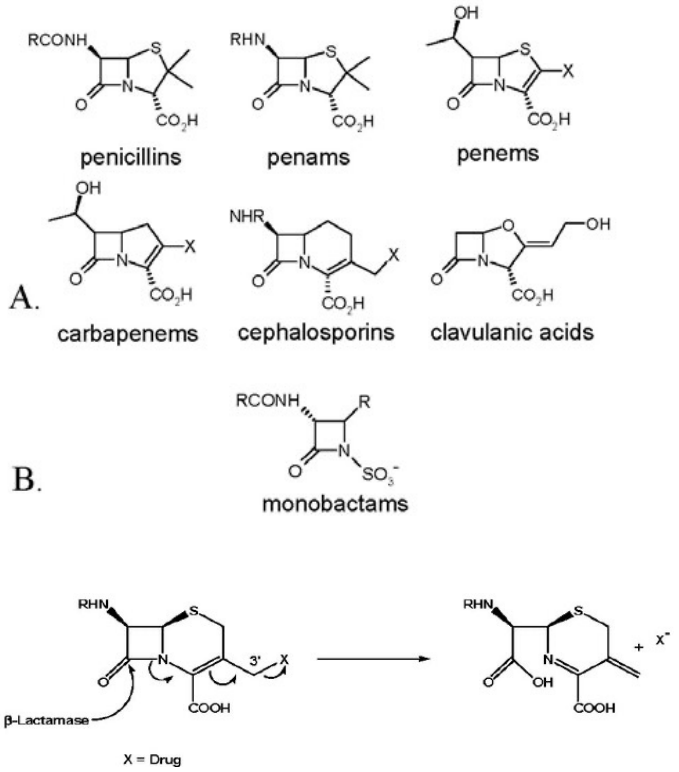
Cefazolin ist ein parenterales Beta-Laktam-Antibiotikum aus der Gruppe der **Cephalosporine der 1. Generation**, dessen Stabilität gegenüber bakteriellen **Beta-Laktamasen** stark vom jeweiligen Erregertyp abhängt.

Da Beta-Laktamasen Enzyme sind, die den für die Wirkung unentbehrlichen Beta-Laktam-Ring spalten, entscheidet das Vorhandensein bestimmter Enzymtypen über die Wirksamkeit von Cefazolin.

Stabilität bei Gram-positiven Erregern

•**Gute Stabilität gegen Penicillinasen**: Cefazolin besitzt eine weitgehende Stabilität gegenüber klassischen Penicillinasen (z. B. von *Staphylococcus aureus*). Es wird daher standardmäßig bei Infektionen durch Methicillin-sensible Staphylokokken (MSSA) eingesetzt.

•**Der Inokulum-Effekt**: Bei einigen Stämmen von *S. aureus* (vor allem Typ-A-Beta-Laktamase-Bildnern) kann es bei einer sehr hohen Bakteriendichte (Inokulum) zu einer teilweisen Inaktivierung des Antibiotikums kommen.

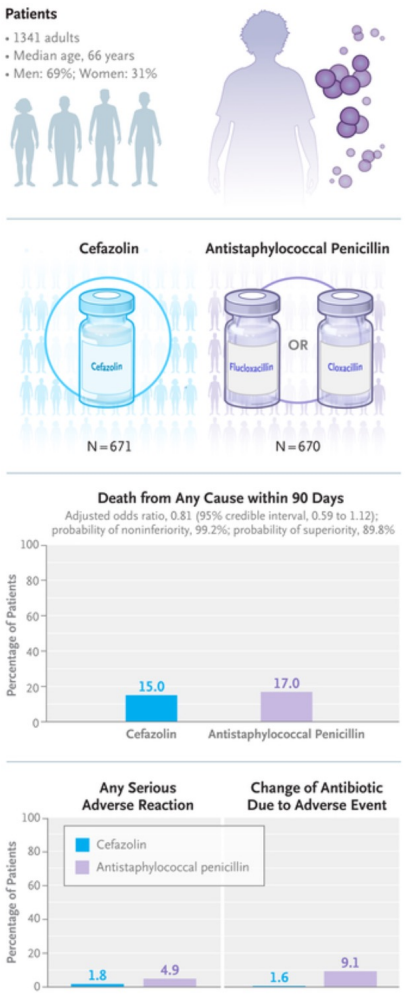


Der Cefazolin-Inokulum-Effekt ist ein Phänomen, bei dem Methicillin-sensible *Staphylococcus aureus*-Stämme (MSSA) bei hoher Bakteriendichte (Inokulum) resistent gegen Cefazolin werden. Obwohl sie im Standardtest sensibel erscheinen, führt die große Erregermenge zu einer massiven Produktion des Enzyms β-Laktamase, wodurch das Antibiotikum unwirksam wird und Therapieversagen droht.

Cefazolin for Methicillin-Susceptible *Staphylococcus aureus* Bacteremia

Staphylococcus aureus bacteremia is associated with high mortality. Whether cefazolin or an antistaphylococcal penicillin should be preferred for the treatment of methicillin-susceptible *S. aureus* bacteremia is unclear.

In an ongoing international Bayesian adaptive platform trial, we conducted an open-label, randomized comparison of cefazolin with an antistaphylococcal penicillin (flucloxacillin or cloxacillin) in adult patients with penicillin-resistant, methicillin-susceptible *S. aureus* bacteremia. The primary outcome, which was evaluated with a hierarchical Bayesian logistic-regression model, was death from any cause within 90 days after enrollment in the platform. We assessed the posterior probability of the noninferiority of cefazolin to flucloxacillin or cloxacillin (with the criterion for noninferiority prespecified as an adjusted odds ratio of <1.2, which approximates an absolute difference in mortality of <2.5 percentage points if mortality in the antistaphylococcal-penicillin group is 15%), as well as the posterior probability of superiority (with the criterion of an adjusted odds ratio of <1.0). Secondary safety outcomes included the development of acute kidney injury within 14 days.



Staphylococcus aureus bacteremia is a leading cause of bacteria-related death worldwide, with more than one in four affected patients dying within 90 days. Although there are accepted best practices in the management of *S. aureus* bacteremia, the preferred antibiotic for the treatment of methicillin-susceptible *S. aureus* bacteremia is unclear. Expert opinion from endocarditis guidelines favors the antistaphylococcal penicillins (e.g., nafcillin, oxacillin, cloxacillin, or flucloxacillin) over cefazolin owing to theoretical concerns about the cefazolin inoculum effect, an in vitro destruction of cefazolin by beta-lactamases, which may be relevant in high-burden infections. However, meta-analyses of observational studies suggest that cefazolin may be superior to antistaphylococcal penicillins for 30-day mortality (odds ratio, 0.73; 95% confidence interval [CI], 0.62 to 0.85), with a more favorable adverse-event profile.

Given that observational analyses may be subject to multiple biases, a randomized clinical trial is the most reliable way to inform disease management. We launched the *Staphylococcus aureus* Network Adaptive Platform (SNAP) trial in 2022 to answer multiple questions related to the treatment of patients with *S. aureus* bacteremia. Within the SNAP trial, we evaluated the efficacy and safety of cefazolin for the treatment of methicillin-susceptible *S. aureus* bacteremia.

Trial Design and Oversight

We used a Bayesian adaptive platform to conduct a pragmatic, open-label, randomized, noninferiority comparison of cefazolin with an antistaphylococcal penicillin (cloxacillin or flucloxacillin, depending on the country) at 91 sites in eight countries (Australia, Canada, Israel, the Netherlands, New Zealand, Singapore, South Africa, and the United Kingdom).

Patients

We enrolled hospitalized patients with *S. aureus* bacteremia in the platform within 72 hours after the collection of the blood sample for the index blood culture (the first culture positive for *S. aureus*). The analyses described here involved adults at least 18 years of age. The pediatric trial is ongoing.

Interventions

The recommended dose was 2 g of cefazolin administered intravenously every 8 hours (or every 6 hours for critical illness or endocarditis), 2 g of flucloxacillin administered intravenously every 6 hours (or every 4 hours for critical illness or endocarditis), or 2 g of cloxacillin administered intravenously every 4 hours, with dose adjustments according to renal function.

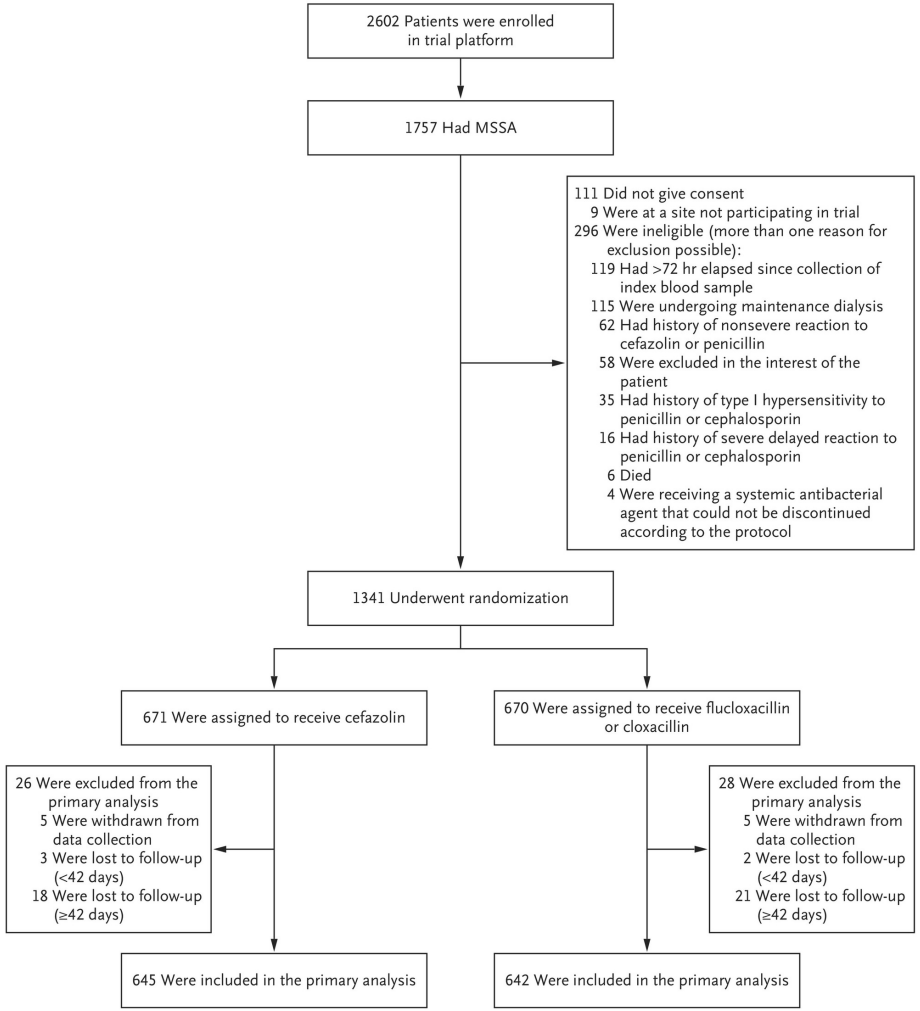
Outcomes

The primary outcome for the platform and domain was death from any cause within 90 days after platform entry. Secondary platform outcomes included death from any cause within 14, 28, and 42 days; microbiologic treatment failure and diagnosis of new foci of infection between days 15 and 90; and *Clostridioides difficile* infection within 90 days.

Patients

Characteristic	Cefazolin (N = 671)	Flucloxacillin or Cloxacillin (N = 670)
Demographic characteristics		
Median age (IQR) — yr	66 (53–76)	66 (52–77)
Female sex — no. (%)	215 (32.0)	206 (30.7)
Median weight (IQR) — kg	82.0 (69.0–96.8)	80.0 (68.0–95.0)
Coexisting conditions — no. (%)		
Diabetes mellitus	231 (34.4)	217 (32.4)
Chronic kidney disease†	96 (14.3)	93 (13.9)
Cirrhosis	34 (5.1)	30 (4.5)
Cancer leading to any surgical or medical therapy within past 12 mo‡	95 (14.2)	76 (11.3)
Dementia	23 (3.4)	32 (4.8)
Iatrogenic immunosuppression§	105 (15.6)	84 (12.5)
Implanted intravascular prosthesis or endovascular device¶	64 (9.5)	58 (8.7)
Previous infective endocarditis	11 (1.6)	10 (1.5)
Underlying cardiac abnormality conferring predisposition to endocarditis‖	50 (7.5)	42 (6.3)
Injection drug use within past 6 mo	31 (4.6)	52 (7.8)
Limitations to care**	80 (11.9)	84 (12.5)
Prognostic factors		
Median time to index blood culture positivity (IQR) — hr	15.7 (12.0–21.0)	15.3 (12.0–20.7)
Median time from index blood culture to entry in trial platform (IQR) — hr	52.3 (43.5–65.5)	50.9 (42.3–64.7)
Median time from index blood culture to entry in silo (IQR) — hr	62.2 (50.2–67.9)	61.1 (50.0–67.5)
Inpatient in intensive care unit at time of recruitment — no. (%)	74 (11.0)	72 (10.7)
Median Pitt bacteremia score (IQR)††	0 (0–1)	0 (0–1)
Median C-reactive protein level (IQR) — mg/liter	192.0 (113.5–266.5)	203.1 (122–283.8)

In most clinical settings, **MSSA (Methicillin-Susceptible *Staphylococcus aureus*)** infections are more common than **MRSA (Methicillin-Resistant *Staphylococcus aureus*)**, typically accounting for about **60–80%** of all *Staphylococcus aureus* infections, while MRSA makes up the remaining **20–40%**

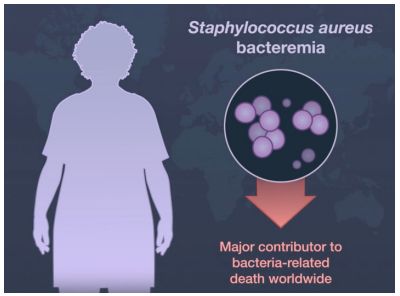


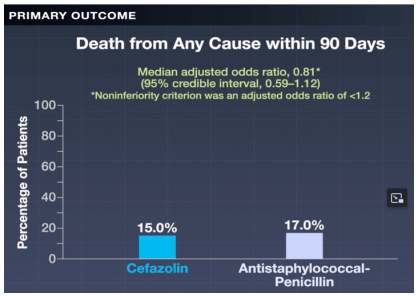
Foci of infection

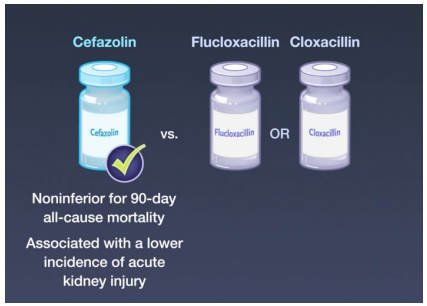
Focus or Type of Infection	Cefazolin (N=671)	Flucloxacillin or Cloxacillin (N=670)
	number of patients (percent)	
Osteoarticular infection	220 (32.8)	210 (31.3)
Septic arthritis or extra-axial osteomyelitis	167 (24.9)	151 (22.5)
Vertebral osteomyelitis, septic discitis, or both	61 (9.1)	59 (8.8)
Epidural abscess	45 (6.7)	49 (7.3)
Orthopedic hardware–associated infection	34 (5.1)	31 (4.6)
Skin and soft-tissue infection	177 (26.4)	204 (30.4)
Isolated skin and soft-tissue infection	127 (18.9)	136 (20.3)
Intravascular catheter–associated infection	103 (15.4)	102 (15.2)
Isolated intravascular catheter–associated infection	91 (13.6)	91 (13.6)
Primary bacteremia, with no other focus identified	81 (12.1)	80 (11.9)
Endocarditis	55 (8.2)	57 (8.5)
Native-valve infection on the left side	35 (5.2)	33 (4.9)
Native-valve infection on the right side	13 (1.9)	19 (2.8)
Prosthetic-valve infection	13 (1.9)	9 (1.3)
Pleuropulmonary infection	40 (6.0)	42 (6.3)
Other deep focus	27 (4.0)	37 (5.5)
Genitourinary infection	24 (3.6)	22 (3.3)
Native vascular or vascular-graft infection	15 (2.2)	16 (2.4)
Unspecified	14 (2.1)	13 (1.9)
Infection associated with cardiac device or other implantable nonorthopedic device	12 (1.8)	16 (2.4)
Central nervous system infection	5 (0.7)	2 (0.3)

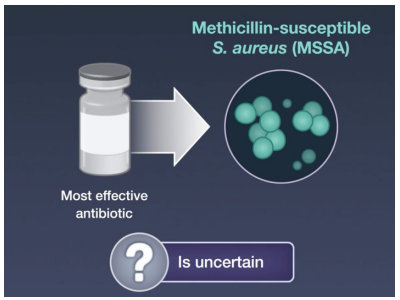
Outcomes

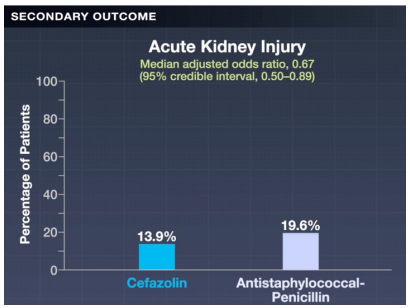
Outcome	Cefazolin (N=671)	Flucloxacillin or Cloxacillin (N=670)	Odds Ratio (95% Credible Interval)*	Probability of Noninferiority†	Probability of Superiority†
	number/total number (percent)			*percent*	
Primary outcome					
Death from any cause within 90 days					
Primary analysis	97/645 (15.0)	109/642 (17.0)	0.81 (0.59–1.12)	99.2	89.8
Analysis with all patients with missing data assumed to be dead	123/671 (18.3)	137/670 (20.4)	0.83 (0.63–1.10)	99.6	90.7
Analysis with all patients with missing data assumed to be alive	97/671 (14.5)	109/670 (16.3)	0.81 (0.59–1.11)	99.3	90.5
Analysis of protocol-adherent population	81/589 (13.8)	73/520 (14.0)	0.88 (0.61–1.26)	95.4	76.0
Secondary outcomes					
Acute kidney injury within 14 days‡	92/660 (13.9)	127/648 (19.6)	0.67 (0.50–0.89)	>99.9	99.7
Acute liver injury within 14 days§	75/574 (13.1)	78/562 (13.9)	0.96 (0.68–1.35)	90.0	59.7
Any serious adverse reaction related to trial drug	12/671 (1.8)	33/670 (4.9)	0.41 (0.21–0.77)	99.9	99.8
Death by day 14	25/667 (3.7)	37/665 (5.6)	0.67 (0.39–1.11)	NR	NR
Death by day 28	47/665 (7.1)	70/665 (10.5)	0.61 (0.41–0.91)	NR	NR
Death by day 42	63/663 (9.5)	86/662 (13.0)	0.66 (0.46–0.94)	NR	NR
Change of antibiotic due to perceived inefficacy	14/671 (2.1)	16/670 (2.4)	1.05 (0.51–2.10)	NR	NR
Microbiologic treatment failure after day 14	18/587 (3.1)	12/566 (2.1)	1.41 (0.71–2.78)	NR	NR
Diagnosis of new foci of infection after day 14	28/623 (4.5)	30/609 (4.9)	0.87 (0.53–1.45)	NR	NR
Change of antibiotic due to adverse event	11/671 (1.6)	61/670 (9.1)	0.21 (0.11–0.38)	NR	NR
Initiation of renal-replacement therapy within 90 days	17/668 (2.5)	27/657 (4.1)	0.61 (0.33–1.11)	NR	NR
Ongoing renal-replacement therapy at 90 days	4/662 (0.6)	3/643 (0.5)	1.00 (0.31–3.16)	NR	NR
Clostridioides difficile infection¶	14/664 (2.1)	10/661 (1.5)	1.28 (0.60–2.66)	NR	NR
Intravenous catheter complication leading to removal‖	22/668 (3.3)	33/665 (5.0)	0.68 (0.39–1.16)	NR	NR

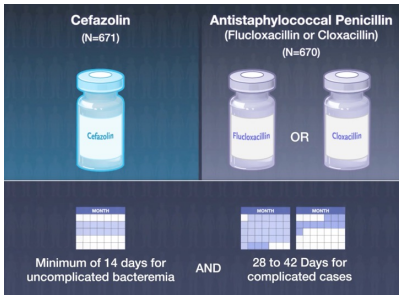


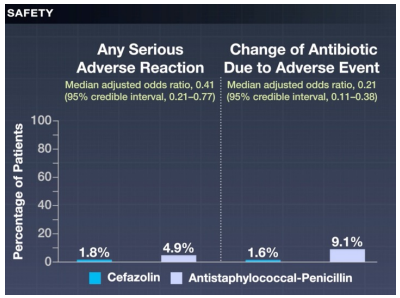






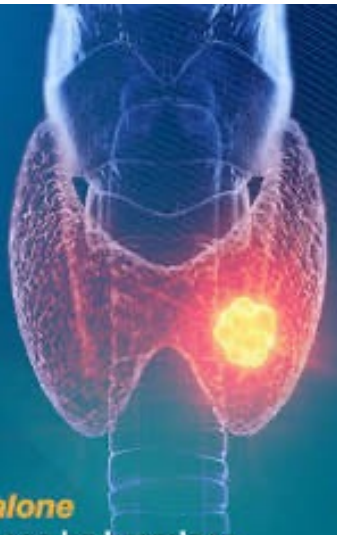






Cefazolin was patented in 1967 and introduced into medical and commercial practice in the early 1970s. It was originally approved for use in the United States in 1973.

THYROID CANCER AWARENESS



SIZE ≠ RISK

A key message for the public is that ***size alone does not determine risk***. Large nodules can be harmless, while small ones may be suspicious. Warning signs include:

- Persistent/enlarging neck lump
- Hoarseness
- Difficulty swallowing
- Swollen lymph nodes

Suspicious nodules may require a ***fine needle aspiration biopsy (FNA)*** for accurate diagnosis.

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THYROID PAPILLARY CARCINOMA: MOST COMMON MALIGNANCY

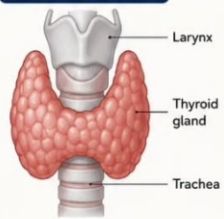
Papillary thyroid carcinoma (PTC) accounts for ~80–85% of all thyroid cancers and is the **most common endocrine malignancy.**

KEY POINT
Generally indolent but with excellent prognosis when diagnosed early.

EPIDEMIOLOGY

- Most common thyroid cancer (~80–85%).
- More common in females (F:M = 3:1).
- Occurs at any age; peak in 30–50 years.
- Incidence increasing worldwide (partly due to detection of small, subclinical tumors).

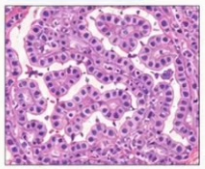
ANATOMY: THYROID



RISK FACTORS

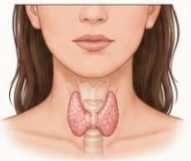
- Ionizing radiation exposure (especially in childhood)
- Genetic predisposition (e.g., BRAF, RET/PTC rearrangements)
- Female sex
- Family history of thyroid cancer or syndromes (e.g., FAP, Cowden)

PATHOLOGY



- Papillary architecture with fibrovascular cores.
- Characteristic nuclear features (hallmarks):
  - Orphan Annie eye nuclei
  - Nuclear grooves
  - Pseudoinclusions
  - Clearing of chromatin
- Psammoma bodies common.

CLINICAL PRESENTATION



- Painless thyroid nodule (often incidental).
- Cervical lymphadenopathy (common; usually metastatic to central compartment).
- Usually no compressive symptoms until late.

DIAGNOSIS

Clinical exam + neck ultrasound (hypoechoic nodule, microcalcifications, irregular margins, taller-than-wide).

USG-guided FNA (Bethesda System): PTC usually reported as Bethesda VI (Malignant).

Molecular markers (may support diagnosis/prognosis): BRAF V600E mutation (~40–60%), RET/PTC rearrangements, NTRK fusions.

TREATMENT

Surgery: Total thyroidectomy (preferred) or lobectomy (selected low-risk cases) with central neck dissection if nodes involved.

Radioactive iodine (RAI): For ablation of residual tissue and treatment of metastases (risk-adapted).

TSH suppression therapy with levothyroxine.

Follow-up: Serum thyroglobulin (Tg) levels + neck ultrasound.

PROGNOSIS

- Excellent overall prognosis.
- 10-year survival >95%.
- Outcomes depend on age, tumor size, extrathyroidal extension, and nodal/distant metastasis.

COMMON SITES OF SPREAD

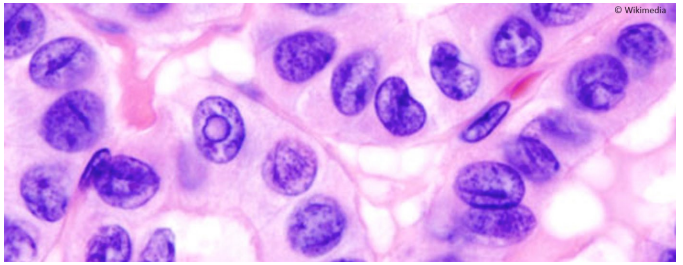
Cervical lymph nodes (central > lateral)

Lungs

Bones (less common)

TAKE-HOME MESSAGE: Papillary thyroid carcinoma is the most common thyroid malignancy with distinctive pathology, excellent prognosis, and highly effective treatment when appropriately managed.

Calcitonin sollte bei der Abklärung von Schilddrüsenknoten, unklaren Dignitätsbefunden (z. B. suspekter Zytologie) oder familiärem Risiko für ein medulläres Schilddrüsenkarzinom (MTC) bestimmt werden. Die S3-Leitlinie Schilddrüsenkarzinom empfiehlt die Bestimmung des Tumormarkers als sensitiven Indikator zur Früherkennung des MTC.



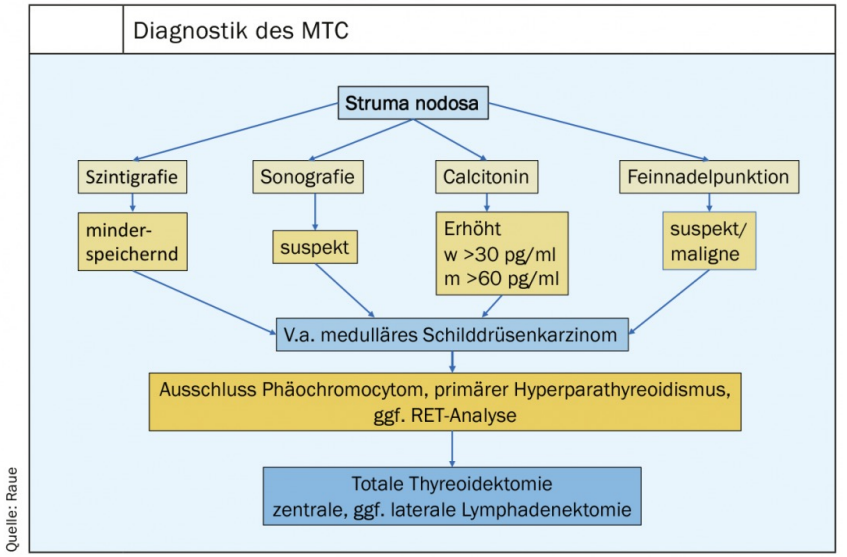
Wann die Messung indiziert ist

•**Diagnostik bei Schilddrüsenknoten:** Zum Ausschluss oder zur Früherkennung eines MTC bei knotigen Veränderungen der Schilddrüse (Struma nodosa).

•**Familiäres Risiko:** Bei genetischer Vorbelastung (z. B. MEN-2-Syndrom, *RET*-Protoonkogen-Mutation).

•**Unklare Zytologie:** Wenn eine Feinnadelpunktion unklare Ergebnisse liefert oder auf einen neuroendokrine Tumor hinweist.

•**Präoperative Planung:** Vor geplanten Schilddrüsenoperationen oder thermischen Ablationen.



Management of Differentiated Thyroid Cancer

Summary

Modern risk-adapted management of thyroid cancer involves risk stratification as an active, dynamic process that begins with the detection of a thyroid nodule and continues throughout the clinical course of diagnosis, active surveillance or treatment, and follow-up. Rooted in clinicopathological staging, which can be further refined with the molecular risk characterization of the tumor, initial management plans are developed and modified over time on the basis of the natural history of the disease and the response to therapy. We present a clinical framework for therapeutic decision making that can be used to compare, contrast, and illustrate the relative risks, benefits, and patient preferences that are integral to the development of a personalized management plan. We examine examples of therapeutic decision making in active surveillance of low-risk papillary thyroid cancer, minimalist therapeutic management options for low- and intermediate-risk thyroid cancer, and systemic therapies for advanced thyroid cancer, showing how the therapeutic decision-making framework can be used to achieve informed consensus and management recommendations.

Management of Differentiated Thyroid Cancer

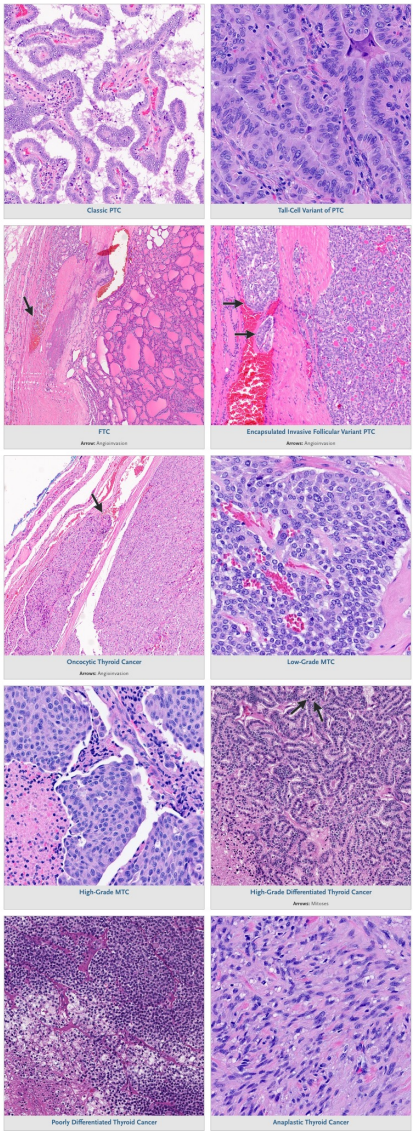
- The dramatic increase in the incidence of thyroid cancer over the past 30 years is largely attributable to the incidental discovery and overdiagnosis of low-risk papillary thyroid cancers, which have led to overtreatment for cancers of limited clinical significance.
- The classification of thyroid cancers has been revised and now stratifies tumors on the basis of histologic features, differentiation status, and molecular profile.
- In contrast to risk stratification viewed as a single, static assessment made after surgical intervention, comprehensive risk stratification is now seen as a dynamic process that begins with the discovery of a thyroid nodule and continues through final follow-up.
- Management recommendations have traditionally been based almost exclusively on estimated risks of disease recurrence and disease-specific death. The emergence of multidisciplinary collaboration and appreciation of the role of guided decision making now allows for clinicians and patients to also integrate the risks and benefits of the proposed therapies (whether immediate or delayed) with the patient's values and goals in order to individualize decision making for the treatment of thyroid cancer.
- Minimalist management options, including active surveillance and ultrasound-guided ablation, are now viewed as acceptable alternatives to thyroidectomy in selected patients with low-risk papillary thyroid cancer.
- Major strides have been made in systemic therapy for patients with advanced thyroid cancer. Gene-specific therapies are available for patients with targetable driver gene alterations, and multikinase inhibitors have activity across the spectrum of advanced thyroid cancers.

Well-Differentiated Cancers

High-Grade

Undifferentiated Cancer

Papillary Thyroid Cancer (PTC)	Follicular Thyroid Cancer (FTC)	Encapsulated Follicular Variant PTC	Oncocytic Thyroid Cancer (OTC)	Medullary Thyroid Cancer (MTC)
Subtypes Classic Encapsulated Tall-cell Infiltrative follicular variant Oncocytic Warthin-like Clear-cell Diffuse sclerosing Solid or trabecular Spindle-cell Columnar-cell Hobnail With fibromatosis, fasciitis-like, or desmoid-type stroma	**Subtypes** Minimally invasive subtype (Capsular invasion only) Encapsulated angioinvasive subtype (<4 vs ≥4 foci of angioinvasion) Widely invasive subtype (Extensive invasion of thyroid or extrathyroidal soft tissues)			**Low-Grade MTC** <5 mitosis per 2 mm^2 Ki-proliferation index <5% and no tumor necrosis
High-Grade Differentiated Thyroid Cancer *Follicular cell–derived nonanaplastic thyroid cancer* Well-differentiated cytologic or architectural phenotype (e.g., papillary, follicular, or oncocytic cancer) Tumor with invasive properties Increased mitotic count (≥5 mitoses/2 mm^2), tumor necrosis, or both, and no anaplastic features		**Poorly Differentiated Thyroid Cancer** *Follicular cell–derived nonanaplastic thyroid cancer* *Oncocytic and nononcocytic subtypes* Solid, trabecular, or insular growth pattern Tumor with invasive properties Increased mitotic count (≥3 mitoses/2 mm^2), tumor necrosis, or both, and convoluted nuclei No nuclear features of PTC, and no anaplastic features		**High-Grade MTC** ≥5 mitosis per 2 mm^2 Ki-proliferation index ≥5% or tumor necrosis
Anaplastic follicular cell–derived thyroid cancer				



Characterization of cancers

Histologic Type	Mutational Profile	Common Metastatic Sites	Likelihood That RAI Will Be Effective	Likelihood That Metastatic Foci Will Be FDG-Avid
Papillary thyroid cancer	*BRAF* V600E (40–80%) *TERT* (5–15%) Gene fusions, commonly *RET*, *NTRK* (5–25%)	Cervical lymph nodes	Likely	Unlikely
Tall-cell subtype, papillary thyroid cancer	*BRAF* V600E (90%)	Cervical lymph nodes	Unlikely	Likely
Follicular thyroid cancer	*RAS* (30–50%) *TERT* (10–35%) Gene fusions, mostly *PAX8/PPARG* (10–50%)	Distant	Very likely	Unlikely
Encapsulated invasive follicular variant papillary thyroid cancer	*RAS* (30–40%)	Distant	Very likely	Unlikely
Infiltrative follicular papillary thyroid cancer	*BRAF* V600E (54%) *RAS* (2–39%)	Cervical lymph nodes	Unlikely	Unlikely
Oncocytic thyroid cancer	Mitochondrial DNA mutations Widespread chromosomal losses Increased mutational burden *RAS* (15%) *EIF1AX* (10%)	Distant	Very unlikely	Very likely
High-grade differentiated thyroid cancer	*BRAF* V600E (30–80%) *TERT* (40%) *NRAS* (30%)	Cervical lymph nodes and distant metastasis	Uncertain	Very likely
Poorly differentiated thyroid cancer	*RAS* (45%) *TERT* (44%) *TP53* (15%) *EIF1AX* (15%)	Cervical lymph nodes and distant metastasis	Uncertain	Very likely
Anaplastic thyroid cancer	*TP53* (40–80%) *TERT* (30–75%) *RAS* (10–50%) *BRAF* V600E (10–50%) *PIKSCA* (5–25%) *PTEN* (10–15%) *EIF1AX* (5–15%)	Cervical lymph nodes and distant metastasis	None	Almost always

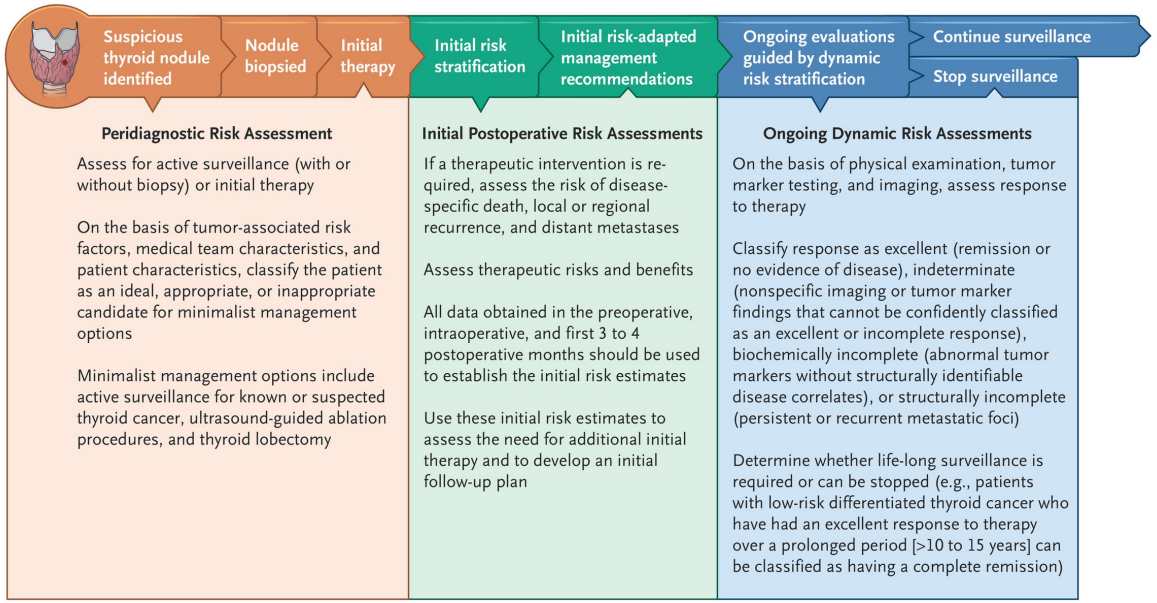
Landmark RAI trials

Trial	Trial Design	Patient Population[a]	Primary Outcome	Key Secondary Efficacy Outcomes	Key Safety Outcomes
HiLo[23,24]	Randomized noninferiority trial comparing low-dose (1.1 GBq [30 mCi]) or high-dose (3.7 GBq [100 mCi]) radioactive iodine with thyrotropin alfa or thyroid hormone withdrawal	438 Patients with differentiated thyroid cancer, T1 to T3 tumors, with or without nodal metastasis, and no distant metastasis who had undergone total thyroidectomy	In analysis of ablation success rate, thyroid ablation with low-dose radioactive iodine was noninferior to high-dose radioactive iodine and thyrotropin alfa was noninferior to thyroid hormone withdrawal; cumulative rates of recurrence were similarly low in the low- and high-dose radioactive iodine groups in long-term follow-up; no difference in recurrence was seen between the thyrotropin alfa and thyroid hormone withdrawal groups	Hospitalization for ≥3 days less common with low-dose than with high-dose radioactive iodine	Adverse events, including anxiety, constipation, difficulty concentrating, and fatigue, were more common in the thyroid hormone withdrawa group
ESTIMABL1[25,26]	Phase 3, randomized 2-by-2 trial comparing low- or high-dose radioactive iodine, and thyrotropin alfa or thyroid hormone withdrawal	752 Patients with differentiated thyroid cancer, pT1pN0, N1 or Nx or pT2N0 with no distant metastasis who had undergone total thyroidectomy	Rate of thyroid ablation and recurrence was not related to the strategy used for ablation		Hypothyroid symptoms measured and deterioration of quality of life were more common in the thyroid hormone withdrawal group
ESTIMABL2[27,28]	Phase 3, randomized trial comparing thyrotropin alfa–stimulated low-dose radioactive iodine with no radioactive iodine	730 Patients with low-risk differentiated thyroid cancer who underwent total thyroidectomy	In analysis of functional, structural, or biologic evidence of recurrence, no radioactive iodine was noninferior to low-dose radioactive iodine		Patients in both groups had similar quality of life, anxiety, and fear of recurrence scores
oN[29]	Phase 3, randomized noninferiority trial comparing no radioactive iodine ablation with radioactive-iodine ablation	504 Patients with low-risk differentiated thyroid cancer who underwent total thyroidectomy	In analysis of recurrence-free survival, no radioactive iodine ablation was noninferior to radioactive-iodine ablation	Avoiding ablation results in substantial cost savings	Fatigue, lethargy, and dry mouth did not differ substantially between groups
ASTRA[30]	Phase 3, double-blind trial comparing thyrotropin alfa–stimulated high-dose radioactive iodine plus pretreatment with selumetinib (a mitogen-activated protein kinase inhibitor) vs. placebo as adjuvant therapy	400 Patients with differentiated thyroid cancer and no distant metastasis at high risk for recurrence after total thyroidectomy	Complete response rate after radioactive iodine was not higher with selumetinib pretreatment than with placebo	No significant difference seen in complete response rate in patients with *BRAF* or *NRAS* mutations	More adverse events occurred with selumetinib than with placebo; the most common selumetinib-related grade 3 adverse events were dermatitis acneiform and increased blood creatine kinase

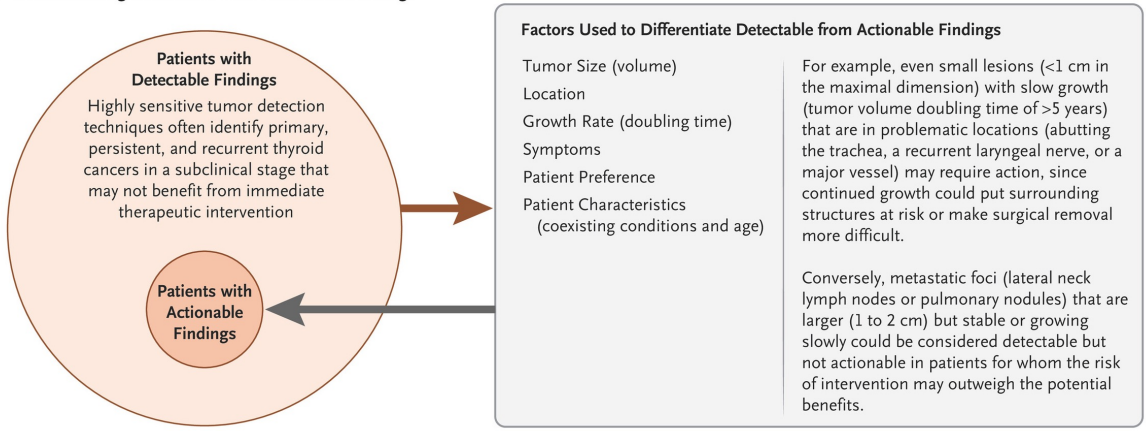
Landmark trials of treatment for advanced cancer

Trial	Trial Design	Patient Population	Primary Outcome	Key Secondary Efficacy Outcomes	Key Safety Outcomes
Multikinase inhibitor for radioactive iodine–refractory DTC					
DECISION[58]	Phase 3, double-blind, randomized trial comparing sorafenib with placebo	417 Patients with progressive, radioactive iodine–refractory DTC who had not received previous systemic therapy except for radioactive iodine	Median progression-free survival was longer with sorafenib (10.8 months) than with placebo (5.8 months)	No difference in median overall survival; 12.2% of patients had a response with sorafenib	The most common adverse events included hand–foot skin reaction, diarrhea, alopecia, rash, fatigue, weight loss, and hypertension; 18.8% of patients discontinued sorafenib owing to adverse events
SELECT[59]	Phase 3, double-blind, randomized trial comparing lenvatinib with placebo	392 Patients with progressive radioactive iodine–refractory DTC who had received ≤1 previous multikinase inhibitor	Median progression-free survival was longer with lenvatinib (18.3 months) than with placebo (3.6 months)	Median overall survival was not calculable in either group; 64.8% of patients had a response with lenvatinib	The most common adverse events included hypertension, diarrhea, fatigue, anorexia, weight loss, nausea, and proteinuria; 14.2% of patients discontinued lenvatinib owing to adverse events
COSMIC-311[62]	Phase 3, double-blind, randomized trial comparing cabozantinib with placebo	227 Patients with radioactive iodine–refractory DTC who had progressive disease during or after treatment with lenvatinib or sorafenib	Median progression-free survival was longer with cabozantinib (median not calculable) than with placebo (1.9 months); the percentage of patients with a response with cabozantinib did not meet the prespecified significance level	Median overall survival not calculable in either group	The most common adverse events included diarrhea, hand–foot skin reaction, hypertension, fatigue, nausea, transaminitis, and anorexia; 5% of patients discontinued cabozantinib owing to adverse events
Gene-specific inhibitor for radioactive iodine–refractory DTC					
NAVIGATE and SCOUT[63]	Pooled data from three phase 1–2 studies of the tropomyosin receptor kinase 1–3 inhibitor larotrectinib	22 Patients (subgroup) with *NTRK* fusion-positive DTC	86% Of patients with DTC had a response	Median progression-free survival in DTC was not calculable; 24-month progression-free survival was 84%	The most common adverse events included myalgia, fatigue, peripheral edema, and dizziness; larotrectinib was not discontinued owing to adverse events in any patient
ALKA-372–001, STARTRK-1 and -2[64]	Pooled data from three phase 1–2 trials of entrectinib, a ROS1 and tropomyosin receptor kinase 1–3 inhibitor	13 Patients (subgroup) with *NTRK* fusion-positive DTC	53.8% Of patients with thyroid cancer had a response	Median progression-free survival was 19.9 months among patients with thyroid cancer	The most common adverse events included dysgeusia, fatigue, diarrhea, constipation, peripheral edema, and dizziness; 4% of patients discontinued entrectinib owing to adverse events
LIBRETTO-001[65]	Phase 1–2 trial of RET inhibitor, selpercatinib	41 Patients (subgroup) with previously treated *RET* fusion-positive thyroid cancer and 24 patients with such cancer that had not been previously treated	95.8% Of patients with fusion-positive thyroid cancer that had not been previously treated with a multikinase inhibitor had a response; 85.4% of those who had received previous treatment had a response	Median progression-free survival in patients with fusion-positive thyroid cancer that had not been previously treated with a multikinase inhibitor was not calculable; median progression-free survival in previously treated patients was 27.4 months; median overall survival was not calculable	The most common adverse events included dry mouth, hypertension, transaminitis, increased creatinine level, and fatigue; 2% of patients discontinued selpercatinib owing to adverse events
ARROW[66]	Phase 1–2 trial of RET inhibitor, pralsetinib	25 Patients (subgroup) with RET fusion-positive thyroid cancer previously treated with ≥1 multikinase inhibitor	89% Of patients had a response	Median progression-free survival was 25.4 months; median overall survival was not calculable	The most common adverse events included transaminitis, anemia, hypertension, constipation, hyperphosphatemia, and neutropenia; 5.7% discontinued pralsetinib owing to adverse events
Dabrafenib vs. dabrafenib + trametinib in *BRAF*-mutated radioactive iodine–refractory DTC[57]	Phase 2, open-label, randomized trial of dabrafenib, a BRAF inhibitor, with or without trametinib, an MEK inhibitor	53 Patients with radioactive iodine–refractory BRAF-mutated differentiated thyroid cancer with progressive disease who had previously received ≥1 multikinase inhibitor	35% Of patients had a response with dabrafenib, and 30% had an objective response with dabrafenib + trametinib	Median progression-free survival with dabrafenib was 10.7 months, median progression-free survival with dabrafenib + trametinib was 15.1 months, and median overall survival was 37.9 and 47.5 months, respectively	The most common adverse events included skin and subcutaneous tissue disorders, fever, hyperglycemia, anemia, hand–foot skin reaction, nausea, alopecia, chills, and fatigue
Multikinase inhibitor for medullary thyroid cancer					
ZETA[60]	Phase 3, double-blind, randomized trial comparing vandetanib with placebo	331 Patients with advanced medullary thyroid cancer	Median progression-free survival was longer with vandetanib (model predicted 30.5 months) than with placebo (19.3 months)	Median overall survival was not calculable; 45% of patients had a response with vandetanib	The most common adverse events included diarrhea, rash, nausea, hypertension, fatigue, headache, and anorexia; 12% of patients discontinued vandetanib owing to adverse events
EXAM[61]	Phase 3, double-blind, randomized trial comparing cabozantinib with placebo	330 Patients with progressive medullary thyroid cancer	Median progression-free survival was longer with cabozantinib (11.2 months) than with placebo (4.0 months)	Median overall survival was not significantly different with cabozantinib vs. placebo; 28% of patients had a response with cabozantinib	The most common adverse events included diarrhea, hand–foot skin reaction, weight loss, anorexia, nausea, fatigue, and dysgeusia; 16% of patients discontinued cabozantinib owing to adverse events
Gene-specific inhibitor for medullary thyroid cancer					
LIBRETTO-531[68]	Phase 3, randomized trial comparing selpercatinib with the physician's choice of cabozantinib or vandetanib (control)	291 Patients with previously untreated progressive *RET*-altered medullary thyroid cancer	Median progression-free survival was longer with selpercatinib (not calculable) than with the control	Median treatment failure–free survival was longer with selpercatinib than with the control; a response occurred with selpercatinib in 69.4% vs. 38.8% with the control	Safety profiles for selpercatinib and the control were similar to those established in the LIBRETTO-001, ZETA, and EXAM trials; selpercatinib was discontinued owing to adverse events in 4.7% vs. 26.8% with the control
Anaplastic thyroid cancer					
ROAR[69]	Phase 2 basket study evaluating dabrafenib plus trametinib in *BRAF* V600E–mutant rare cancers	36 Patients with unresectable or metastatic *BRAF* V600E–mutant anaplastic thyroid cancer enrolled in anaplastic thyroid cancer cohort	56% Of patients had a response	Median progression-free survival was 6.7 months; median overall survival was 14.5 months	Adverse events were consistent with the established safety profile of dabrafenib plus trametinib; dabrafenib plus trametinib was discontinued owing to adverse events in 17%

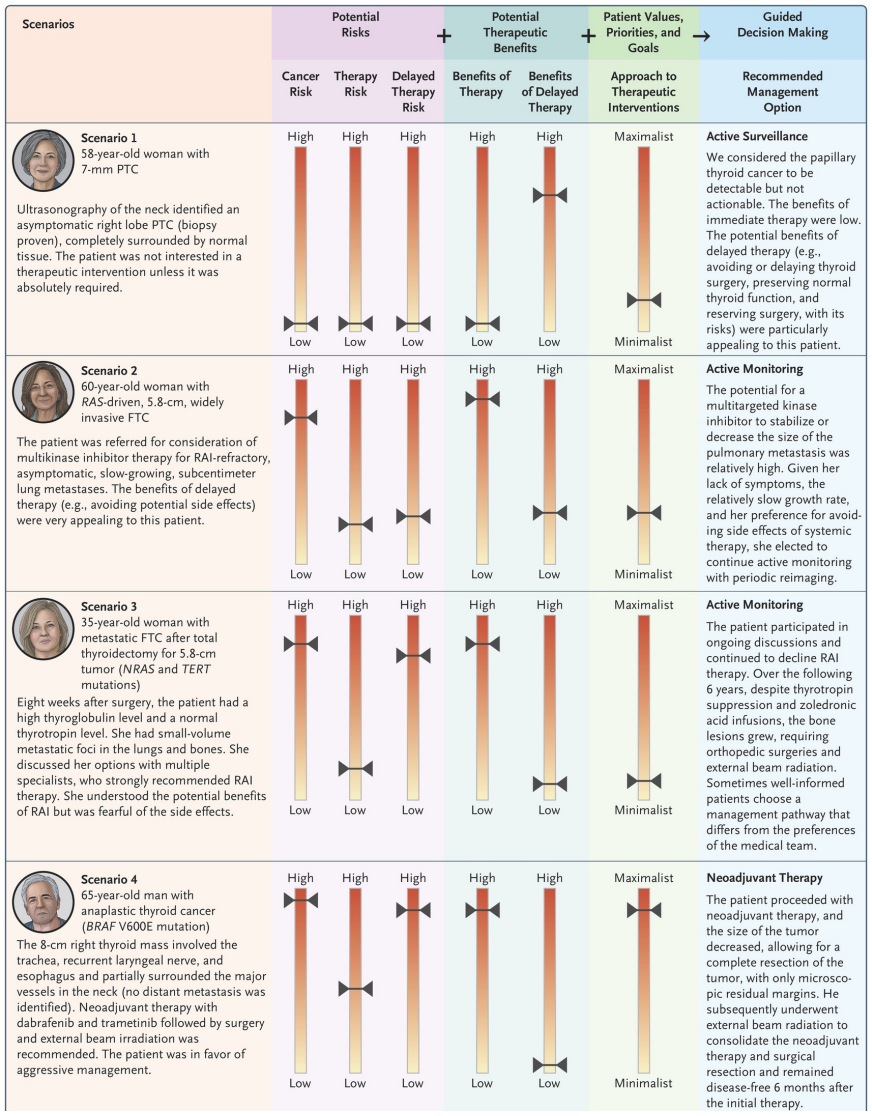
A Risk Assessment at Multiple Time Points to Inform Management Recommendations



B Differentiating Detectable from Actionable Findings



Framework for Therapeutic Decision Making in Thyroid Cancer



A Decision-Making Framework for the Management of Thyroid Cancer.

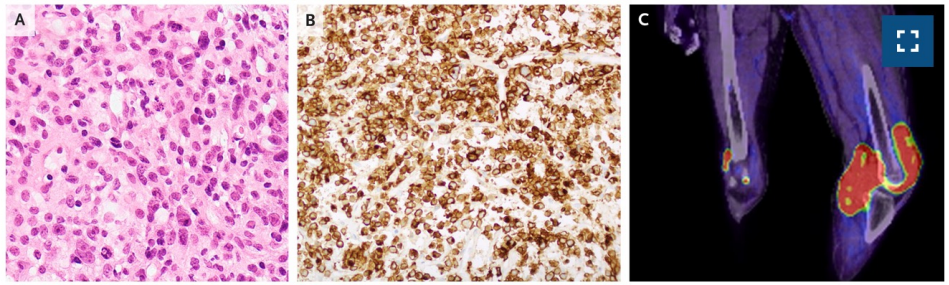
A therapeutic decision-making framework is analogous to an audio mixer sound board in which multiple signal inputs (potential risk, potential therapeutic benefits, and the patient's values, priorities, and goals) are blended with the use of individual faders (sliders) to produce well-balanced sound output through the speakers (guided decision making). The inputs (position of the faders) for potential risks and benefits are primarily estimated by the clinician, and the input for the patient's values, priorities, and goals is expressed as the patient's preferences for management options, ranging from minimalist to maximalist. The output is a range of management options, with the preferred option and alternative options incorporated into the recommendation, which is informed by guided decision making. For each therapeutic scenario, relative risk estimates for each of the potential risks and potential therapeutic benefits are integrated with the patient's preferences to provide a visual representation of the key factors that must be considered in developing an individualized management plan for the patient (a blank framework diagram is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org). The clinician participates in the discussion as a guide, advocating a preferred management option that best integrates the patients values, priorities, and goals with a comprehensive understanding of the risks and benefits associated with each potential management option.[39] Each scenario in the figure describes a specific management decision that needs to be made with a focus on the risks and benefits that are of primary importance to the patient. FTC denotes follicular thyroid cancer, PTC papillary thyroid cancer, and RAI radioactive iodine.

Conclusions

Understanding that risk stratification in thyroid cancer is an active, dynamic process that evolves over time, clinicians and patients must integrate the patient's preferences into their current understanding of the risks and benefits of various diagnostic, therapeutic, and surveillance management options. Unlike management plans that focus almost exclusively on mitigating cancer risks, the development of individualized management plans requires that the patient and the clinician reach consensus on the potential risks and potential benefits, as well as the patient's values, priorities, and goals. When applied properly, a risk-adapted paradigm will lead to individualized patient care by incorporating either minimalist or more aggressive management options designed to minimize risks, maximize benefits, and achieve excellent clinical outcomes. John Maynard Keynes (1883–1946), the British economist and founder of macroeconomics, is credited with saying, "When the facts change, I change my mind. What do you do, sir?" Although a paradigm shift is always challenging, we should acknowledge that when the facts change, we need to change our minds.

„Wenn sich die Fakten ändern, ändere ich meine Meinung. Was tun Sie, mein Herr?"

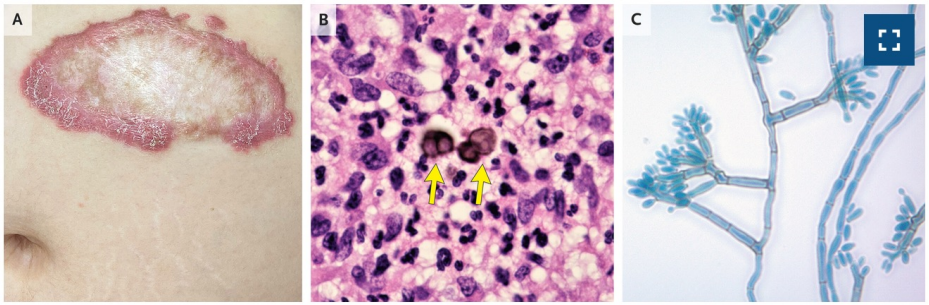
Immunosuppression-Associated Peripheral T-Cell Lymphoma



A 66-year-old man with a history of Crohn's disease treated with long-term adalimumab therapy was admitted to the hospital with an 8-week history of fever and swelling of both knees. Physical examination was notable for cachexia and tenosynovitis in both knees (greater in the left knee than in the right). Owing to concern for septic arthritis, a surgical lavage was performed. Histopathological analysis of a biopsy sample of the left knee synovium showed an atypical T-cell infiltrate (Panel A). Immunohistochemical analysis was positive for CD30 (Panel B), CD2, CD3, CD7, CD4, and CD163 and negative for ALK and CD8 and showed 60% expression of Ki-67. Fluorodeoxyglucose positron-emission tomography showed uptake in both knees, with greater uptake in the left knee (Panel C). T-cell gene rearrangement studies showed a clonal T-cell population, and sequencing showed mutations in *DNMT3A*, *TET2*, *STAT3*, *JAK1*, and *TP53*. Epstein–Barr encoding region in situ hybridization was negative. A diagnosis of immunosuppression-associated peripheral T-cell lymphoma — a rare condition associated with exposure to thiopurines and tumor necrosis factor inhibitors — was made. Adalimumab therapy was discontinued and multiagent chemotherapy was initiated. At a 14-month follow-up, the lymphoma remained in remission but the Crohn's disease had flared, leading to treatment with glucocorticoid agents and ustekinumab.

Adalimumab ist ein biotechnologisch hergestellter, monoklonaler Antikörper, der als starkes Immunsuppressivum (TNF-α-Hemmer) wirkt.

Chromoblastomycosis



A 38-year-old pregnant woman at 30 weeks' gestation was referred to the dermatology clinic for evaluation of a long-standing, itchy lesion on her abdomen. The lesion had first appeared 9 years earlier after the patient had emigrated from Honduras, where she had worked in agriculture. The lesion had subsequently slowly expanded. On physical examination, a 15-cm erythematous, scaly plaque with a raised border and atrophic center was visible on the left upper abdomen (Panel A). Histopathological analysis of a skin-biopsy sample showed pseudoepitheliomatous hyperplasia with dermal granulomatous infiltrates. Thick-walled, brown, septate spores called muriform cells (Panel B, arrows) were also seen. The presence of such cells (also known as Medlar bodies, sclerotic bodies, or copper pennies) is pathognomonic for chromoblastomycosis. Fungal culture grew a pigmented mold, which showed septate hyphae with loosely branched clavate conidia and prominent denticles on microscopy (Panel C). The causative organism was identified as a fonsecaea species. A diagnosis of chromoblastomycosis with cicatricial morphologic features was confirmed. Chromoblastomycosis is a chronic, progressive implantation mycosis caused by dematiaceous fungi in soil and plant matter. It is typically diagnosed in agricultural workers in tropical or subtropical regions. Postpartum treatment with itraconazole was planned, but the patient was lost to follow-up.

Abenteuer DIAGNOSE

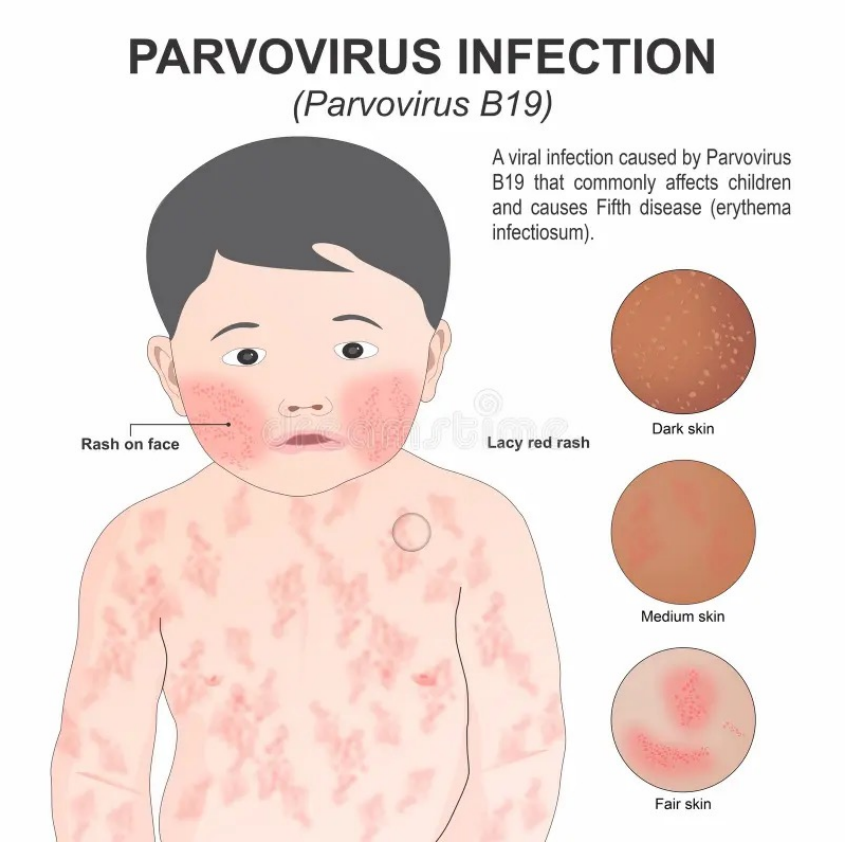
Das humane **Parvovirus B19** ist ein weltweit verbreitetes DNA-Virus, das vor allem als Auslöser der Kinderkrankheit **Ringelröteln** (Erythema infectiosum) bekannt ist.

Typischer Verlauf & Symptome

•**Kinder:** Typisch sind ein girlandenartiger Ausschlag im Gesicht (Wangenröteln) und später am Körper. Oft verläuft die Infektion aber auch unbemerkt oder wie eine leichte Erkältung.

•**Erwachsene:** Häufig treten keine Hautausschläge auf, dafür aber oft schmerzhafte Gelenkschmerzen oder Gelenkentzündungen (Arthralgien).

•**Immunität:** Eine durchgemachte Infektion führt zu einer lebenslangen Immunität.



Scharlach, Masern, Röteln, Windpocken und **Ringelröteln (fifth disease)**

Case 17-2026: A 74-Year-Old Man with Pancytopenia

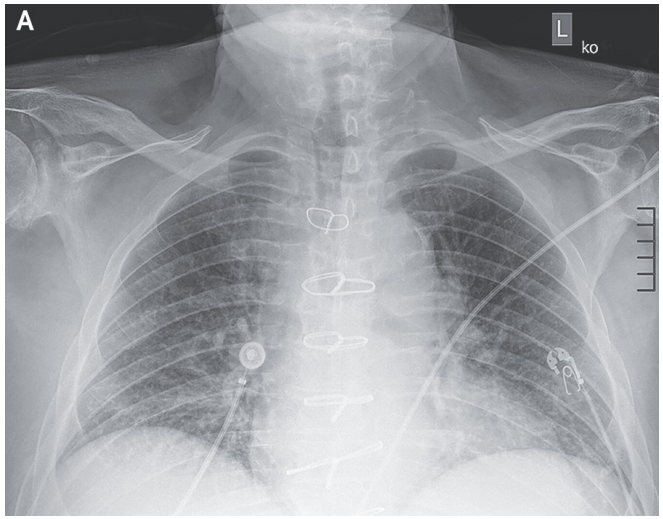
A 74-year-old man was admitted to this hospital because of persistent pancytopenia that had resulted in multiple red-cell transfusions.
Three months before the current presentation, the patient underwent heart transplantation after a prolonged admission in the cardiac intensive care unit of this hospital. He had been admitted for decompensated heart failure due to transthyretin amyloid cardiomyopathy, for which he received treatment with infusions of inotropic and diuretic agents. The preoperative course was notable for anemia, for which he received intravenous iron therapy. In addition, the patient had persistent thrombocytopenia that prompted a switch in treatment from heparin to a direct thrombin inhibitor, despite the fact that testing for antibodies against platelet factor 4 was negative. Serologic testing performed before transplantation was positive for Epstein–Barr virus (EBV) IgG, negative for cytomegalovirus (CMV) IgG, and negative for toxoplasma IgG. Serologic testing in the donor was positive for EBV IgG and CMV IgG and negative for toxoplasma IgG. Laboratory test results are shown.

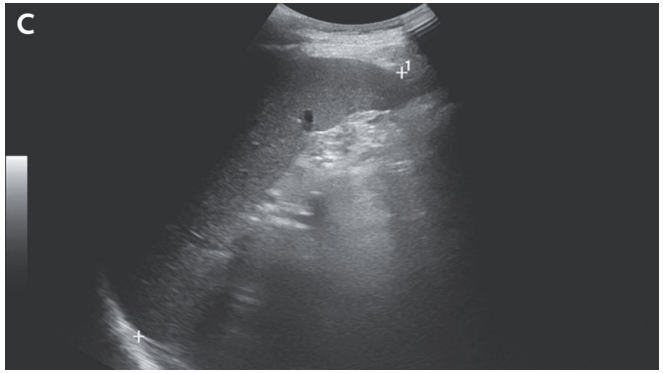
Laboratory data

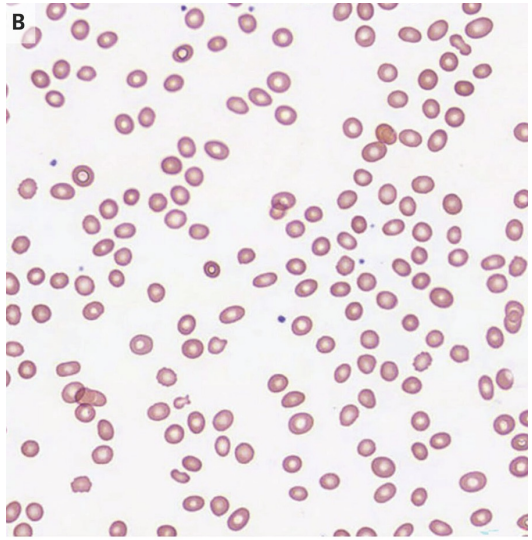
Variable	Reference Range, Adults†	2 Days before Transplantation, ICU	Day 17 after Transplantation	Day 28 after Transplantation	Day 38 after Transplantation	Day 56 after Transplantation	On Readmission, Day 70 after Transplantation	Day 71 after Transplantation
Hemoglobin (g/dl)	13.5–17.5	13.7	8.8	7.7	6.7	5.6	6.6	7.4
Hematocrit (%)	41.0–53.0	40.5	26.3	22.2	20.1	16.9	18.5	21.7
Reticulocyte count (%)	0.5–2.5	—	—	—	<0.5	<0.5	<0.5	—
Mean corpuscular volume (fl)	80.0–100.0	—	97.0	94.9	94.8	90.9	85.6	88.0
White-cell count (per μl)	4500–11,000	6190	5640	3800	5290	2950	3690	2560
Differential count (per μl)								
Neutrophils	1800–7700	—	5200	3310	4700	2320	3080	1410
Lymphocytes	1000–4800	—	270	290	370	310	210	570
Monocytes	200–1200	—	140	140	180	220	290	500
Platelet count (per μl)	150,000–400,000	89,000	95,000	97,000	94,000	62,000	92,000	57,000
Sodium (mmol/liter)	135–145	136	136	136	140	140	136	139
Potassium (mmol/liter)	3.4–5.0	3.8	4.5	4.5	5.3	5.3	5.3	4.4
Chloride (mmol/liter)	98–108	103	101	100	106	107	104	110
Carbon dioxide (mmol/liter)	23–32	21	23	21	17	18	19	19
Urea nitrogen (mg/dl)	8–25	27	50	83	68	75	67	55
Creatinine (mg/dl)	0.60–1.50	1.14	1.90	2.71	2.20	2.44	2.02	1.80
Cystatin C (mg/liter)	0.61–0.95	—	—	3.26	3.00	2.25	3.19	—
Glucose (mg/dl)	70–110	90	81	132	85	—	109	88
Total protein (g/dl)	6.0–8.3	6.3	5.1	—	6.3	5.6	5.1	5.1
Globulin (g/dl)	1.9–4.1	2.7	1.7	—	—	1.9	1.8	1.5
Albumin (g/dl)	3.3–5.0	3.6	3.4	—	3.8	4.2	4.0	3.6
Alanine aminotransferase (U/liter)	10–55	24	60	—	244	75	27	23
Aspartate aminotransferase (U/liter)	10–40	32	36	—	51	30	27	32
Total bilirubin (mg/dl)	0.0–1.0	1.8	1.5	—	1.0	1.8	1.1	1.7
Direct bilirubin (mg/dl)	0.0–0.4	0.6	0.7	—	—	0.8	0.5	0.7
Lactate dehydrogenase (U/liter)	110–210	—	—	—	250	—	385	—
Direct antibody test	Negative	—	—	—	—	Negative	Negative	—

N-terminal pro–B-type natriuretic peptide (pg/ml)	<900	—	—	—	—	4515	—	—
Fibrinogen (mg/dl)	150–400	—	—	—	—	—	2468	—
Haptoglobin (mg/dl)	30–200	—	—	—	134	—	142	—
25-Hydroxyvitamin D (ng/ml)	33–100	—	—	—	—	19	—	—
Iron (μg/dl)	30–160	—	—	—	286	256	297	—
Iron-binding capacity (μg/dl)	230–404	—	—	—	328	276	318	—
Ferritin (μg/liter)	10–200	—	—	—	855	1229	1775	—
Vitamin B_{12} (pg/ml)	>231	—	—	—	492	—	592	—
Folate (ng/ml)	>4.7	—	—	—	6.7	—	5.0	—
Erythropoietin (mIU/ml)	2.6–18.5	—	—	—	—	—	—	465
Zinc (μg/dl)	60–107	—	—	—	—	—	—	48
Rheumatoid factor (IU/ml)	0–14	—	—	—	—	—	—	20
Antinuclear antibody	Negative at 1:40 and 1:160	—	—	—	—	—	—	Positive at 1:40 and 1:160, homogeneous pattern
IgG (mg/dl)	614–1295	—	—	—	—	—	—	523
IgA (mg/dl)	69–309	—	—	—	—	—	—	81
IgM (mg/dl)	53–334	—	—	—	—	—	—	53
Electrophoresis and immunofixation	No M component	—	—	—	—	—	—	Normal pattern, mild diffuse decrease in immune globulin
Free kappa light chain (mg/liter)	3.3–19.4	—	—	—	—	—	—	30.2
Free lambda light chain (mg/liter)	5.7–26.3	—	—	—	—	—	—	20.9
Kappa:lambda ratio	0.30–1.70	—	—	—	—	—	—	1.44
Tacrolimus trough (ng/ml)	10–13 during first year after heart transplantation	—	13.2	—	8.7	13.3	8.0	7.8
Posaconazole (ng/ml)	>1000	—	1290	—	—	—	—	805

After transplantation, the patient had intact allograft function, but transient acute kidney injury developed. Milrinone infusion was administered from the time of transplantation until post-transplantation day 8. Endomyocardial biopsies were performed at 7 and 14 days after transplantation, and both specimens showed mild lymphocyte infiltration without myocardial injury. On post-transplantation day 17, the patient was discharged from the hospital. New medications prescribed at discharge included prednisone, mycophenolate mofetil, tacrolimus, valganciclovir, trimethoprim–sulfamethoxazole, and posaconazole. In addition, the patient continued to receive treatment with tafamidis, famotidine, pravastatin, amlodipine, torsemide, calcium, and vitamin D.
Thirty-eight days after transplantation, the patient was admitted to the cardiac surgical unit because of a hemoglobin level of 6.7 g per deciliter (reference range, 13.5 to 17.5) and a potassium level of 5.3 mmol per liter (reference range, 3.4 to 5.0). Testing for hepatitis B virus DNA, hepatitis C virus RNA, and human immunodeficiency virus (HIV) RNA was negative.
Two units of packed red cells were transfused, and treatment with oral sodium zirconium cyclosilicate was administered. Genetic testing for the H63D and C282Y variants in the gene *HFE* was negative. Transthoracic echocardiography showed normal biventricular function, dilatation of the right ventricle and left atrium, trace interatrial shunting, and no pericardial effusion. Treatment with trimethoprim–sulfamethoxazole was discontinued, and atovaquone was started for prophylaxis against *Pneumocystis jirovecii* pneumonia and toxoplasmosis. The dose of mycophenolate mofetil was decreased. The potassium level normalized, and on the fourth hospital day, he was discharged home.







Chest Radiograph, Peripheral-Blood Smear, and Abdominal Ultrasound.

An image obtained on portable chest radiography on post-transplantation day 38 (Panel A) shows low lung volumes with some retrocardiac bandlike opacities, most likely indicating atelectasis, and no evidence of pleural effusion. The patient had previously undergone median sternotomy. A peripheral-blood smear obtained on post-transplantation day 70 (Panel B) shows anisopoikilocytosis, with an absence of reticulocytes. Images from a limited right-upper-quadrant abdominal ultrasound obtained the next day (Panel C) show splenomegaly, with the spleen measuring 16.7 cm in craniocaudal dimension.

The patient was a retired consultant and lived in coastal Massachusetts. He smoked marijuana and consumed one beer almost daily. He did not use tobacco or illicit drugs. He was not sexually active. The patient had previously visited California but had not traveled in the past year. His father had had coronary artery disease.
On physical examination, the temporal temperature was 36.3°C, the heart rate 100 beats per minute, the blood pressure 100/62 mm Hg, and the oxygen saturation 100% while the patient was breathing ambient air. The body-mass index (the weight in kilograms divided by the square of the height in meters) was 33.4. He had conjunctival pallor. The sternal surgical incision was well approximated. Auscultation of the heart revealed a regular rhythm without murmurs or a friction rub. He had edema in both legs, which was more pronounced in the right leg than in the left; there was no calf tenderness. Neither ecchymosis nor rash was noted. The remainder of the examination was normal.

Differential Diagnosis

This 74-year-old man underwent orthotopic heart transplantation for decompensated heart failure due to transthyretin amyloid cardiomyopathy. In the weeks that followed transplantation, he presented with various combinations of cytopenias, most notably severe transfusion-dependent anemia. Single or multilineage cytopenias occur in 38 to 63% of patients after solid-organ transplantation, usually within the first 100 days after surgery. Decreased cell counts in solid-organ transplant recipients may be classified according to the pathophysiological mechanism, cause, or cell line involved.

Pathophysiological Mechanisms of Cytopenias

The pathophysiological mechanisms of cytopenias are not specific to solid-organ transplant recipients and include decreased production, increased destruction, and splenic sequestration.

Specific Causes of Cytopenias

Specific causes of cytopenias that occur after solid-organ transplantation include medications, infections, inflammation, and immune-mediated processes.

Post-Transplantation Anemia

After heart transplantation, the prevalence of anemia ranges from 20 to 51% at different time points, with a prevalence of about 40% at 1 year after the procedure. Anemia may result from blood loss after surgery, immune- or non–immune-mediated hemolysis, reduced erythropoiesis, or, less commonly, splenic sequestration.

Anemia after transplant

Hyperproliferative Causes

Bleeding
Perioperative bleeding
Frequent blood draws

Hemolytic anemia
Immune causes
- ABO-mismatched solid-organ transplantation (passenger lymphocyte syndrome)
- Drug-induced hemolytic anemia
  - β-lactam antibiotics
  - Trimethoprim–sulfamethoxazole

Nonimmune causes
- Medications associated with thrombotic microangiopathy
  - Cyclosporine
  - Tacrolimus
- Oxidant medications associated with hemolysis in glucose-6-phosphate dehydrogenase deficiency
  - Dapsone
  - Trimethoprim–sulfamethoxazole
- Infections
  - Cytomegalovirus infection
  - Chronic hepatitis C virus infection
  - BK polyomavirus infection
  - Babesiosis
  - Malaria

Hypoproliferative Causes

Inflammation
Anemia of inflammation
Hemophagocytic lymphohistiocytosis

Medications
Mycophenolate mofetil
Tacrolimus
Ganciclovir
Valganciclovir
Trimethoprim–sulfamethoxazole (may induce megaloblastic anemia)

Infections
Parvovirus B19 infection
Viral hepatitis infection
Human immunodeficiency virus infection
Epstein–Barr virus infection
Cytomegalovirus infection
Human herpesvirus-6 infection
Human herpesvirus-8 infection

Post-transplantation lymphoproliferative disorder

Red cell aplasia

Congenital
Diamond–Blackfan anemia
Acquired
Primary (i.e., idiopathic)
Secondary
- Autoimmune disorders
  - Systemic lupus erythematosus
  - Rheumatoid arthritis
- General medications
  - Azathioprine
  - Isoniazid
  - Diphenylhydantoin
  - Recombinant erythropoietin (older preparations)
- Transplantation-related medications
  - Mycophenolate mofetil
  - Tacrolimus
  - Trimethoprim–sulfamethoxazole
- Lymphoproliferative disorders
  - Chronic lymphocytic leukemia
  - Large granular lymphocytic leukemia
- Solid tumors
  - Thymoma
  - Others
- Infections
  - Parvovirus B19 infection
  - Human immunodeficiency virus infection
  - Epstein–Barr virus infection
  - Viral hepatitis infection
  - Cytomegalovirus infection
  - Tuberculosis

Pure Red-Cell Aplasia

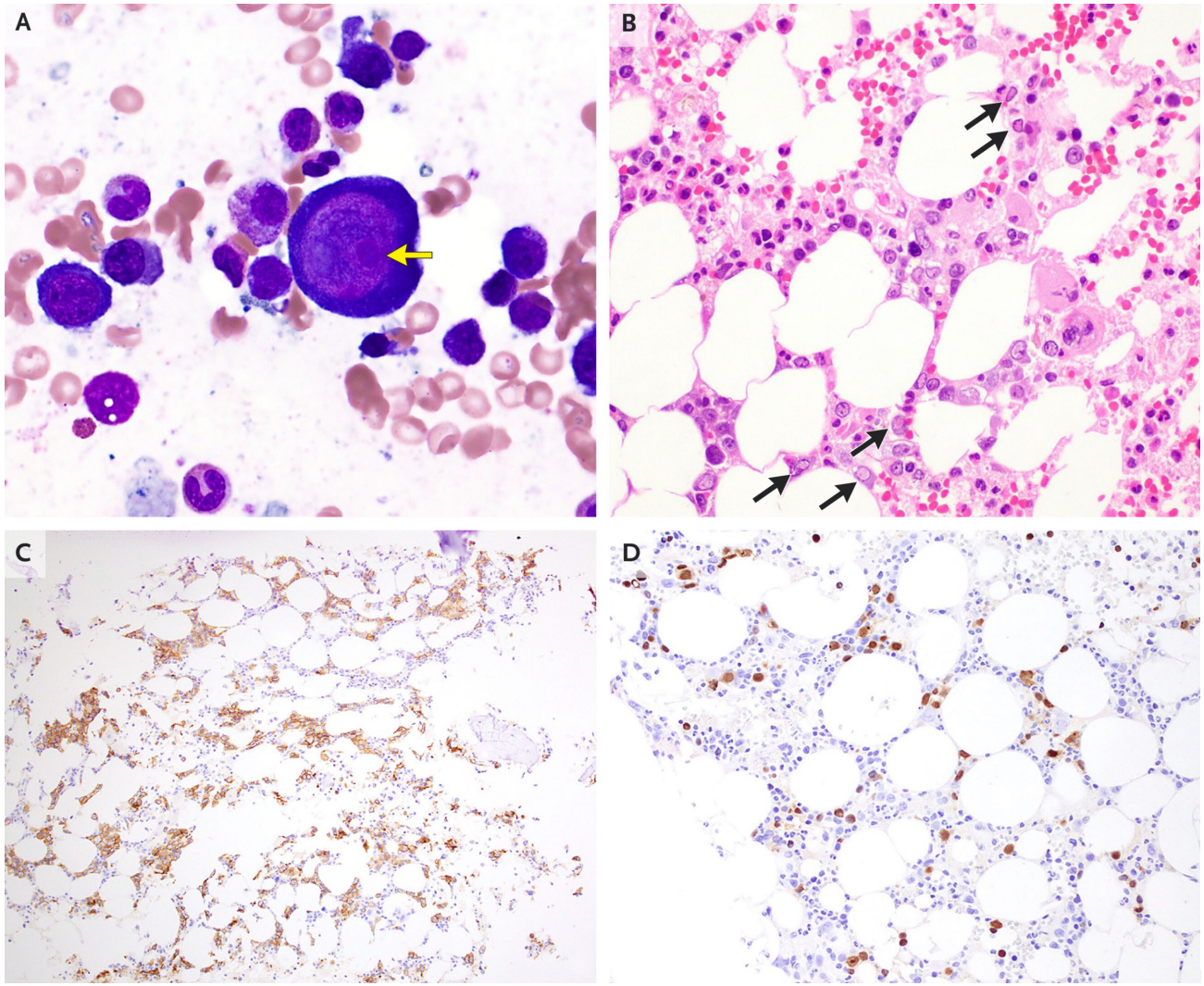
Pure red-cell aplasia is a syndrome characterized by isolated normocytic normochromic anemia (although macrocytic anemia can also occur), severe reticulocytopenia, and marked reduction or absence of erythroid precursors in the bone marrow. Implicit in the definition is that other causes of reduced erythropoiesis, including nutritional deficiency, hypothyroidism, and chronic kidney disease, have been ruled out. This patient received intravenous iron preoperatively, so it is unlikely that he would have been iron-deficient after surgery. In addition, the levels of vitamin B_{12} and thyrotropin were normal, and the creatinine level was only mildly elevated.

Parvovirus B19 Infection

Parvovirus B19 is a single-stranded DNA virus that preferentially infects erythroblasts. It enters the erythroid progenitor cell through the erythrocyte P-antigen receptor. Viral replication produces a distinctive cytopathic effect, which can be seen with the use of light microscopy in the bone marrow and is characterized by giant proerythroblasts. Human parvovirus B19 is ubiquitous; it infects approximately half the population by 15 years of age.

Hemophagocytic Lymphohistiocytosis

The development of pancytopenia and elevated levels of ferritin in a patient who has undergone transplantation increases the possibility of hemophagocytic lymphohistiocytosis (HLH).Previous studies showed that 40% of HLH cases associated with solid-organ transplantation occurred within the first 3 months after transplantation, and approximately 67% occurred within the first year. In many cases, infections, including parvovirus B19 infection, are identified as possible triggers.



Bone Marrow Aspirate and Core-Biopsy Specimen.

Wright–Giemsa staining of the smear of bone marrow aspirate (Panel A) shows a giant proerythroblast with an eosinophilic intranuclear inclusion (arrow), a finding that indicates parvovirus B19 infection. Hematoxylin and eosin staining of the bone marrow core-biopsy specimen (Panel B) reveals trilineage hematopoiesis with maturing myeloid elements, megakaryocytes, and marked left-shifted erythroid elements, which includes many giant proerythroblasts with eosinophilic intranuclear inclusions (arrows). Immunohistochemical staining for E-cadherin performed on the core-biopsy specimen (Panel C) highlights erythroid progenitors, which are increased in number and show frequent clustering. Immunohistochemical staining for parvovirus B19 (Panel D) is strongly positive in many of the erythroid precursors.

Serologic testing for antibodies against parvovirus B19 detected IgM antibodies but not IgG antibodies. Quantitative nucleic acid testing was also performed to measure the amount of parvovirus B19 DNA in the patient's blood, which exceeded the upper limit of the assay (>100,000,000 DNA copies per milliliter). Immunohistochemical staining was performed on the biopsy specimen. Immunohistochemical staining for E-cadherin highlighted erythroid precursors, which were increased in number and showed frequent clustering. Parvovirus B19–specific immunostaining was strongly positive in many erythroid precursors, which confirmed that the patient's severe, persistent anemia was caused by parvovirus B19 infection. Because of the history of chronic pancytopenia and presence of some small megakaryocytes with hypolobated nuclei on the bone marrow biopsy, the possibility of myelodysplastic syndrome was considered. However, cytogenetic analysis of the bone marrow aspirate showed a normal karyotype, and DNA sequencing detected no pathogenic mutations. Therefore, no evidence of a hematopoietic neoplasm was present.

After five doses of IVIG, the parvovirus B19 viral load decreased from 100 million DNA copies per milliliter to 665,200 DNA copies per milliliter. If there had been no response to the first course of IVIG, additional courses of IVIG would have been considered. Routine preemptive use of additional courses of IVIG to prevent recurrences is not recommended.

Parvovirus B19 infection can recur in immunocompromised patients; in one case series, 25% of organ-transplant recipients had a recurrence. Given the risk of recurrence, we monitored quantitative parvovirus B19 DNA levels in this patient, along with the complete blood count, including the reticulocyte count. Several months after the patient's initial treatment, he had a recurrent infection. He received treatment with an additional course of IVIG, which resulted in a return of the reticulocyte count to a normal level and a decrease in his quantitative parvovirus B19 DNA level.

Das humane **Parvovirus B19** ist ein weltweit verbreitetes DNA-Virus, das vor allem als Auslöser der Kinderkrankheit **Ringelröteln** (Erythema infectiosum) bekannt ist.

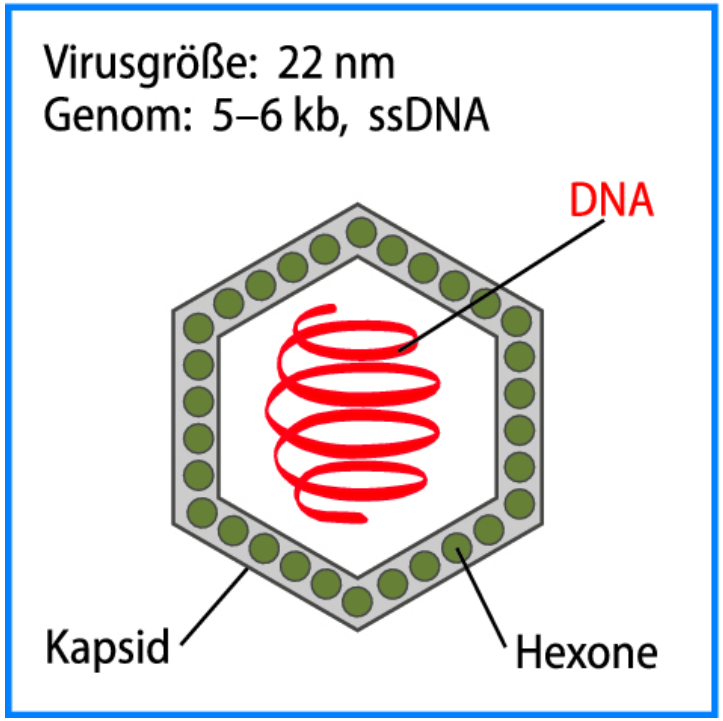
Besondere Risikogruppen

Bei den meisten Menschen heilt die Infektion folgenlos aus. Komplikationen können jedoch auftreten bei:

•**Schwangeren:** Eine Erstinfektion in der Schwangerschaft kann zu schweren Entwicklungsstörungen oder Blutarmut (Anämie) beim Ungeborenen führen, weshalb hier bei Kontakt engmaschige Kontrollen (Ultraschall, Bluttests) erfolgen.

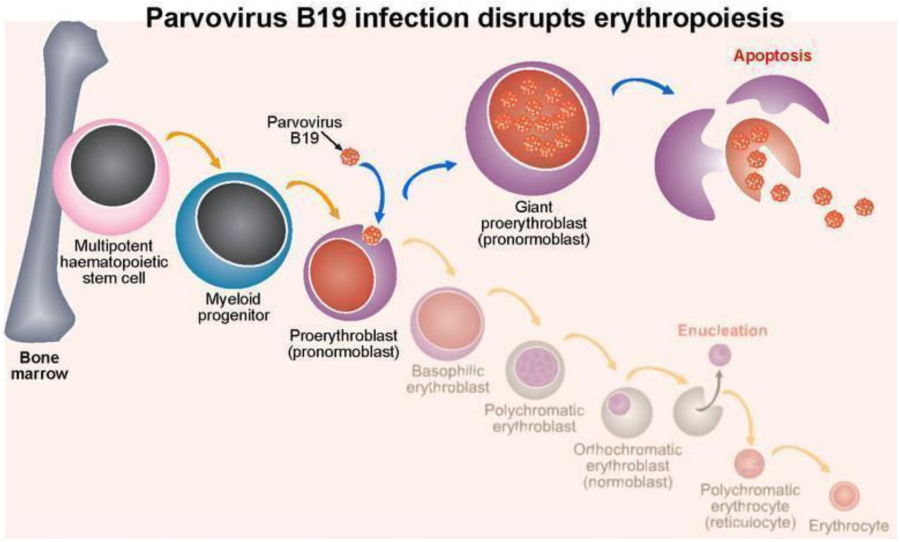
•**Patienten mit chronischer Anämie:** Bei Vorerkrankungen der roten (wie Sichelzellanämie) kann das Virus eine lebensgefährliche Krise auslösen.

•**Immungeschwächten Personen:** Es kann zu einer chronischen Blutarmut führen.



Es gibt derzeit keinen zugelassenen Impfstoff gegen das humane Parvovirus B19 (Auslöser der Ringelröteln). Der Schutz erfolgt ausschließlich über eine bereits durchgemachte Infektion, die eine lebenslange Immunität hinterlässt.

Parvovirus B19 verursacht eine Anämie, indem es sich gezielt in den Vorläuferzellen der roten Blutkörperchen (Erythroblasten) im Knochenmark vermehrt und diese zerstört. Dies führt zu einem sofortigen Stopp der Blutbildung, was besonders bei Patienten mit verkürzter Lebensdauer der roten Blutkörperchen zu lebensbedrohlichen Krisen führt.



Mechanismus im Detail

•**Zellinfektion:** Das Virus dockt an den Rezeptor (Globosid oder Blutgruppen-P-Antigen) auf der Oberfläche der unreifen roten Blutkörperchen im Knochenmark an und dringt in sie ein.

•**Stopp der Erythropoese:** Durch die Vermehrung des Virus in diesen Zellen sterben die Vorläuferzellen ab. Die Produktion neuer Erythrozyten (rote Blutkörperchen) im Knochenmark kommt vorübergehend komplett zum Erliegen.

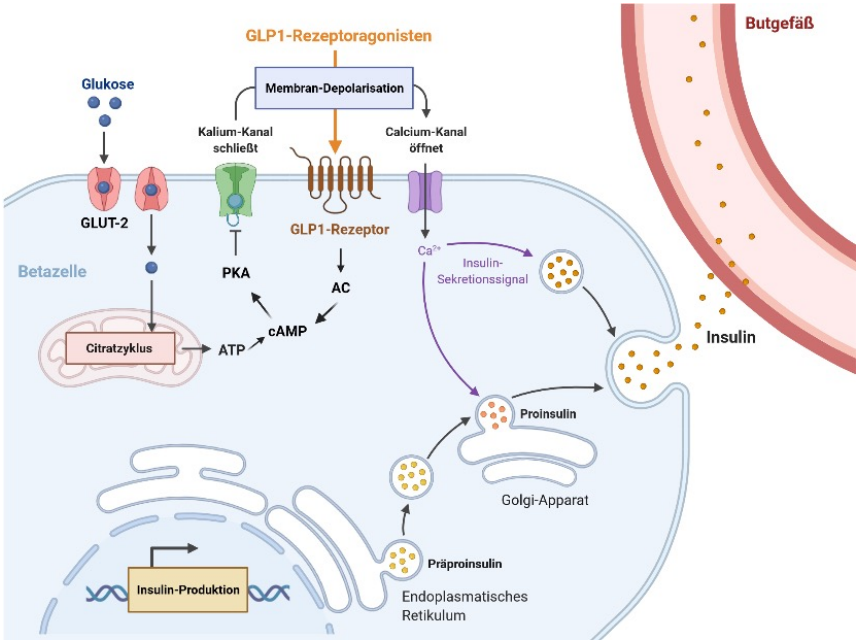
•**Klinische Auswirkung:** Da reife rote Blutkörperchen eine Lebensdauer von rund 120 Tagen haben, fällt der Mangel bei Gesunden kaum auf. Bei Patienten mit chronischen Blutkrankheiten (wie Sichelzellanämie, Thalassämie oder Sphärozytose) oder bei Immunschwäche führt dieser abrupte Produktionsstopp jedoch innerhalb weniger Tage zu einer schweren, sogenannten **aplastischen Krise**.

Der Begriff **„large P antigen“** (großes P-Antigen) taucht in der medizinischen Forschung hauptsächlich im Zusammenhang mit **Ribosomen** auf. Er bezieht sich auf das **humane große P-Antigen** (*human large P-antigen*), welches ein struktureller Kernbestandteil der großen (60S) Untereinheit von Ribosomen in menschlichen Zellen ist

Gesunde Kinder bekommen bei Ringelröteln (Parvovirus B19) in der Regel keine klinisch auffällige Anämie, weil die Zerstörung der roten Blutkörperchen durch die schnelle Neubildung im Knochenmark ausgeglichen wird und die Lebensdauer der bereits vorhandenen Erythrozyten ausreicht

THE LANCET

GLP-1 (Glucagon-like Peptide-1) ist ein natürliches Darmhormon, das nach der Nahrungsaufnahme ausgeschüttet wird. Es senkt den Blutzucker, indem es die Insulinproduktion anregt, und signalisiert dem Gehirn Sättigung. Als Medikament (GLP-1-Rezeptoragonist) wird es intensiv zur Behandlung von Typ-2-Diabetes und Adipositas eingesetzt.



Wirkung und Nutzen

•**Blutzuckerkontrolle:** Es fördert die Insulinausschüttung und hemmt die Ausschüttung von Glucagon, wodurch der Blutzuckerspiegel sinkt.

•**Gewichtsverlust:** Durch die Verlangsamung der Magenentleerung und ein verstärktes Sättigungsgefühl führt es oft zu einer deutlichen Gewichtsabnahme.

•**Herz-Kreislauf-Schutz:** Einige GLP-1-Medikamente senken nachweislich das Risiko für Herzinfarkte oder Schlaganfälle.

Injectable GLP-1 agonists and plastic junk

Elecoglipron, an oral small molecule GLP-1 receptor agonist in adults with obesity or overweight (VISTA): a multicentre, phase 2, randomised, placebo-controlled clinical trial

Oral GLP-1 agnonist

In Type-2 Diabetes

and

Obesity

Summary

Background Elecoglipron (AZD5004) is an oral small-molecule glucagon-like peptide-1 (GLP-1) receptor agonist administered once daily without food or fluid restriction, in development for weight management in people living with obesity or overweight and type 2 diabetes. We assessed the efficacy, safety, and tolerability of elecoglipron versus placebo in participants with obesity or overweight and at least one weight-related condition without diabetes.

Methods In this double-blind, randomised, controlled, phase 2 dose-ranging study with a total treatment duration of 36 weeks, adult participants were recruited from medical research centres and hospitals in Australia, Canada, Germany, Japan, Taiwan, the UK, and the USA. Participants were aged 18 years or older living with obesity (BMI ≥30 kg/m²) or with overweight (BMI ≥27 kg/m²) with at least one weight-related condition and without type 2 diabetes. Eligible participants were randomly assigned in a 2:3:3:3:3:5 ratio to receive 5 mg, 15 mg, 50 mg, 75 mg (weekly titration), or 75 mg (every 2-week titration) of elecoglipron or matching placebo. Elecoglipron was administered as oral once-daily tablets without titration (5 mg and 15 mg) and as three different dose-titration regimens. The daily dose of 50 mg was evaluated using an every-4-weeks dose-escalation schedule, while 75 mg was assessed with weekly or every 2-week dose-escalation schedules. Participants, treating physicians, and sponsor were masked to the treatment allocation. The dual primary endpoints were percent change in bodyweight from baseline and the proportion of patients reaching at least 5% weight loss at week 26. Safety and tolerability were assessed in all participants who received at least one dose of study treatment. This trial is registered at ClinicalTrials.gov (NCT06579092) and is completed.

Findings From Oct 8, 2024, to Feb 18, 2025, 472 individuals were screened for potential study inclusion, 162 did not meet the inclusion criteria, and 310 participants were randomly assigned to the varied elecoglipron groups or placebo. 288 participants (93%) completed the study and 231 (75%) completed the assigned treatment. The mean age of participants was 48·4 years (SD 13·7), 225 (73%) were female, 85 (27%) were male, their mean bodyweight was 106·9 kg (SD 24·1), and their mean BMI was 38·2 kg/m² (SD 7·2). At week 26, the estimated mean change from baseline in bodyweight was between –2·6% (5 mg elecoglipron), and –10·5% (75 mg with weekly titration steps) compared with –0·6% with placebo. The estimated proportion of participants reaching weight reductions of at least 5% at week 26 was 40·4–88·8% with elecoglipron versus 15·6% with placebo. Adverse events were reported by 84% (27 of 32) to 98% (48 of 49) of participants across elecoglipron doses compared with 84% (68 of 81) in the placebo group, the most common being nausea, constipation, diarrhoea, headache, and vomiting.

Interpretation Daily oral elecoglipron demonstrated clinically meaningful weight reductions and a safety and tolerability profile consistent with the GLP-1 receptor agonist class in this phase 2 dose-ranging study, supporting phase 3 investigation in people living with obesity or overweight.

Funding AstraZeneca.

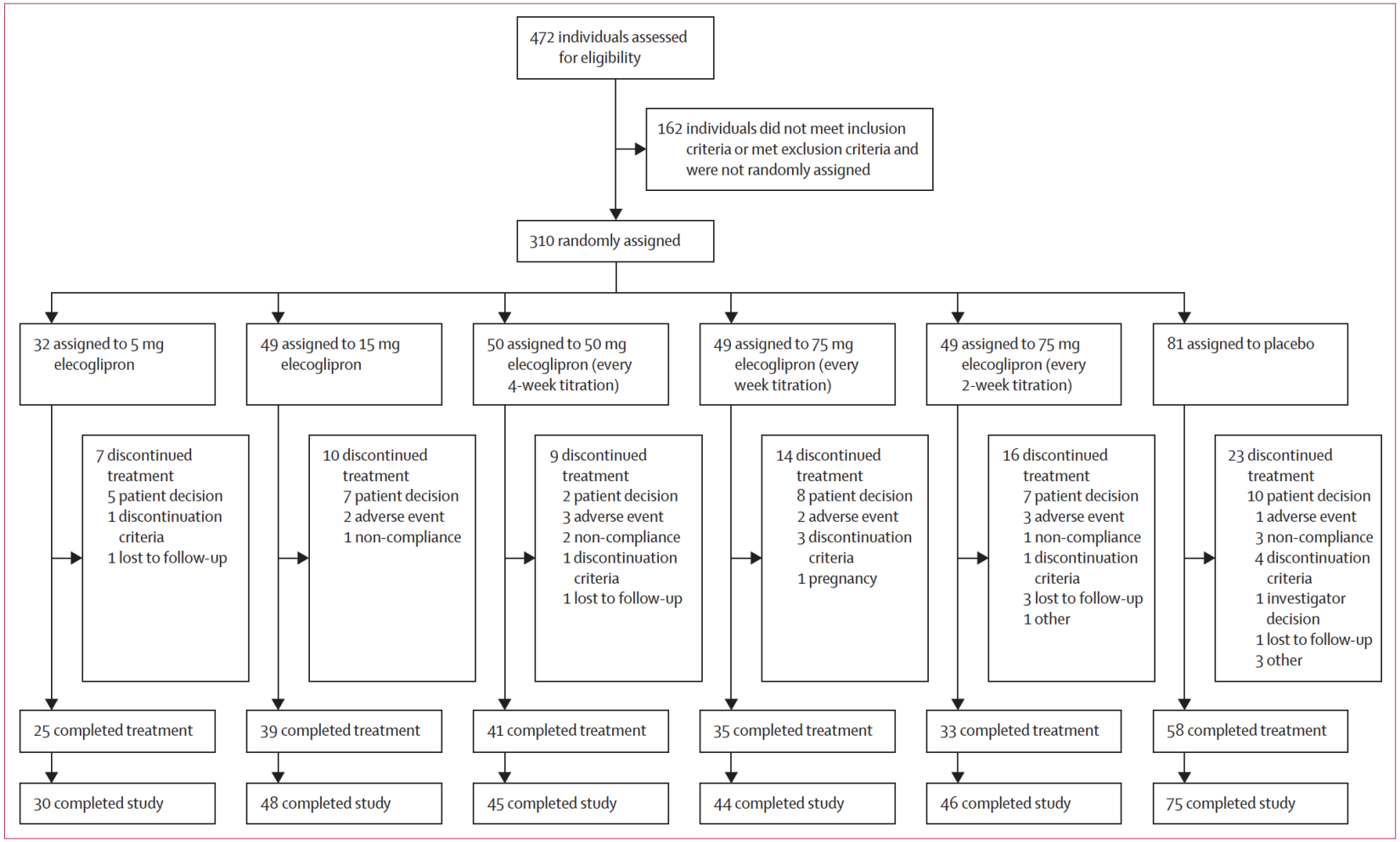


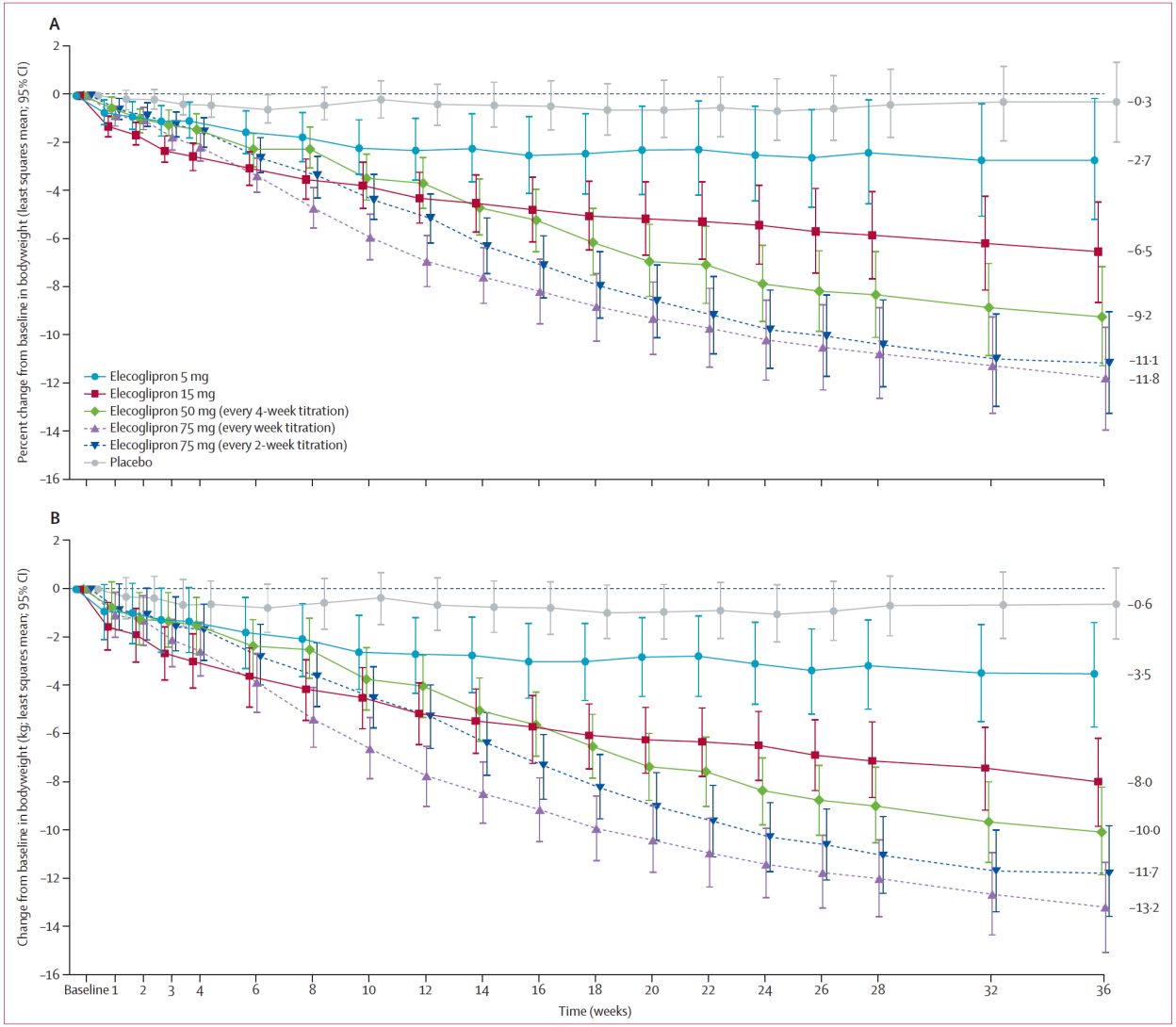
Figure 1: **Trial profile**

	Elecoglipron					Pooled placebo (n=81)	Total (N=310)
	5 mg (n=32)	15 mg (n=49)	50 mg (every 4-week titration; n=50)	75 mg (every week titration; n=49)	75 mg (every 2-week titration; n=49)		
Age, years	50·7 (12·2)	46·7 (13·3)	51·0 (12·7)	48·0 (11·9)	48·9 (15·7)	46·9 (14·7)	48·4 (13·7)
Females	26 (81%)	33 (67%)	40 (80%)	28 (57%)	41 (84%)	57 (70%)	225 (73%)
Males	6 (19%)	16 (33%)	10 (20%)	21 (43%)	8 (16%)	24 (30%)	85 (27%)
Race							
American Indian or Alaska Native	0	0	0	0	0	1 (1%)	1 (<1%)
Asian	4 (13%)	9 (18%)	5 (10%)	9 (18%)	7 (14%)	10 (12%)	44 (14%)
Black or African American	5 (16%)	4 (8%)	10 (20%)	3 (6%)	4 (8%)	11 (14%)	37 (12%)
Native Hawaiian or other Pacific Islander	0	0	0	1 (2%)	0	0	1 (<1%)
Multiple	0	0	1 (2·0%)	0	1 (2%)	0	2 (1%)
White	23 (72%)	35 (71%)	33 (66%)	36 (73%)	37 (76%)	59 (73%)	223 (72%)
Not reported	0	1 (2%)	1 (2%)	0	0	0	2 (1%)
Bodyweight, kg	107·5 (20·7)	109·7 (21·6)	104·4 (20·8)	106·7 (27·5)	103·5 (28·1)	108·7 (24·2)	106·9 (24·1)
BMI, kg/m²	38·7 (5·8)	39·0 (6·8)	37·8 (5·9)	37·4 (8·4)	37·3 (8·3)	38·8 (7·2)	38·2 (7·2)
BMI range							
<30 kg/m²	0	2 (4%)	1 (2%)	4 (8%)	3 (6%)	4 (5%)	14 (5%)
30 to <35 kg/m²	11 (34%)	15 (31%)	17 (34%)	18 (37%)	22 (45%)	21 (26%)	104 (34%)
35 to <40 kg/m²	8 (25%)	10 (20%)	14 (28%)	13 (27%)	9 (18%)	27 (33%)	81 (26%)
≥40 kg/m²	13 (41%)	22 (45%)	18 (36%)	14 (29%)	15 (31%)	29 (36%)	111 (36%)
Obesity-related comorbidities							
Hypertension	8 (25%)	16 (33%)	17 (34%)	17 (35%)	13 (27%)	27 (33%)	98 (32%)
Dyslipidaemia	7 (22%)	10 (20%)	7 (14%)	16 (33%)	8 (16%)	14 (17%)	62 (20%)
Cardiovascular disease	1 (3%)	2 (4%)	0	1 (2%)	1 (2%)	3 (4%)	8 (3%)
Obstructive sleep apnoea	6 (19%)	9 (18%)	8 (16%)	6 (12%)	5 (10%)	8 (10%)	42 (14%)
Waist circumference, cm							
Males	128·5 (10·9)	123·4 (15·5)	119·4 (15·5)	122·6 (17·6)	129·7 (26·9)	122·9 (17·4)	123·5 (17·3)
Females	109·2 (10·8)	112·6 (17·0)	114·2 (18·7)	106·3 (15·8)	108·7 (12·7)	110·4 (15·1)	110·4 (15·4)
Glycated haemoglobin group							
≥5·7%	8 (25%)	17 (35%)	15 (30%)	16 (33%)	16 (33%)	35 (43%)	107 (35%)
Blood pressure, mm Hg							
Systolic	125·3 (14·2)	121·4 (14·7)	127·4 (14·0)	124·1 (12·3)	124·6 (14·7)	125·7 (12·3)	124·9 (13·6)
Diastolic	81·0 (8·4)	78·5 (10·5)	83·6 (9·9)	80·9 (6·9)	80·3 (8·2)	80·7 (8·0)	80·8 (8·7)
Pulse, beats per min	75·6 (10·4)	73·9 (10·0)	71·7 (10·2)	72·3 (10·1)	69·6 (10·0)	70·7 (9·8)	72·0 (10·1)
eGFR, mL/min per 1·73m²	97·2 (15·2)	100·0 (18·7)	97·1 (18·1)	100·4 (15·4)	96·0 (19·4)	102·1 (17·4)	99·2 (17·6)

Data are reported as mean (SD) or n (%). Percentages might not total 100 because of rounding. eGFR=estimated glomerular filtration rate.

Table 1: **Baseline characteristics**

Change in body weight



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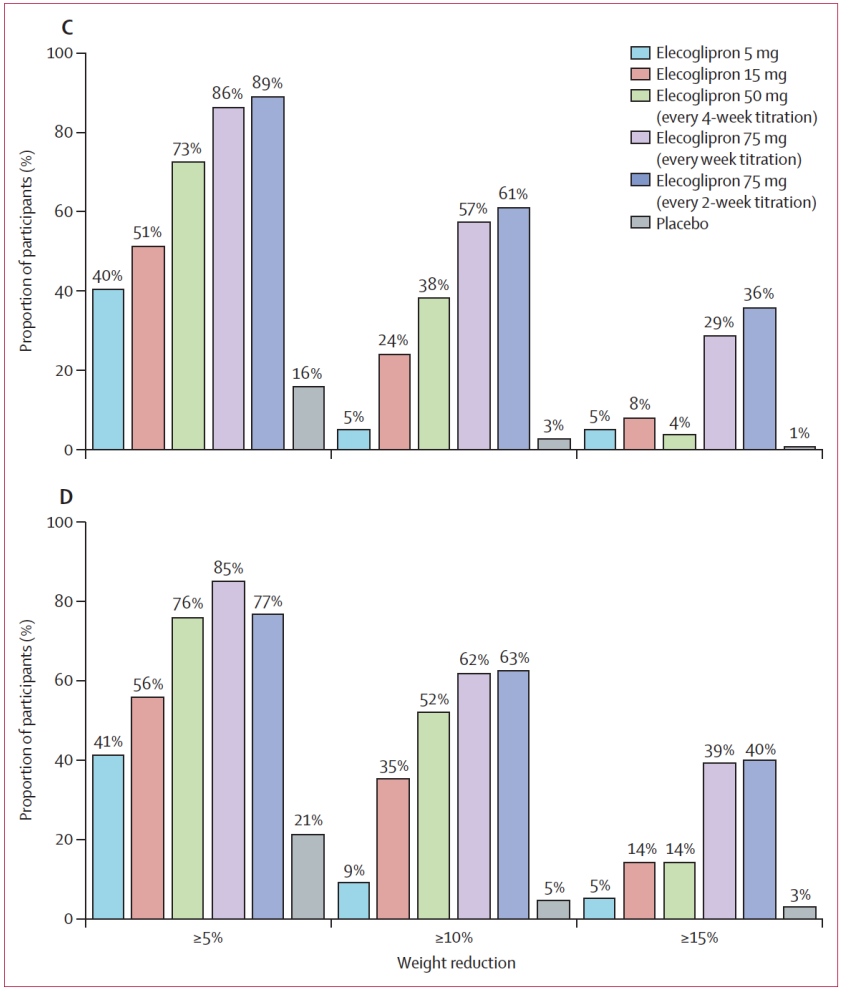


***Figure 2*: Efficacy outcomes**

The percentage change (A) and the absolute change (B) from baseline in bodyweight by week in the efficacy estimand are shown. Least-square means are presented, and bars indicate 95% CI. Proportion of participants who had weight reductions of at least 5%, at least 10%, and at least 15% by week 26 (C) and week 36 (D). The results were calculated according to Rubin's rule.

	Elecoglipron						Pooled placebo (n=81)
	5 mg (n=32)	15 mg (n=49)	50 mg (every 4-week titration; n=50)	75 mg (every week titration; n=49)	75 mg (every 2-week titration; n=49)	75 mg total (n=98)	
Bodyweight change from baseline, %							
Week 26 (dual primary endpoint)							
Number of participants	27	38	44	35	36	71	61
Least squares mean (95% CI)	−2·6 (−4·7 to −0·6)	−5·6 (−7·4 to −3·9)	−8·1 (−9·8 to −6·5)	−10·5 (−12·3 to −8·7)	−10·0 (−11·7 to −8·3)	−10·3 (−11·5 to −9·0)	−0·6 (−1·9 to 0·8)
Least squares mean difference *vs* placebo (95% CI)	−2·1 (−4·5 to 0·4)	−5·1 (−7·2 to −2·9)	−7·6 (−9·7 to −5·5)	−9·9 (−12·1 to −7·8)	−9·4 (−11·6 to −7·3)	−9·7 (−11·5 to −7·9)	..
Week 36 (secondary endpoint)							
Number of participants	24	38	39	35	29	64	54
Least squares mean (95% CI)	−2·7 (−5·2 to −0·2)	−6·5 (−8·6 to −4·4)	−9·2 (−11·3 to −7·2)	−11·8 (−13·9 to −9·6)	−11·1 (−13·2 to −9·0)	−11·5 (−13·0 to −9·9)	−0·3 (−2·0 to 1·3)
Least squares mean difference *vs* placebo (95% CI)	−2·4 (−5·4 to 0·6)	−6·2 (−8·8 to −3·6)	−8·9 (−11·5 to −6·3)	−11·5 (−14·1 to −8·8)	−10·8 (−13·5 to −8·2)	−11·1 (−13·3 to −8·9)	..
Participants reaching at least 5% weight loss							
Week 26 (dual primary endpoint)							
Probability of event, % (95% CI)	40·4 (24·2 to 59·0)	51·3 (36·2 to 66·2)	72·5 (58·0 to 83·5)	86·1 (71·4 to 93·9)	88·8 (74·7 to 95·5)	87·5 (78·1 to 93·2)	15·6 (8·7 to 26·5)
OR (95% CI) *vs* placebo	3·7 (1·4 to 9·9)	5·7 (2·3 to 14·1)	14·3 (5·6 to 36·5)	33·5 (10·8 to 103·6)	42·9 (13·1 to 140·9)	37·9 (14·7 to 97·8)	..
Week 36 (secondary endpoint)							
Probability of event, % (95% CI)	41·3 (24·2 to 60·8)	55·7 (40·3 to 70·1)	76·1 (60·8 to 86·7)	85·1 (70·1 to 93·3)	76·8 (60·2 to 87·8)	81·4 (71·0 to 88·6)	21·4 (12·8 to 33·4)
OR (95% CI) *vs* placebo	2·6 (0·9 to 7·1)	4·6 (1·9 to 11·1)	11·7 (4·6 to 30·0)	21·1 (7·1 to 62·4)	12·2 (4·5 to 32·6)	16·1 (6·9 to 37·2)	..
Participants reaching at least 10% weight loss							
Week 26 (secondary endpoint)							
Probability of event, % (95% CI)	4·9 (1·0 to 21·4)	24·1 (13·5 to 39·1)	38·1 (25·2 to 53·0)	57·2 (40·9 to 72·0)	60·8 (44·4 to 75·0)	59·0 (47·5 to 69·6)	2·7 (0·6 to 11·4)
OR (95% CI) *vs* placebo	1·9 (0·2 to 17·7)	11·4 (2·1 to 61·4)	22·1 (4·3 to 114·0)	48·0 (8·9 to 257·8)	55·6 (10·7 to 290·6)	51·6 (10·4 to 255·7)	..
Week 36 (secondary endpoint)							
Probability of event, % (95% CI)	8·8 (2·5 to 26·5)	35·1 (22·0 to 51·0)	52·0 (37·0 to 66·6)	61·9 (45·4 to 76·0)	62·5 (45·7 to 76·7)	62·2 (50·6 to 72·5)	4·5 (1·4 to 13·3)
OR (95% CI) *vs* placebo	2·1 (0·4 to 12·1)	11·5 (3·0 to 44·5)	23·0 (6·1 to 86·5)	34·5 (9·0 to 131·2)	35·4 (9·1 to 136·8)	34·9 (9·9 to 122·6)	..
Participants reaching at least 15% weight loss							
Week 26 (secondary endpoint)							
Probability of event, % (95% CI)	5·0 (1·0 to 21·7)	8·0 (2·8 to 20·5)	3·5 (0·7 to 15·5)	28·7 (16·2 to 45·6)	35·8 (22·1 to 52·2)	32·1 (22·3 to 43·7)	0·7 (0·0 to 9·2)
OR (95% CI) *vs* placebo	7·9 (0·3 to 192·0)	12·9 (0·7 to 241·4)	5·5 (0·2 to 127·6)	60·2 (3·7 to 994·0)	83·2 (5·1 to 1368·2)	70·7 (4·5 to 1113·2)	..
Week 36 (secondary endpoint)							
Probability of event, % (95% CI)	4·9 (1·0 to 21·4)	14·0 (6·5 to 27·7)	14·1 (6·3 to 28·7)	39·3 (24·4 to 56·4)	39·8 (24·8 to 57·0)	39·5 (28·6 to 51·6)	2·7 (0·6 to 11·5)
OR (95% CI) *vs* placebo	1·8 (0·2 to 17·6)	5·8 (1·0 to 33·8)	5·9 (1·0 to 34·6)	23·1 (4·3 to 125·3)	23·6 (4·3 to 129·0)	23·4 (4·6 to 118·2)	–

Table 2: **Primary and secondary endpoints**

	Elecoglipron					Pooled placebo (n=81)
	5 mg (n=32)	15 mg (n=49)	50 mg (every 4-week titration; n=50)	75 mg (every week titration; n=49)	75 mg (every 2-week titration; n=49)	
Overall adverse event information						
Adverse events	27 (84%)	43 (88%)	44 (88%)	48 (98%)	45 (92%)	68 (84%)
Serious adverse events	0	0	0	4 (8%)	4 (8%)	2 (2%)
Serious adverse events with an outcome of death	0	0	0	0	0	0
Adverse events leading to treatment discontinuation	0	2 (4%)	3 (6%)	3 (6%)	4 (8%)	3 (4%)
Gastrointestinal adverse events leading to treatment discontinuation	0	1 (2%)	2 (4%)	1 (2%)	1 (2%)	0
Adverse events occurring in at least 5% of participants in any group (non-gastrointestinal)						
Headache	3 (9%)	6 (12%)	14 (28%)	15 (31%)	8 (16%)	11 (14%)
Fatigue	2 (6%)	5 (10%)	8 (16%)	4 (8%)	8 (16%)	6 (7%)
Nasopharyngitis	5 (16%)	8 (16%)	5 (10%)	3 (6%)	9 (18%)	9 (11%)
Upper respiratory tract infection	5 (16%)	7 (14%)	8 (16%)	6 (12%)	3 (6%)	10 (12%)
Arthralgia	4 (13%)	2 (4%)	5 (10%)	2 (4%)	4 (8%)	5 (6%)
Back pain	4 (13%)	7 (14%)	3 (6%)	2 (4%)	3 (6%)	7 (9%)
Dizziness	0	3 (6%)	3 (6%)	3 (6%)	3 (6%)	3 (4%)
Influenza	3 (9%)	2 (4%)	3 (6%)	1 (2%)	2 (4%)	3 (4%)
Amylase increased	0	2 (4%)	3 (6%)	1 (2%)	5 (10%)	1 (1%)
Insomnia	1 (3%)	0	5 (10%)	2 (4%)	1 (2%)	2 (2%)
Lipase increased	1 (3%)	1 (2%)	2 (4%)	1 (2%)	5 (10%)	1 (1%)
Blood bilirubin increased	0	0	2 (4%)	4 (8%)	4 (8%)	0
Lethargy	1 (3%)	1 (2%)	1 (2%)	3 (6%)	2 (4%)	0
Rash	2 (6%)	2 (4%)	1 (2%)	2 (4%)	1 (2%)	2 (2%)
Viral upper respiratory tract infection	1 (3%)	3 (6%)	1 (2%)	4 (8%)	1 (2%)	1 (1%)
Gastroenteritis	0	0	4 (8%)	1 (2%)	1 (2%)	3 (4%)
Alopecia	0	1 (2%)	0	3 (6%)	3 (6%)	0
Bilirubin conjugate increased	0	0	0	2 (4%)	6 (12%)	0
Migraine	1 (3%)	1 (2%)	3 (6%)	1 (2%)	2 (4%)	1 (1%)
Cough	3 (9%)	2 (4%)	1 (2%)	0	3 (6%)	1 (1%)
Dysgeusia	0	1 (2%)	4 (8%)	0	2 (4%)	0
Oropharyngeal pain	1 (3%)	0	2 (4%)	3 (6%)	1 (2%)	2 (2%)
Sinusitis	2 (6%)	2 (4%)	0	1 (2%)	2 (4%)	2 (2%)
COVID-19	2 (6%)	0	3 (6%)	2 (4%)	1 (2%)	2 (2%)
Pain in extremity	2 (6%)	1 (2%)	2 (4%)	0	0	1 (1%)

(Table 3 continues on next page)

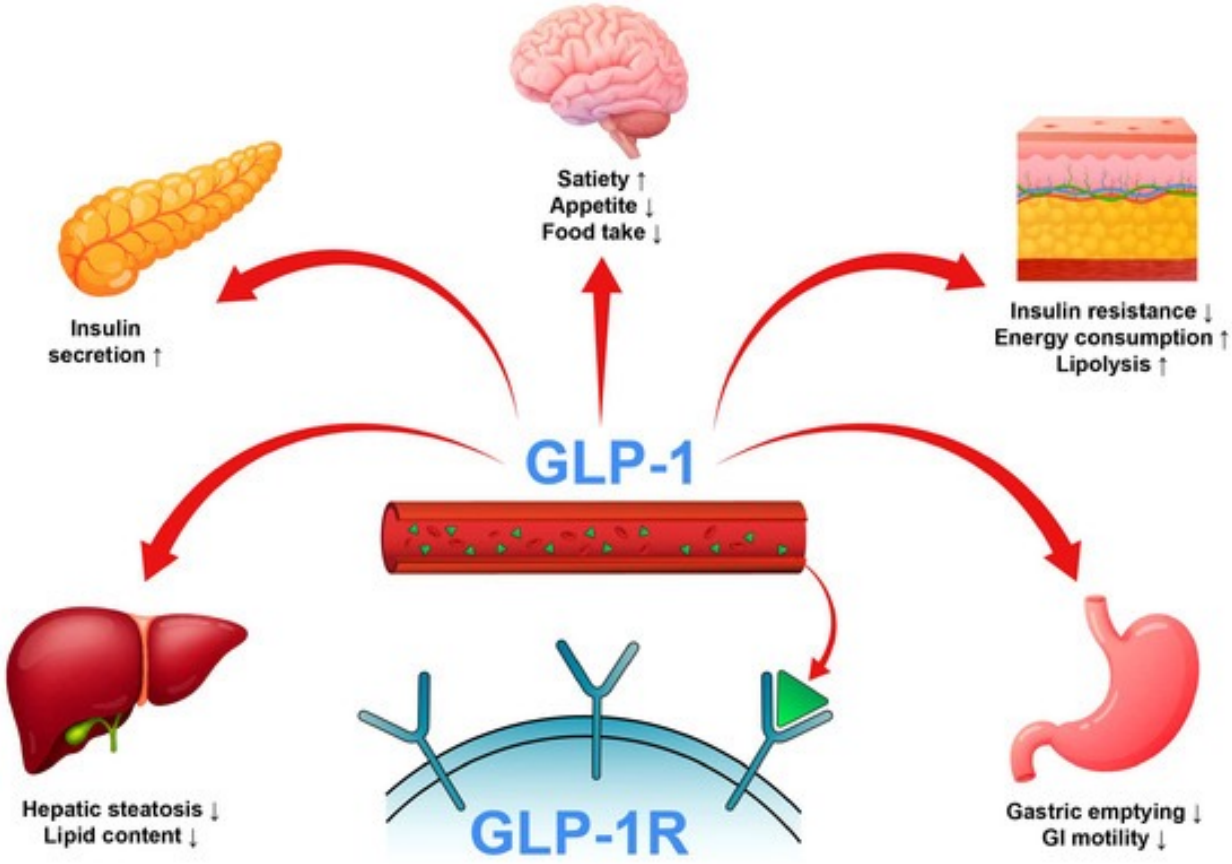
	Elecoglipron					Pooled placebo (n=81)
	5 mg (n=32)	15 mg (n=49)	50 mg (every 4-week titration; n=50)	75 mg (every week titration; n=49)	75 mg (every 2-week titration; n=49)	
(Continued from previous page)						
Gastrointestinal adverse events of special interest occurring in at least 5% of participants in any group						
Any	17 (53%)	38 (78%)	40 (80%)	41 (84%)	38 (78%)	42 (52%)
Nausea	3 (9%)	27 (55%)	28 (56%)	27 (55%)	22 (45%)	16 (20%)
Constipation	4 (13%)	13 (27%)	21 (42%)	20 (41%)	10 (20%)	5 (6%)
Diarrhoea	4 (13%)	13 (27%)	15 (30%)	17 (35%)	11 (22%)	20 (25%)
Vomiting	2 (6%)	6 (12%)	13 (26%)	13 (27%)	14 (29%)	4 (5%)
Dyspepsia	3 (9%)	10 (20%)	8 (16%)	7 (14%)	9 (18%)	2 (2%)
Abdominal pain (upper)	2 (6%)	5 (10%)	5 (10%)	10 (20%)	9 (18%)	4 (5%)
Gastro-oesophageal reflux disease	1 (3%)	5 (10%)	6 (12%)	5 (10%)	6 (12%)	2 (2%)
Abdominal distension	2 (6%)	3 (6%)	6 (12%)	6 (12%)	3 (6%)	6 (7%)
Eructation	0	4 (8%)	2 (4%)	5 (10%)	7 (14%)	0
Flatulence	1 (3%)	2 (4%)	2 (4%)	5 (10%)	4 (8%)	3 (4%)
Decreased appetite	2 (6%)	2 (4%)	3 (6%)	3 (6%)	2 (4%)	5 (6%)
Dry mouth	1 (3%)	2 (4%)	1 (2%)	3 (6%)	4 (8%)	0
Abdominal pain	1 (3%)	2 (4%)	5 (10%)	3 (6%)	1 (2%)	4 (5%)
Abdominal pain (lower)	1 (3%)	0	3 (6%)	2 (4%)	0	0

The table includes adverse events with an onset date on or after the day of the randomisation visit and participants are censored at the earliest of withdrawal of consent, death, or the date of the last clinical assessment. Only the first event per participant in each category is used in the analyses. Serious adverse events were as assessed by the investigator.

Table 3: **Summary of adverse events**

Implications of all the available evidence

Elecoglipron resulted in notable weight loss in adults living with obesity or overweight without type 2 diabetes. The sustained reduction in bodyweight up to 36 weeks without evidence of a plateau suggests that maximal weight loss might not have been reached by 6 months; longer-term evaluation in phase 3 trials is needed to confirm the extent of longer-term weight loss. Elecoglipron does not have food or fluid dosing restrictions and might offer a convenient, effective, and safe oral therapy for people living with obesity or overweight. Phase 3 studies will be required to confirm long-term efficacy and safety.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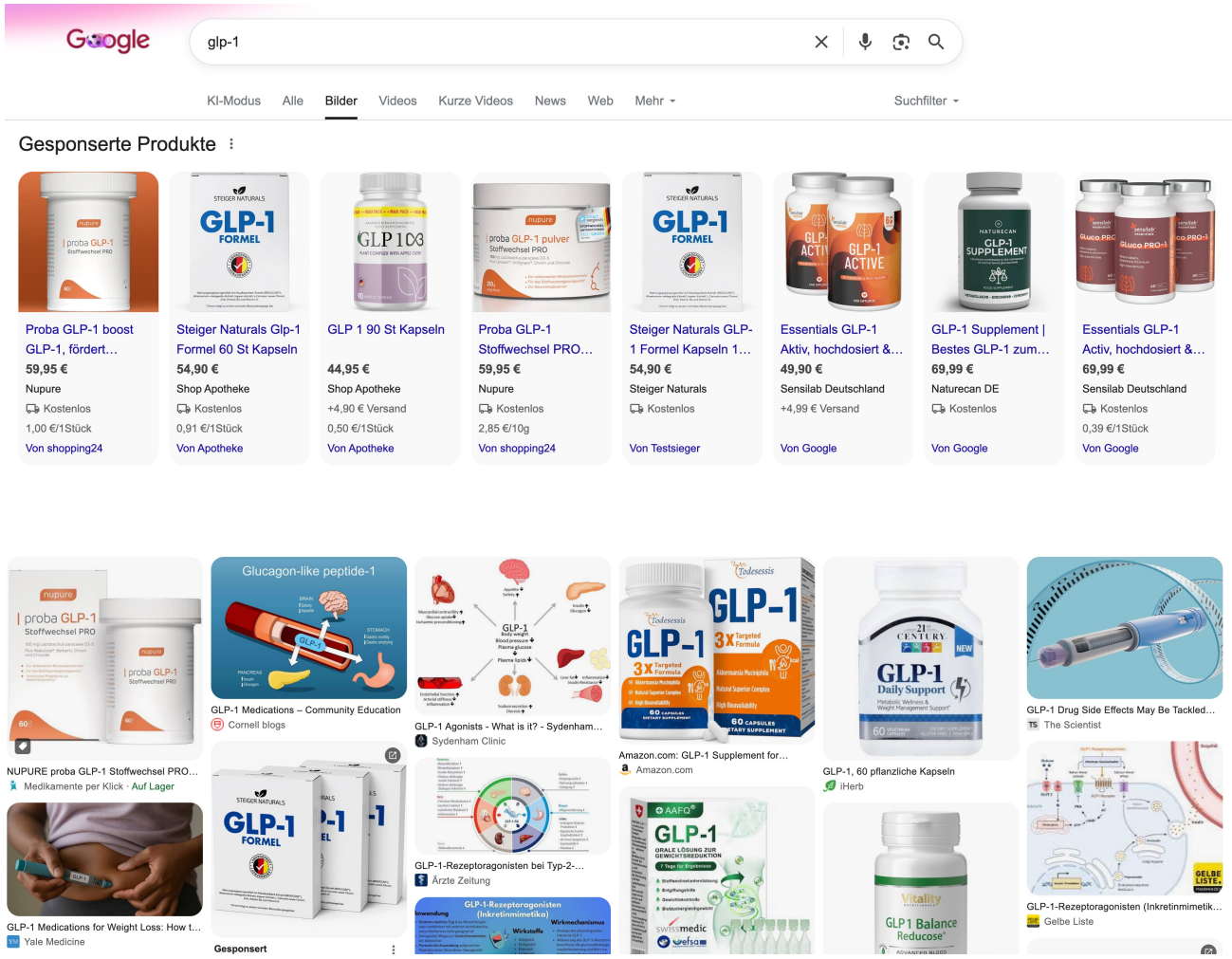
Appetite ↓
Food take ↓
Insulin
secretion ↑
Insulin resistance ↓
Energy consumption ↑
Lipolysis ↑
GLP-1
Hepatic steatosis ↓
Lipid content ↓
GLP-1R
Gastric emptying ↓
GI motility ↓

What is all this stuff ?!?!?



Elecoglipron, an oral small molecule GLP-1 receptor agonist in adults with type 2 diabetes (SOLSTICE): a multicentre, phase 2b, randomised, placebo-controlled trial

Oral GLP-1 agnonist

In Type-2

DM

Summary

Background Elecoglipron is an oral, small molecule glucagon-like peptide (GLP)-1 receptor agonist currently in development for the management of type 2 diabetes. Elecoglipron is orally administered once daily with no food or fluid restrictions. SOLSTICE, a phase 2b study, evaluated the efficacy, safety, and tolerability of elecoglipron versus placebo in participants with type 2 diabetes.

Methods This phase 2b, randomised, double-blind, placebo-controlled trial was conducted in medical research centres and hospitals across nine countries, Canada, Germany, Hungary, Japan, Poland, Slovakia, Spain, the UK, and the USA. Sites were selected based on their capacity to fulfil protocol requirement, including, but not limited to, regulatory and ethics approvals, appropriate infrastructure and personnel, and access to the target patient population. Participants aged 18 years and older with a BMI of 23 kg/m² or higher and type 2 diabetes (glycated haemoglobin [HbA_{1c}] ≥7·0% to ≤10·5%, ≥6·5% to ≤10·5% in the USA) managed with diet and exercise alone or monotherapy with metformin or an SGLT2 inhibitor were enrolled. Participants were randomly assigned (3:5:3:5:3:3:6:4) via an interactive web response system to elecoglipron as oral once-daily tablets without dose escalation (5, 15, or 25 mg) or three different dose-escalation regimens, to target doses of 50 mg and 75 mg. The daily dose of 50 mg was evaluated using an every 2-week dose-escalation schedule, while 75 mg was assessed with every 2-week or every 4-week dose-escalation schedules. Participants could also be randomly assigned to placebo matched to each of the elecoglipron groups, or open-label oral semaglutide titrated to 14 mg once daily for 26 weeks. Participants, the treating physician, and the sponsor were masked to doses of elecoglipron or matched placebo, while semaglutide was open-label. The primary endpoint was percent change in HbA_{1c} from baseline to 26 weeks. Efficacy, safety, and tolerability were assessed in all participants who received at least one dose of trial treatment. The trial is registered with ClinicalTrials.gov (NCT06579105) and clinicaltrials.eu (2024-512562-34-00) and is completed.

Findings From Oct 8, 2024, to June 6, 2025, 863 individuals were screened for study inclusion, 457 were excluded as they did not meet the inclusion criteria or met the exclusion criteria, 406 were enrolled and randomly assigned to one of the eight treatment groups, and 404 participants received at least one dose of trial treatment. Among those who received at least one dose of trial treatment, mean (SD) baseline characteristics were: age 58·4 years (10·7); HbA_{1c} of 7·9% (0·9); bodyweight of 99·8 kg (22·1); and BMI of 34·9 kg/m² (7·5). Of 404 participants, 168 (42%) of participants were female and 236 (58%) were male; 280 (69%) were White. At week 26, the mean change from baseline in HbA_{1c} ranged between –0·91% (95% CI –1·25 to –0·58; 5 mg elecoglipron) and –1·88% (–2·23 to –1·53; 75 mg elecoglipron with every 2-week dose-escalation step) compared with –0·15% (–0·42 to 0·12) with placebo. Adverse events were reported by 63% (24 of 38 in the 5 mg group and 39 of 62 in the 15 mg group) to 87% (33 of 38 in 75 mg every 4-week dose escalation) of participants across elecoglipron doses compared with 63% (45 of 71) in the placebo group. The most common adverse events were gastrointestinal, including nausea, constipation, diarrhoea, and vomiting.

Interpretation Once-daily oral elecoglipron showed reductions in glycaemia and a safety and tolerability profile consistent with the GLP-1 receptor agonist class at a similar phase of development, supporting continued development with phase 3 trials for people living with type 2 diabetes.

Funding AstraZeneca.

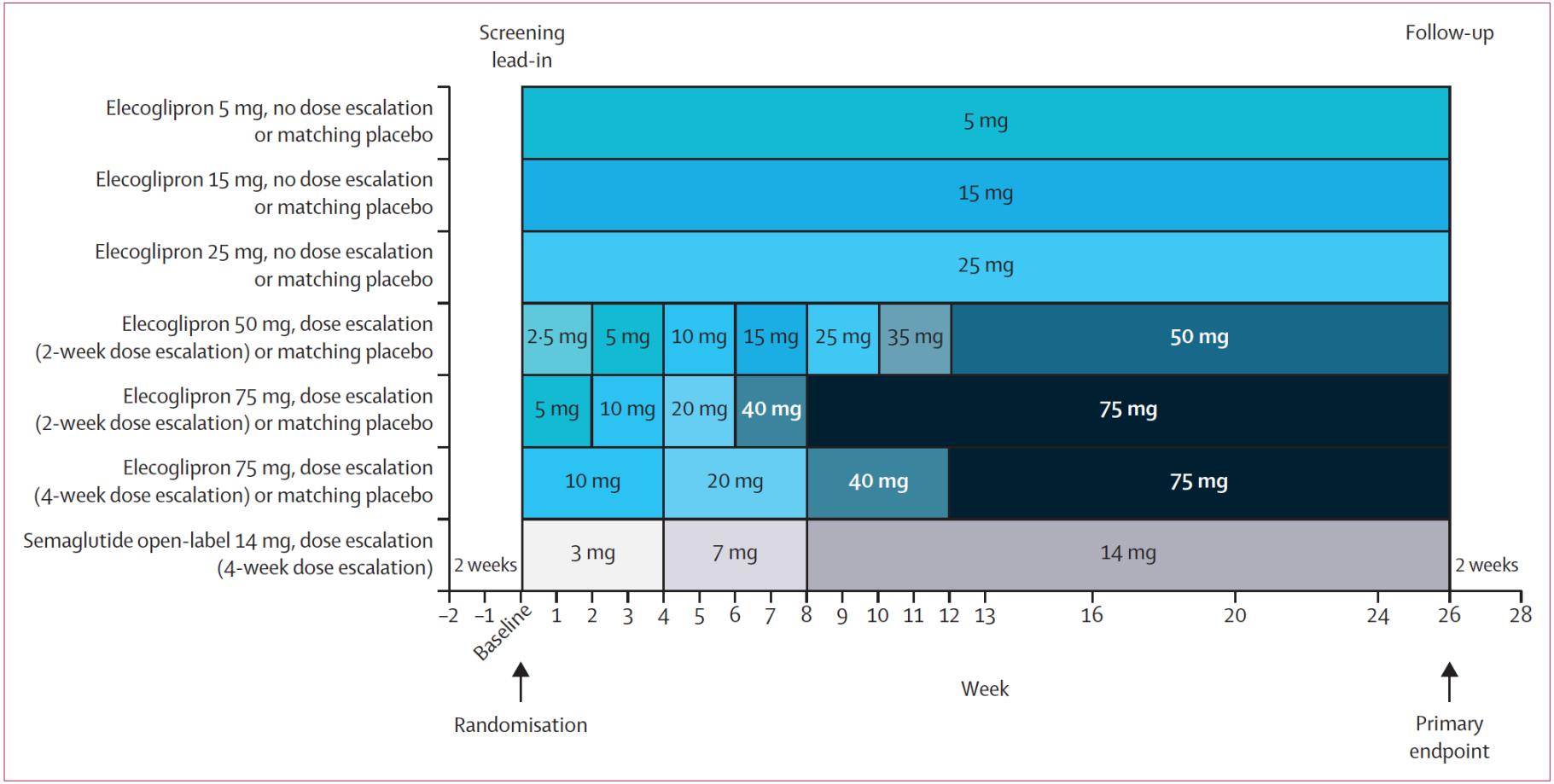


Figure 1: **Dose and dose-escalation schema**

Semaglutide 14 mg bezieht sich auf das orale Medikament **Rybelsus** (Tabletten). Es ist die höchste zugelassene Erhaltungsdosis für die tägliche Einnahme bei Typ-2-Diabetes, die nach einer schrittweisen Steigerung von 3 mg und 7 mg erreicht wird.

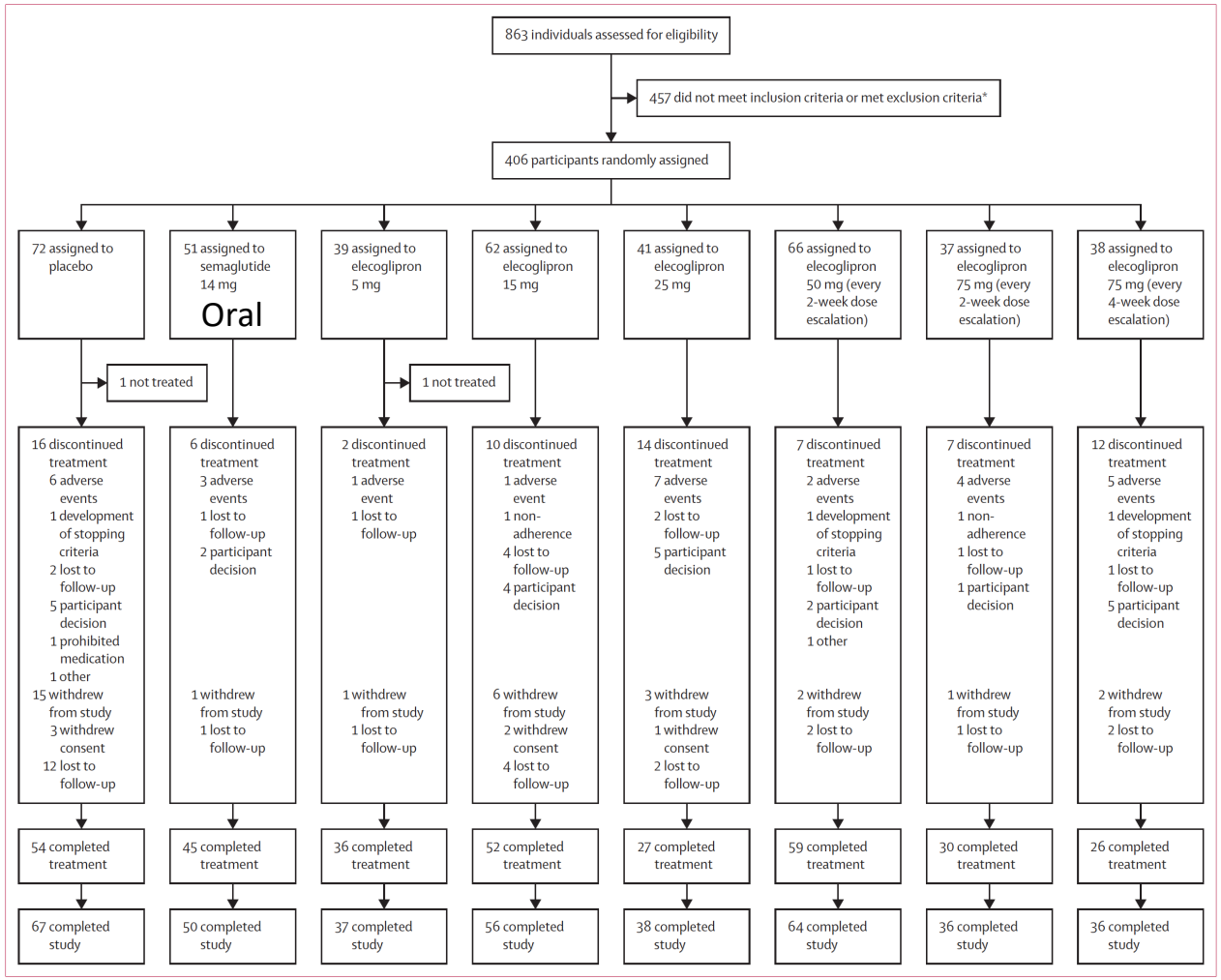


***Figure 2*: Trial profile**

Discontinued treatment categorisation reflects primary reason for discontinuation as assessed by investigator. HbA_{1c}=glycated haemoglobin. *The three most common reasons for screen failure were: inclusion criteria not met for HbA_{1c} value at screening of ≥7·0% and ≤10·5% with diet and exercise alone or with a stable dose of metformin or SGLT2 inhibitor for at least 1 month before screening (n=168); exclusion for being on prohibited background medications (n=51); exclusion for presence of hepatitis B core antibody or hepatitis surface B antigen (n=33).

	Placebo (n=71)	Elecoglipron						Semaglutide 14 mg (every 4-week dose escalation; n=51)
		5 mg (n=38)	15 mg (n=62)	25 mg (n=41)	50 mg (every 2-week dose escalation; n=66)	75 mg (every 2-week dose escalation; n=37)	75 mg (every 4-week dose escalation; n=38)	
Demographic variables								
Sex								
Female	22 (31%)	18 (47%)	29 (47%)	17 (41%)	37 (56%)	10 (27%)	11 (29%)	24 (47%)
Male	49 (69%)	20 (53%)	33 (53%)	24 (59%)	29 (44%)	27 (73%)	27 (71%)	27 (53%)
Age, years	60·1 (10·6)	59·1 (9·6)	56·0 (10·5)	56·8 (12·0)	57·7 (10·2)	58·9 (11·0)	58·6 (10·9)	59·8 (11·1)
Race								
White	47 (66%)	29 (76%)	45 (73%)	33 (80%)	41 (62%)	29 (78%)	17 (45%)	39 (76%)
Black or African American	8 (11%)	4 (11%)	7 (11%)	4 (10%)	16 (24%)	2 (5%)	9 (24%)	10 (20%)
Asian	12 (17%)	5 (13%)	8 (13%)	3 (7%)	7 (11%)	4 (11%)	10 (26%)	2 (4%)
American Indian or Alaska Native	1 (1%)	0	0	0	0	1 (3%)	0	0
Other or unknown	3 (4%)	0	2 (3%)	1 (2%)	2 (3%)	1 (3%)	2 (5%)	0
Ethnicity								
Hispanic or Latino	11 (15%)	3 (8%)	8 (13%)	8 (20%)	6 (9%)	5 (14%)	0	10 (20%)
Not Hispanic or Latino	60 (85%)	35 (92%)	52 (84%)	33 (80%)	60 (91%)	32 (86%)	36 (95%)	39 (76%)
Not reported	0	0	2 (3%)	0	0	0	2 (5%)	2 (4%)
Clinical variables								
HbA_{1c}, %	8·0% (0·8)	7·9% (1·0)	7·9% (1·0)	7·9% (1·0)	7·9% (0·9)	8·1% (1·1)	7·8% (1·0)	7·8% (0·9)
Diabetes duration, years	6·2 (3·2–9·9)	4·8 (2·7–10·4)	6·6 (2·8–10·4)	6·0 (2·7–10·2)	5·3 (2·3–9·9)	7·3 (3·5–13·0)	6·3 (3·3–10·3)	5·9 (1·6–8·3)
Diabetes medication at baseline	52 (73%)	27 (71%)	46 (74%)	34 (83%)	50 (76%)	31 (84%)	34 (89%)	41 (80%)
Bodyweight, kg	100·91 (23·24)	95·74 (22·67)	101·30 (23·49)	107·12 (20·25)	99·85 (23·87)	98·53 (20·40)	96·43 (20·94)	97·35 (18·68)
BMI, kg/m²	34·7 (7·2)	33·7 (6·5)	35·8 (8·5)	37·6 (7·5)	35·8 (9·0)	33·0 (6·5)	32·7 (7·0)	34·4 (5·6)
eGFR, mL/min per 1·73 m²	93·7 (15·3)	92·3 (19·2)	97·6 (14·8)	95·6 (15·8)	91·3 (16·5)	92·8 (14·0)	95·1 (16·8)	89·2 (16·4)
Systolic blood pressure, mm Hg	127·9 (15·9)	129·3 (11·8)	127·5 (13·8)	130·5 (16·4)	130·6 (13·7)	130·7 (12·1)	131·9 (16·6)	129·8 (10·4)

Data are mean (SD), n (%), or median (IQR). Starting dose for elecoglipron 50 mg every 2-week dose escalation: 2·5 mg; for elecoglipron 75 mg every 2-week dose escalation: 5 mg; for elecoglipron 75 mg every 4-week dose escalation: 10 mg; for semaglutide every 4-week dose escalation: 3 mg. Percentages may not add to total 100 because of rounding. eGFR=estimated glomerular filtration rate. HbA_{1c}=glycated haemoglobin.

Table 1: **Baseline characteristics**

HBA1C

Fasting glucose

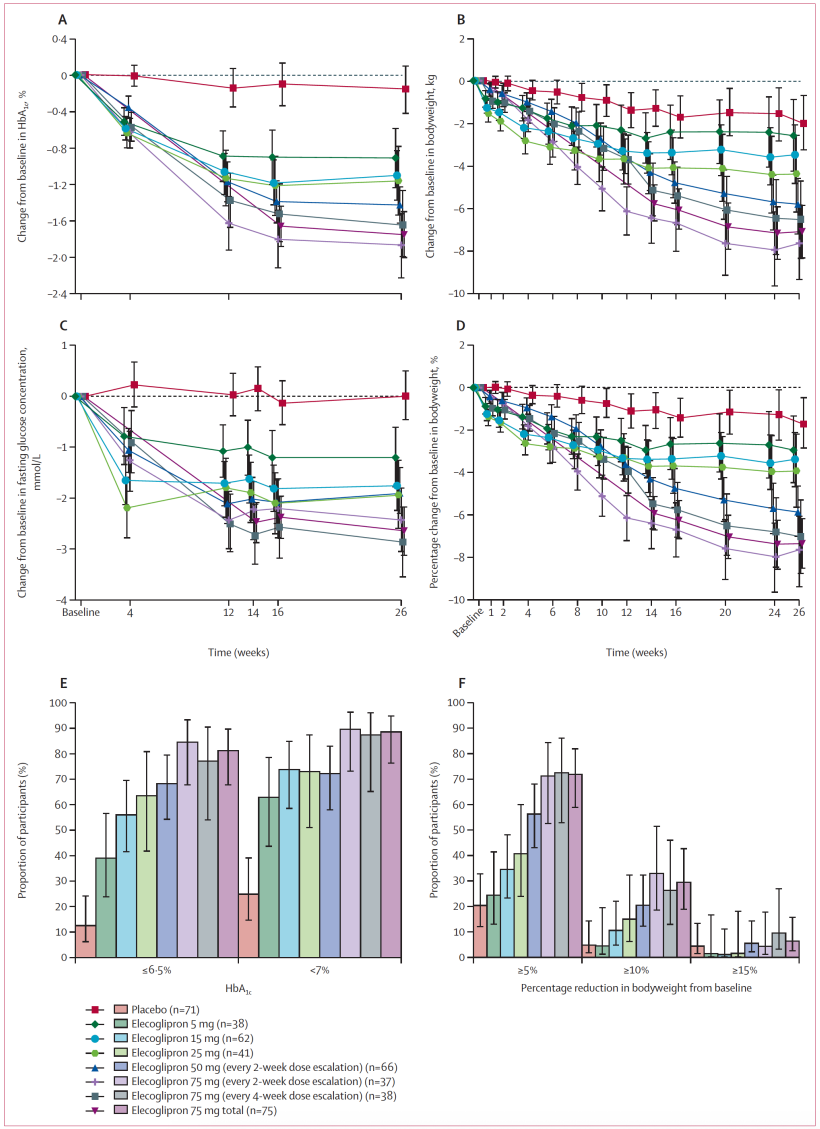


***Figure 3*: Efficacy parameters**
(A) Change from baseline in HbA_{1c}, %. (B) Change from baseline in bodyweight (kg). (C) Change from baseline in fasting glucose concentration (mmol/L). (D) Percentage change from baseline in bodyweight. (E) Proportion of participants reaching HbA_{1c} ≤6·5% and <7% at week 26. (F) Proportion of participants reaching at least 5%, at least 10%, and at least 15% reduction in bodyweight from baseline at week 26. HbA_{1c}=glycated haemoglobin.

	Placebo (n=71)	Elecoglipron							Semaglutide 14 mg (every 4-week dose escalation; n=51)
		5 mg (n=38)	15 mg (n=62)	25 mg (n=41)	50 mg (every 2-week dose escalation; n=66)	75 mg (every 2-week dose escalation; n=37)	75 mg (every 4-week dose escalation; n=38)	75 mg pooled (n=75)	
HbA_{1c}, %									
Baseline	7·96 (0·83)	7·93 (0·95)	7·93 (0·95)	7·92 (0·95)	7·88 (0·94)	8·08 (1·06)	7·78 (1·00)	7·93 (1·03)	7·82 (0·88)
Change from baseline at 26 weeks (95% CI)	−0·15 (−0·42 to 0·12)	−0·91 (−1·25 to −0·58)	−1·11 (−1·38 to −0·83)	−1·16 (−1·54 to −0·79)	−1·42 (−1·68 to −1·16)	−1·88 (−2·23 to −1·53)	−1·64 (−2·00 to −1·27)	−1·76 (−2·01 to −1·50)	−1·28 (−1·58 to −0·98)
Compared with placebo	..	−0·76 (−1·19 to −0·34); p=0·0005	−0·96 (−1·34 to −0·57); p<0·0001	−1·01 (−1·47 to −0·55); p<0·0001	−1·27 (−1·64 to −0·90); p<0·0001	−1·73 (−2·17 to −1·29); p<0·0001	−1·49 (−1·94 to −1·03); p<0·0001	−1·61 (−1·97 to −1·24); p<0·0001	..
Compared with semaglutide	..	0·37 (−0·08 to 0·82)	0·18 (−0·23 to 0·59)	0·12 (−0·36 to 0·60)	−0·14 (−0·54 to 0·26)	−0·60 (−1·06 to −0·13)	−0·35 (−0·83 to 0·12)	−0·47 (−0·87 to −0·08)	..
Fasting serum glucose, mmol/L									
Baseline	8·65 (1·87)	8·98 (2·18)	8·72 (2·38)	8·74 (2·24)	8·93 (2·73)	9·47 (2·42)	8·43 (2·52)	8·96 (2·51)	8·61 (1·94)
Change from baseline at 26 weeks (95% CI)	0·02 (−0·47 to 0·51)	−1·19 (−1·78 to −0·60)	−1·74 (−2·24 to −1·24)	−1·92 (−2·60 to −1·24)	−1·85 (−2·31 to −1·39)	−2·41 (−3·03 to −1·79)	−2·86 (−3·54 to −2·18)	−2·64 (−3·10 to −2·18)	−1·68 (−2·22 to −1·14)
Compared with placebo	..	−1·21 (−1·98 to −0·45); p=0·0020	−1·76 (−2·46 to −1·06); p<0·0001	−1·94 (−2·78 to −1·11); p<0·0001	−1·87 (−2·54 to −1·20); p<0·0001	−2·44 (−3·23 to −1·64); p<0·0001	−2·88 (−3·72 to −2·04); p<0·0001	−2·66 (−3·33 to −1·99) p<0·0001	..
Compared with semaglutide	..	0·49 (−0·31 to 1·29)	−0·06 (−0·79 to 0·67)	−0·24 (−1·10 to 0·63)	−0·16 (−0·87 to 0·54)	−0·73 (−1·55 to 0·09)	−1·18 (−2·04 to −0·31)	−0·96 (−1·67 to −0·25)	..
Fasting serum glucose, percentage change									
Percentage change from baseline at 26 weeks (95% CI)	2·5 (−3·3 to 8·3)	−12·6 (−19·5 to −5·6)	−17·5 (−23·3 to −11·6)	−20·7 (−28·7 to −12·8)	−16·8 (−22·2 to −11·3)	−24·7 (−32·1 to −17·4)	−29·4 (−37·4 to −21·3)	−27·1 (−32·5 to −21·7)	−17·9 (−24·3 to −11·6)
Compared with placebo	..	−15·1 (−24·1 to −6·0); p=0·0012	−20·0 (−28·2 to −11·8); p<0·0001	−23·2 (−33·1 to −13·4); p<0·0001	−19·3 (−27·2 to −11·4); p<0·0001	−27·3 (−36·6 to −17·9); p<0·0001	−31·9 (−41·8 to −22·0); p<0·0001	−29·6 (−37·5 to −21·7); p<0·0001	..
Compared with semaglutide	..	5·4 (−4·1 to 14·8)	0·4 (−8·2 to 9·1)	−2·8 (−13·0 to 7·4)	1·1 (−7·2 to 9·5)	−6·8 (−16·5 to 2·9)	−11·4 (−21·7 to −1·2)	−9·2 (−17·5 to −0·8)	..
Bodyweight, kg									
Baseline	100·91 (23·24)	95·74 (22·67)	101·30 (23·49)	107·12 (20·25)	99·85 (23·87)	98·53 (20·40)	96·43 (20·94)	97·46 (20·56)	97·35 (18·68)
Change from baseline at 26 weeks (95% CI)	−1·94 (−3·25 to −0·64)	−2·54 (−4·25 to −0·83)	−3·42 (−4·81 to −2·03)	−4·35 (−6·19 to −2·50)	−5·79 (−7·09 to −4·48)	−7·61 (−9·39 to −5·84)	−6·52 (−8·36 to −4·68)	−7·06 (−8·34 to −5·78)	−4·69 (−6·19 to −3·18)
Compared with placebo	..	−0·60 (−2·75 to 1·55); p=0·59	−1·48 (−3·39 to 0·43); p=0·13	−2·40 (−4·67 to −0·14); p=0·038	−3·84 (−5·69 to −2·00); p<0·0001	−5·67 (−7·87 to −3·47); p<0·0001	−4·58 (−6·83 to −2·32); p<0·0001	−5·11 (−6·94 to −3·29); p<0·0001	..
Compared with semaglutide	..	2·15 (−0·13 to 4·42)	1·27 (−0·78 to 3·32)	0·34 (−2·04 to 2·73)	−1·10 (−3·09 to 0·89)	−2·92 (−5·25 to −0·60)	−1·83 (−4·20 to 0·54)	−2·37 (−4·34 to −0·40)	..
Bodyweight, percentage change									
% change from baseline at 26 weeks (95% CI)	−1·7 (−2·9 to −0·5)	−2·9 (−4·5 to −1·3)	−3·4 (−4·7 to −2·1)	−4·0 (−5·7 to −2·2)	−5·9 (−7·1 to −4·6)	−7·7 (−9·4 to −6·1)	−7·0 (−8·8 to −5·3)	−7·4 (−8·6 to −6·2)	−5·1 (−6·5 to −3·7)
Compared with placebo	..	−1·3 (−3·3 to 0·8); p=0·22	−1·7 (−3·5 to 0·1); p=0·064	−2·3 (−4·4 to −0·1); p=0·038	−4·2 (−5·9 to −2·4); p<0·0001	−6·1 (−8·1 to −4·0); p<0·0001	−5·3 (−7·5 to −3·2); p<0·0001	−5·7 (−7·4 to −4·0); p<0·0001	..
Compared with semaglutide	..	2·1 (0·0 to 4·3)	1·7 (−0·2 to 3·6)	1·1 (−1·1 to 3·4)	−0·8 (−2·7 to 1·1)	−2·7 (−4·9 to −0·5)	−2·0 (−4·2 to 0·3)	−2·3 (−4·2 to −0·5)	..

Data are mean (SD) or least squares mean differences (95% CI) and p values from mixed models for repeated measures. Starting dose for elecoglipron 50 mg every 2-week dose escalation: 2·5 mg; for elecoglipron 75 mg every 2-week dose escalation: 5 mg; for elecoglipron 75 mg every 4-week dose escalation: 10 mg; for semaglutide every 4-week dose escalation: 3 mg. HbA_{1c}=glycated haemoglobin.

Table 2: **Primary and key secondary efficacy endpoints at week 26**

	Elecoglipron							Semaglutide 14 mg (every 4-week dose escalation; n=51)	Placebo (n=71)
	5 mg (n=38)	15 mg (n=62)	25 mg (n=41)	50 mg (every 2-week dose escalation; n=66)	75 mg (every 2-week dose escalation; n=37)	75 mg (every 4-week dose escalation; n=38)	Total (n=282)		
(Continued from previous page)									
Gastrointestinal adverse events occurring in at least 5% of participants in any group									
Any gastrointestinal adverse events	12 (32%)	23 (37%)	26 (63%)	31 (47%)	17 (46%)	27 (71%)	136 (48%)	16 (31%)	19 (27%)
Nausea	1 (3%)	10 (16%)	11 (27%)	14 (21%)	9 (24%)	14 (37%)	59 (21%)	9 (18%)	2 (3%)
Constipation	5 (13%)	6 (10%)	8 (20%)	11 (17%)	3 (8%)	11 (29%)	44 (16%)	3 (6%)	3 (4%)
Diarrhoea	3 (8%)	5 (8%)	7 (17%)	9 (14%)	2 (5%)	8 (21%)	34 (12%)	1 (2%)	11 (15%)
Vomiting	1 (3%)	6 (10%)	6 (15%)	5 (8%)	4 (11%)	7 (18%)	29 (10%)	2 (4%)	1 (1%)
Dyspepsia	2 (5%)	1 (2%)	3 (7%)	2 (3%)	6 (16%)	3 (8%)	17 (6%)	1 (2%)	2 (3%)
Abdominal pain (upper)	1 (3%)	4 (6%)	1 (2%)	1 (2%)	2 (5%)	3 (8%)	12 (4%)	0	1 (1%)
Eructation	2 (5%)	3 (5%)	2 (5%)	4 (6%)	0	1 (3%)	12 (4%)	1 (2%)	3 (4%)
Flatulence	2 (5%)	2 (3%)	3 (7%)	3 (5%)	0	1 (3%)	11 (4%)	0	2 (3%)
Gastro-oesophageal reflux disease	2 (5%)	1 (2%)	1 (2%)	2 (3%)	0	2 (5%)	8 (3%)	1 (2%)	0
Abdominal pain	0	0	0	0	1 (3%)	2 (5%)	3 (1%)	1 (2%)	1 (1%)
Haemorrhoids	2 (5%)	0	1 (2%)	0	0	0	3 (1%)	0	0
Change of bowel habits	0	0	0	0	0	2 (5%)	2 (1%)	0	0
Adverse events occurring in at least 5% of participants in any group (non-gastrointestinal)									
Decreased appetite	3 (8%)	1 (2%)	5 (12%)	3 (5%)	2 (5%)	2 (5%)	16 (6%)	1 (2%)	3 (4%)
Headache	1 (3%)	2 (3%)	3 (7%)	4 (6%)	1 (3%)	3 (8%)	14 (5%)	0	4 (6%)
Lipase increased	3 (8%)	1 (2%)	0	4 (6%)	4 (11%)	2 (5%)	14 (5%)	0	0
Dizziness	3 (8%)	1 (2%)	2 (5%)	2 (3%)	3 (8%)	2 (5%)	13 (5%)	0	8 (11%)
Upper respiratory tract infection	2 (5%)	4 (6%)	2 (5%)	1 (2%)	0	2 (5%)	11 (4%)	3 (6%)	5 (7%)
Arthralgia	1 (3%)	1 (2%)	2 (5%)	1 (2%)	1 (3%)	4 (11%)	10 (4%)	2 (4%)	4 (6%)
Fatigue	2 (5%)	1 (2%)	2 (5%)	1 (2%)	1 (3%)	3 (8%)	10 (4%)	2 (4%)	4 (6%)
Amylase increased	1 (3%)	1 (2%)	0	2 (3%)	2 (5%)	2 (5%)	8 (3%)	0	0
Nasopharyngitis	1 (3%)	2 (3%)	2 (5%)	1 (2%)	1 (3%)	0	7 (2%)	1 (2%)	4 (6%)
Urinary tract infection	1 (3%)	1 (2%)	1 (2%)	1 (2%)	1 (3%)	2 (5%)	7 (2%)	2 (4%)	1 (1%)
Hypertension	1 (3%)	3 (5%)	0	0	0	2 (5%)	6 (2%)	2 (4%)	4 (6%)
Influenza	0	1 (2%)	0	1 (2%)	2 (5%)	1 (3%)	5 (2%)	0	0
Increased appetite	2 (5%)	0	1 (2%)	0	0	0	3 (1%)	0	0
Insomnia	0	0	1 (2%)	0	0	2 (5%)	3 (1%)	0	0
Rash	0	0	0	0	2 (5%)	1 (3%)	3 (1%)	2 (4%)	0
Gout	0	0	0	0	0	2 (5%)	2 (1%)	0	2 (3%)
Hyperglycaemia	0	0	1 (2%)	1 (2%)	0	0	2 (1%)	1 (2%)	7 (10%)
Neck pain	0	0	0	0	0	2 (5%)	2 (1%)	0	0
Thirst	2 (5%)	0	0	0	0	0	2 (1%)	0	0
Viral infection	2 (5%)	0	0	0	0	0	2 (1%)	0	0

Data are n (%). The table includes adverse events with an onset date on or after the day of the randomisation visit and participants were censored at the earliest of withdrawal of consent, death, or the date of the last clinical assessment. Only the first event per participant in each category is used in the analyses. Starting dose for elecoglipron 50 mg every 2-week dose escalation: 2·5 mg; for elecoglipron 75 mg every 2-week dose escalation: 5 mg; for elecoglipron 75 mg every 4-week dose escalation: 10 mg; for semaglutide every 4-week dose escalation: 3 mg. Data in this table reflect actions taken with study drug for each adverse event while data in figure 2 and appendix 1 (p 13) reflect primary reason for early discontinuation of study drug as assessed by investigator. CTCAE=Common Terminology Criteria for Adverse Events. *Possibly related was defined as a reasonable possibility that the adverse event was caused by trial treatment, as assessed by investigator. †Adverse events of large intestinal haemorrhage.

Table 3: **Adverse events**

Implications of all the available evidence

In the SOLSTICE trial, treatment with elecoglipron, an oral small molecule GLP-1 receptor agonist, showed improvements in glycaemic control and bodyweight in individuals with type 2 diabetes, with results similar to findings observed in phase 2b type 2 diabetes trials with oral peptide and small molecule GLP-1 receptor agonists. Further, elecoglipron demonstrated an acceptable tolerability and safety profile. Elecoglipron administration requires no food or fluid restrictions and could provide a convenient and accessible treatment option for those living with type 2 diabetes. These trial findings support advancement of elecoglipron to a large phase 3 programme, during which long-term efficacy and safety can be further evaluated in people living with type 2 diabetes.

Das **diffus großzellige B-Zell-Lymphom** (engl. *Diffuse Large B-Cell Lymphoma*, kurz **DLBCL**) ist eine bösartige Krebserkrankung des Lymphsystems. Es handelt sich dabei um die **häufigste Form des Non-Hodgkin-Lymphoms** bei Erwachsenen. Das DLBCL ist ein hochmalignes (sehr aggressives), aber **gut behandelbares und oft heilbares** Lymphom. Da die Krebszellen sehr schnell wachsen, muss die Therapie meist zügig nach der Diagnose beginnen.

Symptome

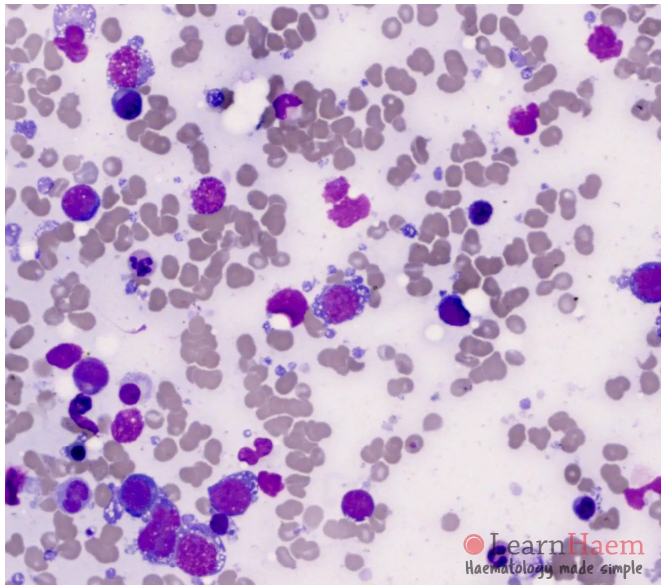
Die Erkrankung äußert sich meist durch ein rasches, schmerzloses Anschwellen von Lymphknoten, oft am Hals, in den Achselhöhlen oder in der Leistengegend. Häufig treten auch sogenannte **B-Symptome** auf:

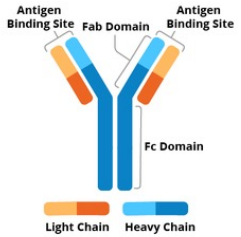
•**Fieber**: Unklare Temperaturen über 38 °C ohne Anzeichen eines Infekts.

•**Nachtschweiß**: Extrem starkes Schwitzen in der Nacht, sodass die Kleidung gewechselt werden muss.

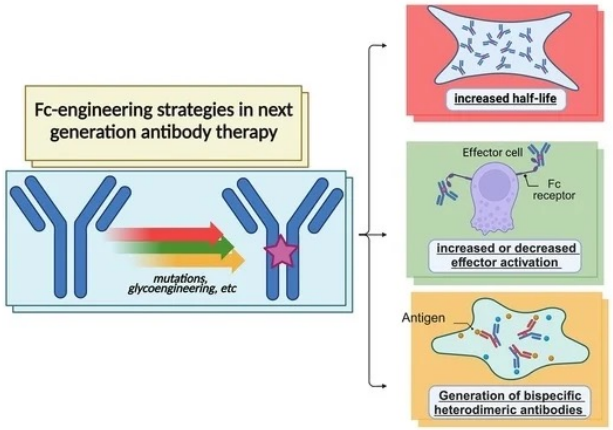
•**Gewichtsverlust**: Ungewollter Verlust von mehr als 10 % des Körpergewichts innerhalb von 6 Monaten.

•**Weitere Beschwerden**: Je nach Befall der Organe können Bauchschmerzen, Reizhusten, Atembeschwerden oder chronische Müdigkeit hinzukommen.





Ein **Fc-optimierter (Fc-enhanced) Antikörper** ist ein therapeutischer Antikörper, dessen konstanter Teil (die Fc-Region) gentechnisch oder durch Glykomodifikation verändert wurde. Ziel ist es, die Bindung an Immunrezeptoren zu verstärken, um die körpereigene Zerstörung von Krebszellen oder Krankheitserregern (über ADCC oder CDC) und die Halbwertszeit im Blut deutlich zu verbessern.

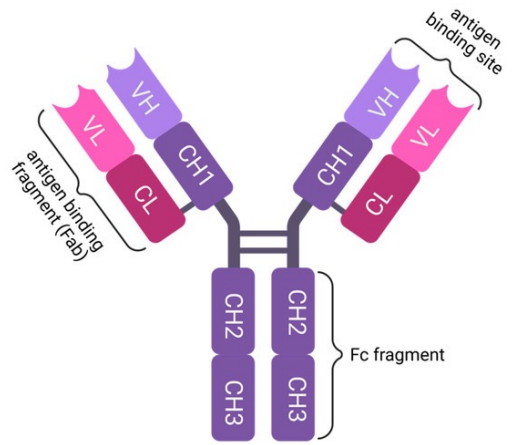


Wie es funktioniert

Ein normaler Antikörper besteht aus zwei Teilen:

•**Fab-Region (Antigen-bindend):** Erkennt das Ziel (z. B. ein Tumorantigen).

•**Fc-Region (kristallisierbares Fragment):** Dient als Signal-Schwanz, der Immunzellen (wie Killerzellen) oder das Komplementsystem aktiviert.



Bei einem **Fc-optimierten Antikörper** wird dieser Schwanzbereich gezielt modifiziert:

•**Aminosäureaustausch (Protein-Engineering):** Gezielte Mutationen erhöhen die Bindungsaffinität zu aktivierenden Fc-Rezeptoren (z. B. FcγRIIIa) auf Immunzellen.

•**Zucker-Modifikation (Glyko-Engineering):** Das Entfernen bestimmter Zuckermoleküle (wie Fucose) aus der Fc-Region („afucosylierte Antikörper“) führt zu einer bis zu 50-150-fach stärkeren Aktivierung der zellulären Zytotoxizität (ADCC).

Do anti CD19
+ Proteosome-
Inhibitor

help

R-CHOP?

Tafasitamab plus lenalidomide and R-CHOP versus R-CHOP for first-line treatment of patients with high-risk diffuse large B-cell lymphoma (frontMIND): a global, phase 3, randomised, double-blind, placebo-controlled trial

Summary

Background Approximately 40% of patients with high-risk diffuse large B-cell lymphoma (DLBCL) are not cured with first-line R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone or prednisolone). We aimed to investigate the addition of tafasitamab (an Fc-enhanced anti-CD19 monoclonal antibody) and lenalidomide to R-CHOP (tafa-len-R-CHOP) in patients with high-risk aggressive B-cell lymphomas.

Methods frontMIND is a phase 3, randomised, double-blind, placebo-controlled study conducted at 298 centres in North America, South America, Europe, and the Asia–Pacific region. Patients aged 18–80 years with previously untreated, high-intermediate-risk or high-risk DLBCL or high-grade B-cell lymphoma (HGBL) were randomly allocated (1:1), stratified by International Prognostic Index (IPI) or age-adjusted IPI and geographical region, to receive six 21-day cycles of standard R-CHOP (rituximab 375 mg/m² intravenous on day 1, cyclophosphamide 750 mg/m² intravenous on day 1, doxorubicin 50 mg/m² intravenous on day 1, vincristine 1·4 mg/m² [maximum 2 mg] intravenous on day 1, and prednisone or prednisolone 100 mg/day orally on days 1–5); patients in the tafa-len-R-CHOP group additionally received tafasitamab (12 mg/kg intravenous on days 1, 8, and 15) plus lenalidomide (25 mg/day orally on days 1–10), while those in the R-CHOP group received matching placebos. The primary endpoint was investigator-assessed progression-free survival (defined as time from randomisation to disease progression or death from any cause), analysed in the intention-to-treat population; safety was included as a secondary endpoint among all patients who received at least one dose of study treatment. The trial is registered with ClinicalTrials.gov (NCT04824092) and EUDRA-CT (2020-002990-84) and is active but no longer enrolling.

Findings Between May 11, 2021, and March 2, 2023, 1229 patients were screened, among whom 899 were randomly allocated: 448 (50%) to the tafa-len-R-CHOP group and 451 (50%) to the R-CHOP group. At the time of primary analysis (median follow-up 35·2 months [95% CI 35·0–35·4]), progression-free survival was improved in the tafa-len-R-CHOP group versus the R-CHOP group (hazard ratio [HR] 0·75 [95% CI 0·59–0·96]; p=0·0194), with 2-year progression-free survival rates of 71·1% (66·3–75·4) with tafa-len-R-CHOP versus 62·9% (57·9–67·5) with R-CHOP. Interim HR for overall survival was 0·85 (0·63–1·14). The overall rate of grade 3 or higher treatment-emergent adverse events was higher with tafa-len-R-CHOP (384 [87%] of 443) than with R-CHOP (340 [76%] of 447). Additionally, a higher rate of fatal treatment-emergent adverse events was observed with tafa-len-R-CHOP (26 [6%]) than with R-CHOP (17 [4%]). However, the number of overall deaths in the study was lower with tafa-len-R-CHOP than with R-CHOP (82 [19%] *vs* 97 [22%]). Based on disposition data, rates of premature discontinuation of all study drugs were similar in the tafa-len-R-CHOP group (71 [16%] of 443) and R-CHOP group (66 [15%] of 447).

Interpretation Progression-free survival was significantly improved with tafa-len-R-CHOP versus R-CHOP; however, the safety profile indicated increases in adverse events, including treatment-emergent adverse events leading to death, with the addition of tafasitamab and lenalidomide. Overall survival data are immature; follow-up is ongoing. Further analyses, including of circulating tumor DNA, will help to assess whether deeper molecular responses are contributing to the progression-free survival benefit observed with tafa-len-R-CHOP. Tafa-len-R-CHOP might represent a potential new first-line treatment for patients with high-risk DLBCL or HGBL.

Funding Incyte Corporation.

C – Cyclophosphamid: Ein Alkylanz (Zytostatikum), das die DNA der Krebszellen beschädigt und so deren Teilung verhindert.
H – Hydroxydaunorubicin: Besser bekannt als **Doxorubicin** (oder Adriamycin), ein Tumorantibiotikum, das die Vermehrung von Krebszellen blockiert.
O – Oncovin®: Der Handelsname des Wirkstoffs **Vincristin**, ein Mitosespindelgift, das die Zellteilung direkt stoppt.
P – Prednison oder Prednisolon: Ein hochdosiertes Glukokortikoid (Cortisonpräparat), das lymphotoxisch wirkt (Lymphomzellen zerstört) und gleichzeitig Nebenwirkungen wie Übelkeit unterdrückt.

Patients

Eligible patients were required to have previously untreated DLBCL or another large B-cell lymphoma subtype (including T-cell or histiocyte-rich large B-cell lymphoma; Epstein–Barr virus-positive DLBCL; *ALK*-positive large B-cell lymphoma; human herpes virus 8-positive DLBCL, not otherwise specified; HGBL with rearrangements in *MYC* and *BCL2* or *BCL6*, or both [double-hit or triple-hit lymphoma]; DLBCL coexistent with either indolent follicular lymphoma or gastric or non-gastric mucosa-associated lymphoid tissue lymphoma; HGBL, not otherwise specified; or grade 3b follicular lymphoma) based on local pathology review, according to the 2016 WHO classification of lymphoid neoplasms.[25] For patients with HGBL based on local pathology review, investigators were asked to indicate the reason that a more intensified regimen was contraindicated. Patients had to be aged 18–80 years, have an ECOG performance status of 0–2, be candidates for R-CHOP, and have at least one measurable PET-positive lesion by local assessment. To capture patients with higher risk, patients were required to be within 28 days of their diagnostic biopsy at treatment initiation and have high-intermediate-risk or high-risk disease (IPI 3–5 or age-adjusted IPI [aaIPI] 2–3 if aged ≤60 years). A full list of eligibility criteria is available in the protocol (appendix p 22).

Consolidative radiotherapy to bulky and extranodal disease sites and CNS prophylaxis with intravenous methotrexate were allowed only if preplanned before randomisation and only if administered after the sixth treatment cycle and after the end-of-treatment response assessment. CNS prophylaxis with intrathecal methotrexate was not recommended, but was permitted once per treatment cycle according to institutional practice and needs; preplanned intrathecal methotrexate had to be reported before randomisation. Unplanned radiotherapy, including changes in preplanned sites of radiotherapy or CNS treatment, were considered as a next antilymphoma treatment. Prophylaxis for lenalidomide-related venous thromboembolism with aspirin or a low-molecular-weight heparin was mandatory.

All patients had to have archival or freshly collected tumour tissue submitted for central pathology and gene expression profiling (GEP). An independent, retrospective, central pathology review was performed by an expert haematopathologist; results of the central

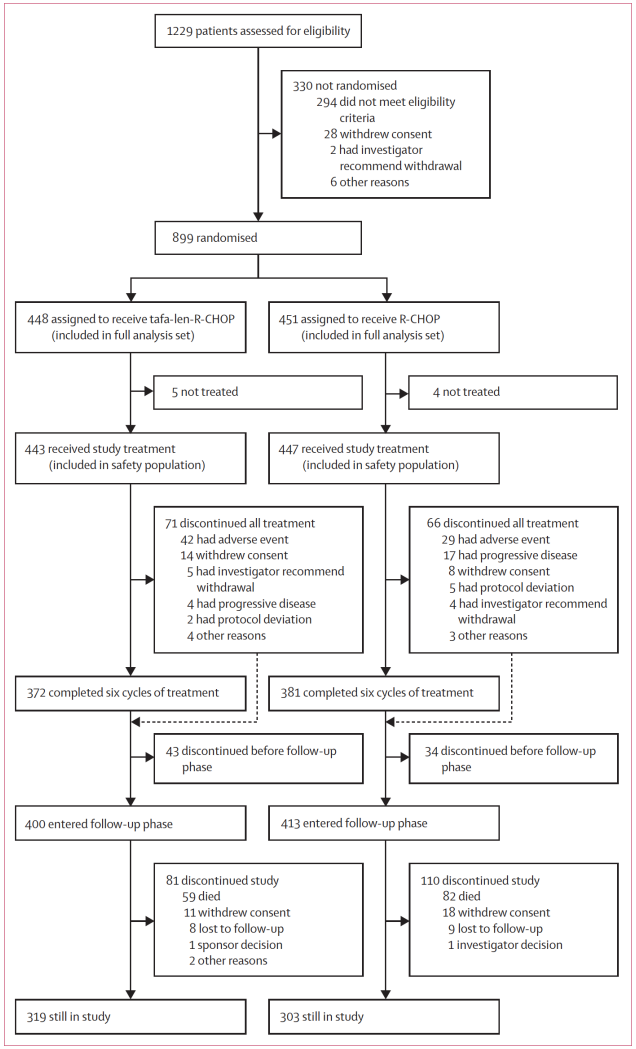


Figure 1: **Trial profile**
Data are presented for the full analysis set and safety populations as of the data cutoff date of Oct 20, 2025. R-CHOP=rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone or prednisolone. Tafa-len-R-CHOP=tafasitamab plus lenalidomide and R-CHOP.

	Tafa-len-R-CHOP group (n=448)	R-CHOP group (n=451)
Age, years		
Median (IQR)	65 (56–71)	65 (56–71)
Range	20–80	18–80
≥65	226 (50%)	233 (52%)
<65	222 (50%)	218 (48%)
Sex		
Male	240 (54%)	233 (52%)
Female	208 (46%)	218 (48%)
Geographical region*		
Asia	90 (20%)	93 (21%)
Europe, USA, Canada, Australia, and New Zealand	324 (72%)	324 (72%)
Rest of world	34 (8%)	34 (8%)
Ann Arbor stage at enrolment		
I or II	16 (4%)	15 (3%)
III or IV	432 (96%)	436 (97%)
Extranodal involvement at two or more sites		
Yes	173 (39%)	175 (39%)
No	123 (27%)	118 (26%)
Missing	152 (34%)	158 (35%)
Presence of bulky disease	254 (57%)	231 (51%)
ECOG performance status at enrolment		
0	132 (29%)	126 (28%)
1	179 (40%)	179 (40%)
2	137 (31%)	146 (32%)
Lactate dehydrogenase level		
Normal	79 (18%)	75 (17%)
Elevated (>ULN)	369 (82%)	376 (83%)
Risk group*		
Low to low-intermediate risk (IPI 0–2 or aaIPI 0–1)	3 (1%)	5 (1%)
IPI 0	0	0
IPI 1	0	0
IPI 2	1 (<1%)	3 (1%)
aaIPI 0	0	0
aaIPI 1	2 (<1%)	2 (<1%)
High-intermediate risk (IPI 3 or aaIPI 2)	259 (58%)	244 (54%)
IPI 3	139 (31%)	118 (26%)
aaIPI 2	120 (27%)	126 (28%)
High risk (IPI 4–5 or aaIPI 3)	186 (42%)	202 (45%)
IPI 4	123 (27%)	137 (30%)
IPI 5	33 (7%)	35 (8%)
aaIPI 3	30 (7%)	30 (7%)

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	Tafa-len-R-CHOP group (n=448)	R-CHOP group (n=451)
Median time from initial diagnostic biopsy to treatment initiation, days	23·5 (17–28)	24·0 (18–28)
Cell of origin†		
Activated B-cell-like	84/239 (35%)	88/245 (36%)
Germinal centre B-cell-like	131/239 (55%)	117/245 (48%)
Unclassified	24/239 (10%)	40/245 (16%)
Results not available	209 (47%)	206 (46%)
Lymphoma subtype (local assessment)		
DLBCL	362 (81%)	361 (80%)
HGBL with *MYC* and *BCL2* and/or *BCL6* rearrangements	34 (8%)	37 (8%)
DLBCL coexistent with indolent follicular or MALT lymphoma	28 (6%)	17 (4%)
Follicular lymphoma grade 3b	9 (2%)	8 (2%)
Other‡	15 (3%)	28 (6%)
Lymphoma subtype (central assessment)		
DLBCL	307/391 (79%)	325/382 (85%)
HGBL§	41/391 (10%)	24/382 (6%)
Other confirmed lymphoma subtype¶	43/391 (11%)	33/382 (9%)

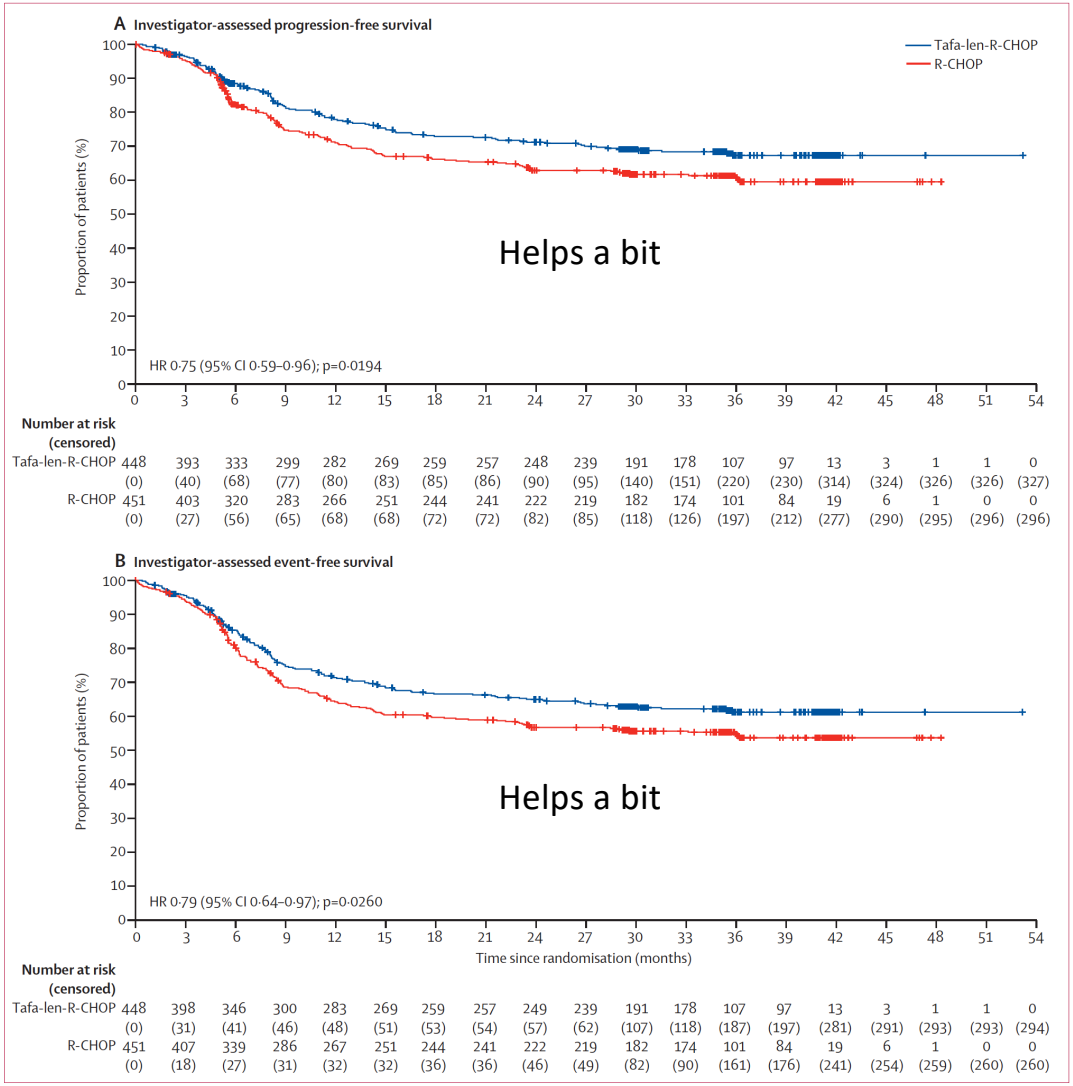
Data are n (%) or median (IQR), or n/N (%), unless otherwise specified. aaIPI=age-adjusted International Prognostic Index. *ALK*=anaplastic lymphoma kinase. DLBCL=diffuse large B-cell lymphoma. EBV=Epstein–Barr virus. ECOG=Eastern Cooperative Oncology Group. HGBL=high-grade B-cell lymphoma. HHV=human herpes virus. IPI=International Prognostic Index. MALT=mucosa-associated lymphoid tissue. R-CHOP=rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone or prednisolone. Tafa-len-R-CHOP=tafasitamab plus lenalidomide and R-CHOP. ULN=upper limit of normal. *Stratification factor. †Based on gene expression profiling (central assessment). ‡Other reported local lymphoma subtypes included T-cell or histiocyte-rich large B-cell lymphoma; EBV-positive DLBCL; *ALK*-positive large B-cell lymphoma; HHV-8-positive DLBCL, not otherwise specified; HGBL with *MYC* and *BCL2* and/or *BCL6* rearrangements (double-hit or triple-hit lymphoma); DLBCL coexistent with either indolent follicular lymphoma or gastric or non-gastric MALT lymphoma; HGBL, not otherwise specified; or grade 3b follicular lymphoma. §All patients with centrally confirmed HGBL had double-hit or triple-hit lymphoma. ¶Other centrally confirmed lymphoma subtypes included T-cell or histiocyte-rich large B-cell lymphoma, EBV-positive DLBCL, *ALK*-positive large B-cell lymphoma, grade 3b follicular lymphoma, and DLBCL coexistent with indolent follicular or MALT lymphoma; inclusion criteria also included HHV-8-positive DLBCL, for which no patients were enrolled.

Table 1: **Baseline demographics and disease characteristics (full analysis set)**

	Tafa-len-R-CHOP group (n=448)	R-CHOP group (n=451)	Hazard ratio (95% CI)	p value*
Progression-free survival				
Patients with an event	121 (27%)	155 (34%)	0·75 (0·59–0·96)	0·0194
Earliest event				
Disease progression	92 (21%)	135 (30%)	..	..
Death	29 (6%)	20 (4%)	..	..
Median progression-free survival, months	NR (NE–NE)	NR (NE–NE)	..	..
Kaplan–Meier estimate at 2 years, %	71·1% (66·3–75·4)	62·9% (57·9–67·5)	..	..
Kaplan–Meier estimate at 3 years, %	67·3% (62·1–71·9)	60·7% (55·6–65·5)	..	..
Event-free survival				
Patients with an event	154 (34%)	191 (42%)	0·79 (0·64–0·97)	0·0260
Earliest event				
Disease progression	92 (21%)	135 (30%)	..	..
Death	29 (6%)	20 (4%)	..	..
New antilymphoma treatment started	33 (7%)	36 (8%)	..	..
Median event-free survival, months	NR (NE–NE)	NR (35·9–NE)	..	..
Kaplan–Meier estimate at 2 years, %	65·0% (60·1–69·4)	56·7% (51·8–61·3)	..	..
Kaplan–Meier estimate at 3 years, %	61·2% (56·1–65·9)	54·8% (49·8–59·5)	..	..
Overall survival				
Patients who died	82 (18%)	95 (21%)	0·85 (0·63–1·14)	0·2703
Median overall survival, months	NR (NE–NE)	NR (NE–NE)	..	..
Kaplan–Meier estimate at 2 years, %	84·1% (80·3–87·3)	80·5% (76·4–83·9)	..	..
Kaplan–Meier estimate at 3 years, %	81·1% (77·0–84·6)	77·8% (73·5–81·5)	..	..

Data are n (%) or point estimate (95% CI). NE=not evaluable. NR=not reached. R-CHOP=rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone or prednisolone. Tafa-len-R-CHOP=tafasitamab plus lenalidomide and R-CHOP. *From stratified log-rank test.

Table 2: **Investigator-assessed efficacy endpoints (full analysis set)**



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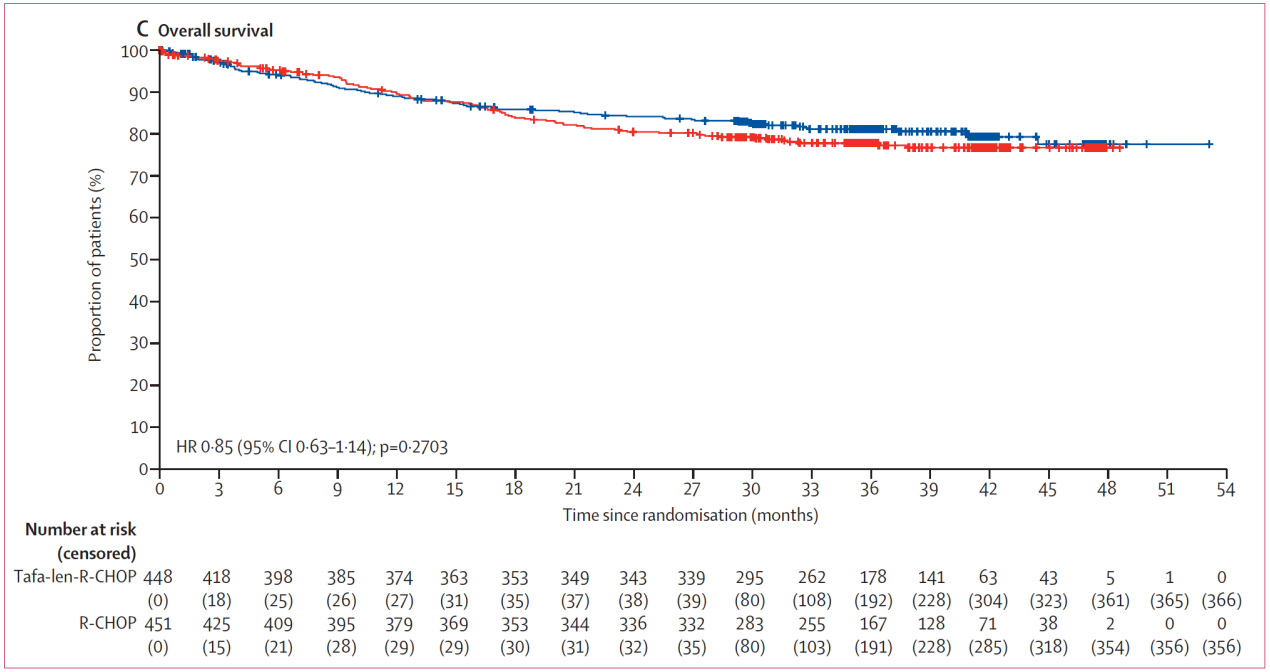


Figure 2: **Kaplan–Meier survival analyses (full analysis set)**
(A) Progression-free survival (defined as time to progression or death from any cause) as assessed by the investigator. (B) Event-free survival (defined as time to first occurrence of disease progression, start of new antilymphoma treatment, or death from any cause) as assessed by the investigator. (C) Overall survival (defined as time to death from any cause). Vertical tick marks indicate censored data. HRs are from stratified Cox proportional hazards models. p values are from stratified log-rank tests. Kaplan–Meier survival rates per group are shown in table 2. HR=hazard ratio. R-CHOP=rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone or prednisolone. Tafa-len-R-CHOP=tafasitamab plus lenalidomide and R-CHOP.

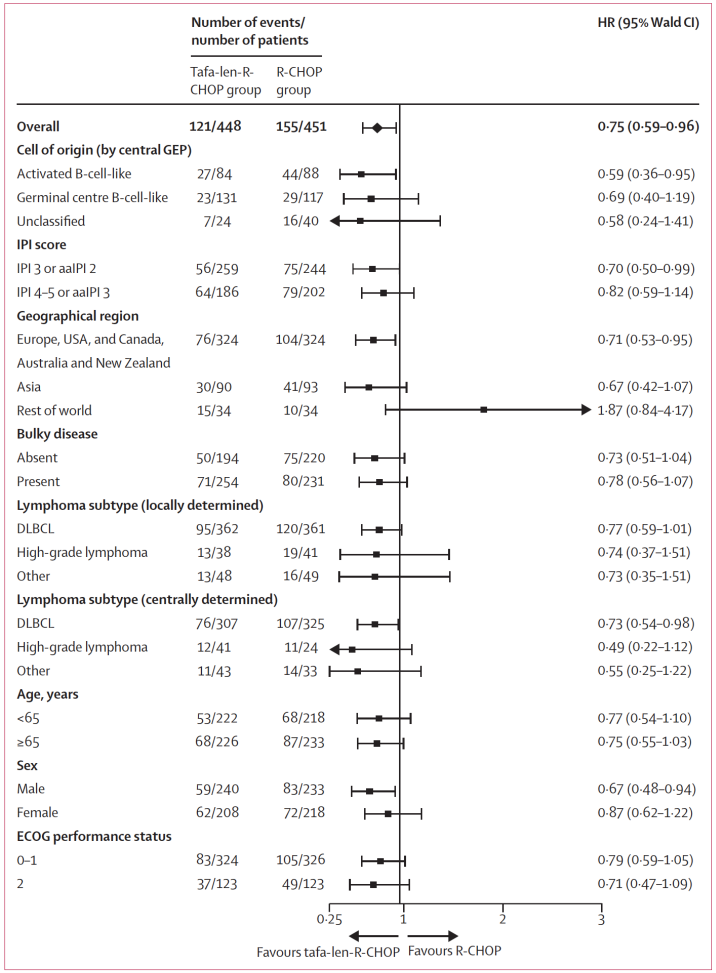


Figure 3: **Subgroup analysis of progression-free survival (full analysis set)**
Subgroup analysis of progression-free survival as assessed by the investigator. HRs were calculated using an unstratified Cox proportional hazards model, except for the overall population for which the HR was calculated using a stratified Cox proportional hazards model. aaIPI=age-adjusted International Prognostic Index. DLBCL=diffuse large B-cell lymphoma. ECOG=Eastern Cooperative Oncology Group. GEP=gene expression profiling. HR=hazard ratio. IPI=International Prognostic Index. R-CHOP=rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone or prednisolone. Tafa-len-R-CHOP=tafasitamab plus lenalidomide and R-CHOP.

	Tafa-len-R-CHOP group (n=443)				R-CHOP group (n=447)			
	Any grade	Grade 3	Grade 4	Grade 5 (death)	Any grade	Grade 3	Grade 4	Grade 5 (death)
Number of treatment-emergent adverse events	437 (99%)	95 (21%)	263 (59%)	26 (6%)	434 (97%)	97 (22%)	226 (51%)	17 (4%)
Treatment-emergent serious adverse events	222 (50%)	107 (24%)	63 (14%)	26 (6%)	174 (39%)	79 (18%)	59 (13%)	17 (4%)
Treatment-related treatment-emergent adverse events	423 (95%)	87 (20%)	264 (60%)	8 (2%)	407 (91%)	82 (18%)	217 (49%)	8 (2%)
Treatment-emergent adverse events leading to discontinuation of all study drug components	23 (5%)	5 (1%)	9 (2%)	1 (<1%)	24 (5%)	13 (3%)	3 (1%)	4 (1%)
Most common treatment-emergent adverse event								
Neutropenia	313 (71%)	55 (12%)	251 (57%)	0	267 (60%)	51 (11%)	208 (47%)	0
Anaemia	205 (46%)	101 (23%)	4 (1%)	0	154 (34%)	71 (16%)	2 (<1%)	0
Thrombocytopenia	172 (39%)	58 (13%)	62 (14%)	0	119 (27%)	30 (7%)	32 (7%)	0
Constipation	152 (34%)	0	0	0	126 (28%)	0	0	0
Nausea	117 (26%)	8 (2%)	0	0	140 (31%)	5 (1%)	0	0
Diarrhoea	109 (25%)	10 (2%)	2 (<1%)	0	74 (17%)	6 (1%)	0	0
Hypokalaemia	96 (22%)	27 (6%)	6 (1%)	0	65 (15%)	15 (3%)	3 (1%)	0
Fatigue	95 (21%)	9 (2%)	0	0	86 (19%)	8 (2%)	0	0
COVID-19	90 (20%)	15 (3%)	1 (<1%)	4 (1%)	104 (23%)	12 (3%)	2 (<1%)	1 (<1%)
Leukopenia	82 (19%)	18 (4%)	47 (11%)	0	57 (13%)	18 (4%)	31 (7%)	0
Pyrexia	82 (19%)	4 (1%)	0	0	54 (12%)	1 (<1%)	1 (<1%)	0
Febrile neutropenia	74 (17%)	44 (10%)	28 (6%)	1 (<1%)	57 (13%)	39 (9%)	18 (4%)	0
Infusion-related reaction	71 (16%)	3 (1%)	0	0	50 (11%)	1 (<1%)	0	0
Neuropathy peripheral*	70 (16%)	4 (1%)	0	0	74 (17%)	4 (1%)	0	0
Oedema peripheral	52 (12%)	1 (<1%)	0	0	41 (9%)	0	0	0
Alopecia	51 (12%)	0	0	0	50 (11%)	1 (<1%)	0	0
Peripheral sensory neuropathy*	50 (11%)	5 (1%)	0	0	42 (9%)	0	0	0
Asthenia	49 (11%)	7 (2%)	0	0	54 (12%)	5 (1%)	0	0
Insomnia	48 (11%)	2 (<1%)	0	0	57 (13%)	1 (<1%)	0	0
Stomatitis	47 (11%)	2 (<1%)	0	0	41 (9%)	3 (1%)	0	0
Vomiting	43 (10%)	6 (1%)	0	0	50 (11%)	3 (1%)	0	0

Further adverse event data are provided in the appendix (pp 12–15). Data are n (%) of patients with at least one event. Individual events shown are those that occurred in ≥10% of patients in either group. Events are preferred terms according to the Medical Dictionary for Regulatory Activities (version 27.1). R-CHOP=rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone or prednisolone. Tafa-len-R-CHOP=tafasitamab plus lenalidomide and R-CHOP. *In an overall grouping for neuropathy peripheral comprising the preferred terms of axonal and demyelinating polyneuropathy, dysaesthesia, hypoaesthesia, third nerve paresis, nervous system disorder, neuralgia, neuritis, neuropathy peripheral, paraesthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, and polyneuropathy, any grade and grade ≥3 treatment-emergent adverse events were reported for 180 (41%) and 13 (3%) patients in the tafa-len-R-CHOP group, and for 175 (39%) and seven (2%) patients in the R-CHOP group, respectively.

Table 3: **Treatment-emergent adverse events (safety population)**

Implications of all the available evidence

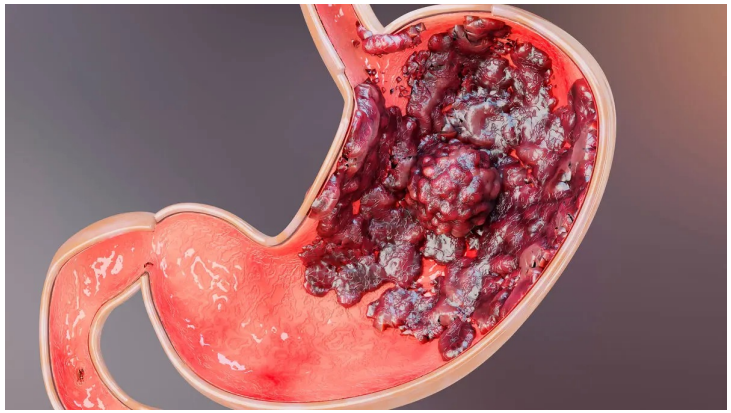
The reduction in the risk of disease progression or death in these patients with tafa-len-R-CHOP, and the possibility of progression-free survival benefit in specific subgroups with needs not met by current first-line treatment regimens, including patients younger than 65 years, those with GCB-like molecular subtype, and those with bulky disease, could expand the first-line armamentarium for these patients with high-risk disease.

Als **neoadjuvant** wird in der Onkologie eine Krebstherapie bezeichnet, die **vor der eigentlichen Hauptbehandlung (meist einer Operation)** stattfindet. Ziel ist es, den Tumor zu verkleinern, um ihn operabel zu machen oder Organe zu schonen.

Eine adjuvante Therapie in der Onkologie ist eine ergänzende, unterstützende Behandlung (wie Chemotherapie, Immuntherapie oder Hormontherapie), die **nach einer erfolgreichen Operation** erfolgt. Ihr Ziel ist es, das Rückfallrisiko zu senken, indem möglicherweise verbliebene, unsichtbare Tumorzellen (Mikrometastasen) im Körper bekämpft werden

Serplulimab ist ein humanisierter monoklonaler PD-1-Checkpoint-Inhibitor. Es wird in Kombination mit Chemotherapie zur Erstlinienbehandlung des fortgeschrittenen kleinzelligen Lungenkarzinoms (ES-SCLC) bei Erwachsenen eingesetzt.

Oxaliplatin ist ein platinbasiertes Chemotherapeutikum (Zytostatikum). Es wird in der Onkologie vorwiegend zur Behandlung von Dickdarm- und Mastdarmkrebs (kolorektale Karzinome) eingesetzt, meist in Kombination mit anderen Medikamenten wie 5-Fluorouracil und Folinsäure (bekannt als FOLFOX-Schema)



Wirkungsweise der Komponenten

Routine

1.S-1 (Tegafur/Gimeracil/Oteracil): Ein perorales Krebsmedikament. Es enthält ein Prodrug von 5-Fluorouracil (5-FU) sowie zwei Modulatoren, welche den Abbau von 5-FU im Körper hemmen und gleichzeitig die gastrointestinale Toxizität (insbesondere Durchfälle) verringern sollen.

2.Oxaliplatin: Ein intravenös verabreichtes Zytostatikum aus der Gruppe der Platinderivate. Es hemmt die Zellteilung, indem es Quervernetzungen in der DNA der Tumorzellen bildet und diese somit schädigt.

Does serplulimab help S1 + oxaliplatin?

Perioperative serplulimab with neoadjuvant chemotherapy versus perioperative chemotherapy in PD-L1-positive gastric cancer (ASTRUM-006): a randomised, double-blind, multicentre, phase 3 study

Summary

Background Perioperative chemo-immunotherapy shows variable outcomes in resectable gastric or gastro-oesophageal junction adenocarcinoma. We evaluated the efficacy and safety of neoadjuvant serplulimab with S-1 plus oxaliplatin (SOX) chemotherapy followed by adjuvant serplulimab versus neoadjuvant placebo plus SOX followed by adjuvant SOX in patients with PD-L1-positive, locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma.

Methods In this randomised, double-blind, multicentre phase 3 ASTRUM-006 study, patients were screened at 75 hospitals in China and Thailand. Eligible patients aged 18–70 years with PD-L1 combined positive score (CPS) ≥5, resectable gastric or gastro-oesophageal junction adenocarcinoma were randomly assigned 1:1 to neoadjuvant serplulimab or placebo (intravenous; 4·5 mg/kg) plus SOX chemotherapy (intravenous oxaliplatin 130 mg/m² on day 1, and oral S1 40–60 mg twice daily on days 1–14) for three cycles (cycle length 21 days), followed by adjuvant serplulimab (up to 17 cycles; serplulimab group) or SOX (five cycles; placebo group). The primary endpoint was investigator-assessed event-free survival (defined as the time from randomisation to the occurrence of progressive disease or local or distant recurrence, other new malignancies, or death), with efficacy first evaluated in PD-L1 CPS ≥10, then in the intention-to-treat (CPS ≥5) population. This study is registered with ClinicalTrials.gov, NCT04139135, and is ongoing.

Findings Between Nov 26, 2019, and April 19, 2024, 1646 patients were screened, of whom 588 patients (median age 61·0 years [IQR 55–66]; 124 [21%] female and 464 [79%] male) at 57 hospitals in China were randomly assigned to the serplulimab group (n=292) or placebo group (n=296). With a median follow-up duration of 42·7 months (IQR 24·3–53·6), median event-free survival was significantly longer with serplulimab than with placebo in the PD-L1 CPS ≥10 population (not reached [NR] *vs* 42·0 months; hazard ratio 0·65 [95% CI 0·47–0·90]; p=0·0082). With a median follow-up of 35·9 months (IQR 23·5–49·4), median event-free survival was also significantly longer with serplulimab than with placebo in the intention-to-treat population (NR *vs* 35·9 months; 0·73 [95% CI 0·56–0·94]; p=0·015). Grade 3 or worse treatment-related adverse events occurred in 136 (47%) patients in the serplulimab group and 172 (59%) patients in the placebo group; 19 (7%) and 31 (11%) patients in the respective groups discontinued treatment due to treatment-related adverse events.

Interpretation Neoadjuvant serplulimab plus SOX followed by adjuvant serplulimab significantly improved event-free survival and demonstrated a better safety profile compared with neoadjuvant and adjuvant SOX in PD-L1-positive, resectable gastric or gastro-oesophageal junction adenocarcinoma. Extended follow-up for the overall survival data is warranted to confirm a survival advantage of this perioperative strategy with a chemotherapy-sparing adjuvant component for this indication.

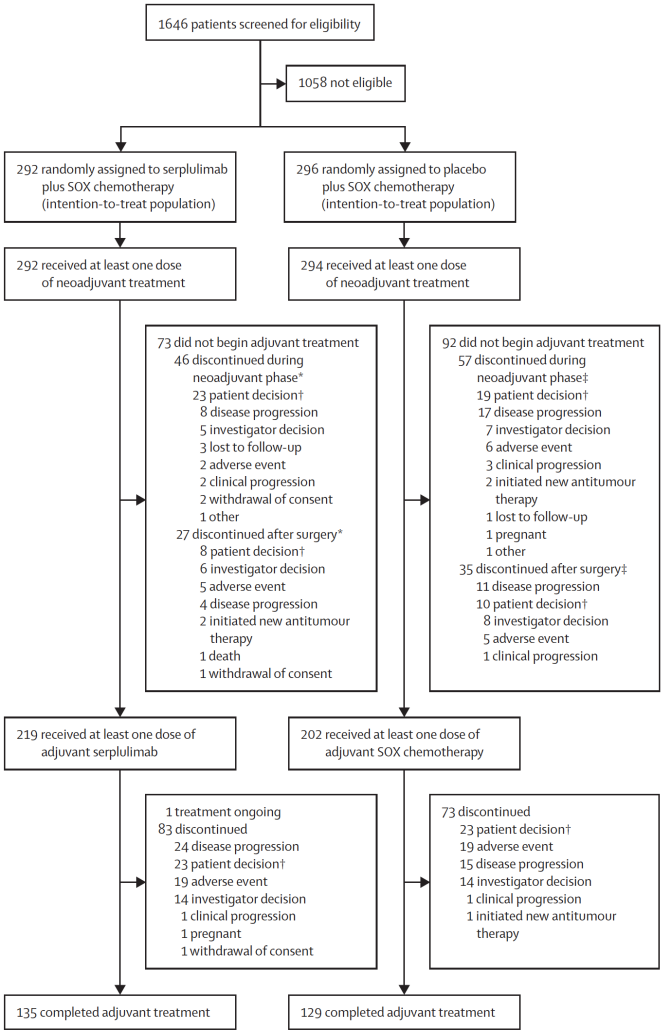


Figure 1: **Trial profile**
SOX=S-1 plus oxaliplatin. *280 completed neoadjuvant phase and 246 completed surgery. †Discontinued treatment but agreed to follow-up. ‡281 completed neoadjuvant phase and 237 completed surgery.

	PD-L1 CPS ≥10			Intention-to-treat population		
	Serplulimab group (N=193)	Placebo group (N=217)	Total (N=410)	Serplulimab group (N=292)	Placebo group (N=296)	Total (N=588)
Age, years	61·0 (56–66)	60·0 (55–65)	61·0 (55–66)	61·5 (55–66)	60·0 (55–65)	61·0 (55–66)
Aged ≥65 years	69 (36%)	63 (29%)	132 (32%)	102 (35%)	86 (29%)	188 (32%)
Sex						
Female	42 (22%)	49 (23%)	91 (22%)	58 (20%)	66 (22%)	124 (21%)
Male	151 (78%)	168 (77%)	319 (78%)	234 (80%)	230 (78%)	464 (79%)
Race or ethnicity						
Asian	193 (100%)	217 (100%)	410 (100%)	292 (100%)	296 (100%)	588 (100%)
ECOG performance status						
0	101 (52%)	116 (53%)	217 (53%)	156 (53%)	157 (53%)	313 (53%)
1	92 (48%)	101 (47%)	193 (47%)	136 (47%)	139 (47%)	275 (47%)
Histological classification						
Diffuse	19 (10%)	24 (11%)	43 (10%)	25 (9%)	30 (10%)	55 (9%)
Intestinal	13 (7%)	15 (7%)	28 (7%)	24 (8%)	24 (8%)	48 (8%)
Unclassified or other	161 (83%)	178 (82%)	339 (83%)	243 (83%)	242 (82%)	485 (82%)
TNM classification						
T3	75 (39%)	77 (35%)	152 (37%)	115 (39%)	116 (39%)	231 (39%)
T4a	109 (56%)	134 (62%)	243 (59%)	163 (56%)	171 (58%)	334 (57%)
T4b	9 (5%)	6 (3%)	15 (4%)	14 (5%)	9 (3%)	23 (4%)
N1	82 (42%)	83 (38%)	165 (40%)	127 (43%)	123 (42%)	250 (43%)
N2	87 (45%)	106 (49%)	193 (47%)	131 (45%)	133 (45%)	264 (45%)
N3	20 (10%)	25 (12%)	45 (11%)	27 (9%)	37 (13%)	64 (11%)
N3a	4 (2%)	2 (1%)	6 (1%)	6 (2%)	2 (1%)	8 (1%)
N3b	0	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	2 (<1%)
Helicobacter pylori infection						
Positive	119 (62%)	129 (59%)	248 (60%)	178 (61%)	178 (60%)	356 (61%)
Negative	74 (38%)	88 (41%)	162 (40%)	114 (39%)	118 (40%)	232 (39%)
PD-L1 expression by CPS						
≥5 to <10	..	..	..	99 (34%)	79 (27%)	178 (30%)
≥10 to <50	147 (76%)	169 (78%)	316 (77%)	147 (50%)	169 (57%)	316 (54%)
≥50	46 (24%)	48 (22%)	94 (23%)	46 (16%)	48 (16%)	94 (16%)

Data are median (IQR) or n (%). CPS=combined positive score. ECOG=Eastern Cooperative Oncology Group.

Table 1: **Baseline and disease characteristics**

Helps a bit

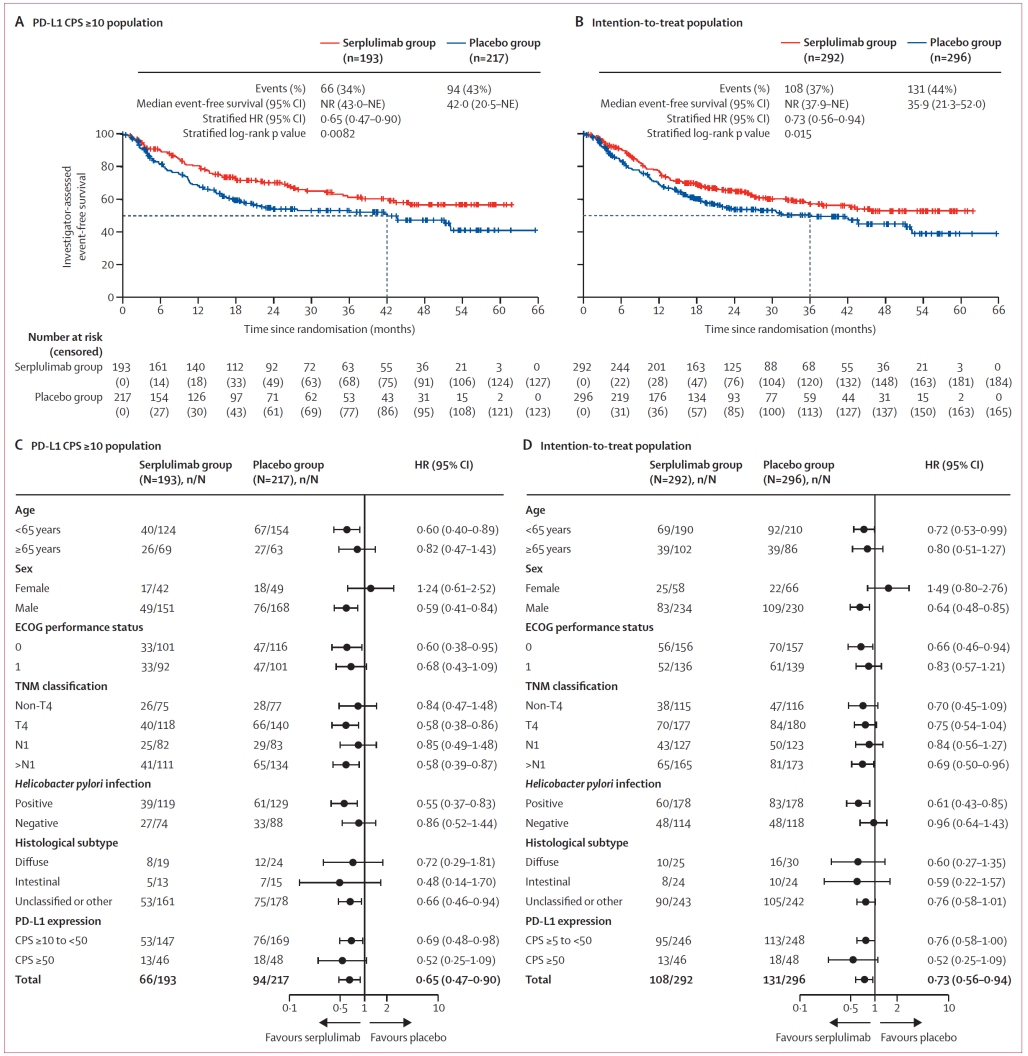


Figure 2: **Event-free survival as assessed by investigator**
Kaplan–Meier estimates of event-free survival in the PD-L1 CPS ≥10 population (A) and the PD-L1 CPS ≥5 population (intention-to-treat) (B). Dashed lines correspond to median event-free survival. Subgroup analysis in the PD-L1 CPS ≥10 population (C), and the PD-L1 CPS ≥5 population (intention-to-treat) (D). CPS=combined positive score. ECOG=Eastern Cooperative Oncology Group. HR=hazard ratio. NE=not estimable. NR=not reached.

Helps a bit

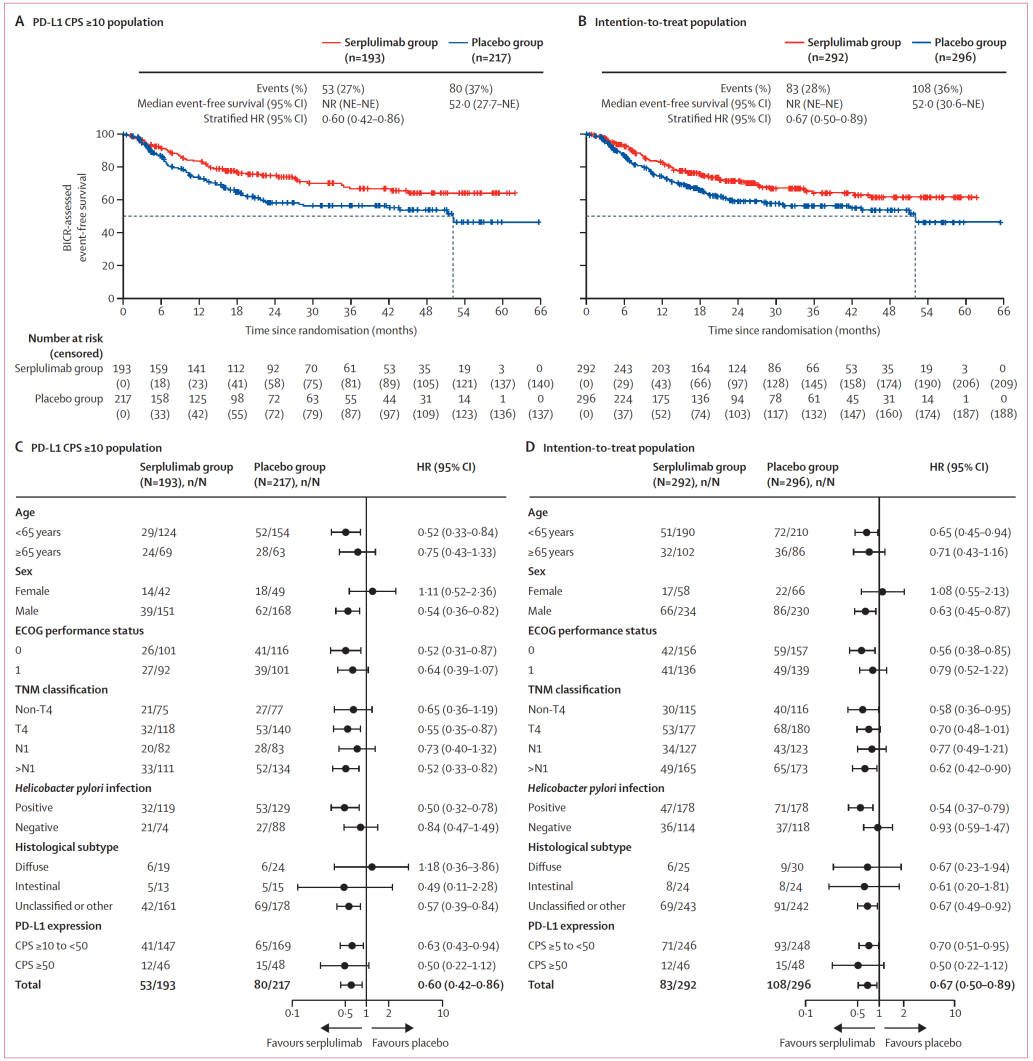


Figure 3: **Event-free survival as assessed by the BICR**
Kaplan–Meier estimates of event-free survival in the PD-L1 CPS ≥10 population (A) and the PD-L1 CPS ≥5 population (intention-to-treat) (B). Dashed lines correspond to median event-free survival. Subgroup analysis in the PD-L1 CPS ≥10 population (C) and the PD-L1 CPS ≥5 population (intention-to-treat) (D). BICR=blinded independent central review. CPS=combined positive score. ECOG=Eastern Cooperative Oncology Group. HR=hazard ratio. NE=not estimable. NR=not reached.

	PD-L1 CPS ≥10		Intention-to-treat population	
	Serplulimab group (N=193)	Placebo group (N=217)	Serplulimab group (N=292)	Placebo group (N=296)
Pathological complete response, n (%; 95% CI)	50 (26%; 20–33)	14 (6%; 4–11)	63 (22%; 17–27)	19 (6%; 4–10)
Stratified odds ratio (95% CI)	4·84 (2·59–9·04)	..	3·95 (2·31–6·76)	..

CPS=combined positive score.

Table 2: **Summary of pathological complete response in patients**

	Serplulimab group (N=292)	Placebo group (N=294)	Total (N=586)
Adverse event of any grade	288 (99%)	292 (99%)	580 (99%)
Related to any study treatment	284 (97%)	288 (98%)	572 (98%)
Adverse event of grade 3 or worse	179 (61%)	201 (68%)	380 (65%)
Related to any study treatment	136 (47%)	172 (59%)	308 (53%)
Serious adverse event	117 (40%)	111 (38%)	228 (39%)
Related to any study treatment	70 (24%)	76 (26%)	146 (25%)
Adverse events leading to discontinuation from any component of the study regimen	23 (8%)	34 (12%)	57 (10%)
Related to any study treatment	19 (7%)	31 (11%)	50 (9%)
Adverse events leading to death	15 (5%)	8 (3%)	23 (4%)
Related to any study treatment	2 (1%)	1 (<1%)	3 (1%)
Related to serplulimab or placebo	2 (1%)	0	2 (<1%)
Related to SOX	2 (1%)	1 (<1%)	3 (1%)
Immune-related adverse event			
Any grade	117 (40%)	19 (6%)	136 (23%)
Grade 3 or worse	18 (6%)	3 (1%)	21 (4%)
Serious	25 (9%)	3 (1%)	28 (5%)
Leading to death	0	0	0
Most common treatment-related adverse events of any grade*			
Neutrophil count decreased	162 (55%)	206 (70%)	368 (63%)
Anaemia	147 (50%)	152 (52%)	299 (51%)
White blood cell count decreased	145 (50%)	174 (59%)	319 (54%)
Nausea	144 (49%)	173 (59%)	317 (54%)
Platelet count decreased	137 (47%)	187 (64%)	324 (55%)
Aspartate aminotransferase increased	135 (46%)	109 (37%)	244 (42%)
Alanine aminotransferase increased	120 (41%)	93 (32%)	213 (36%)
Vomiting	116 (40%)	138 (47%)	254 (43%)
Most common treatment-related adverse events of grade 3 or worse†			
Platelet count decreased	51 (17%)	72 (24%)	123 (21%)
Neutrophil count decreased	26 (9%)	70 (24%)	96 (16%)
Lymphocyte count decreased	21 (7%)	27 (9%)	48 (8%)
Anaemia	18 (6%)	26 (9%)	44 (8%)
White blood cell count decreased	7 (2%)	17 (6%)	24 (4%)

Data are n (%). SOX=S-1 plus oxaliplatin. *Occurring in at least 30% of patients in either group. †Occurring in at least 5% of patients in either group.

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

Added value of this study

ASTRUM-006 is the first study to specifically enrol patients based on PD-L1 combined positive score ≥5 and investigate the use of mono-immunotherapy in the adjuvant setting for gastric cancer. The results show that, compared with neoadjuvant and adjuvant chemotherapy, the chemotherapy-sparing adjuvant strategy following neoadjuvant immunotherapy plus chemotherapy significantly improves event-free survival and pathological complete response rate along with improved tolerability. These findings suggest its potential for the perioperative treatment of this indication.

Implications of all the available evidence

Along with accumulating evidence to support the integration of immune checkpoint blockade into perioperative treatment for resectable gastric and gastro-oesophageal junction cancer, these findings represent some of the first evidence that a less intensive, biomarker-driven treatment strategy involving a PD-1 antibody can be effectively applied in this setting.

The UCL–*Lancet* Commission on Migration and Health: review of the state of progress

Although progress towards implementation of international agreements since publication of the UCL–*Lancet* Commission on Migration and Health in December, 2018, has been slow, global trends in migration and forced displacement have continued to rise. However, the COVID-19 pandemic showed that reaching refugees and migrants with health interventions is feasible with political will. The benefits of refugee-inclusive and migrant-inclusive health-care systems during emergencies (eg, COVID-19 and the war in Ukraine) are apparent, with numerous examples of inclusive policy making being rapidly introduced and innovative models developed to support health-care access, including preventive measures such as vaccination. Lessons from these successes should be learned and incorporated into future policy and practice. However, global political and financial uncertainty and disruption—combined with multiple conflicts and natural disasters—have increased individuals' need to move, which will continue to be exacerbated by the climate crisis. Although new conflicts and exacerbations of existing ones have led to a rise in forced displacement within and across national borders, labour migration has also risen dramatically, with the pandemic highlighting the health and social needs of these groups globally. The need for strong leadership and accountability, engagement of policy makers in the highest-level fora, and improved access to quality health services for refugees and migrants has never been greater. In this Review, nearly 8 years after the UCL–*Lancet* Commission on Migration and Health was published, we renew our call for action to: (1) improve health-care access and optimise outcomes for refugees and migrants by emphasising health in all migration and forced displacement policies; (2) establish data systems to monitor progress, together with appropriate use of new technologies to improve access, prevent harm, and safeguard privacy; (3) support research on adaptation to and mitigation of the health consequences of climate change on refugees and migrants; and (4) renew focus on the political determinants of health outcomes for people on the move. At this pivotal moment, with geopolitical, sociodemographic, and environmental turmoil, political leaders and societies can shape a better future by leveraging the human capital of migrants and upholding the human rights and dignity of all.

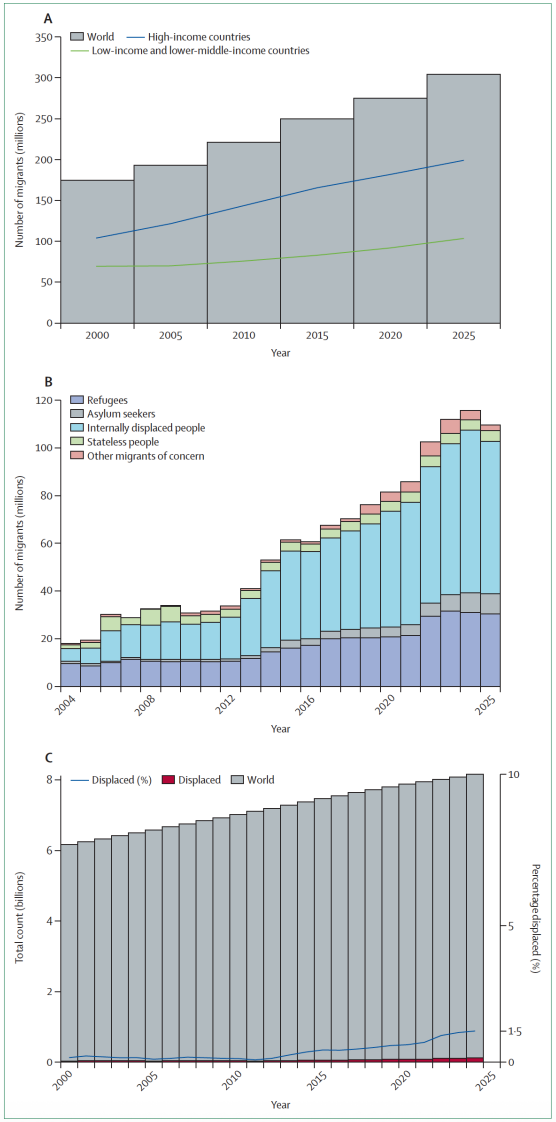


Figure 1: **Trends in overall migrant numbers and forcibly displaced people**
(A) International migration stock by destination country income level, 2000–25. Data are from UN Population Data.[2] (B) Global trends in forcibly displaced people, 2004–23. Data are from the UN High Commissioner for Refugees.[3] (C) Forcibly displaced people worldwide as a percentage of the world's population, 2000–24. Data are from the UN High Commissioner for Refugees Population Statistics Database.[3]

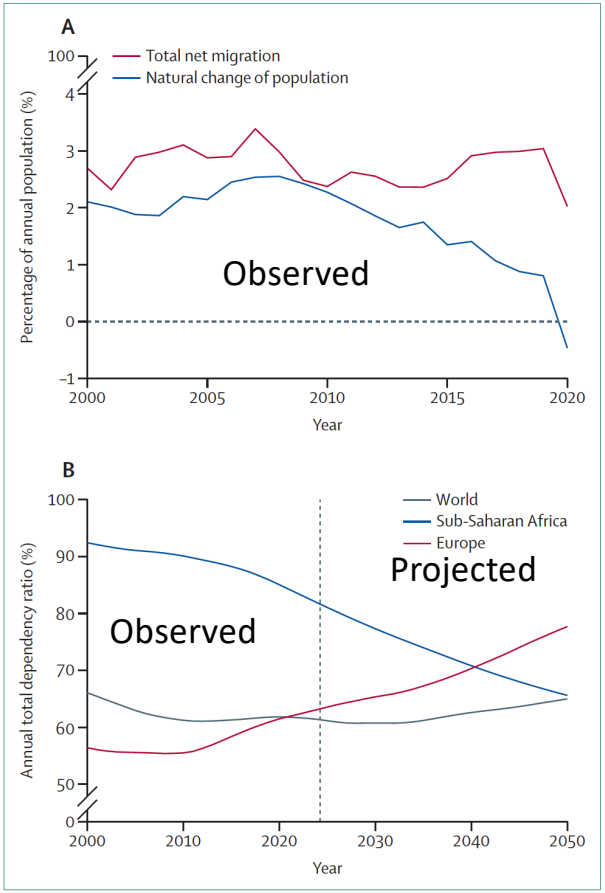


Figure 3: **Trends in net migration and population growth**
(A) Net migration and natural population change in the UK, Canada, Norway, Switzerland, the USA, and the Organisation for Economic Co-operation and Development EU nations. Data are from UN Population Data.[2] (B) Dependency ratio (ie, the ratio of children [aged 0–14 years] and older people [aged ≥65 years] to the working-age population [aged 15–64 years]) in Europe, sub-Saharan Africa, and worldwide over the next three decades. The dashed line indicates the point at which data transition from observed data to projected estimates.

Panel 1: Examples of country policies integrating migrants and refugees during the COVID-19 pandemic

Argentina, Chile, France, Italy, Peru, and Spain
Expedited the recruitment of foreign health-care workers in their respective national health services.[100]

Bahrain and Kuwait
Introduced targeted adaptation policies by providing amnesty for undocumented migrants.[100]

Belgium, Germany, Ireland, Lithuania, Luxembourg, Spain, and Switzerland
Accelerated the recognition of foreign qualifications of health-care professionals.[100]

Colombia
Started the regularisation of undocumented Venezuelan migrants, allowing them to register for the COVID-19 vaccine, and provided medical services to all migrants if they contracted COVID-19.[101]

Lebanon
Ensured the inclusion of refugees, migrants, and stateless people in their national vaccination plans and expanded access to registration platforms beyond mobile or online options.[102,103]

Jordan
Provided free and equitable access to COVID-19 vaccines for migrants and Iraqi and Syrian refugees.[102,104]

Portugal
Regularised the status of migrants with a pending residence application during the pandemic. Continued to offer undocumented migrants the ability to apply for residence and family reunification visa.[105,106]

Senegal, Rwanda, and Uganda
Included refugees in their respective COVID-19 vaccination campaigns, roll-out plans, and programmes.[104]

Spain
Relaxed regularisation programme requirements, including those related to employment status and minimum income.[100]

Russia, South Africa, and Uganda
Waived administrative sanctions and financial penalties for migrants unable to leave due to travel restrictions.[100]

UK
Encouraged undocumented migrants to register with primary care services and national vaccination programmes, emphasising that no immigration checks or fees will be applied to migrants without rights to access non-emergency NHS care.[104]

This panel is not an exhaustive list of all positive examples of action in all countries, but a small selection of states to illustrate what is possible based on published evidence.

Panel 2: Challenging asylum and refugee law

Migration and forced displacement have long been politically charged issues worldwide. Their legal definitions—and these definitions' application—are essential in establishing legal, health, and social protections for displaced people. Forcibly displaced people (ie, asylum seekers, refugees, and internally displaced people) flee persecution, violence, conflict, and disaster to seek safety and protection.[164] Refugees, defined in the 1951 Convention relating to the Status of Refugees and the 1967 Protocol, cross internationally recognised borders, whereas internally displaced people are displaced within their own country's borders. Ensuring that these legal terms are clearly defined and acknowledged by governments is essential for collecting useful displacement data and statistics, better understanding displacement patterns, and supporting evidence-based policy and programming. However, these legal definitions and the protections they entail are being challenged by governments, repudiating their obligations under the Refugee Convention and Protocol. For example, the USA, the UK, and countries in the EU are increasingly requiring asylum seekers to seek asylum outside of their countries. These countries implement this through various mechanisms, including by paying other countries to stop asylum seekers from entering their countries, or by attempting to resettle them to third countries, both of which are being legally challenged in courts.[165–169]

Furthermore, non-Mexican asylum seekers subjected to the US Migrant Protection Protocols, also known as the Remain in Mexico programme, have been required to wait for their immigration court hearings in dangerous Mexican border towns, with many living in squalid conditions or experiencing homelessness.[170–172] The Remain in Mexico programme has been criticised for conflicting with US obligations under international and domestic refugee law, including the 1967 Protocol and the 1980 Refugee Act, which prohibit returning individuals to countries where they risk persecution and establish the statutory right to seek asylum in the USA. The EU also entered into agreements with countries such as Türkiye and Libya to intercept and prevent migrants and asylum seekers from reaching EU territory, in exchange for aid, material, technical assistance, and visa liberalisation.[173–175]

These externalisation approaches undertaken by the USA and Europe have raised sharp criticism over human rights violations, due process concerns, breaches of international law, and outsourcing of asylum procedures.

Although implementing these recommendations might be challenging in the current climate, the urgency to act is undeniable. The adverse role of national policy in many states in exacerbating poor access to health for migrants and refugees shows that our wide-ranging recommendations cannot be directed at a single actor. International and multilateral organisations, civil society actors, and national and local governments all have a responsibility to respond. Human mobility presents an important opportunity to boost economies, strengthen health systems through the inclusion of much-needed health workers across regions, and improve preparedness for global health threats. However, responses must be grounded in rigorous evidence that accounts for the diverse contexts and needs of both migrant populations and host communities. As the world increasingly comprises diverse populations who migrate, inclusive health policies that fully integrate refugees and migrants should be developed and implemented for global health security and the protection of individuals' rights. By doing so, all populations—nationals, refugees, and migrants alike—will benefit, ultimately becoming safer and healthier.

Refining cardiometabolic risk through genomics

Cardiometabolic diseases (CMDs) such as type 2 diabetes, dyslipidemia, and coronary artery disease (CAD) remain the leading causes of morbidity and mortality worldwide. Risk factors for CMD include obesity, insulin resistance and impaired glucose homeostasis, dyslipidemia, and hypertension. Despite therapeutic advances, the prevalence of CMD remains on the rise with earlier onset now observed in adolescents and young adults. Given this trajectory, targeting metabolic dysfunction through early identification and management of insulin resistance, obesity, lipid abnormalities, and elevated blood pressure can delay disease progression, prevent adverse events, and reduce premature mortality. However, CMDs are biologically heterogeneous, and individuals differ substantially in their underlying pathophysiology and long-term risk. Additionally, the precise biological mechanisms linking metabolic dysregulation to cardiovascular damage are not fully understood.

Polygenic risk scores for CAD subtype-informed cardiometabolic risk stratification

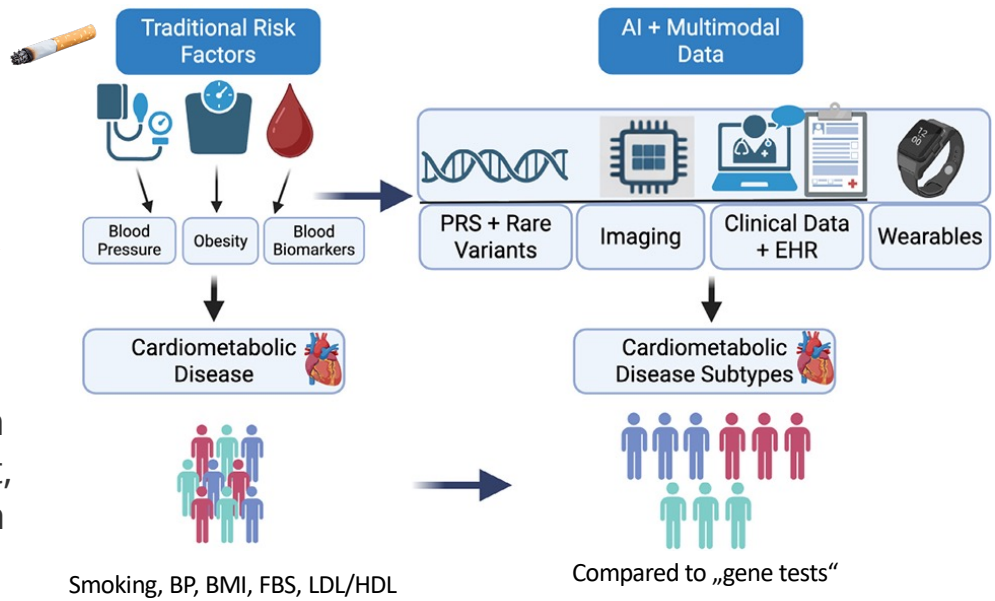
Polygenic risk scores (PRSs) aggregate risk across thousands of common variants and may be useful tools for clinical risk stratification. Unlike conventional risk calculators, PRSs remain stable across the life course and can identify elevated inherited risk before clinical risk factors emerge.

In the case of CAD, current risk models provide moderate discrimination for 10-year risk to inform decisions such as statin initiation. However, these models do not account for the underlying biological heterogeneity of CAD, which limits their ability to support more personalized treatment approaches. Beyond predicting overall CAD risk, genomic information can help parse CAD heterogeneity. For example, in a recent study, we modeled multiple CAD subtypes among 26,036 UK Biobank cases, with external validation in 8,598 cases from the All of Us cohort. Clinical biomarkers (ApoA, ApoB, high-density lipoprotein, triglycerides, C-reactive protein) and both genome-wide and pathway-based PRSs contributed predictive signals for different subtypes. Combining clinical and genomic information improved predictive accuracy, supporting the idea that inherited risk and current biomarker profile status provide complementary, nonredundant information.

A **Polygenic Risk Score (PRS)** is an estimate of a person's genetic susceptibility to a specific disease or trait. It calculates the combined, subtle effects of thousands of genetic variations across your DNA to determine if your overall risk is higher or lower than average.

Monogenic cardiometabolic disease

At the opposite end of the genetic spectrum lie monogenic disorders. Mendelian forms of diabetes and obesity arise from single-gene rare coding variants. Genetic testing of established monogenic diabetes genes (e.g., *GCK, HNF1A, HNF4A*) and obesity genes in the leptin–melanocortin pathway (e.g., *MC4R, LEP*) enables molecular diagnosis that can directly guide care. In select cases, therapy can be tailored to the causal gene—such as sulfonylureas for certain MODY subtypes, leptin replacement therapy for leptin deficiency, or setmelanotide, an MC4 receptor agonist, for mutations in genes upstream of *MC4R* in the leptin melanocortin pathway such as *POMC, PCSK1,* or *LEPR*. Similarly, familial hypercholesterolemia (FH), most commonly caused by pathogenic variants in *LDLR, APOB*, or *PCSK9*, leads to markedly elevated lifelong low-density lipoprotein (LDL) cholesterol and increased CAD risk; genetic testing enables cascade screening among family members and intensive LDL lowering that substantially mitigates this risk. Together, the strategies for ameliorating the effects of these conditions illustrate the tangible clinical impact of genetics-informed care in CMD.



Cardiometabolic disease subtyping through multimodal data integration. Integration of traditional disease biomarkers with multimodal data including genomic profiles, electronic health records (EHR), clinical measurements, wearable-derived metrics, and imaging phenotypes enables the identification of disease subtypes and improves prediction of disease trajectories. Emerging artificial intelligence (AI) and machine learning tools allow for scalable analysis of multimodal data, improving risk stratification and informing more precise preventive strategies. PRS, polygenic risk score.

This exercise ‘sweet spot’ is linked to greater longevity

The links were especially strong for cardiovascular disease and neurological conditions. The data showed that people who lifted weights, no matter how infrequently, were less likely to die from heart attacks or Alzheimer’s disease compared with people who did no resistance training.

Gathering 30 years’ worth of data about exercise habits from more than 147,000 men and women, they looked for associations between the number of minutes people spent lifting weights each week and how long they lived.

According to the results, any amount of resistance exercise, even a few minutes a week, was associated with a lower risk of premature death than never lifting at all, including among people who regularly walked, ran or did other aerobic exercise.

But the scientists also zeroed in on the “Goldilocks” level of weekly lifting — the number of minutes per week that isn’t too little or too much, but just right — associated with the greatest longevity benefit overall, whether people also exercised aerobically or not.

They seem to have found it.

Long-term resistance training with all-cause and cause-specific mortality: assessing dose-response and joint associations with aerobic physical activity

⇒ Using repeated measures of resistance training over up to 30 years of follow-up, we found that performing 90–119 min/week of long-term resistance training was associated with 13% lower all-cause, 19% lower cardiovascular and 27% lower neurological disease mortality, after multivariable adjustment including aerobic activity. Levels higher than 120 min/week did not lower these risks further.

METHODS

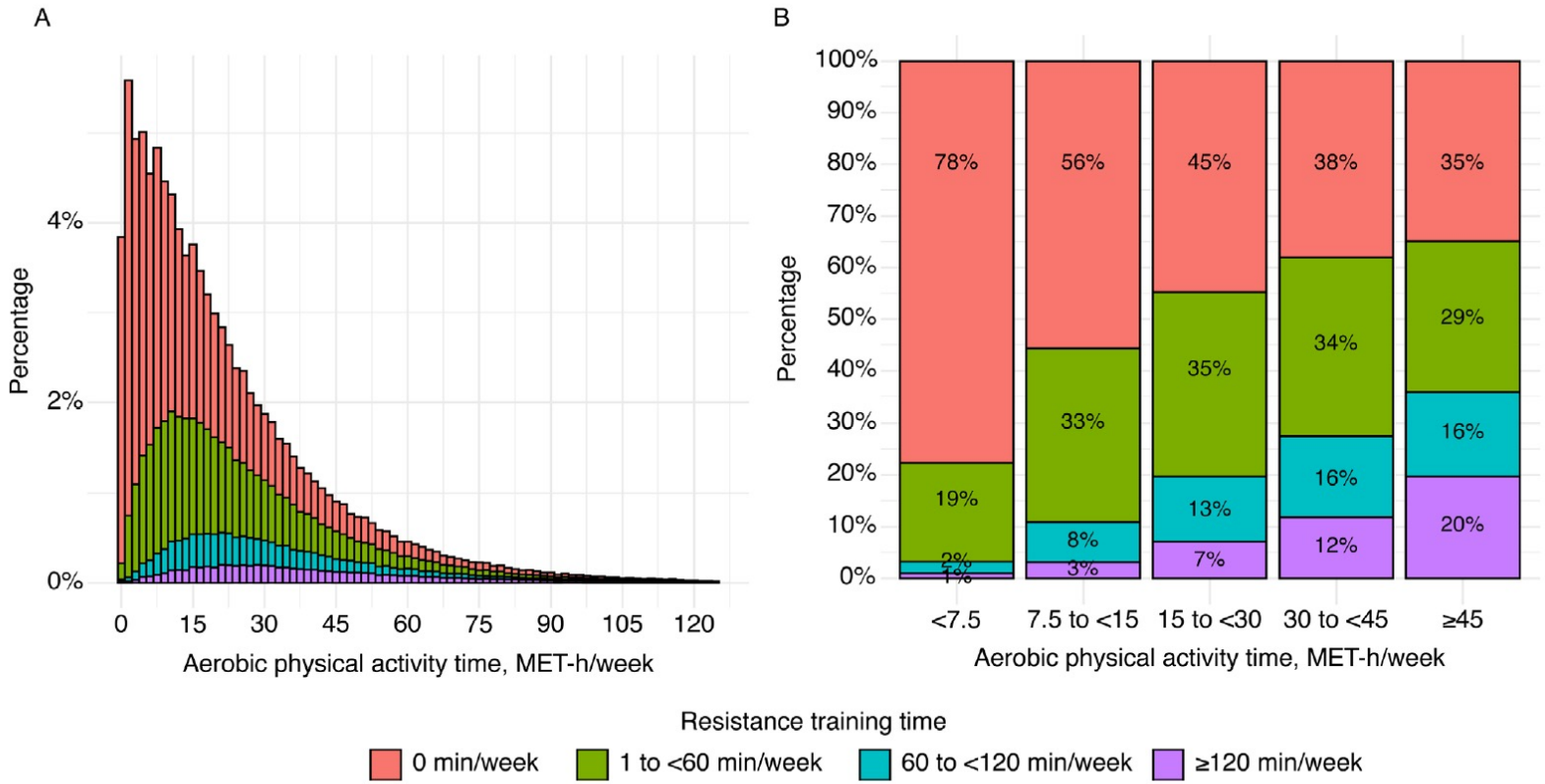
Study population

The Health Professionals Follow-up Study (HPFS) was initiated in 1986 with 51 529 male health professionals, aged 40–75 years at enrolment. The Nurses' Health Study (NHS) was initiated in 1976 with 121 700 female registered nurses, aged 30–55 years

⇒ For cancer mortality, a reduced risk was observed only at lower levels of resistance training (1–59 min/week).

⇒ Engaging in either adequate aerobic activity or resistance training alone was associated with lower mortality, with the risk reduction more pronounced with aerobic activity.

⇒ The lowest mortality risk was observed when both activities were performed at high levels or when aerobic activity level was very high (≥45 metabolic equivalent of task (MET)-hours/week).



Distribution of aerobic physical activity time by resistance training time level throughout follow-up in three cohorts pooled. (A) The distribution resistance training time groups across all aerobic physical activity time level. (B) The percentage of resistance training time groups in each aerobic physical activity time groups. MET, metabolic equivalent of the task.

A Metabolic Equivalent of Task (MET) is an objective, universal unit used to measure the energy expenditure of physical activities. One MET represents resting energy expenditure—the amount of oxygen consumed while sitting quietly (defined as 3.5 mL of oxygen per kg of body weight per minute).

Effects of resistance training corrected for aerobic training (if any)