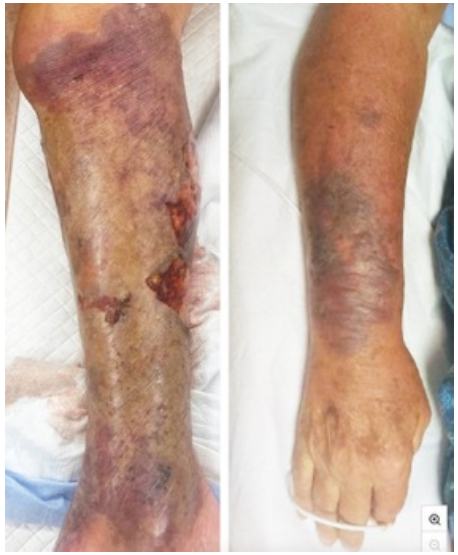
https://www.mdc-berlin.de/de/veroeffentlichungstypen/clinical-journal-club

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



A diagnosis of Vibrio vulnificus necrotizing soft-tissue infection was made. V. vulnificus is found in warm, low-salinity coastal and estuarine waters. Transmission occurs primarily through consumption of undercooked seafood or exposure of open wounds to water containing the bacteria. The abundance and geographic range of V. vulnificus is projected to increase owing to factors related to climate change, including rising water temperatures, storm surges, salinity changes, and algal blooms. The patient underwent amputation and received antibiotic treatment.

A 74-year-old man presented to the emergency department with a 3-day history of a painful laceration on his right leg that he had sustained while jumping into waters off the Gulf Coast of Florida. Two days after the injury to his leg, skin changes had appeared on his right arm. Physical examination is shown of the right lower leg and right forearm. He had no known history of chronic liver disease or an immunocompromising condition. Which of the following is the most likely diagnosis?

Aeromonas cellulitis

Clostridium perfringens gas gangrene

Pseudomonas aeruginosa cellulitis

Mycobacterium marinum skin and soft tissue infection

Vibrio vulnificus skin and soft-tissue infection

Vibrio vulnificus ist ein gramnegatives, stäbchenförmiges Bakterium, das natürlicherweise in warmem Meer- und Brackwasser vorkommt. Es ist vor allem deshalb bekannt, weil es lebensbedrohliche Infektionen verursachen kann, die oft als „fleischfressende Bakterien“ bezeichnet werden, da sie schwere Gewebeschäden (Nekrosen) auslösen.

Vorkommen und Risikofaktoren

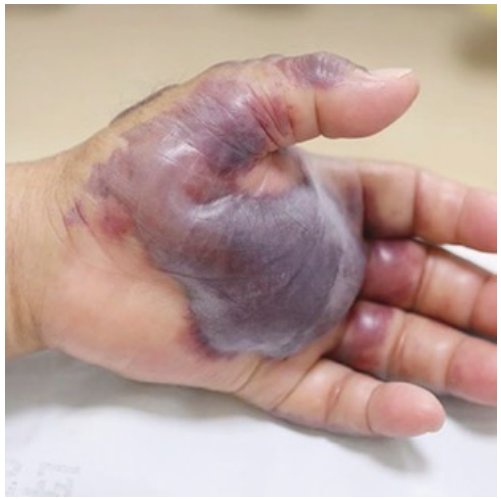
Die Bakterien vermehren sich explosionsartig bei Wassertemperaturen ab etwa 20 grad.

Geografie: Besonders häufig in der **Ostsee**, der **Nordsee** und wärmeren Küstengebieten weltweit (z. B. Florida).

Übertragung:

- **Offene Wunden:** Kontakt mit infiziertem Wasser durch Baden oder Waten.
- **Nahrung:** Verzehr von rohen oder unzureichend gegarten Schalentieren, insbesondere **Austern**.

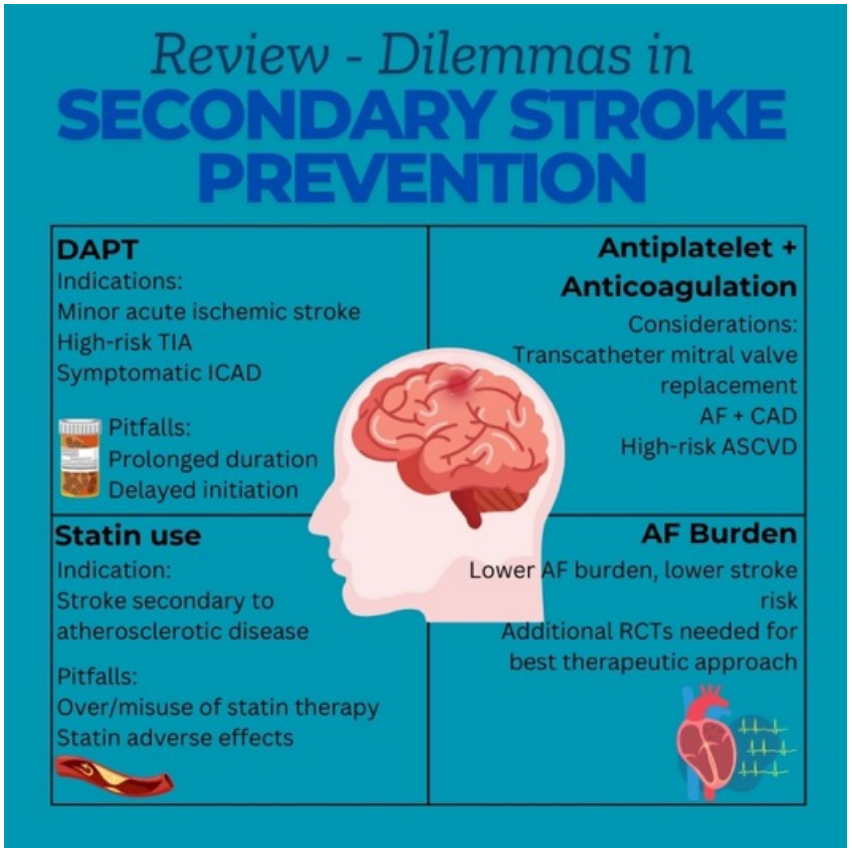
Risikogruppen: Personen mit Immunschwäche, Lebererkrankungen (z. B. durch Alkoholismus), Diabetes oder Krebs tragen ein deutlich höheres Risiko für schwere Verläufe.



Vibrio vulnificus kommt in Europa vor. Das Bakterium findet sich vor allem in den Sommermonaten (bei Wassertemperaturen über 20 grad in salzhaltigen Küstengewässern, besonders in der **Ostsee** (Nordostdeutschland, Dänemark, Schweden), der **Nordsee** und teilweise im Mittelmeer. Durch den Klimawandel und steigende Wassertemperaturen nimmt das Risiko in diesen Regionen zu..

Prophylaxe nach Schlaganfall?

Die Sekundärprävention nach einem Schlaganfall oder einer transitorischen ischämischen Attacke (TIA) zielt darauf ab, das Risiko eines erneuten Ereignisses zu senken, das im ersten Jahr bei etwa 10–16 % liegt. Durch konsequente medizinische und Lebensstil-Anpassungen kann dieses Risiko um bis zu **80 % reduziert** werden.
Zentrale Säulen der Prävention



Medikamentöse Therapie

- **Blutdrucksenkung:** Ein Zielwert von unter **130/80 mmHg** wird für die meisten Patienten empfohlen. Bluthochdruck gilt als der wichtigste veränderbare Risikofaktor.
- **Lipidmanagement (Cholesterin):** Für Patienten mit atherosklerotischem Ursprung ist eine hochintensive Statinterapie (z. B. Atorvastatin 80 mg) Ziel, um das LDL-Cholesterin auf unter **70 mg/dL** (1,8 mmol/L) zu senken.
- **Thrombozytenaggregationshemmung:** Bei nicht-kardioembolischen Schlaganfällen ist eine lebenslange Monotherapie (z. B. Aspirin oder Clopidogrel) Standard. Eine kurzzeitige duale Antiplättchentherapie (**DAPT**) für 21–30 Tage kann bei leichten Schlaganfällen oder Hochrisiko-TIAs vorteilhaft sein.
- **Antikoagulation:** Bei Vorhofflimmern (AF) sind orale Antikoagulanzien (DOACs wie Apixaban oder Rivaroxaban) Mittel der Wahl, um Embolien zu verhindern.

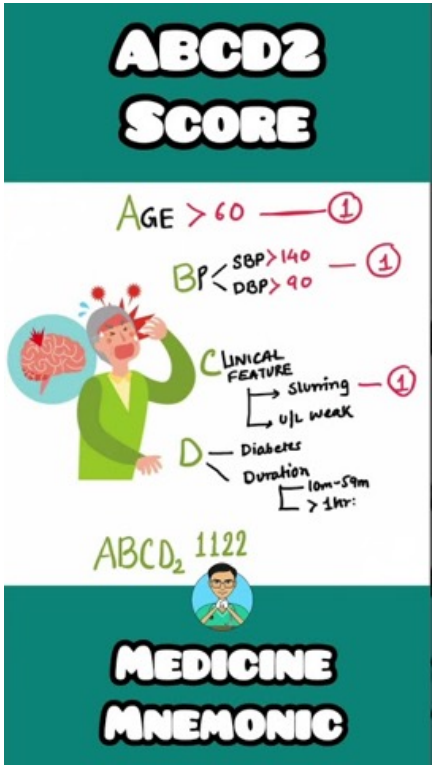
Prophylaxe nach TIA?

Der **ABCD²-Score** ist ein klinisches Bewertungssystem, mit dem Ärzte das kurzfristige Risiko eines Schlaganfalls nach einer **transitorischen ischämischen Attacke (TIA)** (einem "Mini-Schlaganfall") abschätzen. Er hilft dabei, zu entscheiden, wie dringend ein Patient untersucht und stationär aufgenommen werden muss.

Die 5 Kriterien der Berechnung

Der Score wird aus fünf Faktoren berechnet, die zusammen maximal **7 Punkte** ergeben:

Kriterium	Beschreibung	Punkte
A (Age)	**Alter** ≥ 60 Jahre	1
B (Blood Pressure)	**Blutdruck** ≥ 140/90 mmHg	1
C (Clinical features)	**Einseitige Schwäche** (2 Pkt.) oder **Sprachstörung** ohne Schwäche (1 Pkt.)	1–2
D (Duration)	**Dauer** der Symptome: ≥ 60 Min. (2 Pkt.) oder 10–59 Min. (1 Pkt.)	1–2
D (Diabetes)	Bestehender **Diabetes mellitus**	1

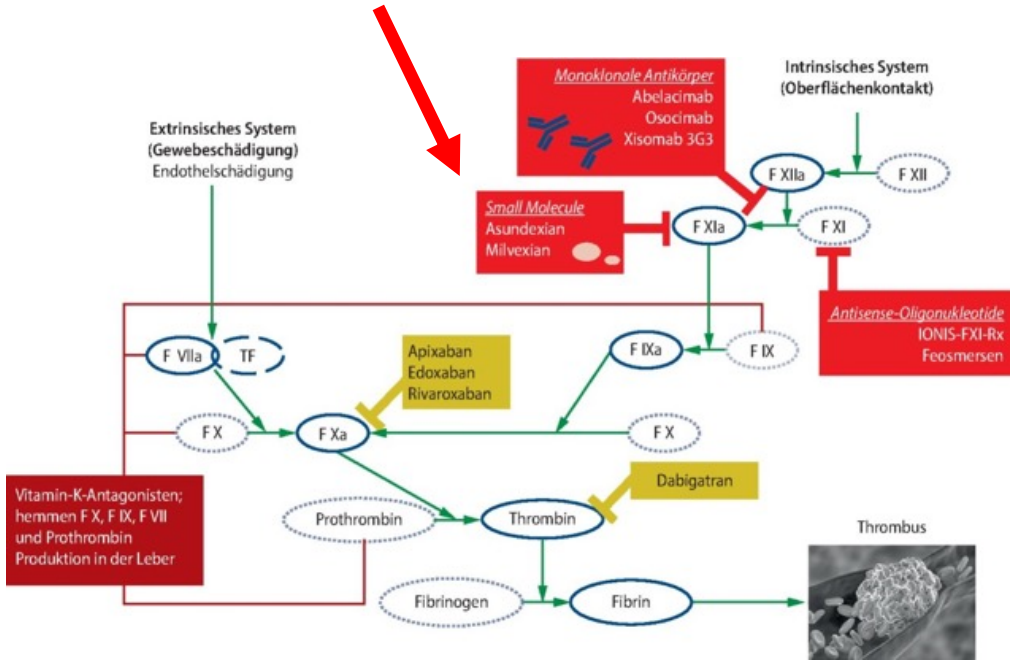


Artificial hemophilia C?

Ein **Faktor-XI-Mangel** (auch als **Hämophilie C** oder **Rosenthal-Syndrom** bezeichnet) ist eine seltene, meist vererbte Gerinnungsstörung. Dabei fehlt dem Blut das Eiweiß „Faktor XI“, das für eine stabile Blutgerinnung notwendig ist.

Wichtige Merkmale

- **Blutungsneigung:** Im Gegensatz zur bekannteren Hämophilie A oder B treten Spontanblutungen (z. B. in Gelenke) selten auf. Blutungen zeigen sich meist erst **nach Verletzungen, Operationen oder Zahneingriffen**.
- **Unvorhersehbarkeit:** Die Schwere der Blutung korreliert oft nur schwach mit der gemessenen Menge des Faktors im Blut. Jemand mit sehr niedrigen Werten kann symptomfrei sein, während eine andere Person mit höheren Werten stärker blutet.
- **Betroffene:** Die Störung tritt bei Männern und Frauen gleichermaßen auf. Besonders häufig ist sie bei Menschen mit **aschkenasisch-jüdischer Herkunft** zu finden.



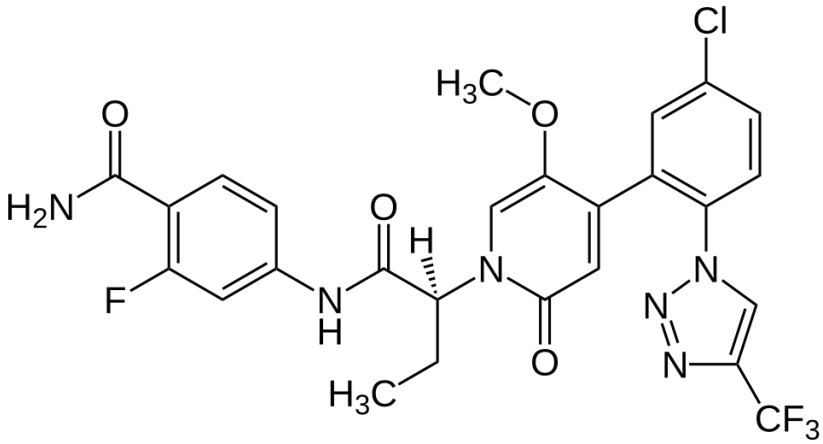
Yes, give them Rosenthal‘s disease!

Asundexian ist ein experimenteller Gerinnungshemmer (Antikoagulans), der vom deutschen Pharmaunternehmen Bayer AG entwickelt wird. Er gehört zu einer neuen Wirkstoffklasse, den **Faktor-XIa-Inhibitoren**.

Aktueller Status und Studienergebnisse (Stand April 2026)

Die Entwicklung von Asundexian war in den letzten Jahren von Höhen und Tiefen geprägt:

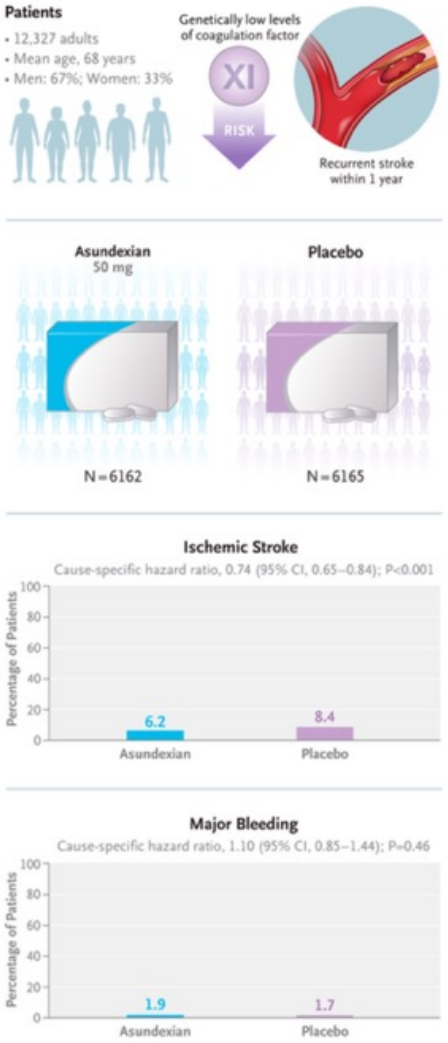
- **Erfolg in der Schlaganfall-Prävention (OCEANIC-STROKE):** Im Februar 2026 wurden positive Ergebnisse der Phase-III-Studie OCEANIC-STROKE präsentiert.
    - Bei Patienten nach einem nicht-kardioembolischen ischämischen Schlaganfall senkte Asundexian das Risiko eines erneuten Schlaganfalls um **26 %** im Vergleich zu Placebo.
    - Besonders bedeutsam: Dies geschah **ohne das Risiko für schwere Blutungen zu erhöhen**, was ein entscheidender Vorteil gegenüber herkömmlichen Blutverdünnern ist.
- **Abbruch bei Vorhofflimmern (OCEANIC-AF):** Bereits Ende 2023 musste Bayer einen Teil der klinischen Entwicklung stoppen. In der Studie an Patienten mit Vorhofflimmern erwies sich Asundexian als **weniger wirksam** als der Standardwirkstoff Apixaban, woraufhin die Studie vorzeitig beendet wurde.



Asundexian for Secondary Stroke Prevention

Patients with noncardioembolic ischemic stroke or transient ischemic attack (TIA) are at risk for recurrent stroke. Low factor XI levels are associated with a reduced risk of ischemic stroke. Asundexian inhibits activated factor XI. Whether the addition of asundexian to antiplatelet therapy would be superior to antiplatelet therapy alone for the secondary prevention of ischemic stroke is unclear.

In this phase 3, double-blind trial, we randomly assigned patients within 72 hours after the onset of a noncardioembolic ischemic stroke or high-risk TIA to receive asundexian (50 mg once daily) or placebo, in addition to planned dual or single antiplatelet therapy. Patients had at least one of the following: a nonlacunar infarct on imaging, a history of atherosclerosis, or evidence of atherosclerotic plaque at any location on cerebrovascular imaging. The primary efficacy outcome was ischemic stroke. The composite of death from cardiovascular causes, myocardial infarction, or stroke was a key secondary outcome. The primary safety outcome was major bleeding.



Despite the use of secondary prevention strategies, 5.1% of patients with an ischemic stroke or transient ischemic attack (TIA) have a recurrent stroke within 1 year. Five years after a minor stroke or TIA, approximately 22% of persons who had survived the event are dead or disabled. The risk is incompletely reduced by antiplatelet therapy. Dual antiplatelet therapy for 21 to 90 days is recommended for minor ischemic stroke or TIA, and antiplatelet monotherapy is recommended for moderate-to-severe stroke and long-term treatment. Long-term use of dual antiplatelet therapy is associated with a higher risk of major hemorrhage than monotherapy, without a lower risk of stroke. Factor XI, a coagulation factor, is part of the intrinsic pathway and appears to have a minor role in hemostasis. Genetic factor XI deficiency is associated with a reduced risk of ischemic stroke without an increase in intracerebral bleeding, and increased levels of factor XI are associated with a higher risk of ischemic stroke. The apparent dissociation of hemostasis and pathologic thrombosis makes factor XI an attractive therapeutic target for stroke prevention. Asundexian is an inhibitor of activated factor XI; at a dose of 50 mg daily, it inhibits activated factor XI by more than 90%. In a phase 2 trial involving patients with noncardioembolic ischemic stroke, asundexian added to antiplatelet therapy appeared to reduce the occurrence of symptomatic ischemic stroke without a significant increase in the incidence of major or clinically relevant nonmajor bleeding. We designed the Oral Factor Eleven A Inhibitor Asundexian as Novel Antithrombotic Stroke (OCEANIC-STROKE) trial to evaluate the efficacy and safety of asundexian for secondary stroke prevention in patients with ischemic stroke or high-risk TIA.

Eligibility

Patients were eligible if they were at least 18 years of age with a noncardioembolic ischemic stroke or high-risk TIA within 72 hours after the onset of symptoms and there was a plan for treatment with dual or single antiplatelet therapy. Patients with ischemic stroke had a maximum score of 15 on the National Institutes of Health Stroke Scale (NIHSS; scores range from 0 to 42, with higher scores indicating more severe stroke), and high-risk TIA was defined as an $ABCD^2$ score of 6 or 7 (on a scale estimating the risk of stroke on the basis of age, blood pressure, clinical features, symptom duration, and the presence of diabetes; scores range from 0 to 7, with higher scores indicating a higher risk of stroke).

Randomization and Treatments

Eligible patients were randomly assigned in a 1:1 ratio to receive asundexian (at a dose of 50 mg once daily) or matching placebo, in addition to planned dual or single antiplatelet therapy.

Outcomes

The primary efficacy outcome was the first occurrence of ischemic stroke. Ischemic stroke was determined to have occurred if there was a new focal neurologic deficit or clinically meaningful worsening of an existing deficit that persisted for at least 24 hours or was associated with imaging evidence of infarction and was not attributable to a nonischemic cause. The primary safety outcome was major bleeding.

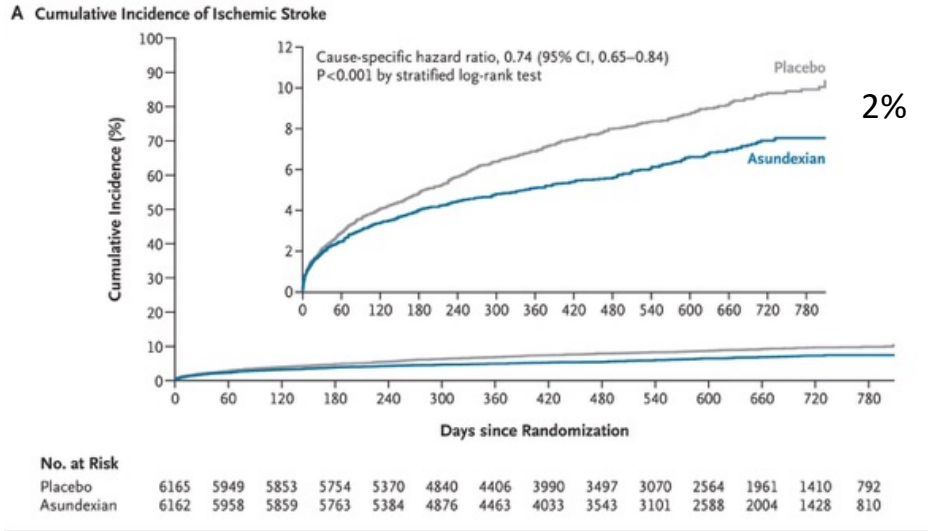
Characteristic	Asundexian (N = 6162)	Placebo (N = 6165)
Age — yr	67.7±10.8	67.5±10.9
Female sex — no. (%)	2063 (33.5)	2047 (33.2)
Geographic region — no. (%)		
North America	783 (12.7)	782 (12.7)
South America	281 (4.6)	286 (4.6)
Australia, Europe, or Israel	3338 (54.2)	3329 (54.0)
Asia–Pacific	1760 (28.6)	1768 (28.7)
Race — no. (%)†		
White	4105 (66.6)	4078 (66.1)
Black	143 (2.3)	139 (2.3)
Asian	1721 (27.9)	1742 (28.3)
Other	193 (3.1)	206 (3.3)
Index event — no. (%)‡		
Ischemic stroke	5839 (94.8)	5838 (94.7)
High-risk TIA	323 (5.2)	325 (5.3)
Stroke subtype — no./total no. (%)§¶		
Large-artery atherosclerosis	2512/5839 (43.0)	2484/5838 (42.5)
Small-vessel occlusion	1290/5839 (22.1)	1349/5838 (23.1)
Stroke of other determined cause	161/5839 (2.8)	188/5838 (3.2)
Stroke of undetermined cause	1786/5839 (30.6)	1710/5838 (29.3)
Cardioembolism	89/5839 (1.5)	107/5838 (1.8)
Time from index event to randomization — hr	50.5±15.4	50.3±15.4
Intravenous thrombolysis, endovascular therapy, or both — no./total no. (%)¶	1608/5839 (27.5)	1593/5838 (27.3)
Intravenous thrombolysis only	1146/5839 (19.6)	1168/5838 (20.0)
Endovascular therapy only	202/5839 (3.5)	169/5838 (2.9)
Median NIHSS score at randomization (IQR)¶‖	2.0 (1.0–4.0)	2.0 (1.0–4.0)
Planned dual antiplatelet therapy with aspirin and P2Y12 inhibitor at randomization — no. (%)**	3859 (62.6)	3853 (62.5)

Efficacy Outcomes.

Outcome	Asundexian (N = 6162)			Placebo (N = 6165)			Cause-Specific Hazard Ratio (95% CI)†	P Value‡
	No. of Patients (%)	No. of Events/ 100 Patient-Yr (95% CI)	Cumulative Incidence at 1 Yr (95% CI)§ %	No. of Patients (%)	No. of Events/ 100 Patient-Yr (95% CI)	Cumulative Incidence at 1 Yr (95% CI)§ %		
Primary efficacy outcome								
Ischemic stroke	384 (6.2)	4.4 (4.0–4.9)	5.1 (4.6–5.7)	518 (8.4)	6.0 (5.5–6.5)	7.0 (6.3–7.6)	0.74 (0.65–0.84)	<0.001
Secondary efficacy outcomes								
Any stroke	404 (6.6)	4.6 (4.2–5.1)	5.3 (4.8–5.9)	545 (8.8)	6.3 (5.8–6.9)	7.3 (6.6–8.0)	0.74 (0.65–0.84)	<0.001
Death from cardiovascular causes, myocardial infarction, or stroke	568 (9.2)	6.6 (6.0–7.1)	7.3 (6.7–8.0)	685 (11.1)	8.0 (7.4–8.6)	9.0 (8.3–9.7)	0.83 (0.74–0.92)	<0.001
Death from any cause, myocardial infarction, or stroke	649 (10.5)	7.5 (6.9–8.1)	8.3 (7.6–9.0)	757 (12.3)	8.8 (8.2–9.4)	9.7 (9.0–10.5)	0.85 (0.77–0.95)	0.003
Ischemic stroke in the first 90 days¶	183 (3.0)	12.4 (10.7–14.2)	3.0 (2.6–3.4)	218 (3.5)	14.8 (12.9–16.8)	3.5 (3.1–4.0)	0.84 (0.69–1.02)	0.08
Disabling or fatal stroke‖	128 (2.1)	1.4 (1.2–1.7)	1.7 (1.4–2.0)	185 (3.0)	2.1 (1.8–2.4)	2.5 (2.1–2.9)	0.69 (0.55–0.87)	—
Death from any cause	248 (4.0)	2.7 (2.4–3.1)	2.8 (2.4–3.3)	253 (4.1)	2.8 (2.4–3.1)	2.7 (2.3–3.2)	0.98 (0.83–1.17)	—
Transient ischemic attack	124 (2.0)	1.4 (1.2–1.6)	1.6 (1.3–1.9)	145 (2.4)	1.6 (1.4–1.9)	1.9 (1.6–2.3)	0.86 (0.67–1.09)	—
Exploratory efficacy outcome								
Death from cardiovascular causes	148 (2.4)	1.6 (1.4–1.9)	1.6 (1.3–2.0)	163 (2.6)	1.8 (1.5–2.1)	1.8 (1.5–2.2)	0.91 (0.73–1.14)	—

Safety Outcomes.

Outcome	Asundexian (N = 6124)			Placebo (N = 6130)			Cause-Specific Hazard Ratio (95% CI)†
	No. of Patients (%)	No. of Events/ 100 Patient-Yr (95% CI)	Cumulative Incidence at 1 Yr (95% CI)‡	No. of Patients (%)	No. of Events/ 100 Patient-Yr (95% CI)	Cumulative Incidence at 1 Yr (95% CI)‡	
Primary safety outcome							
ISTH major bleeding	117 (1.9)	1.6 (1.4–2.0)	1.6 (1.3–1.9)	107 (1.7)	1.5 (1.2–1.8)	1.6 (1.3–2.0)	1.10 (0.85–1.44)
Secondary safety outcomes							
ISTH major or clinically relevant non-major bleeding	339 (5.5)	4.9 (4.4–5.4)	4.8 (4.3–5.4)	307 (5.0)	4.4 (3.9–4.9)	4.4 (3.9–4.9)	1.12 (0.96–1.30)
Clinically relevant nonmajor bleeding	231 (3.8)	3.3 (2.9–3.8)	3.3 (2.9–3.8)	210 (3.4)	3.0 (2.6–3.4)	2.9 (2.5–3.4)	1.11 (0.92–1.34)
Symptomatic intracranial hemorrhage, including intracerebral hemorrhage	41 (0.7)	0.6 (0.4–0.8)	0.5 (0.4–0.7)	36 (0.6)	0.5 (0.3–0.7)	0.5 (0.4–0.7)	1.15 (0.74–1.80)
Hemorrhagic stroke	13 (0.2)	0.2 (0.1–0.3)	0.2 (0.1–0.3)	20 (0.3)	0.3 (0.2–0.4)	0.3 (0.2–0.5)	0.66 (0.33–1.32)
Fatal bleeding	14 (0.2)	0.2 (0.1–0.3)	0.1 (0.1–0.3)	8 (0.1)	0.1 (0.0–0.2)	0.1 (0.1–0.2)	1.77 (0.74–4.23)
Minor bleeding	479 (7.8)	7.2 (6.5–7.8)	6.8 (6.1–7.4)	512 (8.4)	7.6 (7.0–8.3)	7.4 (6.7–8.0)	0.94 (0.83–1.07)



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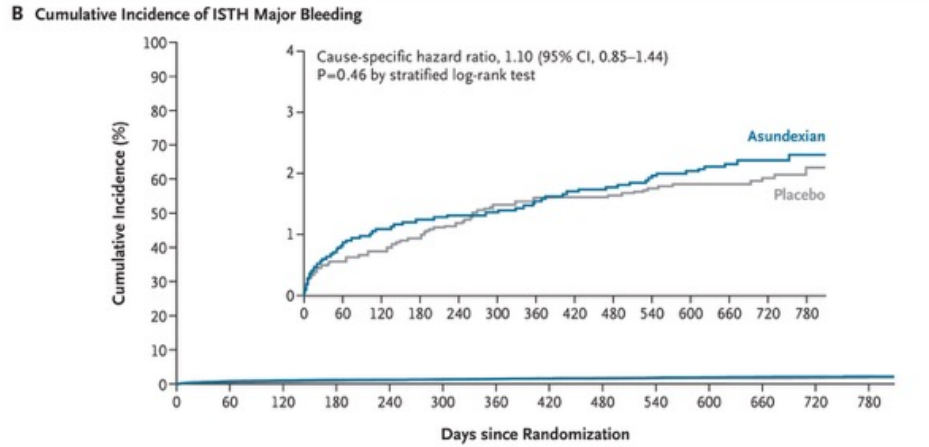
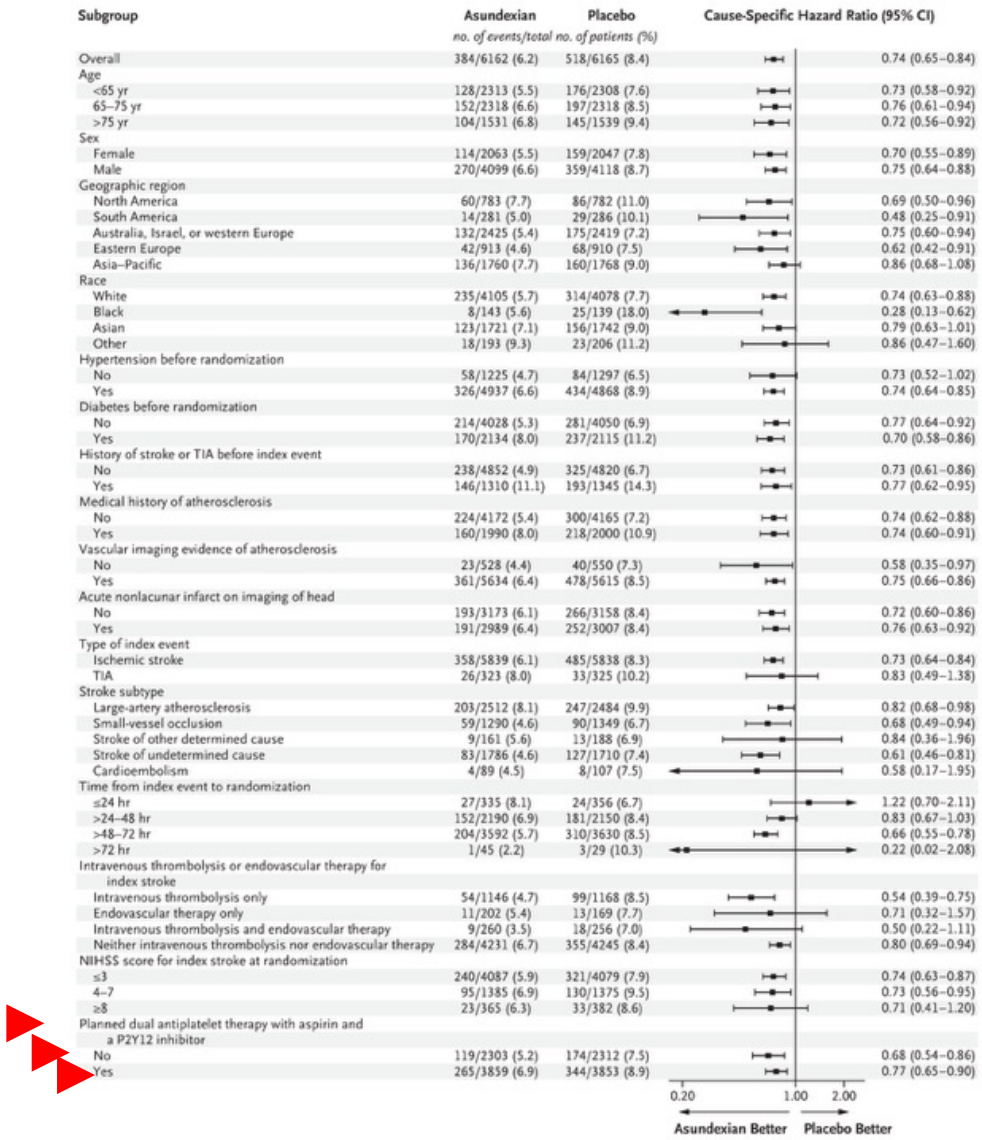
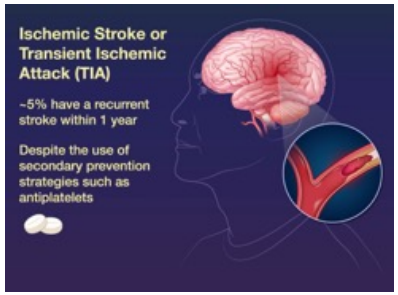




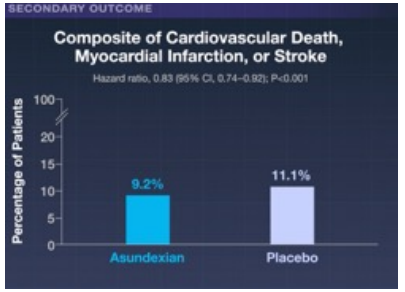
Subgroup	Asundexian	Placebo	Cause-Specific Hazard Ratio (95% CI)
	no. of events/total no. of patients (%)		
Overall	384/6162 (6.2)	518/6165 (8.4)	0.74 (0.65–0.84)
Age			
<65 yr	128/2313 (5.5)	176/2308 (7.6)	0.73 (0.58–0.92)
65–75 yr	152/2318 (6.6)	197/2318 (8.5)	0.76 (0.61–0.94)
>75 yr	104/1531 (6.8)	145/1539 (9.4)	0.72 (0.56–0.92)
Sex			
Female	114/2063 (5.5)	159/2047 (7.8)	0.70 (0.55–0.89)
Male	270/4099 (6.6)	359/4118 (8.7)	0.75 (0.64–0.88)
Geographic region			
North America	60/783 (7.7)	86/782 (11.0)	0.69 (0.50–0.96)
South America	14/281 (5.0)	29/286 (10.1)	0.48 (0.25–0.91)
Australia, Israel, or western Europe	132/2425 (5.4)	175/2419 (7.2)	0.75 (0.60–0.94)
Eastern Europe	42/913 (4.6)	68/910 (7.5)	0.62 (0.42–0.91)
Asia–Pacific	136/1760 (7.7)	160/1768 (9.0)	0.86 (0.68–1.08)
Race			
White	235/4105 (5.7)	314/4078 (7.7)	0.74 (0.63–0.88)
Black	8/143 (5.6)	25/139 (18.0)	0.28 (0.13–0.62)
Asian	123/1721 (7.1)	156/1742 (9.0)	0.79 (0.63–1.01)
Other	18/193 (9.3)	23/206 (11.2)	0.86 (0.47–1.60)
Hypertension before randomization			
No	58/1225 (4.7)	84/1297 (6.5)	0.73 (0.52–1.02)
Yes	326/4937 (6.6)	434/4868 (8.9)	0.74 (0.64–0.85)
Diabetes before randomization			
No	214/4028 (5.3)	281/4050 (6.9)	0.77 (0.64–0.92)
Yes	170/2134 (8.0)	237/2115 (11.2)	0.70 (0.58–0.86)
History of stroke or TIA before index event			
No	238/4852 (4.9)	325/4820 (6.7)	0.73 (0.61–0.86)
Yes	146/1310 (11.1)	193/1345 (14.3)	0.77 (0.62–0.95)
Medical history of atherosclerosis			
No	224/4172 (5.4)	300/4165 (7.2)	0.74 (0.62–0.88)
Yes	160/1990 (8.0)	218/2000 (10.9)	0.74 (0.60–0.91)
Vascular imaging evidence of atherosclerosis			
No	23/528 (4.4)	40/550 (7.3)	0.58 (0.35–0.97)
Yes	361/5634 (6.4)	478/5615 (8.5)	0.75 (0.66–0.86)
Acute nonlacunar infarct on imaging of head			
No	193/3173 (6.1)	266/3158 (8.4)	0.72 (0.60–0.86)
Yes	191/2989 (6.4)	252/3007 (8.4)	0.76 (0.63–0.92)
Type of index event			
Ischemic stroke	358/5839 (6.1)	485/5838 (8.3)	0.73 (0.64–0.84)
TIA	26/323 (8.0)	33/325 (10.2)	0.83 (0.49–1.38)
Stroke subtype			
Large-artery atherosclerosis	203/2512 (8.1)	247/2484 (9.9)	0.82 (0.68–0.98)
Small-vessel occlusion	59/1290 (4.6)	90/1349 (6.7)	0.68 (0.49–0.94)
Stroke of other determined cause	9/161 (5.6)	13/188 (6.9)	0.84 (0.36–1.96)
Stroke of undetermined cause	83/1786 (4.6)	127/1710 (7.4)	0.61 (0.46–0.81)
Cardioembolism	4/89 (4.5)	8/107 (7.5)	0.58 (0.17–1.95)
Time from index event to randomization			
≤24 hr	27/335 (8.1)	24/356 (6.7)	1.22 (0.70–2.11)
>24–48 hr	152/2190 (6.9)	181/2150 (8.4)	0.83 (0.67–1.03)
>48–72 hr	204/3592 (5.7)	310/3630 (8.5)	0.66 (0.55–0.78)
>72 hr	1/45 (2.2)	3/29 (10.3)	0.22 (0.02–2.08)
Intravenous thrombolysis or endovascular therapy for index stroke			
Intravenous thrombolysis only	54/1146 (4.7)	99/1168 (8.5)	0.54 (0.39–0.75)
Endovascular therapy only	11/202 (5.4)	13/169 (7.7)	0.71 (0.32–1.57)
Intravenous thrombolysis and endovascular therapy	9/260 (3.5)	18/256 (7.0)	0.50 (0.22–1.11)
Neither intravenous thrombolysis nor endovascular therapy	284/4231 (6.7)	355/4245 (8.4)	0.80 (0.69–0.94)
NIHSS score for index stroke at randomization			
≤3	240/4087 (5.9)	321/4079 (7.9)	0.74 (0.63–0.87)
4–7	95/1385 (6.9)	130/1375 (9.5)	0.73 (0.56–0.95)
≥8	23/365 (6.3)	33/382 (8.6)	0.71 (0.41–1.20)
Planned dual antiplatelet therapy with aspirin and a P2Y12 inhibitor			
No	119/2303 (5.2)	174/2312 (7.5)	0.68 (0.54–0.86)
Yes	265/3859 (6.9)	344/3853 (8.9)	0.77 (0.65–0.90)

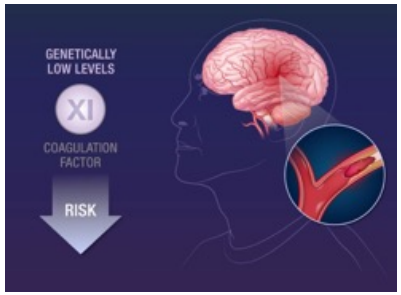
Subgroup Analyses of the Primary Efficacy Outcome: Ischemic Stroke.

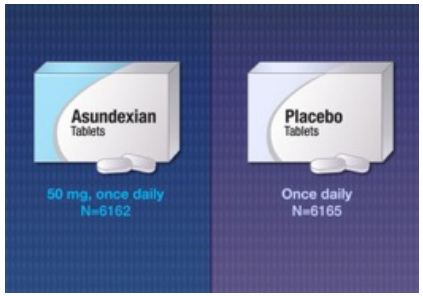
Shown are subgroup analyses for the primary efficacy outcome, ischemic stroke. Cause-specific hazard ratios are shown (with a competing risk of death). Confidence intervals are not adjusted for multiplicity and may not be used for inference. Race was reported by the patient. The stroke subtype was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria. National Institutes of Health Stroke Scale (NIHSS) scores range from 0 to 42, with higher scores indicating more severe stroke. Arrows indicate that the confidence interval extends outside the graphed area. P2Y12 denotes purinergic receptor Y12, and TIA transient ischemic attack.

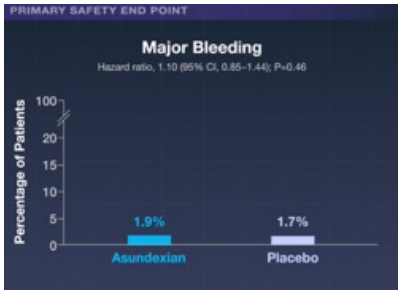

Ischemic Stroke or Transient Ischemic Attack (TIA)
~5% have a recurrent stroke within 1 year
Despite the use of secondary prevention strategies such as antiplatelets

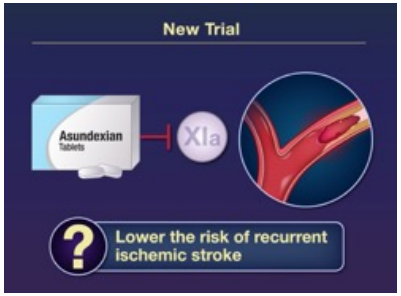

12,327 Adults
Noncardioembolic ischemic stroke or high-risk TIA
Within 72 hours after symptom onset

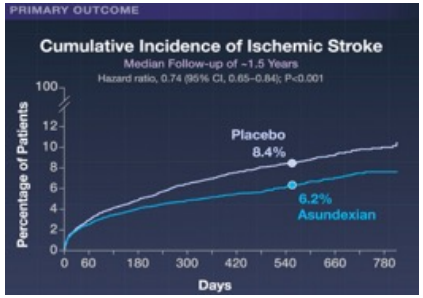

SECONDARY OUTCOME
Composite of Cardiovascular Death, Myocardial Infarction, or Stroke
Hazard ratio, 0.83 (95% CI, 0.74–0.92); P<0.001
Percentage of Patients
9.2%
11.1%
Asundexian
Placebo

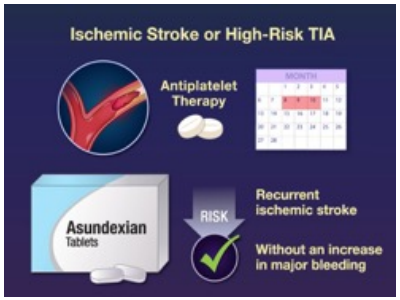

GENETICALLY LOW LEVELS
XI
COAGULATION FACTOR
RISK


Asundexian Tablets
50 mg, once daily N=6162
Placebo Tablets
Once daily N=6165


PRIMARY SAFETY END POINT
Major Bleeding
Hazard ratio, 1.10 (95% CI, 0.85–1.44); P=0.46
Percentage of Patients
1.9%
1.7%
Asundexian
Placebo


New Trial
Asundexian Tablets
XIa
Lower the risk of recurrent ischemic stroke


PRIMARY OUTCOME
Cumulative Incidence of Ischemic Stroke
Median Follow-up of ~1.5 Years
Hazard ratio, 0.74 (95% CI, 0.65–0.84); P<0.001
Percentage of Patients
Placebo
8.4%
6.2%
Asundexian
Days


Ischemic Stroke or High-Risk TIA
Antiplatelet Therapy
Asundexian Tablets
RISK
Recurrent ischemic stroke
Without an increase in major bleeding

Distinguish this strawberry tongue from scarlet fever!

Das Kawasaki-Syndrom ist eine akute, fieberhafte Gefäßentzündung (Vaskulitis) bei Kleinkindern, die vorwiegend die Herzkranzgefäße betrifft. Typisch sind hohes Fieber über 5 Tage, Hautausschlag, rote Augen, entzündete Lippen/Zunge und geschwollene Hände/Füße. Eine rasche Behandlung mit Immunglobulinen (IVIG) ist entscheidend, um lebensbedrohliche Herzschäden zu verhindern.

Diagnose und Symptome

Die Diagnose erfolgt klinisch, wenn das Fieber länger als 5 Tage anhält und mindestens 4 der 5 Hauptsymptome auftreten:

- **Augen:** Bindehautentzündung (nicht-eitrig).
- **Mund/Rachen:** Hochrote, trockene, aufgesprungene Lippen, Erdbeerzunge.
- **Haut:** Polymorpher Hautausschlag (Rumpf, Extremitäten).
- **Extremitäten:** Rötung/Schwellung der Hände und Füße, später Schuppung.
- **Lymphknoten:** Einseitige Halslymphknotenschwellung (> 1,5 cm).
- **Weiteres:** Starke Reizbarkeit.

Ursache und Krankheitsbild

Infectious agent is still unknown!

Die 2017 von der **American Heart Association (AHA)** veröffentlichten Diagnosekriterien für das **Kawasaki-Syndrom (KS)** basieren primär auf klinischen Merkmalen. Da es keinen spezifischen Labortest gibt, wird zwischen dem "kompletten" und dem "inkompletten" Verlauf unterschieden.

Komplettes Kawasaki-Syndrom

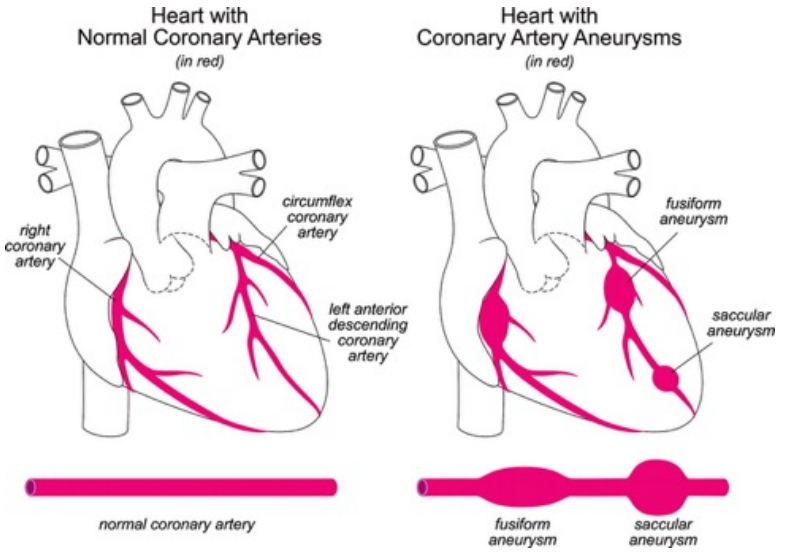
Die Diagnose erfordert **Fieber für mindestens 5 Tage** (bei Vorliegen klassischer Symptome kann die Diagnose bereits nach 4 Tagen durch Experten gestellt werden) zusammen mit mindestens **4 der folgenden 5 Hauptmerkmale**:

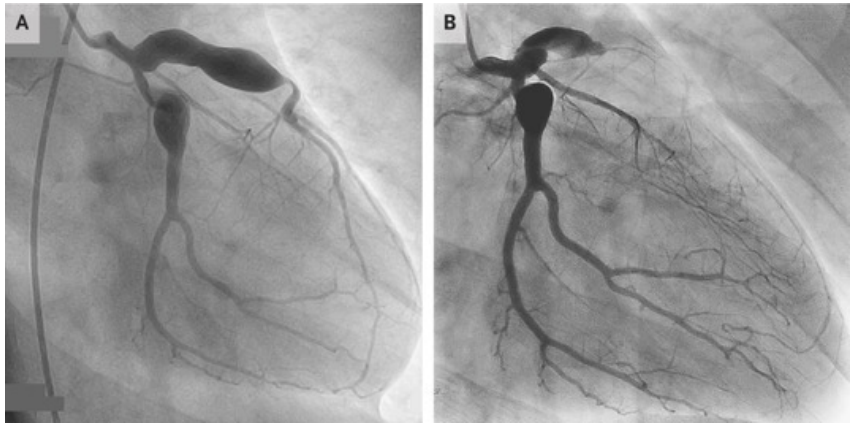
- **Veränderungen der Extremitäten**:
  - *Akut:* Erythem (Rötung) und Ödem (Schwellung) von Handflächen und Fußsohlen.
  - *Subakut:* Schälung der Haut (Desquamation) an den Fingerspitzen und Zehen in der 2. bis 3. Woche. (HFMD Coxsackie and Echo viruses?)
- **Polymorphes Exanthem**: Ein vielgestaltiger Hautausschlag, meist am Rumpf.
- **Bilateralen Konjunktivitis**: Beidseitige Rötung der Augenbindehaut (nicht eitrig).
- **Veränderungen an Lippen und Mundhöhle**: Trockene, rissige Lippen, "Erdbeerzunge" oder Rötung der Rachenschleimhaut.
- **Zervikale Lymphadenopathie**: Einseitige Schwellung der Halslymphknoten (mindestens ein Knoten >1,5 cm Durchmesser).

Dreaded complications

Wichtigste Auswirkungen auf die Koronararterien

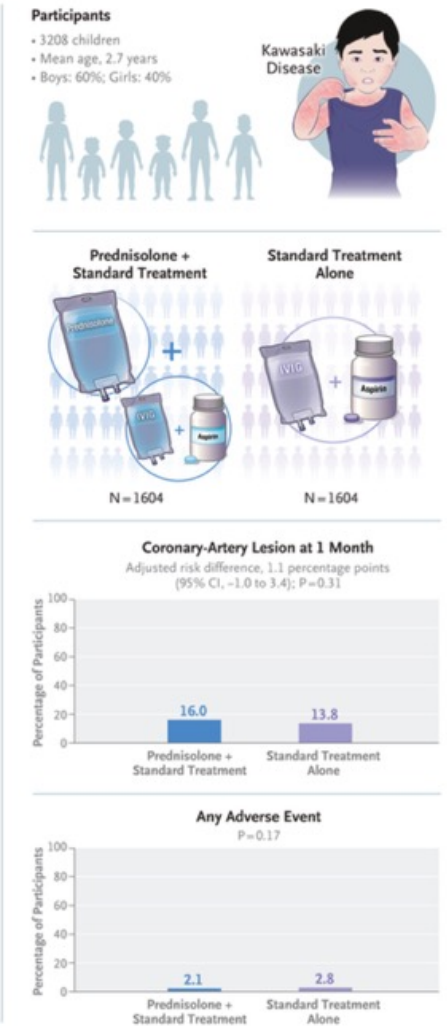
- **Aneurysmen:** Die Entzündung schädigt die elastischen Fasern und Muskelschichten der Arterienwand. Dies führt zu Erweiterungen, die in verschiedene Schweregrade unterteilt werden (basierend auf dem Z-Score, der die Gefäßgröße im Verhältnis zur Körperoberfläche misst):
  - **Kleine Aneurysmen:** Z-Score ≥ 2,5 bis < 5.
  - **Mittlere Aneurysmen:** Z-Score ≥ 5 bis < 10.
  - **Riesenameurysmen (Giant CAA):** Z-Score ≥ 10 oder ein absoluter Durchmesser von > 8 mm.
- **Thrombosen und Stenosen:** In den erweiterten Abschnitten ist der Blutfluss gestört, was zur Bildung von Blutgerinnseln (Thrombosen) führen kann. Langfristig können Vernarbungen und Gewebewucherungen (luminale myofibroblastische Proliferation) zu Engpässen (Stenosen) führen.
- **Myokardinfarkt:** Verstopft ein Gerinnsel oder eine Engstelle das Gefäß komplett, kann es bereits im Kindes- oder später im jungen Erwachsenenalter zu einem Herzinfarkt kommen.





Randomized Trial of Adjunctive Prednisolone for Kawasaki Disease

The effect of adjunctive glucocorticoids in the primary treatment of Kawasaki disease in unselected patients remains unknown.
In this multicenter, open-label, randomized, controlled trial in China, we assigned participants with newly diagnosed Kawasaki disease in a 1:1 ratio to receive prednisolone plus standard treatment or standard treatment alone. The primary outcome was the occurrence of coronary-artery lesions at 1 month after illness onset.
Prespecified key secondary outcomes, for which analyses were not controlled for multiplicity, included receipt of rescue therapy, duration of fever, change in the C-reactive protein (CRP) level, and changes in coronary-artery z scores.



The effect of adjunctive glucocorticoids in the primary treatment of Kawasaki disease remains controversial. A 2006 randomized, controlled trial suggested superiority of IVIG plus glucocorticoids to IVIG alone in preventing coronary-artery lesions. Subsequently, two landmark randomized, controlled trials provided conflicting evidence. The North American trial involving unselected patients showed no benefit from additional single-pulsed intravenous methylprednisolone in reducing coronary-artery lesions. The Randomized Controlled Trial to Assess Immunoglobulin plus Steroid Efficacy for Kawasaki Disease (RAISE) focused on Japanese patients at high risk for resistance to IVIG (Kobayashi score, ≥5) and showed that adjunctive longer-course (for 15 days after C-reactive protein [CRP] normalization) prednisolone significantly reduced the incidence of coronary-artery lesions, a finding that was supported by several meta-analyses. On the basis of this evidence, current guidelines recommend adjunctive glucocorticoids for patients at high risk for resistance to IVIG.

However, critical gaps in research remain. First, the generalizability of the RAISE regimen is limited by the poor predictive performance of the Kobayashi score and other risk scores in non-Japanese populations, which makes identification of high-risk patients outside Japan challenging. Second, most randomized, controlled trials, including RAISE, excluded patients with early-onset coronary-artery lesions, which predict poor prognosis. Retrospective studies suggested that this subgroup might benefit from adjunctive glucocorticoids. To resolve these gaps, we conducted a nationwide, multicenter, randomized, controlled trial to evaluate whether adjunctive glucocorticoids would reduce the occurrence of coronary-artery lesions and improve clinical outcomes in unselected patients with Kawasaki disease across China.

Participants

Eligible patients were children 1 month of age or older who met the 2017 American Heart Association (AHA) diagnostic criteria for Kawasaki disease, had received a diagnosis within 10 days after illness onset (with day 1 defined as the day of fever onset), and had not received IVIG treatment. Among the key exclusion criteria were the presence of large or giant coronary-artery aneurysms (with large or giant defined as any z score of ≥10 or internal diameter of ≥8 mm), a history of Kawasaki disease, being afebrile for at least 24 hours before enrollment, and receipt of glucocorticoids or other immunosuppressive drugs within 30 days before enrollment.

Randomization and Blinding

Eligible patients were randomly assigned in a 1:1 ratio to receive prednisolone plus standard primary treatment or standard primary treatment alone.

Interventions

In the group assigned to standard treatment alone, participants received IVIG (2 g per kilogram of body weight; maximum dose, 60 g) and oral aspirin (30 mg per kilogram per day divided into three doses). Once fever had resolved for 3 days and the CRP level had normalized, the aspirin dose was reduced to 3 to 5 mg per kilogram per day and maintained for at least 6 weeks. In the group assigned to prednisolone plus standard treatment, participants received adjunctive prednisolone (2 mg per kilogram per day; maximum dose, 60 mg) administered concurrently with the IVIG infusion.

Assessments and Outcomes

Assessments included two-dimensional echocardiography, measurement of body temperature, laboratory tests, and safety assessments. All the participants received echocardiography at enrollment, 2 weeks, 1 month, and 3, 6, and 12 months after illness onset. Five coronary-artery segments — including the left main coronary artery, left anterior descending artery, left circumflex coronary artery, and proximal and middle segments of the right coronary artery — were evaluated by means of echocardiography.

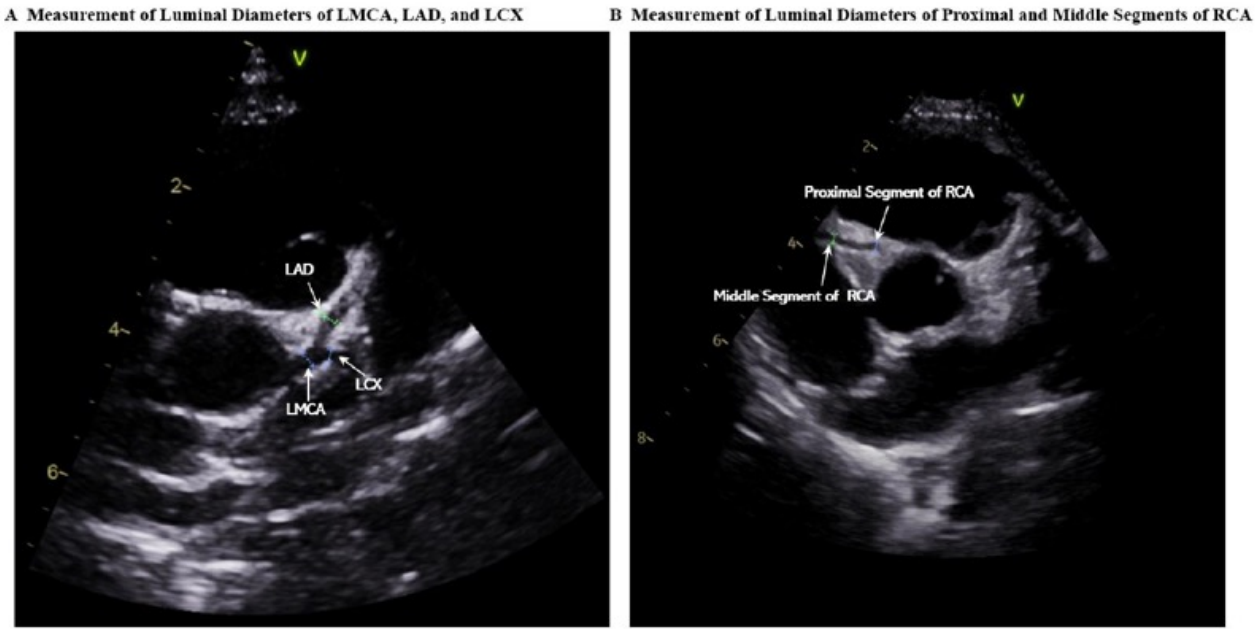


Figure S2. Measurement of Luminal Diameters of LMCA, LAD, LCX, Proximal and Middle Segments of RCA by Two-Dimensional Echocardiography.

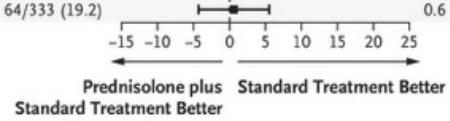
LMCA left main coronary artery, LAD left anterior descending artery, LCX left circumflex coronary artery, RCA right coronary artery.

Characteristic	Prednisolone plus Standard Treatment (N=1604)	Standard Treatment (N=1604)
Age — yr	2.7±1.8	2.7±1.9
Male sex — no. (%)	973 (60.7)	967 (60.3)
Weight — kg	13.4±4.7	13.6±5.0
Height — cm†	91.0±16.1	91.2±16.8
Duration of illness at enrollment‡	6.4±1.5	6.5±1.5
Incomplete Kawasaki disease — no. (%)§	298 (18.6)	308 (19.2)
Diameter of coronary arteries — mm¶		
Left main coronary artery	2.3 (2.1–2.6)	2.3 (2.0–2.6)
z Score	0.9±1.2	0.8±1.1
Left anterior descending artery	1.9 (1.7–2.1)	1.9 (1.7–2.1)
z Score	1.1±1.2	1.0±1.2
Left circumflex coronary artery	1.5 (1.4–1.8)	1.5 (1.4–1.7)
z Score	0.2±0.9	0.2±0.9
Proximal segment of right coronary artery	2.0 (1.8–2.3)	2.0 (1.8–2.3)
z Score	0.8±1.1	0.8±1.1
Middle segment of right coronary artery	1.8 (1.6–2.1)	1.8 (1.6–2.0)
z Score	1.0±1.2	0.9±1.1
Coronary-artery lesion detected at baseline — no./total no. (%)¶	455/1592 (28.6)	415/1592 (26.1)
No. of coronary-artery segments with lesion — no./total no. (%)¶		
1	208/1592 (13.1)	199/1592 (12.5)
2	114/1592 (7.2)	102/1592 (6.4)
3	61/1592 (3.8)	56/1592 (3.5)
4	52/1592 (3.3)	38/1592 (2.4)
5	20/1592 (1.3)	20/1592 (1.3)
Classification of coronary-artery lesion — no./total no. (%)‖		
Large or giant aneurysm	1/1592 (0.1)	3/1592 (0.2)
Medium aneurysm	39/1592 (2.4)	17/1592 (1.1)
Small aneurysm	235/1592 (14.8)	224/1592 (14.1)
Dilation only	180/1592 (11.3)	171/1592 (10.7)
Any z score of ≥2.5 — no./total no. (%)	275/1592 (17.3)	244/1592 (15.3)

Adverse Events.

Safety Outcome	Prednisolone plus Standard Treatment (N=1604)	Standard Treatment (N=1602)	P Value
	no. of participants (%)		
Any adverse event†	33 (2.1)	45 (2.8)	0.17
Any adverse event leading to discontinuation or adjustment of treatment dose	11 (0.7)	12 (0.7)	
Types of adverse events			
Skin allergy	18 (1.1)	30 (1.9)	
Nasal hemorrhage	5 (0.3)	6 (0.4)	
Hematochezia	2 (0.1)	0	
Liver-enzyme elevation	5 (0.3)	11 (0.7)	
Hemolytic anemia	3 (0.2)	0	
Aseptic meningitis	1 (<0.1)	0	

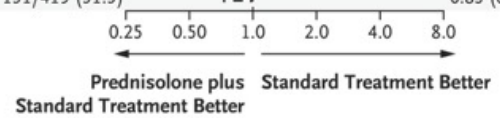
Analysis	Prednisolone plus Standard Treatment	Standard Treatment	Adjusted Risk Difference (95% CI)
	no./total no. (%)		*percentage points*
Primary analysis			
Intention-to-treat population	245/1533 (16.0)	210/1525 (13.8)	1.1 (−1.0 to 3.4)
Sensitivity analysis			
Per-protocol population	242/1490 (16.2)	204/1476 (13.8)	0.9 (−1.4 to 3.2)
Covariate-adjusted analysis	245/1533 (16.0)	210/1525 (13.8)	1.0 (−1.2 to 3.2)
With cluster effects of sites	245/1533 (16.0)	210/1525 (13.8)	2.2 (−1.2 to 4.6)
Best-case scenario	245/1604 (15.3)	210/1604 (13.1)	1.1 (−1.1 to 3.3)
Worst-case scenario	316/1604 (19.7)	290/1604 (18.1)	1.0 (−1.2 to 3.2)
Japanese criteria for coronary-artery lesions	80/1533 (5.2)	61/1525 (4.0)	0.3 (−1.0 to 1.5)
z-Score threshold ≥2.5 for coronary-artery lesions	141/1533 (9.2)	112/1525 (7.3)	0.7 (−1.0 to 2.4)
Coronary-artery lesion based on left anterior descending artery and proximal right coronary artery	158/1533 (10.3)	149/1525 (9.8)	0.5 (−1.3 to 2.4)
Adjusting for the baseline maximum z score	245/1533 (16.0)	210/1525 (13.8)	0.6 (−1.6 to 2.8)
Generalized linear model	245/1533 (16.0)	210/1525 (13.8)	2.2 (−0.3 to 4.7)
Subgroup analysis			
Age			
≤1 yr	76/261 (29.1)	84/269 (31.2)	−1.8 (−8.5 to 4.9)
>1 yr	169/1272 (13.3)	126/1256 (10.0)	1.9 (−0.3 to 4.2)
Sex			
Male	179/929 (19.3)	147/916 (16.0)	2.6 (−0.4 to 5.6)
Female	66/604 (10.9)	63/609 (10.3)	−1.1 (−4.3 to 2.1)
Body-mass index			
Underweight, <10th percentile	58/282 (20.6)	44/257 (17.1)	1.1 (−4.5 to 6.8)
Normal weight, 10th to 85th percentile	137/975 (14.1)	125/992 (12.6)	2.1 (−0.6 to 4.8)
Overweight and obese, >85th percentile	50/276 (18.1)	41/276 (14.9)	−2.2 (−7.5 to 3.0)
Kawasaki disease subtype			
Complete	189/1249 (15.1)	153/1232 (12.4)	1.2 (−1.3 to 3.6)
Incomplete	56/284 (19.7)	57/293 (19.5)	1.0 (−4.4 to 6.3)
Response to IVIG			
Yes	212/1460 (14.5)	170/1369 (12.4)	1.0 (−1.4 to 3.1)
No	33/73 (45.2)	40/156 (25.6)	13.5 (2.7 to 24.3)
Coronary-artery lesion present at baseline			
Yes	176/431 (40.8)	158/394 (40.1)	1.3 (−4.9 to 7.6)
No	69/1101 (6.3)	49/1124 (4.4)	1.7 (0.0 to 3.4)
Duration of illness			
≤4 days	26/118 (22.0)	10/119 (8.4)	0.8 (−6.8 to 8.4)
5–7 days	157/1065 (14.7)	136/1073 (12.7)	1.3 (−1.3 to 3.9)
≥8 days	62/350 (17.7)	64/333 (19.2)	0.6 (−4.3 to 5.5)



Primary, Sensitivity, and Subgroup Analyses of the Primary Outcome.

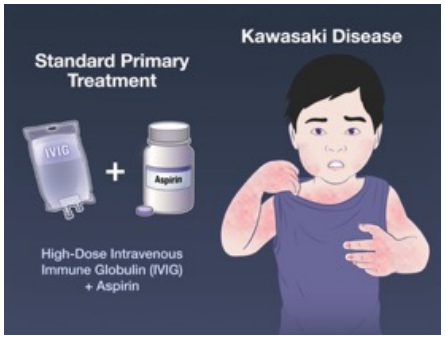
Risk differences and 95% confidence intervals for the primary outcome (coronary-artery lesions detected at 1 month after illness onset) were calculated in the primary analysis (intention-to-treat population, including all the participants who had undergone randomization), two prespecified sensitivity analyses (per-protocol [including all the participants who had undergone randomization and received at least one dose of trial-related treatment] and covariate-adjusted), eight post hoc sensitivity analyses, and subgroup analyses. Prespecified subgroups included age group, sex, category of body-mass index (weight in kilograms divided by square of height in meters), complete or incomplete Kawasaki disease, response or nonresponse to intravenous immune globulin (IVIG response), and presence or absence of coronary-artery lesion at baseline. Another post hoc subgroup analysis involved duration of illness. In the subgroup with coronary-artery lesions detected at baseline, 24 participants receiving prednisolone plus standard treatment and 21 receiving standard treatment alone did not complete the 1-month follow-up. At 1 month, data regarding coronary-artery segments with lesions were as follows: in the group receiving prednisolone plus standard treatment, one segment in 138 participants, two segments in 59 participants, three segments in 22 participants, four segments in 15 participants, and five segments in 11 participants; in the group receiving standard treatment alone, one segment in 112 participants, two segments in 47 participants, three segments in 24 participants, four segments in 14 participants, and five segments in 13 participants (Table S12). Confidence intervals for sensitivity and subgroup analyses were not adjusted for multiplicity and should not be used to infer definitive treatment effects.

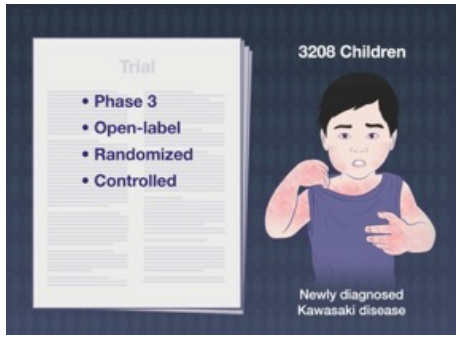
Outcome	Prednisolone plus Standard Treatment	Standard Treatment	Risk Ratio or Hazard Ratio (95% CI)
Prespecified secondary outcomes			
Coronary-artery lesion detected at 3 mo — no./total no. (%)	172/1365 (12.6)	142/1354 (10.5)	1.07 (0.91–1.27)
Median duration of fever (IQR) — hr	8.4 (7.9–9.1)	13.2 (12.4–14.1)	0.67 (0.61–0.73)
Post hoc exploratory outcomes			
Medium-to-giant coronary-artery aneurysm — no./total no. (%)			
At 1 mo	35/1533 (2.3)	29/1525 (1.9)	0.85 (0.50–1.72)
At 3 mo	26/1365 (1.9)	15/1354 (1.1)	0.98 (0.62–2.06)
Large or giant coronary-artery aneurysm — no./total no. (%)			
At 1 mo	12/1532 (0.8)	6/1522 (0.4)	1.40 (0.50–3.92)
At 3 mo	8/1365 (0.6)	4/1351 (0.3)	1.65 (0.49–5.63)
Progression of coronary-artery lesion — no./total no. (%)			
All participants	459/1604 (28.6)	463/1604 (28.9)	0.96 (0.89–1.03)
Participants with coronary-artery lesion present at baseline	121/460 (26.3)	131/419 (31.3)	0.85 (0.73–0.98)

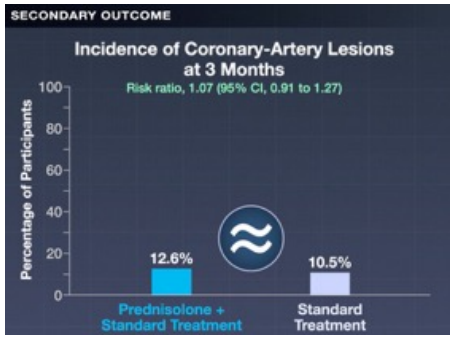


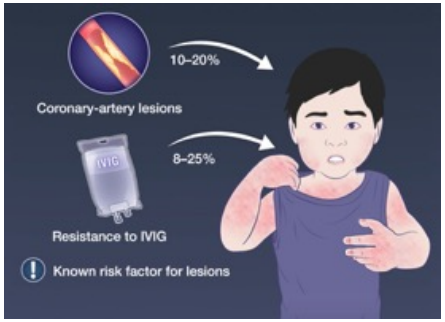
Secondary and Exploratory Outcomes.

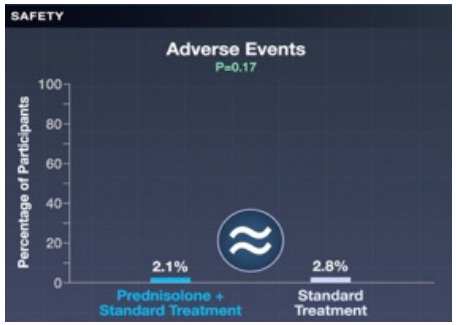
Shown are results of prespecified secondary outcomes and post hoc exploratory outcomes. Unless otherwise specified, analyses were conducted in the intention-to-treat population. Risk ratios and 95% confidence intervals are reported for coronary-artery lesions detected at 3 months, medium-to-giant coronary-artery aneurysm, large or giant coronary-artery aneurysm, and progression of coronary-artery lesions; hazard ratio and 95% confidence interval are reported for duration of fever. No adjustment for multiplicity was made, so 95% confidence intervals should not be used for hypothesis testing. Duration of fever was recorded from initiation of initial IVIG to 96 hours thereafter. Progression of coronary-artery lesions was defined as a z score increment of at least 1 in any coronary artery within 3 months after illness onset. Classification of coronary-artery lesions followed the 2017 American Heart Association guideline.

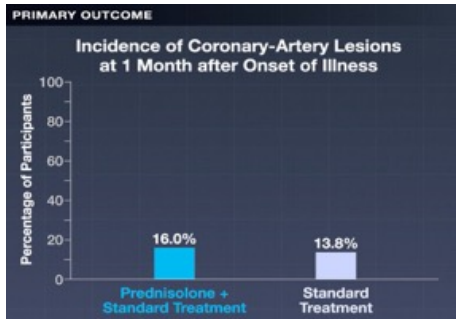












Steroids did not help!

Die **idiopathische thrombozytopenische Purpura (ITP)**, heute meist als **Immunthrombozytopenie** bezeichnet, ist eine Autoimmunerkrankung, bei der das Immunsystem die körpereigenen Blutplättchen (Thrombozyten) zerstört. Da Thrombozyten für die Blutgerinnung zuständig sind, führt ein Mangel zu einer erhöhten Blutungsneigung.

•**Definition:** Ein Abfall der Thrombozytenzahl auf unter 100.000/µl Blut ohne erkennbare andere Ursache.

•**Symptome:**

- **Petechien:** Punktförmige, stecknadelkopfgroße Hauteinblutungen, oft an den Beinen.
- **Hämatome:** Neigung zu blauen Flecken schon bei leichten Stößen.
- **Schleimhautblutungen:** Häufiges Nasen- oder Zahnfleischbluten sowie verstärkte Regelblutungen.

•**Formen:**

- **Akute ITP:** Tritt oft bei Kindern nach einem Infekt auf und heilt meist von selbst wieder aus.
- **Chronische ITP:** Betrifft häufiger Erwachsene und bleibt oft dauerhaft bestehen, was eine langfristige medizinische Begleitung erfordert.

•**Behandlung:** Eine Therapie ist meist erst notwendig, wenn die Thrombozytenzahl sehr niedrig ist oder starke Blutungen auftreten. Klassische Erstmaßnahmen sind Kortikosteroide (Cortison) oder Immunglobuline.

•**Lebensführung:** Bei niedrigen Werten sollten Sportarten mit hohem Verletzungsrisiko (z. B. Fußball oder Kampfsport) gemieden werden. Die Lebenserwartung ist bei korrekter Behandlung in der Regel normal.

Paul Gottlieb Werlhof

Die wichtigsten Zielantigene sind bestimmte **Glykoproteinkomplexe** auf der Thrombozytenmembran:

•**GP IIb/IIIa** (Fibrinogenrezeptor): Dies ist das am häufigsten betroffene Antigen-Ziel.

•**GP Ib/IX/V** (vWF-Rezeptor): Ein weiteres häufiges Ziel der Autoantikörper.

•**GP Ia/IIa** sowie **GP IV** und **GP V**: Diese können ebenfalls als Antigene fungieren.

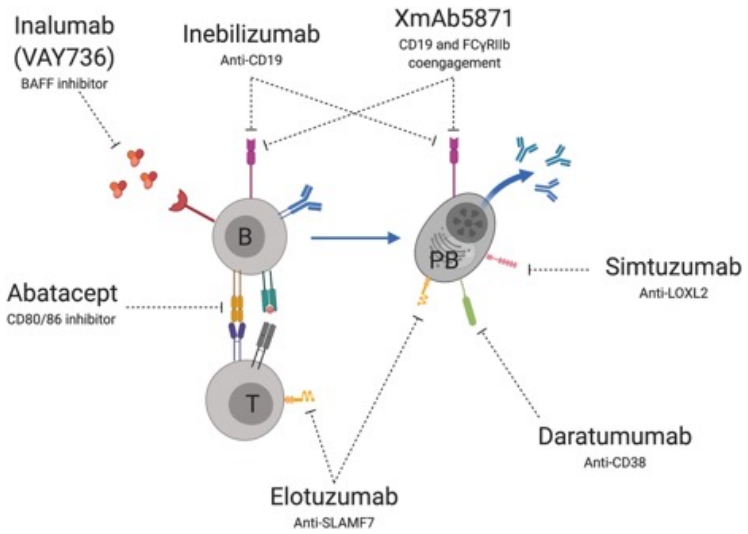
BAFF and BLYS are the same thing!

Ianalumab (auch bekannt als **VAY736** oder unter dem Markennamen **XinYue** in China) ist ein neuartiger monoklonaler Antikörper, der von **Novartis** zur Behandlung **Autoimmunerkrankungen** entwickelt wird.

Wirkmechanismus

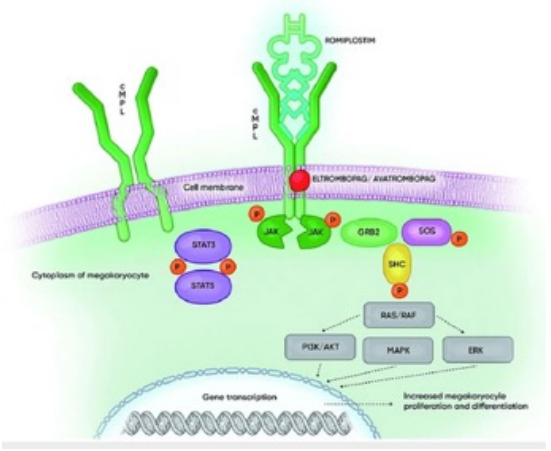
Ianalumab wirkt über zwei Wege gleichzeitig, um krankheitsverursachende B-Zellen zu reduzieren:

- **BAFF-Rezeptor-Blockade:** Es blockiert den Rezeptor für den B-Zell-Aktivierungsfaktor (BAFF), was das Überleben der B-Zellen verhindert.
- **B-Zell-Depletion:** Es führt direkt zum Abbau von B-Zellen im Körper.



Eltrombopag wird verschrieben, wenn die Anzahl der Blutplättchen zu niedrig ist (**Thrombozytopenie**). Dies betrifft insbesondere:

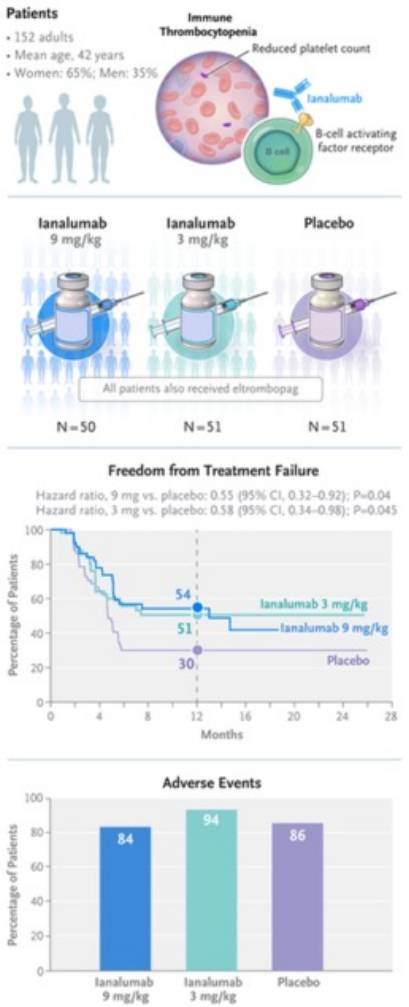
- **Primäre Immunthrombozytopenie (ITP):** Für Patienten (ab 1 Jahr), die auf andere Behandlungen wie Kortikosteroide nicht ansprechen.
- **Schwere aplastische Anämie (SAA):** Bei Erwachsenen, wenn andere Immunsuppressiva nicht geholfen haben.



Ianalumab plus Eltrombopag in Immune Thrombocytopenia

Current second-line treatments for immune thrombocytopenia (ITP) require long-term administration. Ianalumab, a monoclonal antibody targeting B cells, is being assessed as a short-course second-line therapy in ITP.

In this phase 3, randomized, double-blind trial, we assigned, in a 1:1:1 ratio, adults with primary ITP and an insufficient response or a relapse after first-line glucocorticoid therapy to receive ianalumab at a dose of 9 mg or 3 mg per kilogram of body weight or placebo once monthly for 4 months. Eltrombopag, an oral thrombopoietin-receptor agonist, was administered once daily in each group according to local prescribing information; the dose was tapered until discontinuation by the end of week 24 in eligible patients. The primary end point was freedom from treatment failure, as determined in a time-to-event analysis, with treatment failure defined by a platelet count of less than 30×10^9 per liter more than 8 weeks after randomization, initiation of rescue therapy more than 8 weeks after randomization, initiation of new ITP therapy, inability to taper or discontinue eltrombopag because of an inadequate platelet count, or death from any cause, whichever occurred first. The key secondary end point was a stable response at 6 months, defined by a platelet count of at least 50×10^9 per liter in at least 75% of the measurements between weeks 19 and 25 without use of rescue therapy or new ITP therapy. Safety was assessed.



Immune thrombocytopenia (ITP) is a rare autoimmune disease that is characterized by a low platelet count (<100×10^9 per liter). ITP is associated with severe, potentially life-threatening bleeding events; the most common manifestations include mucocutaneous bleeding and fatigue.

B cells play a key role in the pathophysiology of primary ITP. The B-cell activating factor (BAFF) signaling pathway is crucial for B-cell proliferation, differentiation, and survival. Serum BAFF levels are increased in patients with untreated ITP, highlighting BAFF and its receptor as promising therapeutic targets. Ianalumab is a glycoengineered, fully human IgG1 monoclonal antibody that binds to and blocks BAFF receptors, leading to enhanced depletion of B cells through antibody-dependent cellular cytotoxicity and to inhibition of B-cell activation, maturation, proliferation, and survival. These mechanisms of action have the potential to modify the course of ITP by suppressing and eliminating pathogenic, autoreactive B cells.

Here, we report the primary results of VAYHIT2, a phase 3 trial that assessed the efficacy and safety of short-course ianalumab in combination with the oral thrombopoietin-receptor agonist eltrombopag in adult patients with primary ITP who had an insufficient response or a relapse after first-line glucocorticoid therapy.

Patients

Patients who were 18 years of age or older with a diagnosis of primary ITP and an insufficient response or a relapse after first-line glucocorticoid therapy were eligible for the trial. An insufficient response was defined as a platelet count of less than 30×10^9 per liter or the need for glucocorticoids for more than 8 weeks. Relapse was defined as a platelet count of less than 30×10^9 per liter after an initial response. Patients who received any second-line therapy for ITP other than glucocorticoids, with or without intravenous immune globulin, were excluded. Use of a thrombopoietin-receptor agonist for a limited duration (up to 1 week) before screening was permitted.

End Points and Assessments

The primary end point was freedom from treatment failure, as determined in a time-to-event analysis, with treatment failure defined by a platelet count of less than 30×10^9 per liter more than 8 weeks after randomization, initiation of rescue therapy more than 8 weeks after randomization, initiation of new ITP therapy, inability to taper or discontinue eltrombopag because of an inadequate platelet count.

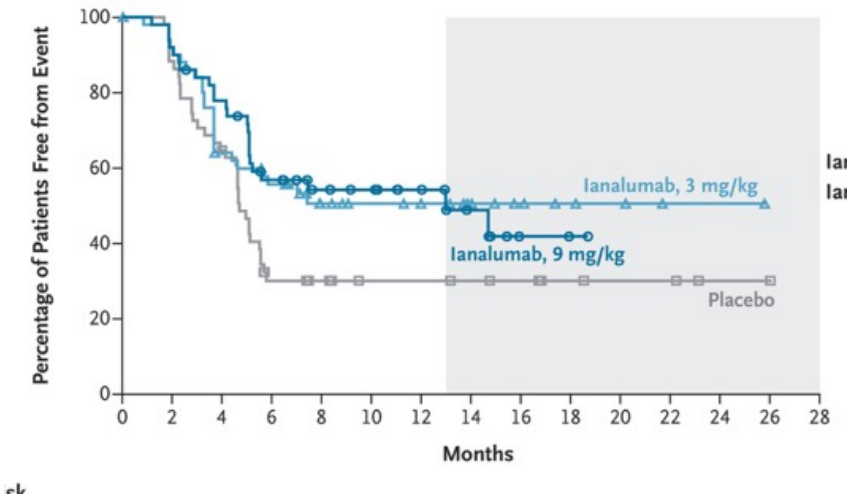
Characteristic	Ianalumab, 9 mg/kg (N=50)	Ianalumab, 3 mg/kg (N=51)	Placebo (N=51)
Age — yr	40.2±15.3	45.5±19.7	40.5±16.6
Age group — no. (%)			
18 to <65 yr	48 (96)	43 (84)	46 (90)
65 to <85 yr	2 (4)	8 (16)	5 (10)
Female sex — no. (%)	33 (66)	31 (61)	35 (69)
Race or ethnic group — no. (%)†			
White	25 (50)	26 (51)	22 (43)
Asian	22 (44)	24 (47)	25 (49)
American Indian or Alaska Native	0	1 (2)	3 (6)
Unknown	3 (6)	0	1 (2)
Body-mass index‡	27.7±7.0	25.8±5.5	27.6±7.6
Median time since initial ITP diagnosis (range) — mo§	3.6 (0.4–482.8)	4.2 (0.3–160.8)	3.4 (0.5–259.3)
Received IVIG before screening — no. (%)	17 (34)	15 (29)	11 (22)
Received platelet transfusion before screening — no. (%)	12 (24)	11 (22)	17 (33)
Received TPO-RAs before screening — no. (%)¶	5 (10)	4 (8)	4 (8)

Stable Response at 6 Months.

Trial Group	Stable Response at 6 Months		Risk Difference (95% CI)†	P Value‡
	no. with event/ total no.	% with event (95% CI)§		
Ianalumab, 9 mg/kg	31/50	62 (47 to 75)	22.7 (3.8 to 41.5)	0.045
Ianalumab, 3 mg/kg	29/51	57 (42 to 71)	17.7 (–0.9 to 36.2)	0.07
Placebo	20/51	39 (26 to 54)	—	—

Adverse Events.

Adverse Events	Ianalumab, 9 mg/kg (N=50)		Ianalumab, 3 mg/kg (N=50)		Placebo (N=51)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)					
At least 1 event						
Overall	42 (84)	12 (24)	47 (94)	10 (20)	44 (86)	2 (4)
Related to trial dose	17 (34)	4 (8)	12 (24)	2 (4)	9 (18)	0
Serious adverse event						
Overall	8 (16)	5 (10)	3 (6)	1 (2)	2 (4)	1 (2)
Related to trial dose	0	0	1 (2)†	0	0	0
Leading to trial dose interruption or reduction or reduction in infusion rate	2 (4)	1 (2)	4 (8)	2 (4)	1 (2)	0
Headache	7 (14)	1 (2)	5 (10)	0	4 (8)	0
Infusion-related reaction	7 (14)	0	4 (8)	0	4 (8)	0
Ecchymosis	6 (12)	0	6 (12)	0	5 (10)	0
Epistaxis	6 (12)	0	4 (8)	0	6 (12)	0
Petechiae	6 (12)	0	6 (12)	0	8 (16)	0
Anemia	5 (10)	2 (4)	4 (8)	0	5 (10)	0
Mouth hemorrhage	5 (10)	2 (4)	1 (2)	0	3 (6)	0
Upper respiratory tract infection	5 (10)	0	8 (16)	0	8 (16)	0
Fatigue	4 (8)	1 (2)	5 (10)	0	4 (8)	0
Urinary tract infection	4 (8)	0	5 (10)	0	2 (4)	1 (2)
Increased alanine aminotransferase level	2 (4)	0	5 (10)	2 (4)	0	0
Diarrhea	2 (4)	0	5 (10)	0	6 (12)	0
Purpura	1 (2)	0	5 (10)	0	2 (4)	0



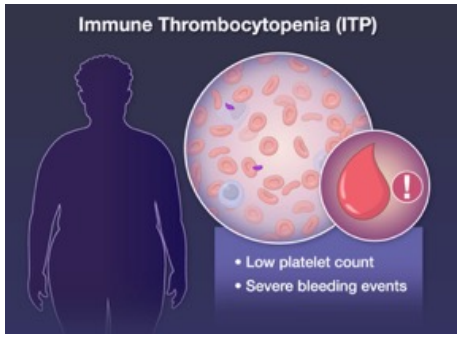
	No. of Patients with Event/Total No. of Patients	Median Event-free Survival (95% CI)
		mo
Ianalumab, 3 mg/kg	24/51	NE (3.7–NE)
Ianalumab, 9 mg/kg	24/50	13.0 (5.1–NE)
Placebo	35/51	4.7 (3.9–5.6)

Ianalumab, 3 mg/kg vs. placebo
Hazard ratio for treatment failure, 0.58 (95% CI, 0.34–0.98)
P=0.045 by log-rank test

Ianalumab, 9 mg/kg vs. placebo
Hazard ratio for treatment failure, 0.55 (95% CI, 0.32–0.92)
P=0.04 by log-rank test

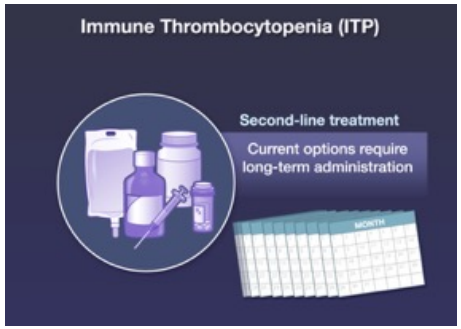
Kaplan–Meier Estimates of the Primary End Point.

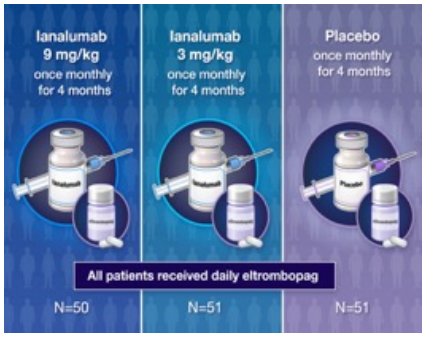
Shown is the probability of being free from treatment failure in a time-to-event analysis, with treatment failure defined by a platelet count of less than 30×10^9 per liter more than 8 weeks after randomization, initiation of rescue therapy more than 8 weeks after randomization, initiation of new immune thrombocytopenia therapy, inability to taper or discontinue eltrombopag, or death from any cause, whichever occurred first. Eltrombopag was administered once daily in each group according to local prescribing information. The shaded area indicates the period during which data from scheduled assessments were missing for more than half the patients (follow-up was ongoing for these patients). P values were considered to be significant at the overall 5.0% level. Circles, triangles, and squares indicate censored data. NE denotes could not be estimated.

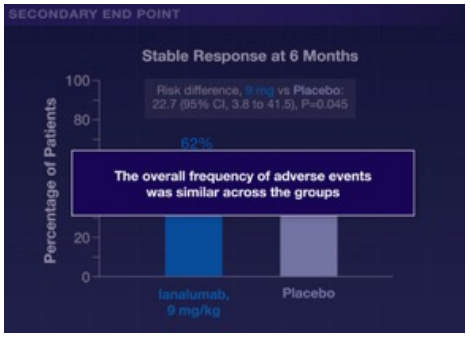

Immune Thrombocytopenia (ITP)
• Low platelet count
• Severe bleeding events

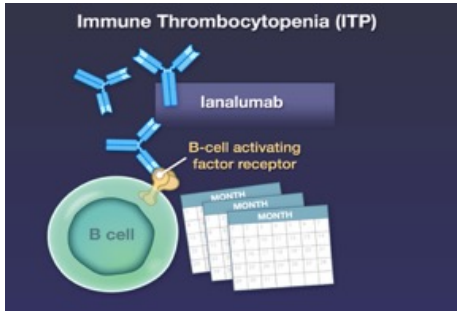

VAYHIT2 Trial
• Phase 3
• Double-blind
• Randomized
152 Adults
• Primary immune thrombocytopenia
• Insufficient response or relapse after first-line glucocorticoid therapy

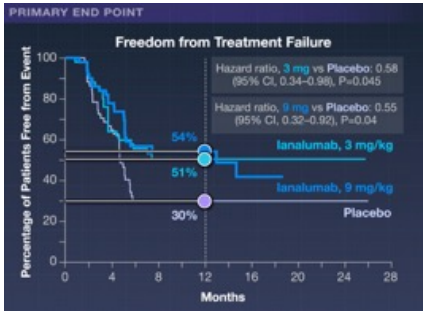

SECONDARY END POINT
Stable Response at 6 Months
Risk difference, 9 mg vs Placebo: 22.7 (95% CI, 3.8 to 41.5), P=0.045
Percentage of Patients
100
80
60
40
20
0
62%
39%
Ianalumab, 9 mg/kg
Placebo

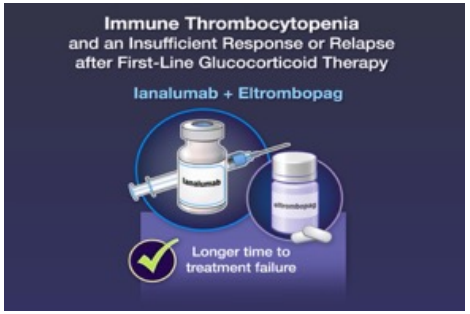

Immune Thrombocytopenia (ITP)
Second-line treatment
Current options require long-term administration
MONTH


Ianalumab 9 mg/kg once monthly for 4 months
Ianalumab 3 mg/kg once monthly for 4 months
Placebo once monthly for 4 months
All patients received daily eltrombopag
N=50
N=51
N=51


SECONDARY END POINT
Stable Response at 6 Months
Risk difference, 9 mg vs Placebo: 22.7 (95% CI, 3.8 to 41.5), P=0.045
Percentage of Patients
100
80
20
0
62%
The overall frequency of adverse events was similar across the groups
Ianalumab, 9 mg/kg
Placebo


Immune Thrombocytopenia (ITP)
Ianalumab
B-cell activating factor receptor
B cell
MONTH
MONTH
MONTH


PRIMARY END POINT
Freedom from Treatment Failure
Hazard ratio, 3 mg vs Placebo: 0.58 (95% CI, 0.34–0.98), P=0.045
Hazard ratio, 9 mg vs Placebo: 0.55 (95% CI, 0.32–0.92), P=0.04
Percentage of Patients Free from Event
100
80
60
40
20
0
54%
51%
30%
Ianalumab, 3 mg/kg
Ianalumab, 9 mg/kg
Placebo
0
4
8
12
16
20
24
28
Months


Immune Thrombocytopenia and an Insufficient Response or Relapse after First-Line Glucocorticoid Therapy
Ianalumab + Eltrombopag
Longer time to treatment failure

Die selektive Dekontamination des Verdauungstrakts (**Selective Decontamination of the Digestive Tract**, kurz **SDD**) ist eine präventive Infektionskontrollstrategie für erwachsene Patienten auf Intensivstationen (ICU), die künstlich beatmet werden.

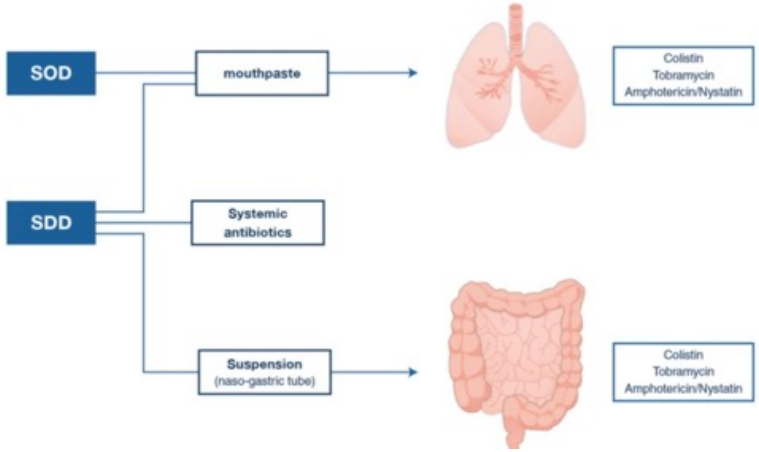
✅ **Kernbotschaft**

Neuere Metaanalysen (Stand 2025/2026) bestätigen mit **hoher Wahrscheinlichkeit**, dass SDD bei beatmeten Erwachsenen das Risiko für **Todesfälle im Krankenhaus senkt**. Der Nutzen scheint jedoch am stärksten zu sein, wenn das Protokoll eine **kurzzeitige intravenöse Antibiotikagabe** einschließt.

Das Protokoll (Die 4 Säulen)

SDD zielt darauf ab, die Besiedlung des Oropharynx und des Darms mit potenziell pathogenen Mikroorganismen (z. B. gramnegative Stäbchen, Hefepilze) zu verhindern oder zu beseitigen.

- **Topische Pasten:** Anwendung von Antibiotika (oft Colistin, Tobramycin) und Antimykotika (Nystatin/Amphotericin B) in der Mundhöhle.
- **Enterale Suspension:** Gabe derselben Wirkstoffe über die Magensonde in den Magen/Darm.
- **Intravenöse Prophylaxe:** Ein 4-tägiger Kurs eines systemischen Antibiotikums (meist ein Cephalosporin der 3. Generation wie Cefotaxim) zu Beginn der Behandlung.
- **Mikrobiologische Überwachung:** Regelmäßige Abstriche (Hals/Rektum), um die Wirksamkeit zu prüfen und Resistenzen frühzeitig zu erkennen.



Components of SDD and SOD. *SDD* selective digestive tract decontamination, *SOD* selective oropharyngeal decontamination

NEJM Evidence

Uncomfortable for patients and much work in ICU

Selective Decontamination of the Digestive Tract in Adult Mechanically Ventilated Patients — An Updated Systematic Review with Bayesian Meta-Analysis

Abstract

Background

There is uncertainty whether the use of selective decontamination of the digestive tract (SDD) as a preventive antimicrobial strategy reduces mortality in adult patients receiving mechanical ventilation in the intensive care unit (ICU). Following the publication of new data from a contemporary randomized clinical trial, an updated systematic review and meta-analysis was conducted to determine whether the use of SDD reduced hospital mortality compared to standard care.

Methods

An updated systematic review of a previously published meta-analysis was conducted including a search from September 12, 2022, to August 18, 2025, for randomized clinical trials (RCTs) of adults receiving mechanical ventilation in an ICU that compared SDD to standard care. Data were pooled using a Bayesian framework. The primary outcome was hospital mortality or closest approximation.

Results

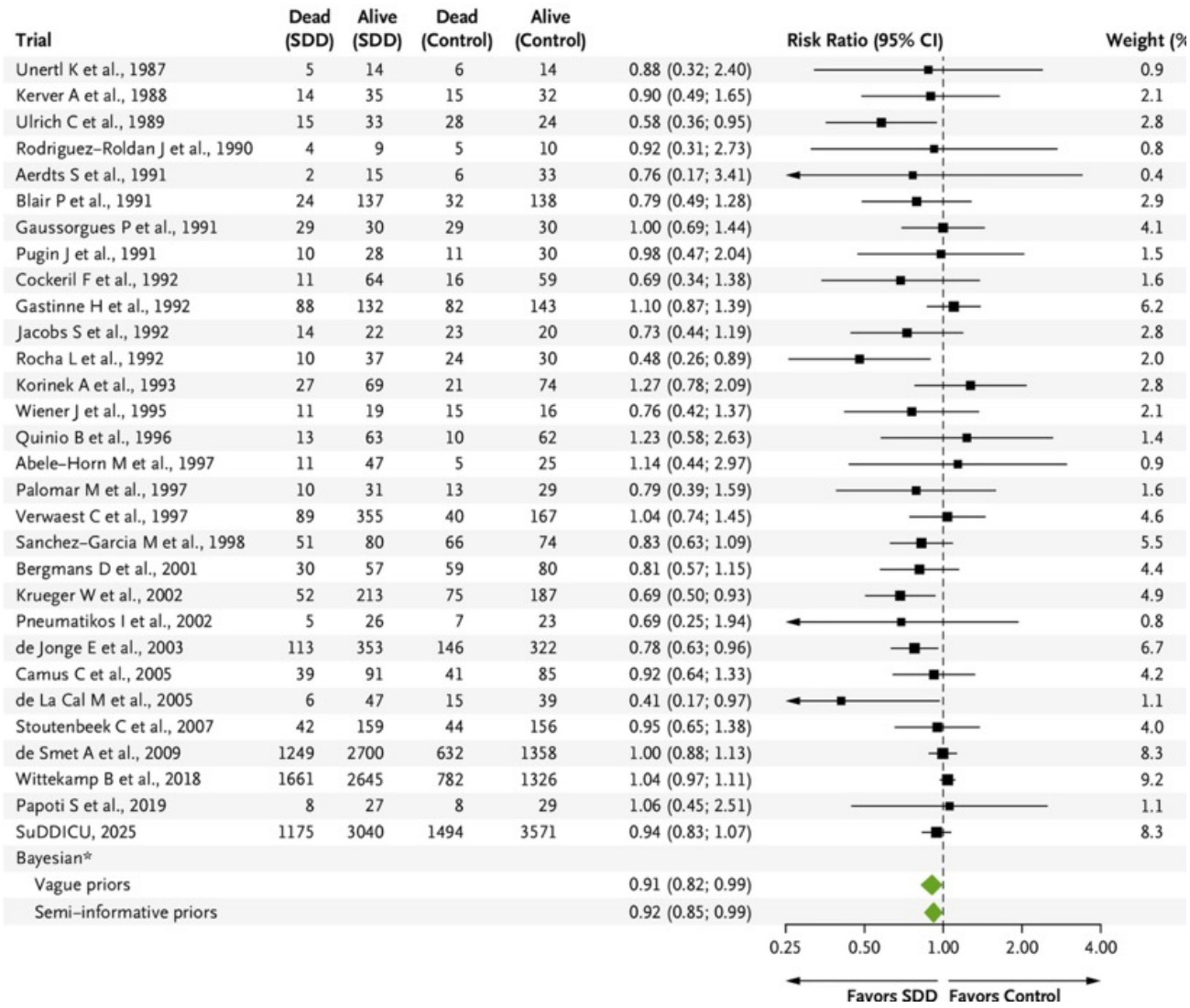
One additional trial was identified, giving a total of 32 RCTs (27,687 participants), with 30 of the 32 RCTs (27,332 participants) contributing data to the primary outcome. The pooled estimated relative risk of hospital mortality for SDD compared to usual care or placebo was 0.91; 95% credible interval, 0.82 to 0.99, I^2=33.3%; with a 99.2% posterior probability that SDD was associated with lower hospital mortality compared to standard care.

Conclusions

There is a high probability that in mechanically ventilated adults in the ICU, SDD, compared to standard care, is associated with a reduction in the risk of in-hospital death.

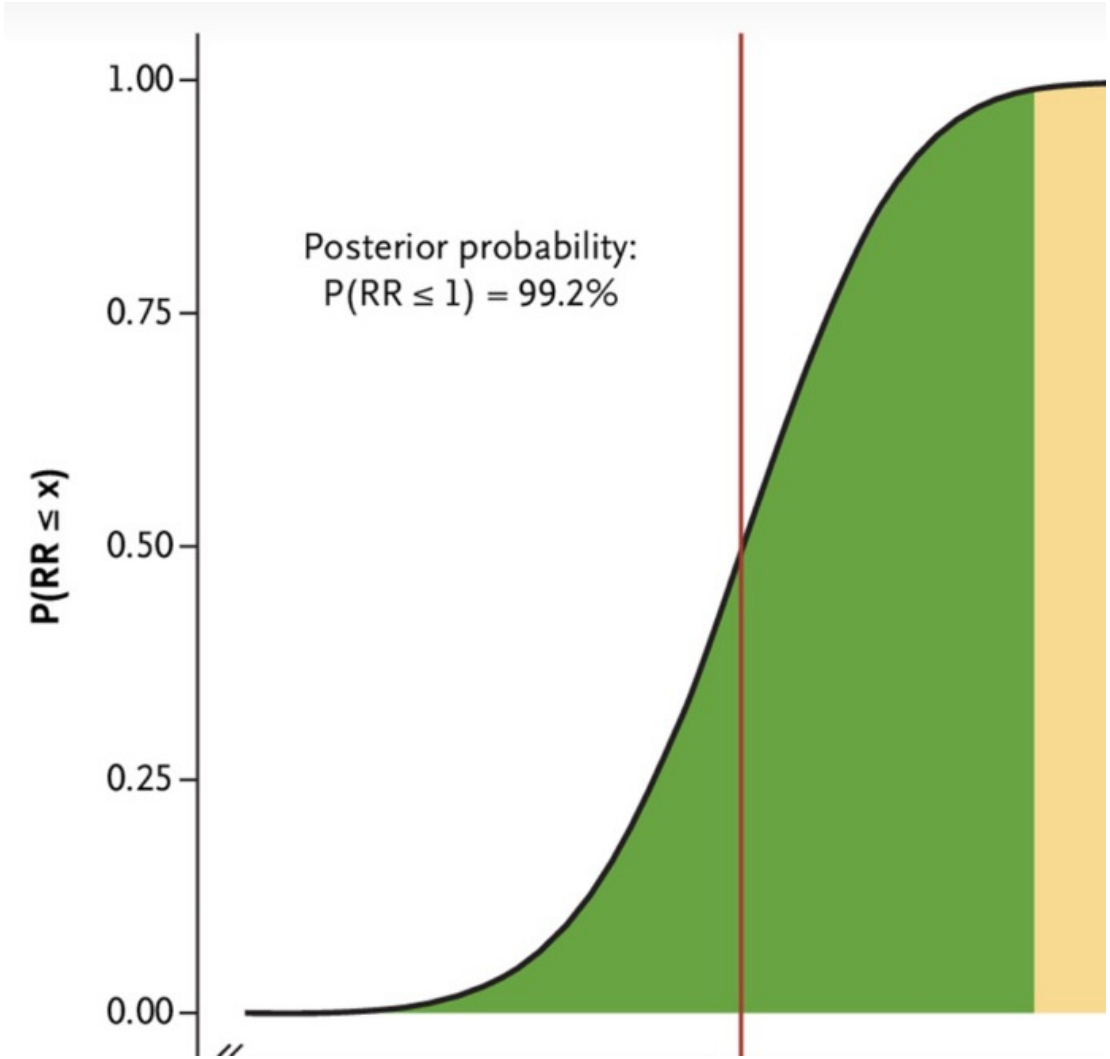
Introduction

Selective decontamination of the digestive tract (SDD) is a preventative infection-control strategy that has been used in intensive care units since the 1980s. It includes the administration of nonabsorbable antimicrobial agents to the oropharynx and upper gastrointestinal tract that is usually combined with a short course of broad-spectrum intravenous antibiotics. The intervention is aimed to prevent the overgrowth of pathogenic, gram-negative bacteria that are known to colonize the upper digestive tract of critically ill patients, in particular those receiving invasive mechanical ventilation, thus reducing the incidence of hospital-acquired infections, duration of mechanical ventilation, and, potentially, in-hospital mortality. Adoption of SDD has been variable across regions with persisting concerns related to the generalizability of the evidence and the potential for SDD to affect the microbial ecology of intensive care units (ICUs) that implemented the intervention.



Forest Plot for Hospital Mortality for the Updated Pooled Analysis.

SDD denotes selective digestive decontamination. CI: Confidence intervals *95% credible intervals provided for Bayesian pooled estimate. Black boxes represent point estimate. Black horizontal line represents confidence intervals. Green diamond represents all trials pooled estimated confidence interval or credible intervals and the middle point the point estimate. The 95% prediction interval for the primary outcome is from 0.69 to 1.15.



Cumulative Incidence Plot for the Posterior Probability of the Risk Ratio for Mortality for the Pooled Analysis.

The plot shows the cumulative distribution of the posterior probability of the estimated relative risk for mortality with 99.2% of the distribution falling below an estimated RR of 1, (green shaded area) with a median estimated RR of 0.91 (red vertical line).

10% reduction in risk with a
very high degree of being right

Primary, Secondary, and Subgroup Outcomes.

Outcome	Trials	Participants	t	I^2	Pooled Estimate	95% CrI	RRR
Primary outcome							
Hospital mortality (vague priors)	30	27,332	0.10	33.3%	RR 0.91	0.82 to 0.99	—
Sensitivity analysis for the primary outcome							
Hospital mortality (semi-informative priors)	30	27,332	0.10	30.7%	RR 0.92	0.85 to 0.99	—
SuDDICU Australia and Canada (analyzed separately)	31	27,332	0.10	31.1%	RR 0.91	0.83 to 0.99	—
Trial sequential analysis	30	27,332	0.01	19.6%	RR 0.92	0.81 to 1.04†	
Secondary outcomes							
Incidence of antibiotic-resistant organism cultured	5	16,148	0.14	16.0%	RR 0.63	0.44 to 0.90	—
Incidence of *Clostridioides difficile*	3	15,629	0.30	8.4%	RR 0.58	0.19 to 1.75	—
Incidence of positive blood cultures (bacteraemia)	21	25,383	0.16	18.5%	RR 0.68	0.57 to 0.81	—
Duration of MV	20	24,034	0.42	19.3%	MD −0.76	−1.34 to −0.14	—
Duration of ICU stay	24	26,496	1.13	50.8%	MD −0.89	−1.75 to −0.06	—
Duration of hospital stay	5	21,890	0.31	2.3%	MD −0.48	−2.13 to 1.17	—
Subgroup analysis for the primary outcome							
Cluster crossover‡	3	21,633	0.07	62.9%	RR 1.00	0.86 to 1.22	1.17 (1.01 to 1.35)
Individual patient randomly assigned‡	27	5699	0.08	12.3%	RR 0.85	0.77 to 0.94	
SDD with no intravenous agent§	14	11,037	0.05	9.5%	RR 1.01	0.91 to 1.11	1.17 (1.03 to 1.36)
SDD with intravenous agent§	17	16,295	0.11	31.1%	RR 0.84	0.73 to 0.94	
Surgical ICUs‖	5	1544	0.20	44.2%	RR 0.92	0.67 to 1.30	Surgical vs. mixed 1.01 (0.79 to 1.32)
Trauma ICUs¶	4	717	0.26	34.8%	RR 0.84	0.48 to 1.37	Trauma vs. mixed 0.95 (0.67 to 1.36)
Mixed-population ICUs¶	21	25,071	0.10	39.3%	RR 0.91	0.81 to 1.00	
Publication year: 1987–1999**	19	3115	0.11	14.9%	RR 0.89	0.78 to 1.02	0.98 (0.83 to 1.17)
Publication year: 2000–2025**	11	24,217	0.12	58.2%	RR 0.92	0.78 to 1.02	

GRADE Summary of Findings for SDD in Mechanically Ventilated Patients in the ICU.

Outcome	Effect Estimate (95% CrI) Number of trials Number of participants	Absolute Effect Estimates: SDD (95% CrI)	Absolute Effect Estimates: Standard care	Certainty of Evidence (quality of the evidence)	Plain Language Summary†
Mortality in hospital	Relative risk 0.91 (0.82 to 0.99) 30 trials 27,332 participants	286 per 1000 28 fewer per 1000 (3 fewer to 57 fewer)	314 per 1000	Moderate Due to inconsistency‡	The use of SDD probably reduces the risk of in-hospital mortality
Incidence of positive blood cultures (bacteraemia)	Relative risk 0.68 (0.57 to 0.81) 21 trials 25,383 participants	62 per 1000 29 fewer per 1000 (17 fewer to 39 fewer)	91 per 1000	Low Due to indirectness and risk of bias§	The use of SDD may result in a reduction in ICU-acquired bacteraemia
Incidence of antibiotic-resistant organism cultured	Relative risk 0.63 (0.44 to 0.90) 5 trials 16,148 participants	124 per 1000 73 fewer per 1000 (20 fewer to 110 fewer)	197 per 1000	Very low Due to inconsistency, indirectness, risk of bias¶	The evidence is uncertain about the effect of SDD on the emergence of antimicrobial-resistant organisms
Incidence of *Clostridioides difficile*	Relative risk 0.58 (0.19 to 1.75) 3 trials 15,629 participants	6 per 1000 4 fewer per 1000 (8 fewer to 8 more)	10 per 1000	Low Due to indirectness, and imprecision‖	The evidence is uncertain about the effect of SDD on the incidence of *Clostridioides difficile*
Duration of mechanical ventilation	Mean difference −0.76 days (−1.34 to −0.14 days) 20 trials 24,034 participants	8.3 days (7.8 days to 9.0 days)	9.1 days	Moderate Due to indirectness**	The use of SDD probably results in a small reduction in the duration of ventilation
Duration of ICU admission	Mean difference −0.89 days (−1.75 to −0.06 days) 24 trials 26,496 participants	11.7 days (10.9 days to 12.5 days)	12.6 days	Low Due to indirectness and imprecision††	The use of SDD may result in a slight reduction in duration of ICU admission
Duration of hospital admission	Mean difference −0.48 days (−2.13 to 1.17 days) 5 trials 21,890 participants	25.3 days (23.7 days to 27.0 days)	25.8 days	Moderate Due to imprecision‡‡	The use of SDD probably results in little to no difference in the duration of hospital admission

Discussion

This updated systematic review and Bayesian meta-analysis that incorporated the results of the completed international SuDDICU trial demonstrates that there is a high probability that SDD is associated with a reduction in the risk of in-hospital mortality compared to standard care in mechanically ventilated adults in the ICU. There is moderate certainty about this effect due to inconsistency in the way various trials have delivered the SDD intervention and reported and assessed the association between the administration of SDD and standard care. These results are in accordance with previously published pooled summaries.

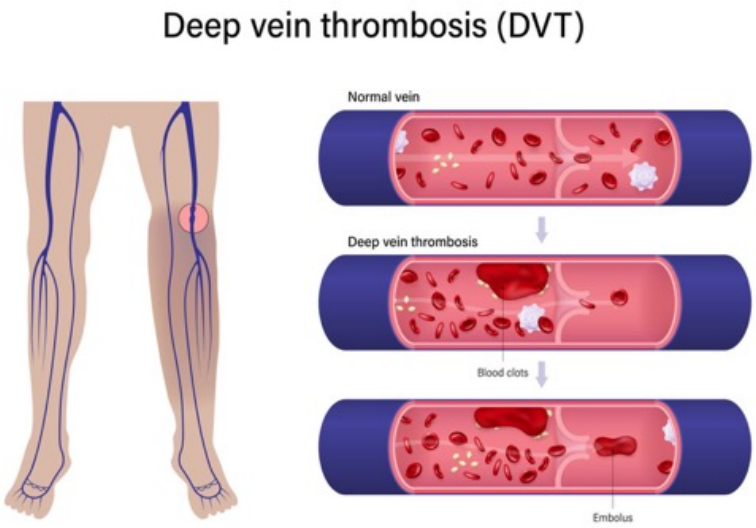
The results of this review confirm that SDD is also associated with a reduction in the incidence of positive blood cultures (bacteremia) and a reduction in the incidence of antimicrobial-resistant organisms and a reduction in the duration of mechanical ventilation and duration of ICU admission.

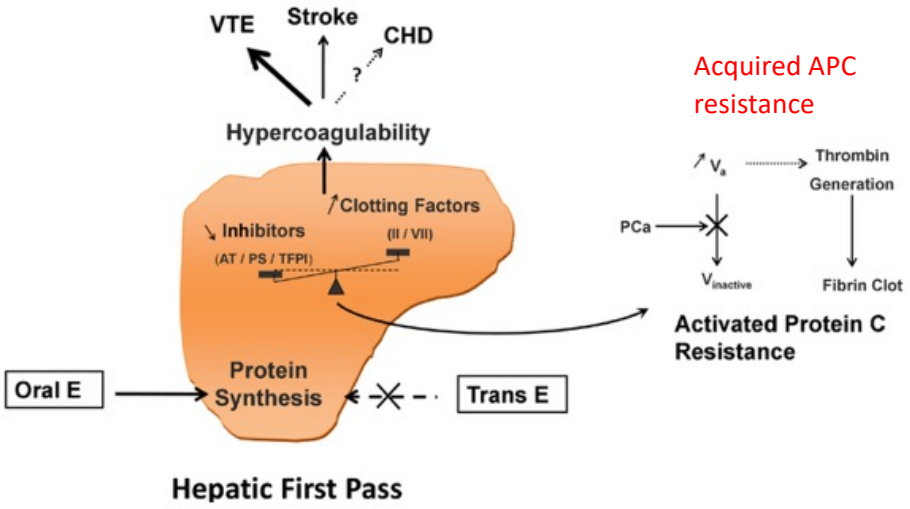
Die Anwendung einer Hormonersatztherapie (**HRT**) geht mit einem erhöhten Risiko für venöse Thromboembolien (**VTE**) einher, insbesondere in der oralen Anwendungsform. Eine Thromboseprophylaxe ist vor allem in Situationen mit erhöhtem Risiko (z. B. Operationen) oder bei Patienten mit bestehenden Risikofaktoren entscheidend.

Risikoprofil der Hormontherapie

Das Thromboserisiko wird maßgeblich durch die Art der Hormone und den Verabreichungsweg beeinflusst:

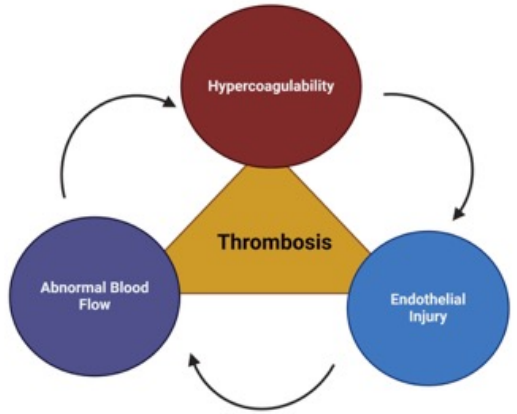
- **Oral vs. Transdermal**: Orale Östrogene erhöhen das VTE-Risiko um das **2- bis 4-fache**, da sie durch den "First-Pass-Effekt" in der Leber die Produktion von Gerinnungsfaktoren fördern. **Transdermale Präparate** (Pflaster, Gele) erhöhen das Risiko nach aktuellen Erkenntnissen **nicht** signifikant.
- **Kombinationspräparate**: Die Kombination aus Östrogen und bestimmten Gestagenen (insb. synthetische Gestagene wie Medroxyprogesteronacetat) ist risikoreicher als eine reine Östrogentherapie.
- **Zeitfaktor**: Das Risiko ist im **ersten Jahr** der Anwendung am höchsten.





Thromboseprophylaxe und Management Für Anwenderinnen einer HRT gelten spezifische Empfehlungen zur Vorbeugung von Blutgerinnseln:

Situation	Empfohlene Maßnahme
Vor chirurgischen Eingriffen	Es wird oft empfohlen, die HRT **4–6 Wochen vor** größeren Operationen abzusetzen, um das perioperative Risiko zu minimieren.
Bestehendes VTE-Risiko	Bei Patientinnen mit Adipositas, Rauchen oder bekannter Thrombophilie (z. B. Faktor-V-Leiden) sollte bevorzugt die **transdermale Route** gewählt werden.
Thrombose unter HRT	Tritt eine Thrombose auf, muss die HRT nicht zwingend sofort gestoppt werden, sofern eine **therapeutische Antikoagulation** (Blutverdünnung) erfolgt.
Allgemeine Prävention	Die Verwendung der **niedrigsten effektiven Dosis** ist entscheidend.



Virchow's Triad in the pathophysiology of thrombosis

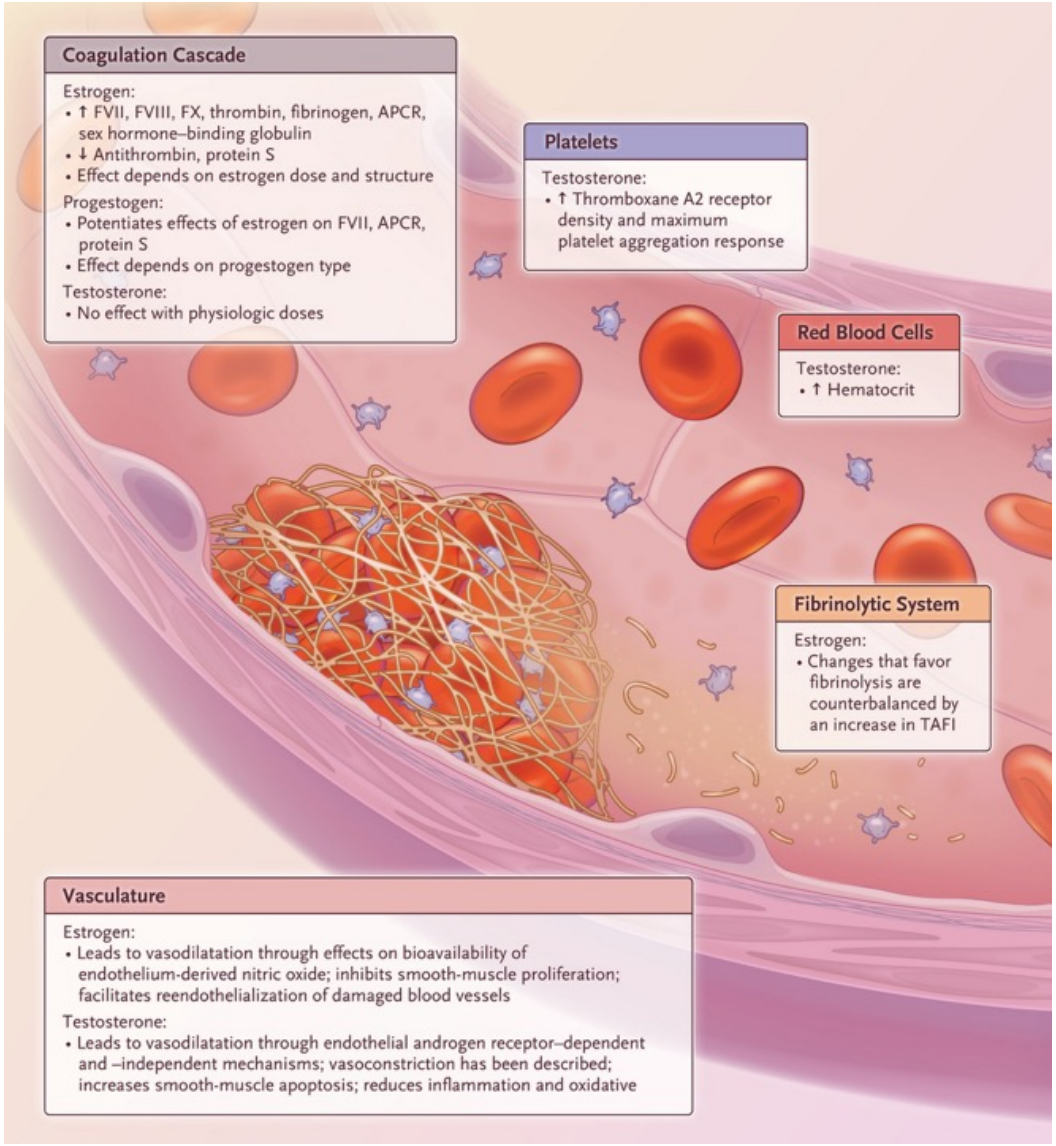
Sex Hormone Influences on Venous Thrombotic and Cardiovascular Risk

Summary

Thrombosis is a recognized complication of sex hormone therapy, which includes hormone replacement for deficiencies, contraceptive therapy, treatment of heavy menstrual bleeding, gender-affirming hormone therapy, suppression of ovulation, oncologic hormone therapy, and assisted reproduction. This review examines the effects of sex hormones on hemostasis and the vasculature and summarizes current evidence on thrombotic risk, including the effects of hormone formulation, thrombophilias, previous thrombosis, and common clinical factors. Practical guidance on the prevention and treatment of hormone-associated venous thromboembolism, as well as on perioperative care of patients receiving sex hormone therapy, is also provided.

Sex Hormone Influences on Venous Thrombotic and Cardiovascular Risks

- Oral contraceptives with a combination of hormones increase the risk of venous thromboembolism (VTE) by a factor of 3.5, and hormone-replacement therapy increases the risk by a factor of 2; in most cases, the absolute risk is low.
- For persons at increased risk for VTE who are considering contraception, a levonorgestrel-releasing intrauterine system or low-dose progestin may be preferred. Information about risks associated with progestin implants is limited. For hormone-replacement therapy or gender-affirming hormone therapy, transdermal estradiol is preferred. Micronized progesterone is associated with a low thrombotic risk.
- Most persons with hormone-associated VTE can stop anticoagulant therapy after 3 to 6 months, as long as hormone therapy has been stopped.
- Ongoing, well-managed anticoagulant therapy can allow for continued use of hormone therapy (contraceptive therapy, hormone-replacement therapy, or gender-affirming hormone therapy).
- Testosterone replacement does not increase the risk of VTE; less is known about the risk in the transmasculine population than in the general population, and information about the cardiovascular risk is limited.



Interaction between Hormones and the Coagulation, Fibrinolytic, and Vascular Systems.

APCR denotes acquired protein C resistance, FVII factor VII, FVIII factor VIII, FX factor X, and TAFI thrombin activatable fibrinolysis inhibitor.

Types of Hormone Therapy and Formulations.

Type of Hormone Therapy	Estrogen	Progestogen	Other Hormones
Combined hormone therapy†			
Combined oral contraceptives			
First generation	Ethinyl estradiol	Norethindrone, ethynodiol diacetate, lynestrenol, norethynodrel	—
Second generation	Ethinyl estradiol	Levonorgestrel, lynestrenol	—
Third generation	Ethinyl estradiol	Desogestrel, gestodene, norgestimate‡	—
Fourth generation or unclassified	Ethinyl estradiol, estrogen valerate, estradiol, estetrol	Cyproterone acetate, drospirenone, segesterone acetate, trimegestone, dienogest, nomegestrol acetate, drospirenone	—
Transdermal therapy	Ethinyl estradiol	Norelgestromin, levonorgestrel	—
Vaginal ring	Ethinyl estradiol	Etonogestrel, segesterone acetate	—
Progestin-only therapy			
Oral therapy	—	Norethindrone, desogestrel, drospirenone	—
Parenteral therapy	—	DMPA	—
Subdermal implant	—	Etonogestrel, levonorgestrel	—
Intrauterine system	—	Levonorgestrel	—
HRT for cisgender women			
Oral therapy	17β-Estradiol, estradiol valerate, conjugated equine estrogens	Micronized progesterone (Prometrium), pregnane derivatives (dydrogesterone, medrogestone, chlormadinone acetate, cyproterone acetate, MPA), norpregnane derivatives (nomegestrol acetate, promegestone, trimegestone, segesterone acetate), nortestosterone derivatives	—
Transdermal patch or gel	17β-Estradiol	Progestogen may or may not be included	—
Low-dose vaginal therapy	17β-Estradiol	—	—
Testosterone therapy for hypogonadal cisgender men and transmasculine persons§			
Oral therapy	—	—	Testosterone undecanoate
Transdermal therapy	—	—	Testosterone gel, testosterone enanthate or cypionate
GAHT for transfeminine persons			
Estrogen therapy¶			
Oral or sublingual therapy	17β-Estradiol	—	—
Transdermal gel or patch	17β-Estradiol	—	—
Parenteral therapy	Estradiol valerate, estradiol cypionate	—	—
Antiandrogen therapy	—	—	Spironolactone, cyproterone acetate, finasteride, GnRH agonist
Progestogen therapy	—	Micronized progesterone, MPA	—

Sex Hormone Action and the Mechanism of Thrombosis.

Hormone Type	Therapeutic Uses	Sex Hormone Action†	Mechanism of Thrombosis
Estrogen	Contraception, management of menstrual bleeding, GAHT, HRT	When used for contraception, estrogen exerts negative feedback on gonadotropin secretion, stabilizes the endometrium to prevent irregular shedding and breakthrough bleeding, and increases the potency of the progestogen component (see below). In women with abnormal menstrual bleeding, estrogen helps stabilize the endometrial lining; in postmenopausal women, it replaces estrogen the body no longer makes. Estrogen is used in GAHT for development of secondary sex characteristics.	The procoagulant effect of estrogen is mediated through decreased levels of inhibitors of coagulation (e.g., protein S, antithrombin, and tissue factor pathway inhibitor) and increased production of coagulation factors (e.g., fibrinogen, prothrombin, factor VII, factor VIII, and factor X), as well as through development of acquired APCR, which is a lack of response to APC, a protein that normally helps prevent blood from clotting excessively. Decreased levels of PAI-1 may lead to decreased fibrinolysis, but this effect may be counterbalanced by increased levels of TAFI.[6]
Progestogen	Contraception, management of menstrual bleeding, GAHT, HRT	When used for contraception, progestogens inhibit ovulation through negative feedback on the hypothalamic–pituitary–ovarian axis and have local effects on cervical mucus and the endometrium. Continuous exposure to synthetic progestins leads to endometrial glandular atrophy and control of menstrual bleeding, whereas DMPA works through endometrial effects and inhibition of gonadotropin secretion from the pituitary.	Progestogens potentiate the effects of estrogen on factor VII, APCR, and protein S, with the effect dependent on the progestogen dose and type.[6]
Testosterone	HRT, GAHT	Testosterone is given to replace hormones not produced in persons with hypogonadism or for secondary sex characteristics as part of GAHT.	Supraphysiologic therapy is associated with a sustained decrease in the fibrinogen level and increase in the hematocrit level; testosterone increases platelet thromboxane A2 receptor density and the maximum platelet aggregation response.[7]

Risk of VTE with Hormone Therapy in Cisgender Persons.

Type of Hormone Therapy	Baseline Incidence of VTE (95% CI)†	Adjusted Risk with Hormone Use vs. Nonuse (95% CI)‡	Incidence of VTE with Hormone Use (95% CI)
	no. of events/10,000 person-yr		
Combined hormone therapy			
Combined oral contraceptives§			
Overall	Unexposed population: 1.9–3.7[23,24]; 2.0 (1.9–2.1)[25]	3.5 (2.9–4.3)[33]	6.2 events/10,000 exposure-yr[26]
Ethinyl estradiol, 20 μg, plus levonorgestrel	—	2.5 (1.3–4.6)[25]	5.0 events (1.4–12.5)/10,000 person-yr[25]
Ethinyl estradiol, 20 μg, plus desogestrel	—	6.3 (5.2–7.6)[25]	12.8 events (9.6–16.9)/10,000 person-yr[25]
Ethinyl estradiol, 20 μg, plus gestodene	—	5.8 (4.8–7.0)[25]	15.4 events (11.2–20.6)/10,000 person-yr[25]
Ethinyl estradiol, 20 μg, plus drospirenone	—	4.9 (3.2–7.3)[25]	6.7 events (3.5–11.7)/10,000 person-yr[25]
Ethinyl estradiol, 30–40 μg, plus norethisterone	—	2.24 (1.12–4.51)[25]	2.9 events/10,000 exposure-yr[25]
Ethinyl estradiol, 30–40 μg, plus levonorgestrel	—	3.6 (3.2–4.0)[25]	7.6 events (6.6–8.6)/10,000 person-yr[25]
Ethinyl estradiol, 30–40 μg, plus norgestimate	—	5.4 (4.3–6.9)[25]	13.2 events (8.4–19.7)/10,000 person-yr[25]
Ethinyl estradiol, 30–40 μg, plus desogestrel	—	7.9 (6.0–10.3)[25]	16.2 events (11.6–22.2)/10,000 person-yr[25]
Ethinyl estradiol, 30–40 μg, plus gestodene	—	6.7 (5.6–7.9)[25]	14.7 events (11.6–18.3)/10,000 person-yr[25]
Ethinyl estradiol, 30–40 μg, plus drospirenone	—	5.8 (4.3–7.8)[25]	13.6 events (9.0–19.7)/10,000 person-yr[25]
Ethinyl estradiol, 30–40 μg, plus cyproterone	—	5.9 (4.3–7.8)[25]	11.6 events (7.0–17.9)/10,000 person-yr[25]
Ethinyl estradiol, 50 μg, plus NEA	—	6.24 (2.95–13.2)[25]	10.2 events/10,000 exposure-yr[25]
Ethinyl estradiol, 50 μg, plus levonorgestrel	—	4.49 (2.94–6.85)[25]	9.3 events/10,000 exposure-yr[25]
Estradiol plus nomegestrol or dienogest	—	3.6 (1.9–6.7)[25]	5.0 events (2.3–9.7)/10,000 person-yr[25]
Transdermal contraceptives	Unexposed population: 2.0[25]	5.0 (2.1–12.0)[25]	8.1 events (1.5–25.1)/10,000 person-yr[25]
Vaginal ring	Unexposed population: 2.0[25]	4.5 (3.1–6.5)[25]	8.0 events (4.6–12.8)/10,000 person-yr[25]
Progestin-only therapy			
Oral (low dose for contraception)			
Overall	General population, 25–29 yr of age: 2.4[25]	0.9 (0.6–1.5)[27]	2.2 events/10,000 person-yr¶
Desogestrel	Unexposed population: 2.0[25]	1.8 (1.4–2.3)[25]	3.6 events (2.8–4.7)/10,000 person-yr[25]
Oral (higher dose for management of bleeding in women <50 yr of age[28])	General population, 25–29 yr of age: 2.4[25]; 45–49 yr of age: 5.4[25]	5.3 (1.5–18.7)[28]‖ 5.9 (1.2–30.1)[28]**	General population, 25–29 yr of age: 12.7 events/10,000 person-yr¶; 45–49 yr of age: 28.6 events/10,000 person-yr¶
Injectable DMPA	Unexposed population: 2.0[25]; general population, 25–29 yr of age: 2.4[25]	5.7 (3.5–9.3)[25] 2.7 (1.3–5.5)[27]	11.9 events (4.4–25.6)/10,000 person-yr[25] 6.5 events/10,000 person-yr¶
Intrauterine system	Unexposed population: 2.0[25]; general population, 25–29 yr of age: 2.4[25]	1.0 (0.8–1.1)[25] 0.6 (0.2–1.5)[27]	2.1 events (1.7–2.6)/10,000 person-yr[25] 1.4 events/10,000 person-yr¶
Subdermal implant	Unexposed population: 2.0[25]	2.4 (1.4–4.0)[25]	3.4 events (1.7–6.3)/10,000 person-yr[25]
HRT in cisgender women			
Oral estrogen alone			
Overall	Unexposed population: 16.0[29]	1.4 (1.3–1.5)[29,30]	—
Conjugated equine estrogen	—	1.5 (1.4–1.6)[29]	8 additional events/10,000 women in 1 yr[29]
Estradiol	—	1.3 (1.2–1.4)[29]	4 additional events/10,000 women in 1 yr[29]
Oral estrogen plus progestogen			
Overall	Unexposed population: 16.0[29]	2.4 (1.9–2.9)[30] 1.7 (1.7–1.8)[29]	—
Conjugated equine estrogen plus MPA	Placebo group: 17[31]††	2.1 (1.9–2.3)[29]	35 events/10,000 person-yr[31]‡‡ 18 additional events/10,000 women in 1 yr[29]
Conjugated equine estrogen plus NG	—	1.7 (1.6–1.9)[29]	12 additional events/10,000 women in 1 yr[29]
Estradiol plus MPA	—	1.4 (1.1–1.9)[29]	7 additional events/10,000 women in 1 yr[29]
Estradiol plus dydrogesterone	—	1.2 (0.98–1.4)[29]	—
Estradiol plus NEA	—	1.7 (1.6–1.8)[29]	11 additional events/10,000 women in 1 yr[29]
Estradiol plus NG or estradiol plus drospirenone	—	1.4 (1.0–2.0)[29]	—
Transdermal estrogen alone	General population, 50–54 yr of age: 11.8[25]	0.96 (0.88–1.04)[29]	11.3 events/10,000 person-yr¶
Transdermal estrogen plus progestogen			
Overall	General population, 50–54 yr of age: 11.8[25]	0.86 (0.73–1.01)[29]	—
Micronized progesterone	—	0.93 (0.65–1.33)[32]	11 events/10,000 person-yr¶
Norpregnane derivatives (nomegestrol acetate or promegestone)	—	2.42 (1.84–3.18)[32]	28.3 events/10,000 person-yr¶
Pregnane and nortestosterone derivatives	—	1.37 (0.97–1.93)[32]	16.5 events/10,000 person-yr¶

Future Directions

Evidence-supported strategies are needed for discussing the risks of hormone therapy with patients, including transgender and gender-diverse persons. Awareness among health care providers of the risk of thrombosis with gender-affirming hormone therapy is important. Further research is needed to better understand the VTE risk with hormone therapy in persons with multiple risk factors, younger women with premature ovarian insufficiency, and those with previous VTE who are considering transdermal hormone-replacement therapy. Additional data are needed to provide more definitive statements on the safety of the progestogen subdermal implant. Finally, data are still needed to characterize the risks of VTE and cardiovascular disease among transgender and gender-diverse persons, especially those who are older or who have additional risk factors for thrombosis.

Case 11-2026: A 24-Year-Old Man with Depression, Anhedonia, and Fatigue

On the day of the current presentation, the patient noted anhedonia with a lack of motivation and severe fatigue that limited his ability to complete tasks during the workday. He reported falling asleep several times per day, sometimes for up to 20 hours. He also noted ongoing anxiety, which usually occurred in social situations, and that he sometimes felt weakness in his hands when he laughed, which he attributed to anxiety in social situations. The patient reported that he had had visual and tactile hallucinations while falling asleep, and he also described awakening and feeling paralyzed multiple times per night. He stated that his partner had not told him of any apneic spells or snoring, and he did not have early morning headaches. In addition, the patient said that he had not recently used any opioids other than buprenorphine but indicated that he had begun using ketamine several times per week and drinking two or three alcoholic beverages once per week.

The patient presented with anhedonia, depression, anxiety, fatigue, and sleep abnormalities in the context of ongoing polysubstance use disorder. This constellation of symptoms is consistent with an episode of major depressive disorder. The patient started treatment with several medications for these conditions, such as buprenorphine for opioid dependence, venlafaxine for depression and anxiety, and prazosin to mitigate his nightmares. Although the patient's mood improved and anxiety decreased, his daytime somnolence and fatigue persisted, which prompted medication adjustments.

On examination, the blood pressure was 126/59 mm Hg, the heart rate 81 beats per minute, the respiratory rate 16 breaths per minute, and the oxygen saturation 98% while the patient was breathing ambient air. The weight was 77 kg, and the body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) was 21.
Urinalysis was normal, and blood and urine toxicology testing was positive for buprenorphine and norbuprenorphine but negative for other opioids, benzodiazepines, or stimulants. Serologic testing for human immunodeficiency virus, hepatitis B and hepatitis C viruses, and syphilis was negative.

A diagnosis was made.

The labs are all normal

Variable	Reference Range, Adults†	On Current Presentation
Hemoglobin (g/dl)	13.5–17.5	12.6
Hematocrit (%)	41.0–53.0	37.7
White-cell count (per μl)	4500–11,000	5870
Platelet count (per μl)	150,000–400,000	363,000
Sodium (mmol/liter)	135–145	140
Potassium (mmol/liter)	3.4–5.0	4.6
Chloride (mmol/liter)	98–108	106
Carbon dioxide (mmol/liter)	23–32	27
Urea nitrogen (mg/dl)	8–25	19
Creatinine (mg/dl)	0.60–1.50	0.80
Glucose (mg/dl)	70–110	106
Globulin (g/dl)	1.9–4.1	3.8
Albumin (g/dl)	3.3–5.0	4.8
Alanine aminotransferase (U/liter)	10–40	10
Aspartate aminotransferase (U/liter)	10–55	14
Alkaline phosphatase (U/liter)	45–115	63
Total bilirubin (mg/dl)	0.0–1.0	0.3
Iron (μg/dl)	45–160	102
Transferrin saturation (%)	14–50	27
Total iron-binding capacity (μg/dl)	230–404	381
Ferritin (μg/liter)	20–300	40

In developing a differential diagnosis to explain the features of this case, I will focus on the most distressing and impairing symptoms reported by the patient — namely, extreme fatigue and intrusive somnolence. Although the severity of his depression and substance use fluctuated over the course of months of treatment, I am most concerned by his sleep-related problems, especially sleeping up to 20 hours a day, falling asleep several times per day, and severe fatigue, all of which limited his ability to complete tasks. These are the core features of excessive daytime sleepiness, and I will review its causes systematically. First, I will review the most common causes of excessive daytime sleepiness in the general population, followed by the most likely causes in this patient on the basis of his coexisting conditions. Then, I will review the rare causes of excessive daytime sleepiness that may be considered if other diagnoses have been ruled out, with a focus on central hypersomnolence disorders.

Narcolepsy

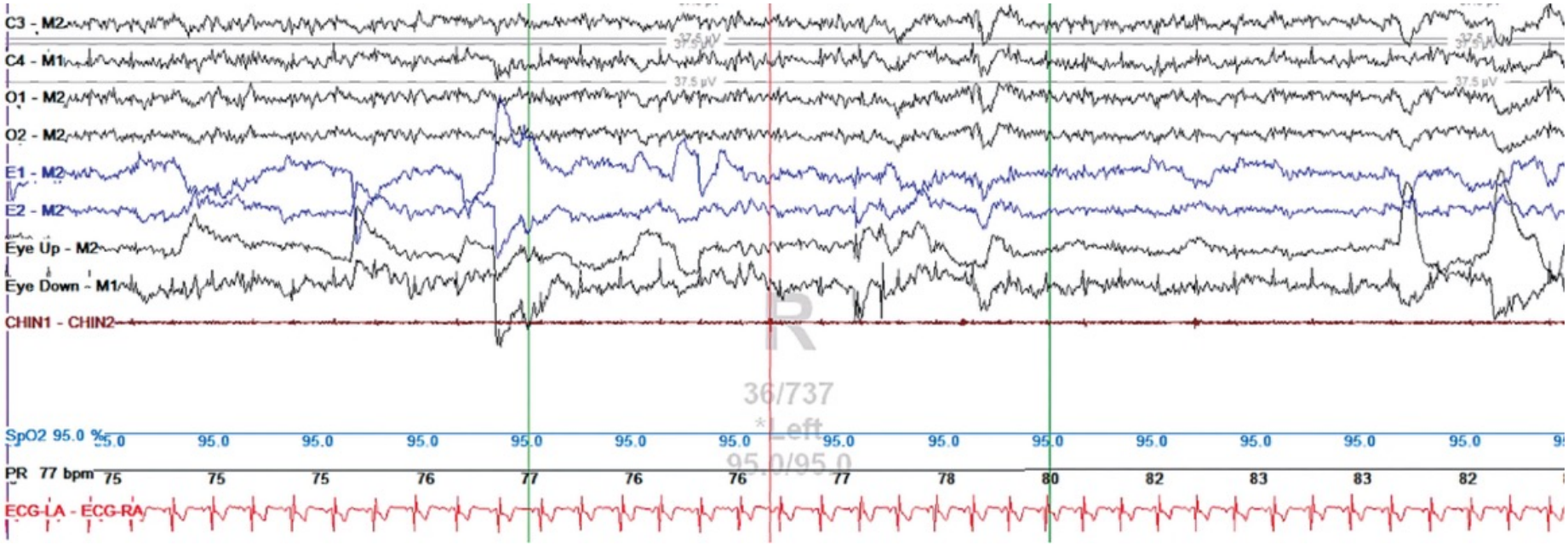
Narcolepsy is characterized by the sudden onset of REM sleep at any time of the day. Sleep episodes in patients with narcolepsy are often irresistible, usually short, frequently associated with dreaming, and typically restore normal wakefulness for up to several hours after an episode. Narcolepsy can be considered a primary or secondary disorder, with the latter resulting from structural damage (e.g., stroke, injury, or mass).

Primary narcolepsy is divided into two types. Narcolepsy type 1 is associated with very low levels of orexin-A in the cerebrospinal fluid (CSF) due to a loss of neurons that produce this neuropeptide in the lateral hypothalamus. It is unclear what causes the loss of neurons, but it is highly associated with specific HLA types, and an underlying autoimmune cause has been suggested.

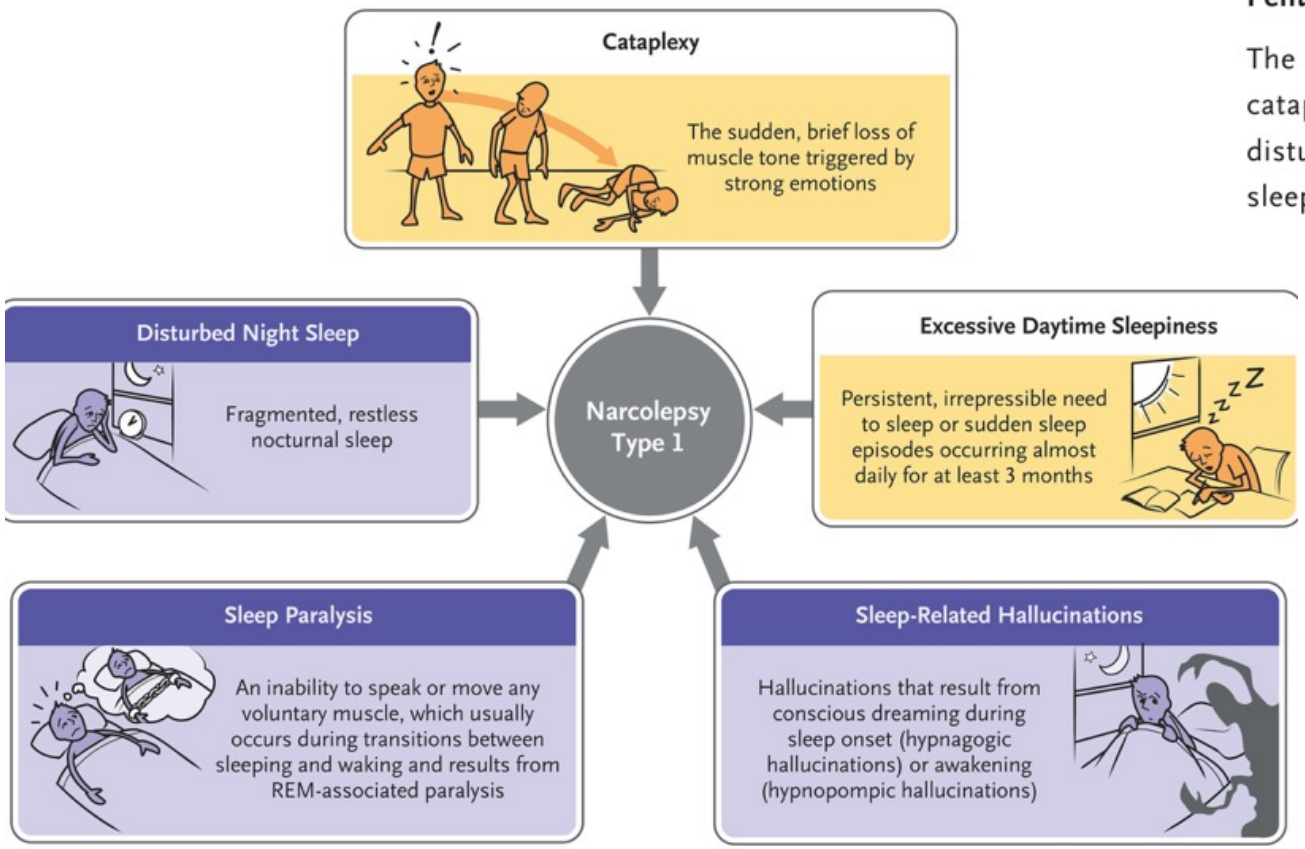
Patients with narcolepsy type 1 also commonly have cataplexy, a sudden loss of muscle tone that is most often triggered by strong emotions that are usually positive. Most striated skeletal muscles, with the exception of the diaphragm, are affected, which may lead to sudden collapse without loss of consciousness. Partial manifestations, limited to specific areas such as the face or arms, can lead to a sudden onset of localized weakness. Narcolepsy is also associated with hypnagogic or hypnopompic hallucinations, which refer to hallucinatory phenomena that occur while falling asleep or waking up, as well as sleep paralysis, which is an inability to move while either waking up or falling asleep. Narcolepsy type 2, on the other hand, can often have milder clinical manifestations and is not associated with low orexin-A levels or cataplexy.

This patient had many features that are consistent with narcolepsy type 1. In addition to excessive daytime sleepiness, the patient reported cataplexy, hypnagogic hallucinations, and sleep paralysis. Coexisting depression is commonly seen in patients with narcolepsy, and the patient also had a family history of sleep disorders, which further suggests a genetic component. The presence of cataplexy rules out narcolepsy type 2. Although this patient had two opioid overdoses and we are not aware of whether clinically significant hypoxia of the central nervous system occurred during these episodes, the absence of any other localized neurologic symptoms makes secondary narcolepsy very unlikely.

To establish the diagnosis of narcolepsy type 1 in this patient, I would recommend performing polysomnography, followed by a multiple sleep latency test. I would expect to see an early transition to REM sleep (typically within 15 minutes after sleep onset) on polysomnography and a short time to fall asleep (≤8 minutes) on the multiple sleep latency test.



Polysomnogram and Multiple Sleep Latency Test.
Shown is a 30-second sleep segment, which includes data for the following electrophysiological channels: electroencephalogram (central leads, C3–M2 and C4–M1; occipital leads, O1–M2 and O2–M2), chin electromyogram, electro-oculogram (EOG; leads, E1–M2 and E2–M2), electrocardiogram (ECG; leads, LA [left arm] and RA [right arm]), pulse rate (PR), and oxygen saturation (SpO_2). The sleep-onset rapid-eye-movement (REM) period is characterized by conjugate rapid eye movements in the EOG channels and REM sleep with atonia in the chin electromyogram channel.



Pentad of Symptoms of Narcolepsy Type 1.

The main symptoms of narcolepsy type 1 are cataplexy, excessive daytime sleepiness, disturbed night sleep, sleep paralysis, and sleep-related hallucinations.

After the diagnosis was confirmed, the patient received a prescription for modafinil for the management of excessive daytime sleepiness associated with narcolepsy type 1.

Follow-up

Within several weeks after starting treatment with modafinil, the patient reported a marked reduction in daytime fatigue and an improved ability to sustain wakefulness during routine activities. His total sleep time normalized, and the frequency of sleep paralysis and hypnagogic hallucinations markedly diminished. He described increased concentration and engagement in daily tasks and noted a renewed capacity to participate in work and academic planning.
The patient characterized the change as transformative, stating, "I feel like I have another chance at life" and "this is how life could have been all along." His symptoms of social anxiety persist, and he continues to receive treatment with escitalopram and weekly psychotherapy.

Final Diagnosis

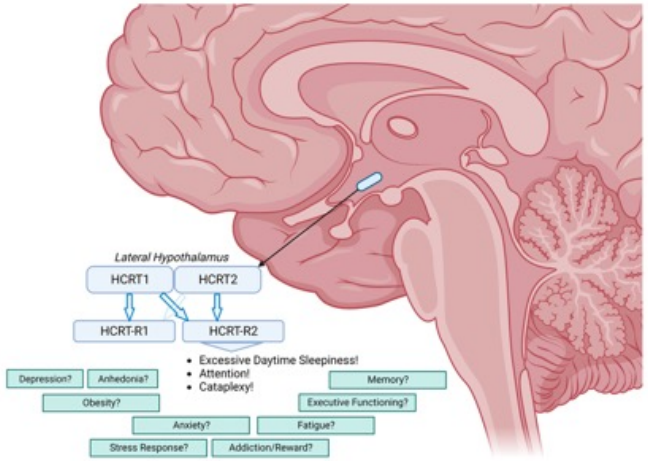
Narcolepsy type 1.

Modafinil hemmt die Wiederaufnahme von Dopamin im Gehirn, was zu einer erhöhten Konzentration im synaptischen Spalt führt. Es wirkt weniger stark auf Noradrenalin und Serotonin.

Die Narkolepsie Typ 1 (NT1) ist eine komplexe Erkrankung, bei der genetische Faktoren eine entscheidende Rolle spielen, auch wenn sie meist nicht direkt vererbt wird. Die wichtigste genetische Komponente ist das **HLA-System**, das das Immunsystem steuert.
Der "Haupt-Risikofaktor" (HLA-DQB1*06:02):
Über 98 % aller Patienten mit Narkolepsie Typ 1 tragen die Genvariante HLA-DQB1*06:02. Diese Variante ist jedoch auch bei ca. 12–38 % der gesunden Bevölkerung vorhanden, weshalb sie allein nicht die Krankheit auslöst, aber eine notwendige Voraussetzung darstellt.

Seltene direkte Mutationen (Monogenetisch)
In extrem seltenen Fällen (meist bei sehr frühem Krankheitsbeginn) können direkte Mutationen in bestimmten Genen die Ursache sein:
- **HCRT-Gen:** Eine Mutation in diesem Gen (kodiert für das Hormon Hypocretin/Orexin) wurde bei einem Fall von frühkindlicher Narkolepsie gefunden.
- **DNMT1-Gen:** Mutationen hier führen zu einer speziellen Form (ADCA-DN), die neben Narkolepsie auch Taubheit und Demenz umfasst.

DNMT1 (DNA-Methyltransferase 1) ist das Hauptenzym zur Aufrechterhaltung der DNA-Methylierungsmuster nach der Replikation, indem es hemimethylierte DNA erkennt und auf den Tochterstrang überträgt.



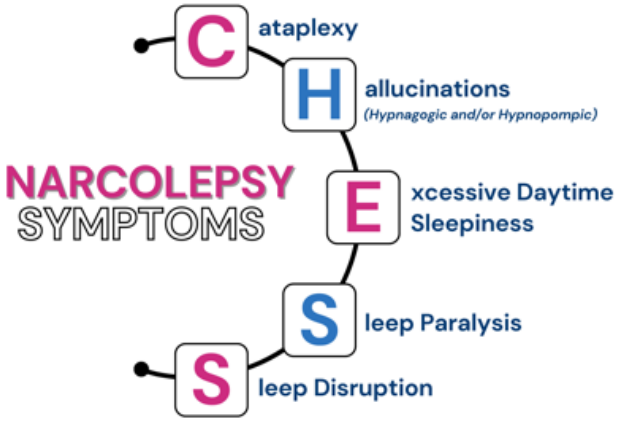
Hypocretin-1 (Biologie): Ein Neuropeptid (auch Orexin-A), das im Hypothalamus produziert wird. Es ist entscheidend für die Wach-Schlaf-Regulierung und Aufmerksamkeit.

Die Verbindung zwischen **Masashi Yanagisawa** und den „schlafenden Dobermanns“ markiert einen der bedeutendsten Durchbrüche in der modernen Schlafforschung.

Die wissenschaftliche Entdeckung

Ende der 1990er Jahre lieferten sich zwei Teams ein wissenschaftliches Wettrennen, um die Ursache der Schlafkrankheit **Narkolepsie** zu finden: das Team um **Masashi Yanagisawa** an der University of Texas und das Team um **Emmanuel Mignot** in Stanford.

- **Yanagisawas Beitrag:** Er entdeckte zwei Neuropeptide im Gehirn, die er **Orexine** nannte (auch bekannt als Hypocretine). Er stellte fest, dass Mäuse, denen das Gen für Orexin fehlte, plötzlich „einfach umkippten“ – ein klassisches Symptom der Narkolepsie.
- **Die Dobermann-Verbindung:** Gleichzeitig untersuchte Emmanuel Mignot eine berühmte Kolonie von Dobermann-Pinschern in Stanford, die an erblicher Narkolepsie litten. Seine Forschung ergab, dass diese Hunde eine Mutation im Gen für den **Orexin-Rezeptor 2** (Hcrtr2) hatten.



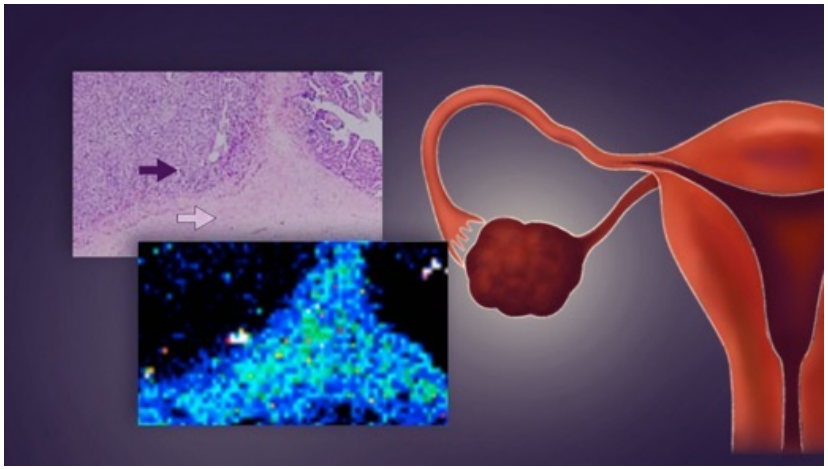
THE LANCET

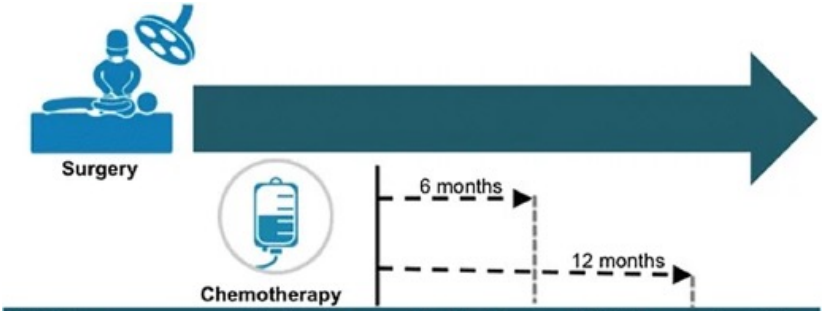
Platinresistenter Eierstockkrebs (Ovarialkarzinom) liegt vor, wenn die Erkrankung während einer platinhaltigen Chemotherapie (z. B. mit Cisplatin oder Carboplatin) oder innerhalb von **weniger als sechs Monaten** nach deren Abschluss erneut auftritt.
Diese Einstufung ist entscheidend für die weitere Therapieplanung, da sie darauf hindeutet, dass der Tumor auf Standard-Platinpräparate nicht mehr ausreichend anspricht.

Definition und Klassifizierung

Die Einteilung erfolgt traditionell anhand des **platinfreien Intervalls (PFI)**:

- **Platin-refraktär:** Fortschreiten der Krankheit noch während der Behandlung oder innerhalb von 4 Wochen danach.
- **Platin-resistent:** Rückfall innerhalb von 1 bis 6 Monaten nach Behandlungsende.
- **Platin-sensitiv:** Rückfall nach mehr als 6 (oft definiert als >12) Monaten.





Platinum sensitivity classification	Refractory	Resistant	Partially sensitive	Sensitive
Probability of second platinum response	0%	<10%	30%	>50%

Aktuelle Behandlungsmöglichkeiten

Da Platinpräparate allein meist nicht mehr wirken, setzen Mediziner auf alternative Strategien:

- **Andere Chemotherapien:** Einsatz von Wirkstoffen ohne Platin, wie **Pegyliertes liposomales Doxorubicin (PLD)**, **Paclitaxel** (meist wöchentlich), **Topotecan** oder **Gemcitabin**.
- **Antikörper-Wirkstoff-Konjugate (ADCs):** Eine neuere gezielte Option ist **Mirvetuximab-Soravtansin**, das speziell für Tumore mit hoher Folat-Rezeptor-alpha (FRα)-Expression zugelassen wurde.
- **Anti-Angiogenese-Therapie:** Der Wirkstoff **Bevacizumab** wird häufig mit der Chemotherapie kombiniert, um die Blutversorgung des Tumors zu hemmen.
- **Immuntherapie:** Neuere Zulassungen (Stand Anfang 2026) umfassen Kombinationen wie **Pembrolizumab** mit Paclitaxel für Patienten mit PD-L1-positiven Tumoren.
- **PARP-Inhibitoren:** Bei bestimmten genetischen Voraussetzungen (z. B. BRCA-Mutationen) können Wirkstoffe wie **Niraparib** oder **Olaparib** eine Option sein.

Relacorilant ist ein neuartiges Medikament, das als selektiver Antagonist des **Glukokortikoidrezeptors (GR)** wirkt. Es blockiert gezielt die Wirkung des Stresshormons **Cortisol** an diesem Rezeptor, ohne andere Hormonrezeptoren (wie den Progesteronrezeptor) zu beeinflussen.

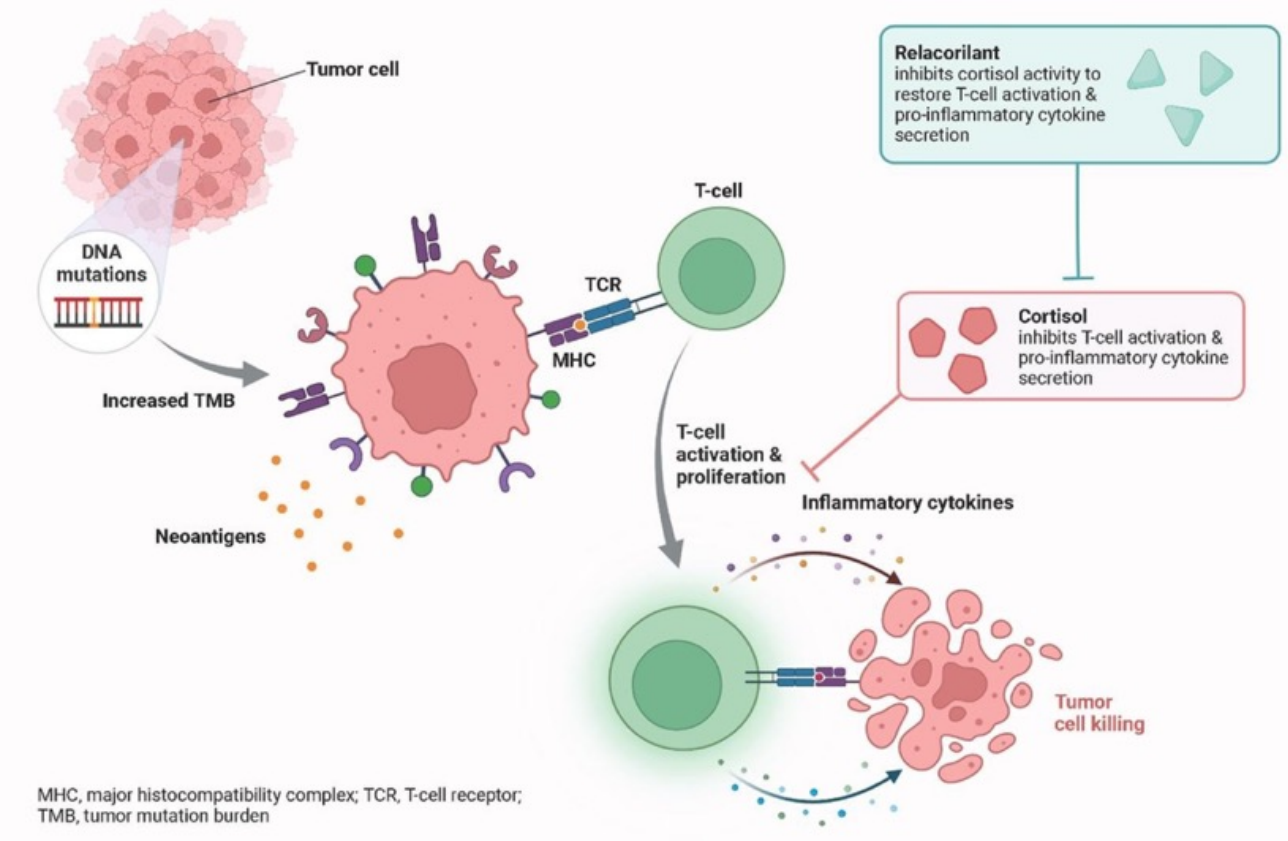
Haupteinsatzgebiete und Zulassungsstatus

Das Medikament wird primär für zwei medizinische Bereiche entwickelt:

- **Onkologie (Krebstherapie):**
  - **Eierstockkrebs:** Am 25. März 2026 erteilte die FDA die Zulassung für Relacorilant in Kombination mit **nab-Paclitaxel** zur Behandlung von platinresistentem Ovarialkarzinom.
  - **Wirkweise:** Cortisol kann Tumore resistent gegen Chemotherapie machen. Durch die Blockade des GR-Rezeptors erhöht Relacorilant die Empfindlichkeit der Krebszellen gegenüber der Behandlung.
- **Risiko einer Addison-Krise:** Da Morbus Addison durch einen Cortisolmangel gekennzeichnet ist, müssen Betroffene lebenslang Cortisol-Ersatzmedikamente (wie Hydrocortison) einnehmen. Relacorilant blockiert die Rezeptoren, an denen diese Ersatzmedikamente wirken müssen. Dies kann eine akute Nebennierenrindeninsuffizienz (Addison-Krise) auslösen, die einen medizinischen Notfall darstellt.

Relacorilant is a potent and selective GR modulator (SGRM) that antagonizes the effects of cortisol activity. Relacorilant binds to the GR with a K_i of 0.15 nM, with no measurable binding with the progesterone, estrogen, mineralocorticoid, or androgen receptors.

Relacorilant, administered orally at doses that achieved systemic exposure similar to those seen in phase 1 (healthy volunteer) studies has shown efficacy in multiple *in vivo* models of Cushing syndrome and solid tumor cancers

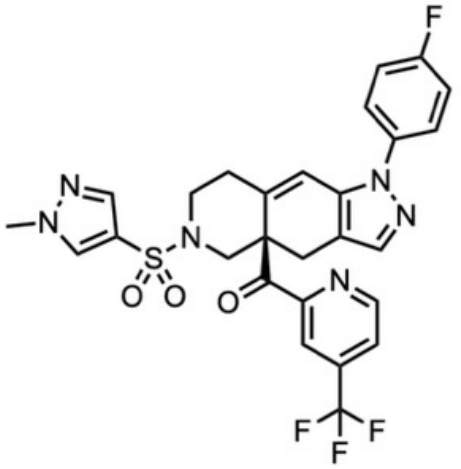


Relacorilant und Cortisol-Ersatztherapie

Eine Cortisol-Ersatztherapie (Substitution) ist in der Regel das Gegenteil dessen, was Relacorilant bewirkt. Während Relacorilant Cortisol-**Überschuss** bekämpft, wird eine Ersatztherapie bei einem Cortisol-**Mangel** (Adrenalinsuffizienz) angewendet.

Wichtige Zusammenhänge zwischen beiden:

- **Vermeidung von Adrenalinsuffizienz:** Da Relacorilant die Cortisol-Rezeptoren blockiert, besteht theoretisch das Risiko, dass die Cortisolwirkung *zu stark* unterdrückt wird, was eine künstliche Adrenalinsuffizienz auslösen könnte. In klinischen Studien traten jedoch bisher keine Fälle von klinisch manifester Adrenalinsuffizienz unter Relacorilant auf.
- **Kein "Stress-Dose"-Ersatz:** Patienten, die Relacorilant einnehmen und unter schweren körperlichen Stress (z. B. eine Operation oder schwere Infektion) geraten, benötigen möglicherweise eine vorübergehende Unterbrechung des Medikaments oder eine zusätzliche Gabe von Steroiden ("Stress-Dosis"), da ihr Körper die blockierten Rezeptoren in Stresssituationen nicht effektiv nutzen kann.
- **Abgrenzung zu Mifepriston:** Im Gegensatz zum älteren Medikament Mifepriston (Korlym) wirkt Relacorilant selektiver. Es blockiert nicht die Progesteron-Rezeptoren, was Nebenwirkungen wie abnormale Gebärmutterblutungen vermeidet.



Overall survival with relacorilant and nab-paclitaxel in patients with platinum-resistant ovarian cancer (ROSELLA): a phase 3 randomised controlled trial

Summary

Background Relacorilant is a selective glucocorticoid receptor antagonist that increases the sensitivity of many cancer cell types to chemotherapy. The efficacy and safety of relacorilant plus nab-paclitaxel were assessed in the phase 3 ROSELLA (GOG-3073, ENGOT-ov72, APGOT-Ov10, and LACOG-0223) trial; the combination showed significant improvement in progression-free survival among patients with platinum-resistant ovarian cancer compared with nab-paclitaxel monotherapy. Results of the final overall survival analysis are reported here.

Methods In this open-label phase 3 trial, patients were randomly assigned 1:1 to receive relacorilant (150 mg orally the day before, day of, and day after nab-paclitaxel infusion) plus nab-paclitaxel (80 mg/m^2 intravenously on days 1, 8, and 15 of each 28-day cycle) or nab-paclitaxel monotherapy (100 mg/m^2 intravenously on the aforementioned schedule). Patients, aged 18 years or older, with one to three lines of previous anticancer therapy and platinum-resistant disease (progression <6 months from their last dose of platinum) were eligible. The trial was conducted at 117 hospitals and community oncology centres in 14 countries across Australia, Europe, Latin America, North America, and South Korea. Progression-free survival, assessed by blinded independent central review, and overall survival (time from randomisation to death from any cause) were dual primary endpoints. Additional prespecified endpoints included safety, second progression-free survival (time from randomisation to disease progression on subsequent anticancer therapy or death due to any cause, whichever occurred first), and patient-reported outcomes. This trial is registered at ClinicalTrials.gov, NCT05257408, and is ongoing.

Findings Between Jan 5, 2023, and April 8, 2024, 381 patients were randomly assigned to the relacorilant combination group (n=188) or the nab-paclitaxel monotherapy group (n=193). All patients had received bevacizumab; 167 (44%) had received three previous lines of therapy, and 234 (61%) had received a poly(ADP-ribose) polymerase inhibitor. At a median follow-up of 24·8 months (95% CI 23·6–25·7), the addition of relacorilant to nab-paclitaxel resulted in a statistically and clinically significant improvement in overall survival compared with nab-paclitaxel monotherapy (hazard ratio for death 0·65 [95% CI 0·51–0·83]; p=0·0004); 18-month overall survival was 46% and 27%, respectively. The median overall survival in the relacorilant combination group was extended by 4·1 months compared with the nab-paclitaxel monotherapy group (16·0 [95% CI 13·0–18·3] *vs* 11·9 months [10·0–13·8]). Subsequent anticancer treatments were similar across study groups. Adverse events were similar in both groups when adjusted for duration of study treatment. Neutropenia (121 [64%]), anaemia (115 [61%]), fatigue (101 [54%]), and nausea (82 [44%]) were the most common adverse events in the relacorilant combination group. No new safety signals were observed with additional follow-up since the primary analysis.

Interpretation The addition of relacorilant to nab-paclitaxel led to significantly longer overall survival in patients with platinum-resistant ovarian cancer, without the need for biomarker selection. The findings support relacorilant plus nab-paclitaxel as a potential new standard treatment option for patients with platinum-resistant ovarian cancer.

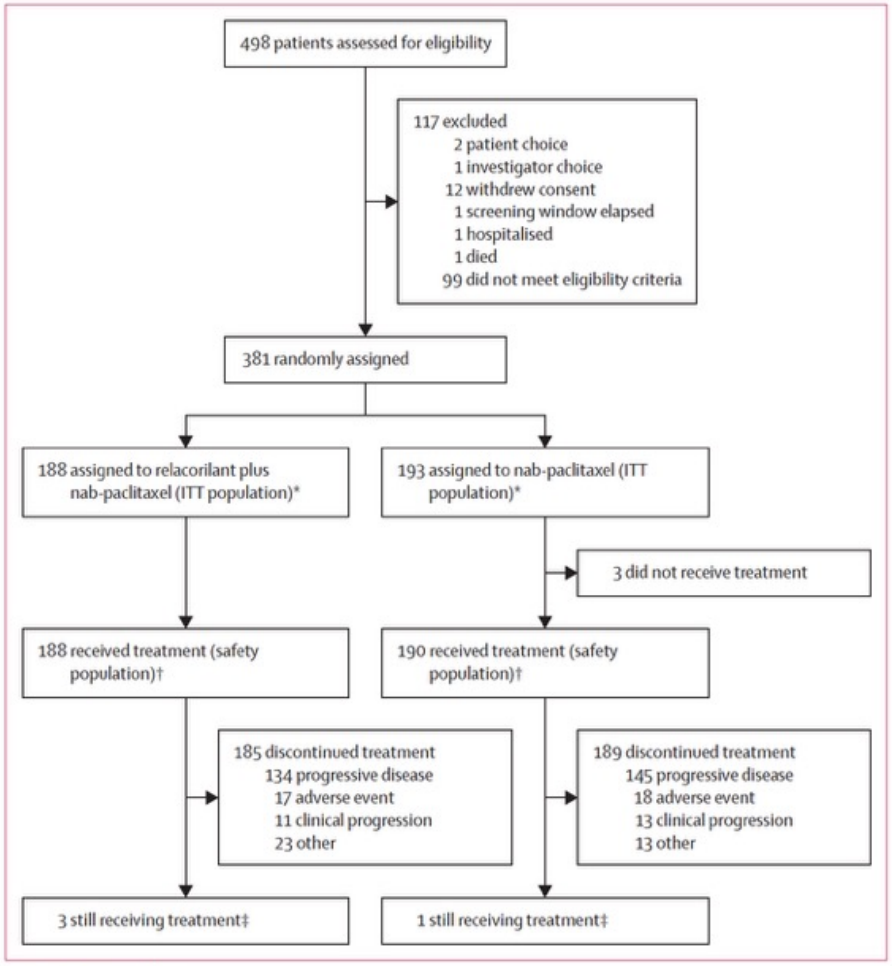


Figure 1: **Trial profile**

Three patients in the nab-paclitaxel monotherapy group withdrew consent and did not receive treatment. ITT=intention-to-treat. *All randomly assigned patients were analysed according to the randomised treatment group. †All randomly assigned patients who received at least one dose of study treatment (ie, relacorilant plus nab-paclitaxel or nab-paclitaxel monotherapy). ‡Refers to patients on nab-paclitaxel at the data cutoff of Jan 8, 2026.

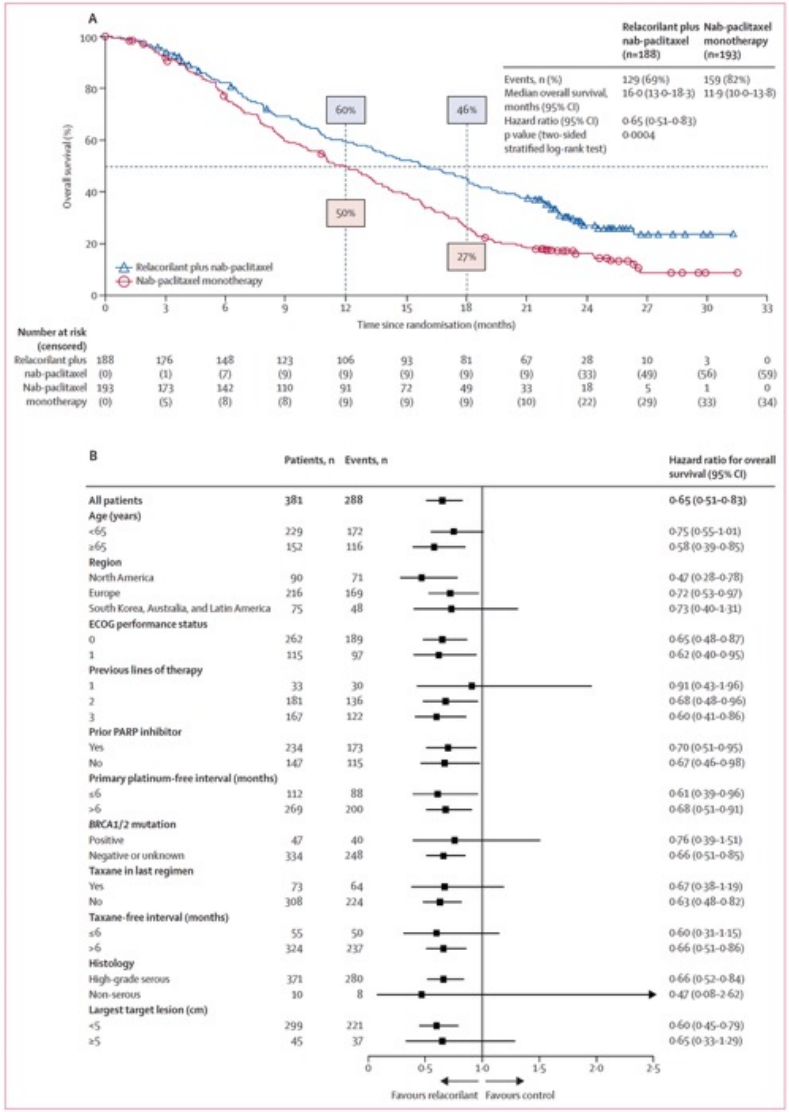


Figure 2: **Overall survival**

(A) Kaplan–Meier estimates of overall survival (time from randomisation to death from any cause) among patients who received relacorilant plus nab-paclitaxel and those who received nab-paclitaxel monotherapy. (B) Results of exploratory subgroup analyses of overall survival in the intention-to-treat population represented as forest plots. The HRs reported throughout the figure are based on a Cox proportional hazards model, stratified according to the randomisation factors that were collected in the interactive response technology system, except when the randomisation factor was the subgroup under analysis; in which case, only a single stratification variable was used. Under the assumption of proportional hazards, a HR of less than 1 indicates a reduction in the hazard in favour of the combination group. Circles and triangles indicate censored data. BRCA=breast cancer gene. HR=hazard ratio. ECOG=Eastern Cooperative Oncology Group. PARP=poly(ADP-ribose) polymerase.

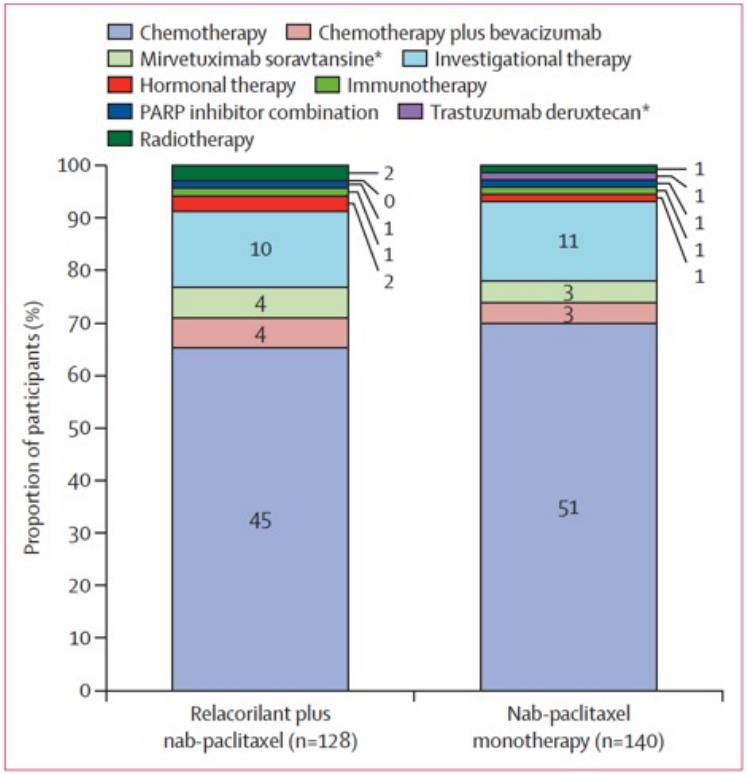


Figure 3: **First subsequent anticancer therapies**

First subsequent therapy received by 128 (68%) of 188 patients from the relacorilant combination group and 140 (73%) of 193 patients from the nab-paclitaxel monotherapy group who discontinued their assigned trial treatment and received subsequent therapy. Chemotherapy included both monotherapy and combination regimens. The most-used chemotherapy agents in the first subsequent regimen in the relacorilant combination group (n=188) versus the nab-paclitaxel monotherapy group (n=193) were gemcitabine (34 [18%] *vs* 38 [20%]), pegylated liposomal doxorubicin (31 [17%] *vs* 31 [16%]), carboplatin (eight [4%] *vs* 11 [6%]), and topotecan (four [2%] *vs* ten [5%]). PARP=poly(ADP-ribose) polymerase. *Monotherapy or combination therapy.

	Relacorilant plus nab-paclitaxel (n=188)		Nab-paclitaxel monotherapy (n=190)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any adverse event	188 (100%)	141 (75%)	189 (99%)	113 (59%)
Any serious adverse event	66 (35%)	60 (32%)	45 (24%)	39 (21%)
Any adverse event resulting in death	4 (2%)*	..	..	..
Any adverse event leading to relacorilant discontinuation	19 (10%)	..	..	..
Any adverse event leading to nab-paclitaxel discontinuation	18 (10%)	..	15 (8%)	..
Adverse events reported in ≥20% of the patients in either group (by preferred term)				
Neutropenia†	121 (64%)	82 (44%)	93 (49%)	48 (25%)
Anaemia‡	115 (61%)	34 (18%)	106 (56%)	17 (9%)
Fatigue§	101 (54%)	17 (9%)	85 (45%)	3 (2%)
Nausea	82 (44%)	7 (4%)	68 (36%)	6 (3%)
Diarrhoea	74 (39%)	7 (4%)	52 (27%)	3 (2%)
Alopecia	72 (38%)	1 (1%)	59 (31%)	0
Constipation	62 (33%)	1 (1%)	51 (27%)	0
Abdominal pain	55 (29%)	4 (2%)	54 (28%)	2 (1%)
Vomiting	49 (26%)	5 (3%)	43 (23%)	3 (2%)
Decreased appetite	41 (22%)	3 (2%)	22 (12%)	1 (1%)
Hypomagnesaemia	40 (21%)	3 (2%)	36 (19%)	2 (1%)

*There were four deaths on study treatment (or within 30 days of the last dose of study drug) due to adverse events, all in the combination group (one each due to cardiac arrest, intestinal perforation, ischaemic stroke, and septic shock). One death (septic shock, on study day 87 in a patient with febrile neutropenia) was considered related to nab-paclitaxel by the investigator, and none of the deaths were related to relacorilant. The cause of death for the other three patients was attributed to their advanced ovarian cancer. †Combined term including neutropenia, decreased neutrophil count, and febrile neutropenia. ‡Combined term including anaemia, decreased haemoglobin, and decreased red blood cell count. §Combined term including fatigue and asthenia.

Table 1: **Adverse events in the safety population**

	Relacorilant plus nab-paclitaxel (n=188)	Nab-paclitaxel monotherapy (n=190)
Alanine aminotransferase or aspartate aminotransferase increase		
>3–5 × ULN	3 (2%)	13 (7%)
>5–8 × ULN	4 (2%)	3 (2%)
>8–10 × ULN	2 (1%)	0
>10 × ULN	1 (1%)	2 (1%)
Total bilirubin increase		
>2 × ULN	3 (2%)	4 (2%)
Alkaline phosphatase increase		
>2 × ULN	16 (9%)	24 (13%)
Hy's law* criteria met	0	0

ULN=upper limit of normal. *Hy's Law is a clinical rule stating that a drug is likely to cause serious liver injury when a patient develops alanine aminotransferase or aspartate aminotransferase 3 × or greater the upper limit of normal together with total bilirubin greater than 2 × the upper limit of normal, without evidence of cholestasis or another explanation.

Table 2: **Summary of liver function test abnormalities in the safety population**

Implications of all the available evidence

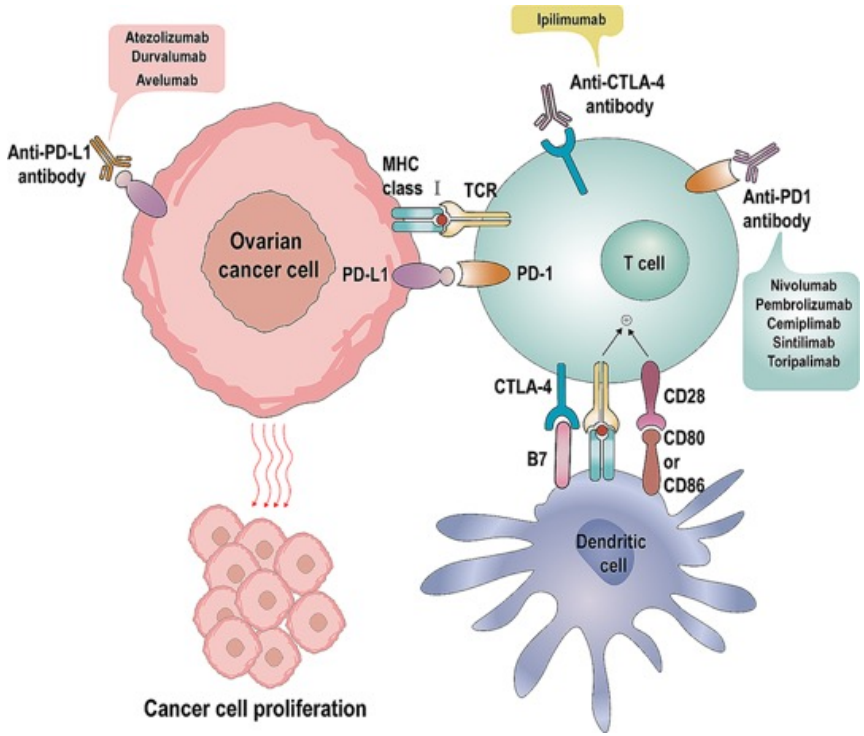
Combined with the evidence from previous studies, these positive overall survival data support relacorilant plus nab-paclitaxel as a potential new standard treatment option for patients with platinum-resistant ovarian cancer, without the need for biomarker selection. This study is the first positive clinical trial conducted with registrational intent for a selective glucocorticoid receptor antagonist in patients with cancer. The data supports the ongoing evaluation of relacorilant in other solid tumour indications and in combination with other classes of anticancer agents. In the AURELIA trial, the VEGF inhibitor bevacizumab also extends progression-free survival in combination with chemotherapy in this setting but has not shown a statistically significant overall survival benefit—probably owing, in part, to crossover to the investigational group at progression—and is predominantly used in earlier lines of therapy for patients with ovarian cancer. Furthermore, mirvetuximab soravtansine has shown an overall survival benefit in a third of patients with high-grade serous folate receptor α–positive ovarian cancer. The addition of pembrolizumab to weekly paclitaxel (with or without bevacizumab) has reported an overall survival benefit in a less pre-treated population. Additional studies will be needed to determine the appropriate sequencing of these agents.

Die Wirksamkeit von Immun-Checkpoint-Inhibitoren (ICI) bei Eierstockkrebs wird intensiv untersucht, hat jedoch bisher in klinischen Studien im Vergleich zu anderen Krebsarten eher **bescheidene Ergebnisse** gezeigt. Dennoch gibt es spezifische Patientenuntergruppen und Kombinationstherapien, die vielversprechende Ansätze bieten.

Zugelassene und häufig untersuchte ICI

Die meisten klinischen Studien konzentrieren sich auf die Blockade der PD-1/PD-L1- und CTLA-4-Signalwege.

- **Pembrolizumab (Keytruda):** Ein PD-1-Inhibitor, der von der FDA gewebeagnostisch für fortgeschrittenen Eierstockkrebs mit **hoher Mikrosatelliteninstabilität (MSI-H)**, **Mismatch-Reparatur-Defizienz (dMMR)** oder **hoher Tumormutationslast (TMB-H)** zugelassen ist.
- **Dostarlimab (Jemperli):** Ein PD-1-Inhibitor, zugelassen für Patientinnen mit fortgeschrittenem oder rezidivierendem Eierstockkrebs, der eine **dMMR** aufweist.
- **Nivolumab:** Ein PD-1-Inhibitor, der in Studien als Monotherapie oder in Kombination (z.B. mit Ipilimumab) untersucht wird, aber noch keine generelle Zulassung für Eierstockkrebs hat.
- **Avelumab & Durvalumab:** PD-L1-Inhibitoren, die vor allem in Kombination mit Chemotherapie oder PARP-Inhibitoren getestet werden.



Pembrolizumab plus weekly paclitaxel in platinum-resistant recurrent ovarian cancer (ENGOT-ov65/KEYNOTE-B96): a multicentre, randomised, double-blind, phase 3 study

Summary

Background Epithelial ovarian cancer frequently recurs and becomes resistant to platinum chemotherapy. We investigated whether adding pembrolizumab to weekly paclitaxel, with or without bevacizumab, improves progression-free survival and overall survival compared with weekly paclitaxel, with or without bevacizumab, in participants with platinum-resistant recurrent ovarian cancer who had received one to two previous systemic regimens.

Methods ENGOT-ov65/KEYNOTE-B96 is a randomised, double-blind, phase 3 study conducted at 187 gynaecologic oncology centres in 25 countries in the Americas, Asia, Europe, and Oceania. Adults (≥18 years) with histologically confirmed epithelial ovarian, fallopian tube, or primary peritoneal carcinoma, who received one to two previous systemic therapies including at least one platinum regimen and who progressed 6 months or less after the last platinum regimen, were eligible. Participants were randomly assigned 1:1 to intravenous pembrolizumab 400 mg every 6 weeks for up to 18 cycles plus open-label intravenous paclitaxel 80 mg/m² on days 1, 8, and 15 of each 21-day cycle or intravenous placebo (saline solution) every 6 weeks for up to 18 cycles plus open-label intravenous paclitaxel 80 mg/m² on days 1, 8, and 15 of each 21-day cycle; intravenous bevacizumab 10 mg/kg every 2 weeks was permitted per investigator. Randomisation was stratified by planned bevacizumab use, region, and PD-L1 combined positive score (CPS). The primary endpoint was investigator-assessed progression-free survival per RECIST version 1.1; the key secondary endpoint was overall survival. Results from two interim analyses and the final analysis are included in this Article. This study is registered with ClinicalTrials.gov, NCT05116189, and is now completed.

Bevacizumab (Handelsname **Avastin®**) ist ein therapeutischer Antikörper, der als Angiogenese-Hemmer das Wachstum neuer Blutgefäße in Tumoren blockiert, indem er den Wachstumsfaktor VEGF hemmt.

Findings Between Dec 13, 2021, and July 3, 2023, 643 female participants were randomly assigned; 322 to pembrolizumab plus paclitaxel and 321 to placebo plus paclitaxel. At the first interim analysis, pembrolizumab plus paclitaxel significantly improved progression-free survival versus placebo plus paclitaxel in both the PD-L1 CPS 1 or higher (median 8·3 months *vs* 7·2 months; hazard ratio [HR] 0·72, 95% CI 0·58–0·89; p=0·0014 [α=0·012]) and overall populations (median 8·3 months *vs* 6·4 months; HR 0·70, 95% CI 0·58–0·84; p<0·0001 [α=0·0023]), meeting the prespecified criteria for confirmatory efficacy. At the second interim analysis, overall survival was significantly improved in the PD-L1 CPS 1 or higher population (median 18·2 months *vs* 14·0 months; HR 0·76, 95% CI 0·61–0·94; p=0·0053 [α=0·0083]). At the final analysis, overall survival was significantly improved in the overall population (median 17·7 months *vs* 14·0 months; HR 0·82, 95% CI 0·69–0·97; p=0·011 [α=0·024]). Grade 3 or worse treatment-related adverse events occurred in 217 (68%) of 320 participants in the pembrolizumab plus paclitaxel group versus 176 (55%) of 318 participants in the placebo plus paclitaxel group. The most common treatment-related adverse events (any grade) included anaemia, peripheral neuropathy, alopecia, fatigue, and nausea. Treatment-related adverse events resulted in death in four participants (1%) in the pembrolizumab plus paclitaxel group (colitis, interstitial lung disease, acute myeloid leukaemia, and intestinal perforation) and in five participants (2%) in the placebo plus paclitaxel group (cardiac failure, intestinal perforation [in two participants], and large-intestine perforation [in two participants]).

Interpretation Pembrolizumab plus weekly paclitaxel, with or without bevacizumab, significantly improved progression-free survival and overall survival in participants with platinum-resistant recurrent ovarian cancer who had received one to two previous systemic regimens, supporting this regimen as a new treatment option for this population.

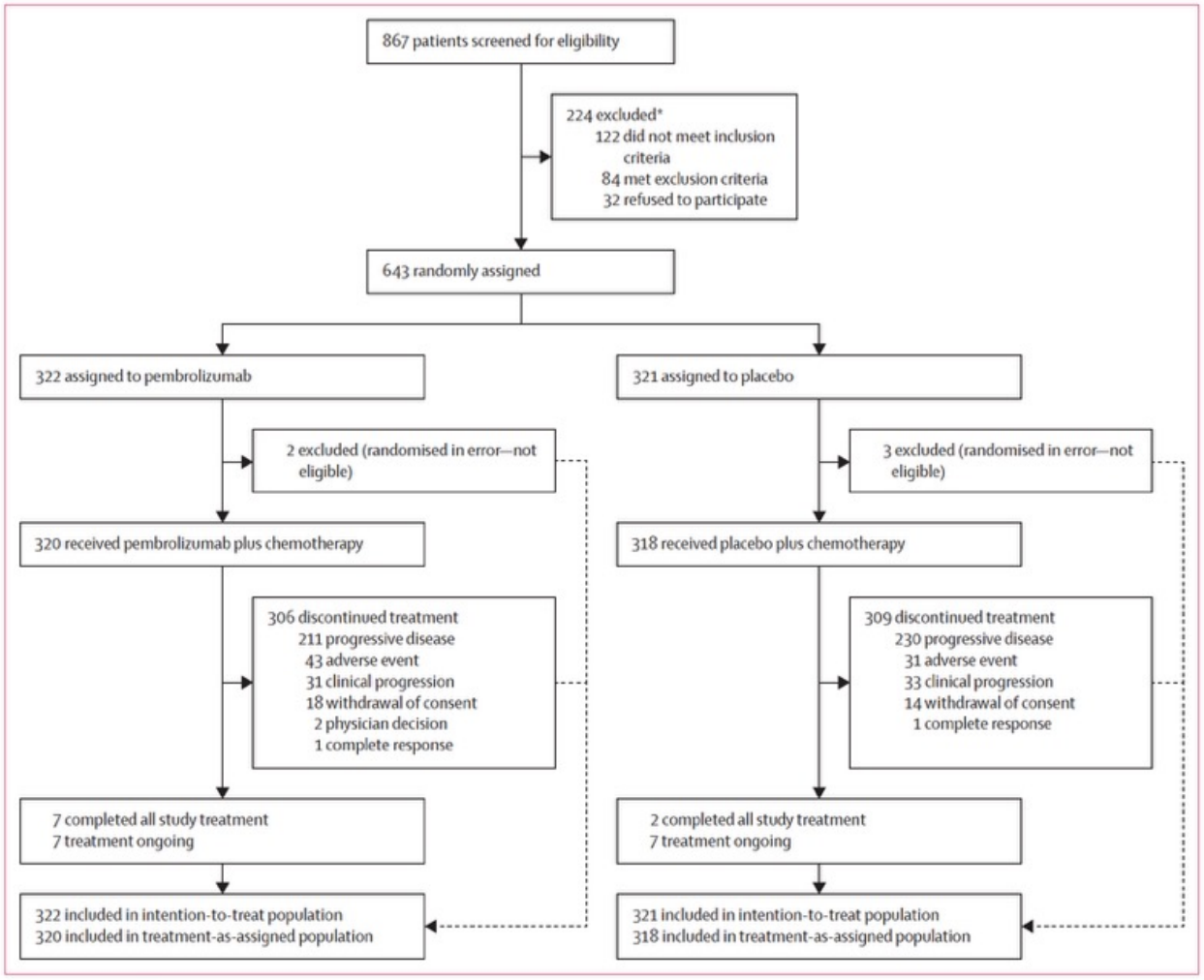


***Figure 1*: Trial profile**

*Participants might have failed screening for more than one reason. The reason for failing screening was not recorded for three participants.

	Pembrolizumab plus paclitaxel (n=322)	Placebo plus paclitaxel (n=321)
Age, years		
Median (IQR)	62 (53-69)	61 (53-68)
≥65	122 (38%)	114 (36%)
Race		
Asian	72 (22%)	58 (18%)
Black or African American	8 (2%)	6 (2%)
Multiple	12 (4%)	17 (5%)
Native Hawaiian or Other Pacific Islander	1 (<1%)	1 (<1%)
White	207 (64%)	217 (68%)
Missing	22 (7%)	22 (7%)
ECOG performance status score*		
0	179 (56%)	175 (55%)
1	142 (44%)	144 (45%)
Missing	1 (<1%)	2 (1%)
Bevacizumab use		
Planned	235 (73%)	236 (74%)
Actual	235 (73%)	236 (74%)
PD-L1 combined positive score		
<1	88 (27%)	89 (28%)
1 to <10	133 (41%)	132 (41%)
≥10	101 (31%)	100 (31%)
FIGO 2014 stage at diagnosis		
IA to IIB	24 (7%)	26 (8%)
IIIA to IIIC	183 (57%)	189 (59%)
IVA to IVB	115 (36%)	106 (33%)
Histology		
High-grade serous	278 (86%)	275 (86%)
Clear cell	24 (7%)	26 (8%)
Endometrioid	9 (3%)	4 (1%)
Low-grade serous	6 (2%)	10 (3%)
Carcinosarcoma	3 (1%)	5 (2%)
Other	2 (1%)	1 (<1%)
Prior lines of therapy		
One line	121 (38%)	113 (35%)
Two lines	200 (62%)	207 (64%)
Three lines	1 (<1%)	1 (<1%)
Prior exposure		
Anti-PD-1 or PD-L1	7 (2%)	7 (2%)
Bevacizumab	149 (46%)	146 (45%)
PARP inhibitor	112 (35%)	123 (38%)
Platinum-free interval, months		
<3	137 (43%)	161 (50%)
3 to 6	183 (57%)	155 (48%)
>6	2 (1%)	5 (2%)

Data are n (%) or median (IQR). ECOG=Eastern Cooperative Oncology Group. FIGO=International Federation of Gynecology and Obstetrics. PARP=poly(ADP-ribose) polymerase. *ECOG performance status scores range from 0 to 5, with 0 indicating no symptoms and higher scores indicating greater disability.

***Table 1*: Baseline demographic and disease characteristics in the intention-to-treat population**

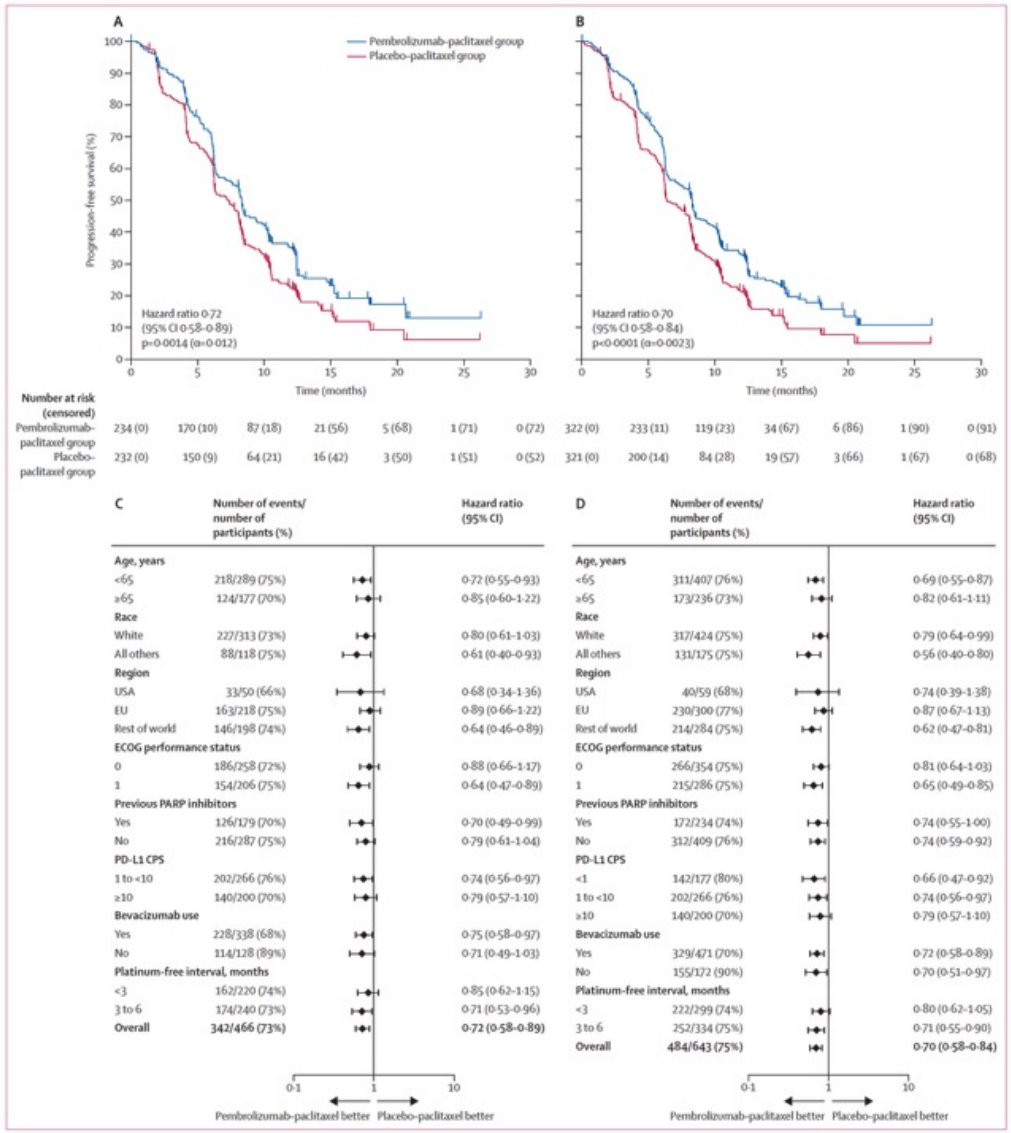


Figure 2: **Progression-free survival**

(A) Kaplan–Meier estimates of progression-free survival in the PD-L1 CPS of 1 or higher population at the first interim analysis. (B) Kaplan–Meier estimates of progression-free survival in the overall population at the first interim analysis. (C) Analysis of progression-free survival in protocol-specified subgroups of the PD-L1 CPS of 1 or higher population. (D) Analysis of progression-free survival in protocol-specified subgroups of the overall population. CPS=combined positive score. ECOG=Eastern Cooperative Oncology Group. PARP=poly(ADP-ribose) polymerase.

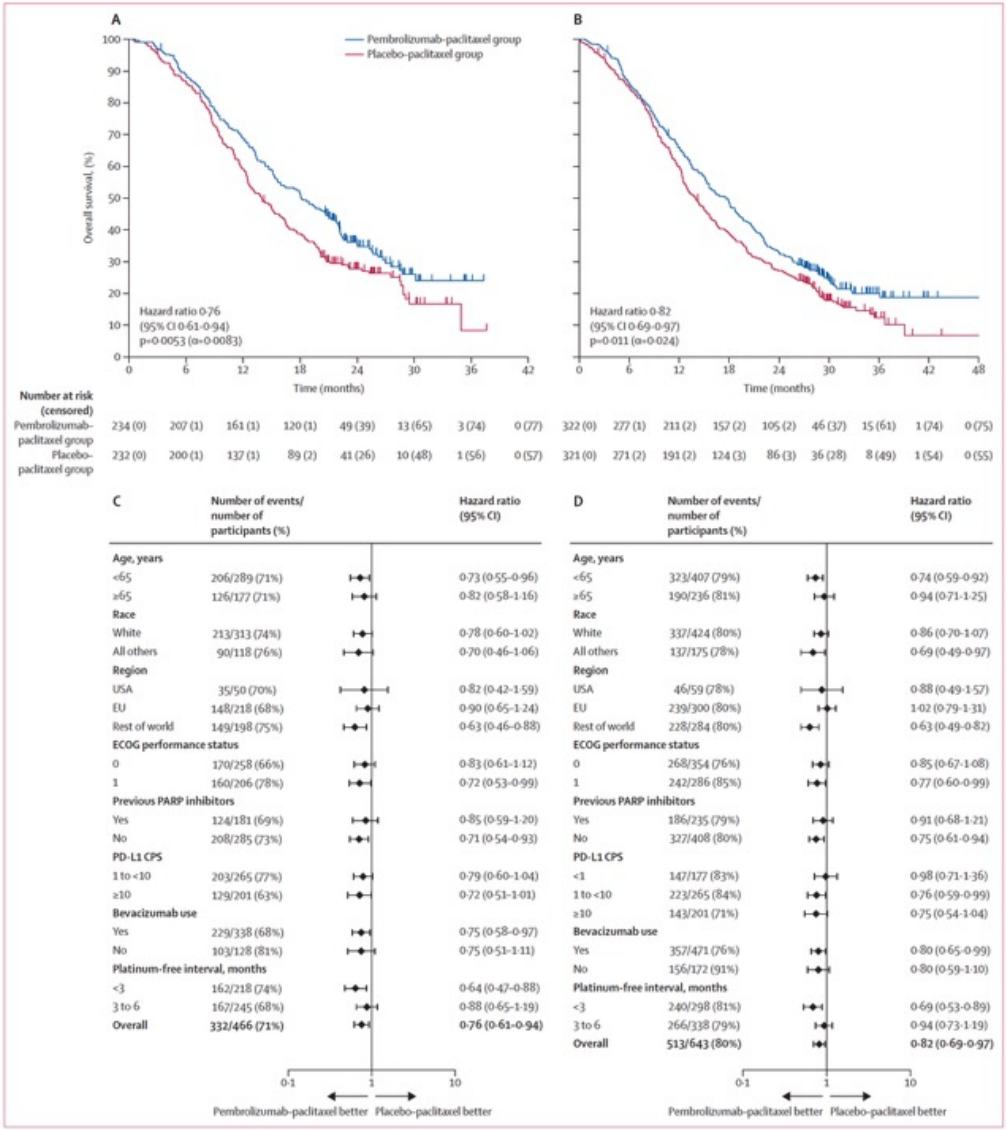


Figure 3: **Overall survival**

(A) Kaplan–Meier estimates of overall survival in the PD-L1 CPS of 1 or higher population at the second interim analysis. (B) Kaplan-Meier estimates of overall survival in the overall population at the final analysis. (C) Analysis of overall survival in protocol-specified subgroups of the PD-L1 CPS of 1 or higher population. (D) Analysis of overall survival in protocol-specified subgroups of the overall population. CPS=combined positive score. ECOG=Eastern Cooperative Oncology Group. PARP=poly(ADP-ribose) polymerase.

	Pembrolizumab plus paclitaxel (n=320)		Placebo plus paclitaxel (n=318)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any adverse event*	319 (100%)	265 (83%)	316 (99%)	225 (71%)
Any treatment-related adverse event†	313 (98%)	217 (68%)	303 (95%)	176 (55%)
Serious adverse event‡	180 (56%)	..	123 (39%)	..
Serious treatment-related adverse event†	107 (33%)	..	63 (20%)	..
Adverse event leading to discontinuation	136 (43%)	..	109 (34%)	..
Treatment-related adverse event leading to discontinuation	120 (38%)	..	90 (28%)	..
Adverse event leading to death	16 (5%)	..	14 (4%)	..
Treatment-related adverse event leading to death	4 (1%)	..	5 (2%)	..
Treatment-related adverse events occurring in ≥20% of participants in a trial group				
Anaemia	159 (50%)	38 (12%)	134 (42%)	25 (8%)
Peripheral neuropathy	124 (39%)	17 (5%)	99 (31%)	19 (6%)
Alopecia	121 (38%)	0	108 (34%)	0
Fatigue	113 (35%)	17 (5%)	105 (33%)	19 (6%)
Nausea	100 (31%)	4 (1%)	87 (27%)	4 (1%)
Epistaxis	94 (29%)	1 (<1%)	69 (22%)	0
Diarrhoea	93 (29%)	10 (3%)	79 (25%)	3 (1%)
Neutrophil count decreased	92 (29%)	59 (18%)	71 (22%)	43 (14%)
White blood cell count decreased	75 (23%)	38 (12%)	57 (18%)	28 (9%)
Neutropenia	73 (23%)	45 (14%)	78 (25%)	44 (14%)
Immune-mediated adverse event§	126 (39%)	38 (12%)	60 (19%)	11 (3%)
Hypothyroidism	58 (18%)	0	19 (1%)	0
Infusion reaction	19 (6%)	6 (2%)	15 (5%)	2 (1%)
Hyperthyroidism	16 (5%)	0	2 (1%)	0
Adrenal insufficiency	15 (5%)	7 (2%)	0	0
Pneumonitis	15 (5%)	2 (1%)	6 (2%)	3 (1%)

*Listed are adverse events that occurred during the treatment period or within 30 days after the treatment period (within 90 days for serious events). The as-treated population included all the participants who had undergone randomisation and received at least one dose of study treatment. The severity of adverse events was graded according to the Common Terminology Criteria for Adverse Events, version 5.0, of the National Cancer Institute. †Treatment-related adverse events were events that were attributed to the trial treatment by the investigators; treatment-related adverse events that occurred in at least 20% of the participants are reported; the events are listed in descending order of frequency in the pembrolizumab-paclitaxel group; participants can have had more than one event. ‡Defined as any untoward medical occurrence that was life-threatening, required hospitalisation, or resulted in disability or death. §Immune-mediated adverse events were determined according to a list of terms specified by the sponsor, regardless of attribution to any trial treatment by the investigators; adverse events of interest that occurred in at least 15 participants are reported.

Table 2: **Adverse events in either treatment group of the as-treated population**

Added value of this study

The randomised, placebo-controlled phase 3 ENGOT-ov65/KEYNOTE-B96 study showed that adding pembrolizumab to weekly paclitaxel, with or without bevacizumab, significantly prolongs progression-free survival and overall survival in platinum-resistant recurrent ovarian cancer in both the PD-L1 combined positive score 1 or higher and the overall populations, representing the first demonstration of an overall survival benefit with an immune checkpoint inhibitor regimen in ovarian cancer. The magnitude and consistency of benefit across clinically relevant subgroups—including older patients, those previously treated with poly(ADP-ribose) polymerase inhibitors, and those with short platinum-free intervals—underscore the robustness of these findings. Safety outcomes were consistent with the known profiles of pembrolizumab and weekly paclitaxel, with no new safety signals and manageable immune-mediated adverse events.

Implications of all the available evidence

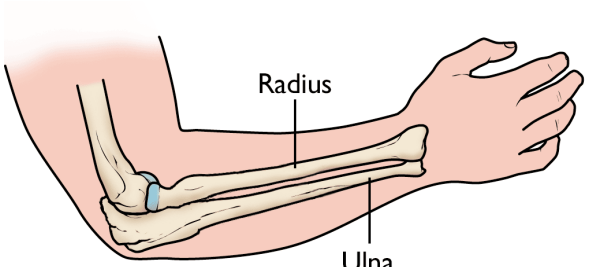
Taken together with previous negative phase 3 trials of immune checkpoint inhibitors combined with non-metronomic chemotherapy in platinum-resistant recurrent ovarian cancer, the findings from ENGOT-ov65/KEYNOTE-B96 indicate that the choice and schedule of chemotherapy are critical determinants of immunotherapy effectiveness. Weekly (metronomic) paclitaxel appears to potentiate checkpoint blockade, consistent with translational data suggesting enhanced antigen presentation, reduced immunosuppressive cell populations, and a more immunogenic tumour microenvironment with metronomic dosing. These results establish pembrolizumab plus weekly paclitaxel, with or without bevacizumab, as an effective treatment option for platinum-resistant recurrent ovarian cancer, provide the first randomised evidence of an overall survival benefit with immunotherapy in ovarian cancer, and support this regimen as a new standard of care.

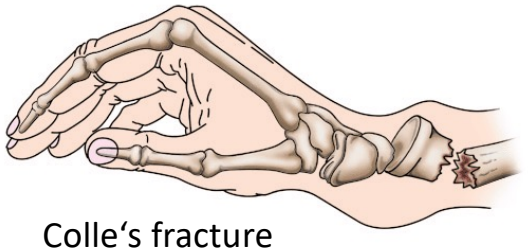
Schwer verschobene distale Radiusfrakturen sind komplexe Brüche der Speiche nahe dem Handgelenk, bei denen die Knochenenden deutlich aus ihrer anatomischen Position verschoben sind. Solche Verletzungen entstehen oft durch hochenergetische Traumata wie Stürze aus großer Höhe oder Verkehrsunfälle und erfordern eine spezialisierte Behandlung, um die langfristige Funktion des Handgelenks zu erhalten.

Wichtige Merkmale und Diagnostik

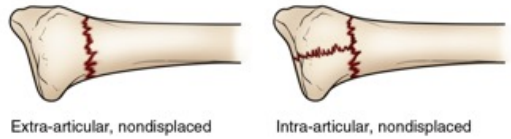
Eine starke Verschiebung (Dislokation) ist oft schon äußerlich durch eine deutliche Fehlstellung des Handgelenks erkennbar, wie etwa die typische „Bajonett-Stellung“ oder „Dinner-Fork-Deformität“.

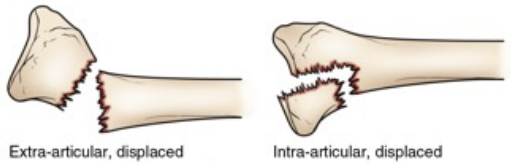
- **Diagnose:** Die Bestätigung erfolgt durch Röntgenaufnahmen in zwei Ebenen. In komplexen Fällen wird oft ein **CT-Scan** durchgeführt, um das Ausmaß der Gelenkbeteiligung und Trümmerzonen genau zu beurteilen.
- **Notfallsymptome:** Sofortige ärztliche Hilfe ist notwendig bei Taubheitsgefühlen in den Fingern (Hinweis auf Nervenkompression), Blässe der Hand oder offenen Wunden.

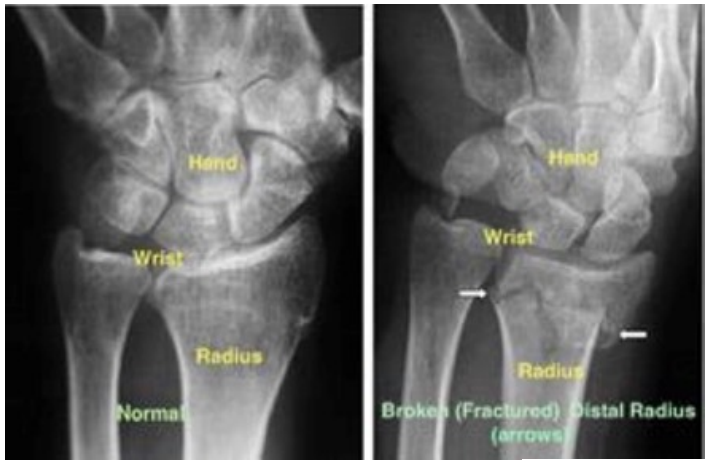




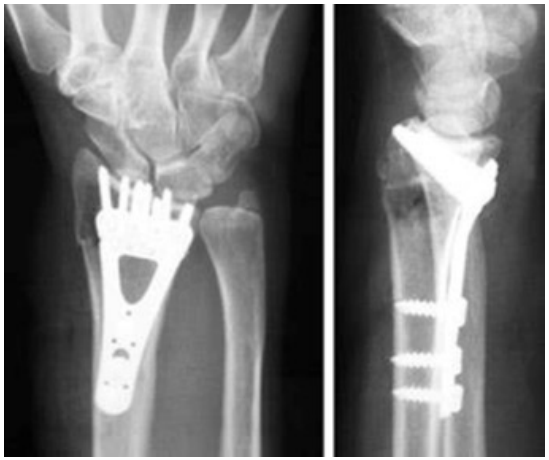
Colle‘s fracture



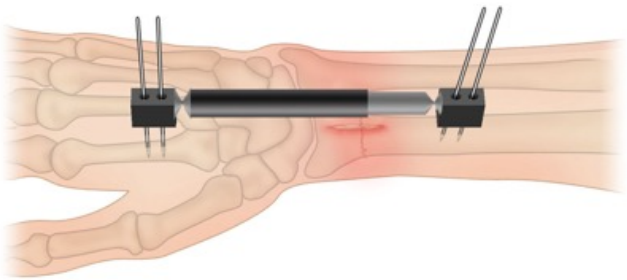




Normal Distale Radius-Fraktur



Platte mit Schrauben



Externe Fixation

Non-surgical casting versus surgical reduction for children with severely displaced distal radial fractures (the CRAFFT Study): a multicentre, randomised, controlled non-inferiority trial and economic evaluation

Summary

Background Severely displaced distal radial fractures are among the most common and controversial injuries in children. Despite observational evidence of reliable remodelling with growth in younger children, their alarming radiographic appearance—particularly when completely displaced (off-ended)—has driven routine surgical reduction and fixation. The Children's Radius Acute Fracture Fixation Trial (CRAFFT) aimed to evaluate the clinical and cost-effectiveness of surgical reduction compared with non-surgical casting.

Methods This pragmatic, multicentre, randomised, non-inferiority trial included participants (aged 4–10 years) with a severely displaced distal radial fracture from 49 hospitals in the UK. Recruiting centres were secondary or tertiary care hospitals providing acute paediatric trauma care. Participants were randomly assigned to either non-surgical casting or surgical reduction, using a minimisation algorithm with a random element and stratification factors were centre, age group, fracture location, and displacement severity. Participants and their parents and carers could not be masked to treatment. Surgical reduction was performed under general anaesthesia or conscious sedation, to restore anatomical alignment, with fixation permitted at the discretion of the surgeon. Non-surgical care involved immobilisation of the fracture in a plaster cast without general anaesthesia or sedation, and without purposeful manipulation of the fracture position. Immobilisation of the fracture beyond 6 weeks post-randomisation was not recommended. The primary outcome was upper limb function at 3 months, measured using the Patient Report Outcomes Measurement System (PROMIS) Upper Extremity Score for Children in the intention-to-treat population, which included all participants in the groups to which they were randomly assigned, irrespective of treatment received. The non-inferiority margin was conservatively set at –2·5 points for the main trial population. A prespecified subgroup analysis was powered to assess whether non-surgical casting could exclude a larger more clinically relevant margin of –5 points among children with completely off-ended fractures. Complications and serious adverse events were summarised in a safety (as-treated) population defined by treatment received. A within-trial economic evaluation was undertaken from the perspective of the UK National Health Service (NHS) and Personal Social Services over a 12-month time period. The trial was registered with the ISRCTN registry, ISRCTN10931294, recruitment is complete and extended follow-up to 3-years post-randomisation is ongoing.

Findings Between Aug 11, 2020, and May 30, 2024, 1227 children were screened for eligibility across 49 UK hospitals. 477 children were excluded (54 met exclusion criteria and 423 did not enter the study, the majority for lack of clinical or parental equipoise). 750 participants were randomly assigned, 375 to the non-surgical casting group and 375 to the surgical reduction group. 456 (61%) participants were male, 294 (39%) were female, and the median age of participants was 7·9 years (IQR 6·5–9·5). 329 (44%) of the 750 participants had completely off-ended fractures. Primary outcome data were collected from 640 (85%) participants. At 3 months post-randomisation, the mean PROMIS Upper Extremity score was 44·9 (SD 8·7) in the non-surgical casting group and 46·6 (8·8) in the surgical reduction group (adjusted mean difference –1·64 [95% CI –2·84 to –0·44]), with the confidence interval favouring surgical reduction but extending beyond the prespecified non-inferiority margin of –2·5 points. In children with completely off-ended fractures, findings were consistent with non-inferiority against the wider, prespecified margin for this group. Most complications within 8 weeks occurred in the surgical reduction group, including pressure damage (n=2), wound infections (n=6), scarring (n=5), and nerve irritation (n=1). During the 12-months of follow-up, refracture occurred in 13 participants (nine after non-surgical casting and four after surgical reduction). From an NHS and Personal Social Services perspective, non-surgical casting was associated with a significant reduction in mean cost per patient of £1665 (95% CI 1487 to 1843) and a marginal incremental reduction in quality-adjusted life-years (QALYs; –0·023 [95% CI –0·037 to –0·009]). The probability of non-surgical casting being cost-effective at the £20 000 and £30 000 per QALY threshold was 100%, indicating that the small short-term functional advantage of surgical reduction was not cost-effective.

Interpretation The CRAFFT trial did not demonstrate non-inferiority of non-surgical casting at 3 months against a conservative margin; however, the observed difference in favour of surgical reduction was small, below thresholds that families considered meaningful, and did not persist beyond early recovery. Surgical reduction was associated with higher costs, early procedural complications, and only a modest improvement in cosmetic appearance, supporting consideration of a cast-first strategy for most children.

Nicht „nicht-schlechter-als“ OP (aber)

Funding National Institute for Health and Care Research (NIHR) Health Technology Assessment programme (17/22/02) and the NIHR Oxford Biomedical Research Centre.

Introduction

Distal radial fractures are the most common bony injury in children, accounting for about half of paediatric long-bone fractures.[1] Severely displaced injuries are typically treated by closed reduction under sedation or general anaesthesia, often followed by Kirschner wire or plate fixation.[2] This procedure restores immediate alignment, at the cost of anaesthesia, procedural pain, and frequent complications, including re-displacement and wire-related problems.[3,4] Despite this established practice, there is a growing uncertainty about whether surgical reduction is necessary.

Children's bones have a remarkable capacity to remodel, distinguishing them from adult bones. Through this process, deformity corrects as the child grows, with the greatest potential for remodelling found close to areas of active growth, particularly the growth plates (physes). Remodelling is greatest in younger children and close to active growth plates.

Observational studies of distal radial fractures in children up to age 10 years suggest that even completely displaced fractures—including those termed as completely off-ended fractures—can correct over time with restoration of function and little long-term deformity.[5,6] Although such fractures appear visibly bent and alarming to families and clinicians, these sometimes realign naturally without manipulation or fixation. A small UK comparative cohort found more complications in children undergoing surgical reduction than in those treated with simple casting.[7] The only randomised trial to date, published only as an abstract and based on radiographic outcomes, reported no advantage for surgical reduction in children younger than 11 years.[8]

This uncertainty led the British Society for Children's Orthopaedic Surgery to prioritise the treatment of these fractures for future research, resulting in the development of the Children's Radius Acute Fracture Fixation Trial (CRAFFT).

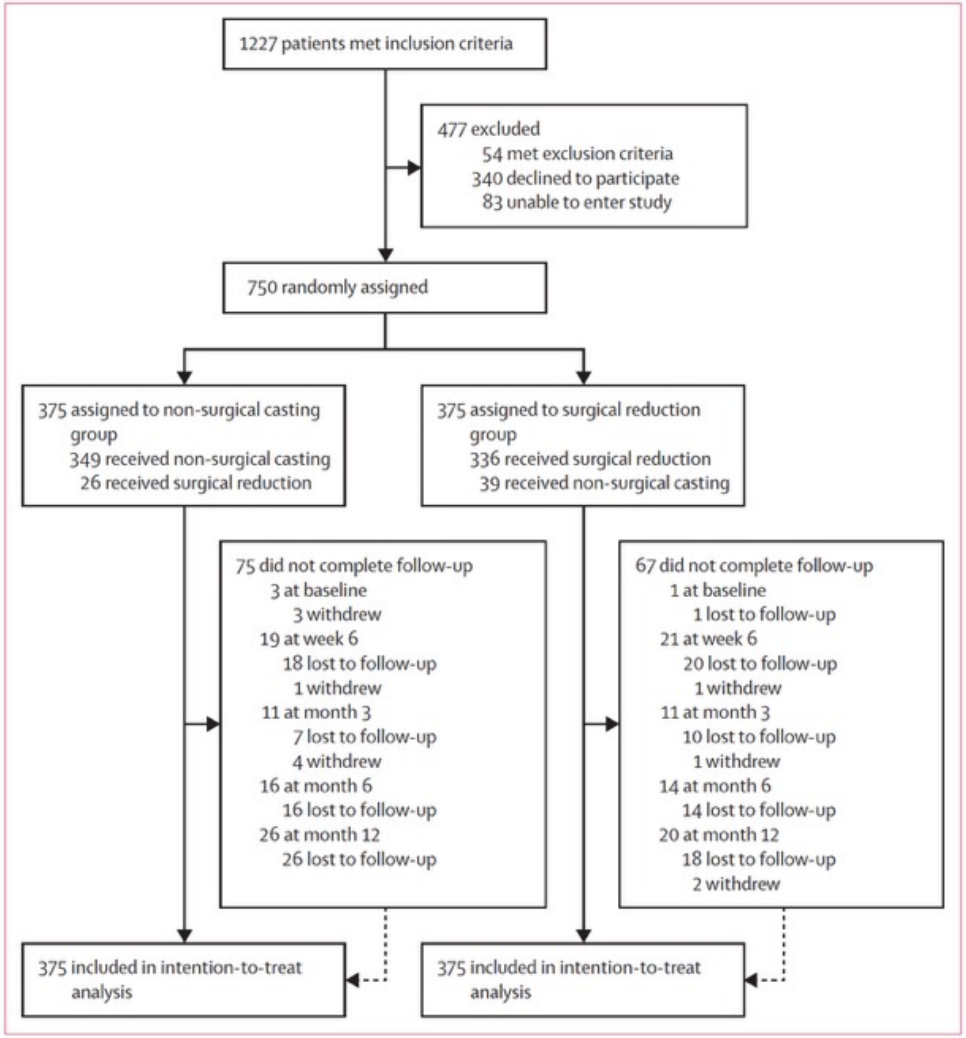


Figure 1: **Trial profile**
Withdrawal indicates that the participant actively declined further study participation from that point onwards.

	Non-surgical casting group (n=375)	Surgical reduction group (n=375)	Total (N=750)
Sex			
Male	225 (60%)	231 (62%)	456 (61%)
Female	150 (40%)	144 (38%)	294 (39%)
Age, years			
Median (IQR)	7·8 (6·5–9·5)	8·0 (6·5–9·6)	7·9 (6·5–9·5)
Age group			
7–10 years	249 (66%)	249 (66%)	498 (66%)
4–6 years	126 (34%)	126 (34%)	252 (34%)
Mechanism of injury*			
High energy fall	192 (51%)	202 (54%)	394 (53%)
Low energy fall	183 (49%)	173 (46%)	356 (47%)
Side of injury			
Left	213 (57%)	224 (60%)	437 (58%)
Right	162 (43%)	151 (40%)	313 (42%)
Injury to dominant arm			
No	195 (52%)	208 (55%)	403 (54%)
Yes	172 (46%)	160 (43%)	332 (44%)
Unsure or ambidextrous	7 (2%)	7 (2%)	14 (2%)
Missing	1 (<1%)	0	1 (<1%)
Displacement severity			
Completely off-ended	165 (44%)	164 (44%)	329 (44%)
Not completely off-ended	210 (56%)	211 (56%)	421 (56%)
Fracture location			
Metaphyseal fracture	303 (81%)	302 (81%)	605 (81%)
Physeal fracture	72 (19%)	73 (19%)	145 (19%)

Data are n (%). *The mechanism of injury was determined by the treating clinician for each participant.

Table 1: **Baseline characteristics**

	Non-surgical casting	Surgical reduction	PROMIS Upper Extremity Score treatment difference	Mean difference (95% CI)
All patients	**44·9**	**46·6**		**−1·64 (−2·84 to −0·44)**
Fracture location				
Physeal fracture	45·8	47·4		−1·66 (−2·89 to −0·43)
Metaphyseal	44·7	46·3		−1·52 (−3·47 to 0·44)
Displacement severity				
Completely off-ended	44·2	45·8		−1·39 (−2·86 to 0·09)
Incompletely off-ended	45·4	47·1		−1·79 (−3·07 to −0·51)
Age (years)				
6·5 (25th percentile)				−1·58 (−2·90 to −0·25)
7·9 (50th percentile)				−1·62 (−2·82 to −0·42)
9·5 (75th percentile)				−1·67 (−3·06 to −0·29)

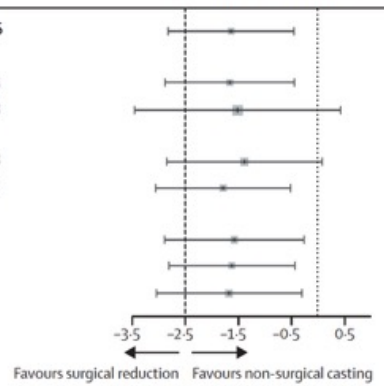


***Figure 2*: PROMIS Upper Extremity Score treatment difference at 3 months by subgroups, including fracture location, displacement severity, and participant age at randomisation**
Surgical reduction is the reference group. PROMIS=Patient Report Outcomes Measurement System.

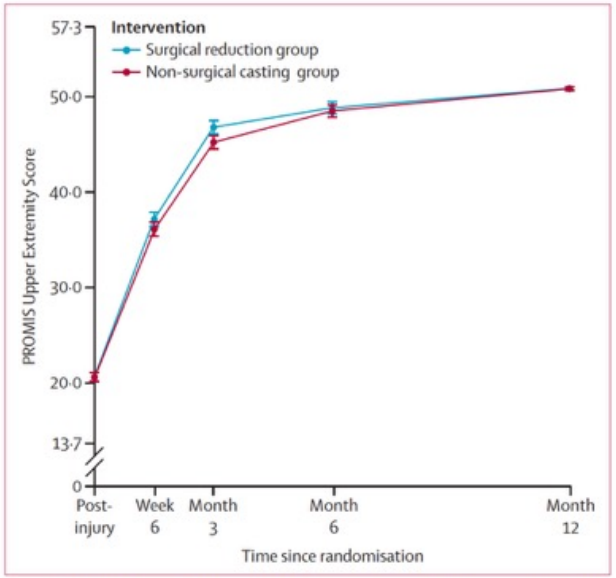


***Figure 3*: PROMIS Upper Extremity Scale Scores at each trial timepoint in the surgical reduction and non-surgical casting groups**
Data are PROMIS Upper Extremity Scale Scores (95% CI). Higher scores indicate better upper extremity function. PROMIS=Patient Report Outcomes Measurement System.

Die **PROMIS Upper Extremity (UE)** Skala ist ein klinisch validiertes System zur Messung der **Funktionsfähigkeit der oberen Extremitäten** (Arme, Schultern, Hände) aus Patientenperspektive. Sie ist Teil des größeren *Patient-Reported Outcomes Measurement Information System* (PROMIS), das von den National Institutes of Health (NIH) entwickelt wurde.

	Non-surgical casting (n=388)	Surgical reduction (n=362)	Total (N=750)
Unplanned surgery	0	31 (9%)	31 (4%)
Child or parent decision*	0	17 (5%)	17 (2%)
Clinician decision*	0	8 (2%)	8 (1%)
Fracture lost position, better-fitting cast required, or cast adjustment†	0	6 (2%)	6 (<1%)
Intra-operative complications			
Nerve injury	0	0	0
Vascular injury	0	0	0
Wire or screw breakage	0	0	0
Other	0	0	0
Cast complications			
Pressure areas	0	2 (1%)	2 (<1%)
Other	0	0	0
Other complications			
Wound infection	0	6 (2%)	6 (1%)
Scarring problems	0	5 (1%)	5 (1%)
Refracture after removal of cast	3 (1%)	1 (<1%)	4 (1%)
Nerve irritation	0	1 (<1%)	1 (<1%)

*Each of these participants were allocated to non-surgical casting but received surgical reduction within 2 weeks. †Five participants were randomly assigned to surgery, received surgery within 2 weeks, and then had an additional surgery owing to loss of fracture position or cast adjustment; one participant was initially randomly assigned to non-surgical casting and received surgical reduction within 2 weeks.

Table 2: **Complications up to 8 weeks, by treatment received**

	Non-surgical casting (n=388)	Surgical reduction (n=362)	Total (N=750)
Complications			
Refracture	6 (2%)	3 (1%)	9 (1%)
Adjacent to previous fracture location	1 (<1%)	1 (<1%)	2 (<1%)
Through old fracture site	5 (1%)	2 (1%)	7 (1%)
Wound infection with antibiotics prescription	0	1 (<1%)	1 (<1%)
Unplanned surgery			
Due to refracture	5 (1%)	2 (1%)	7 (1%)
Other	0	0	0

Table 3: **Complications between 8 weeks and 12 months, by treatment received**

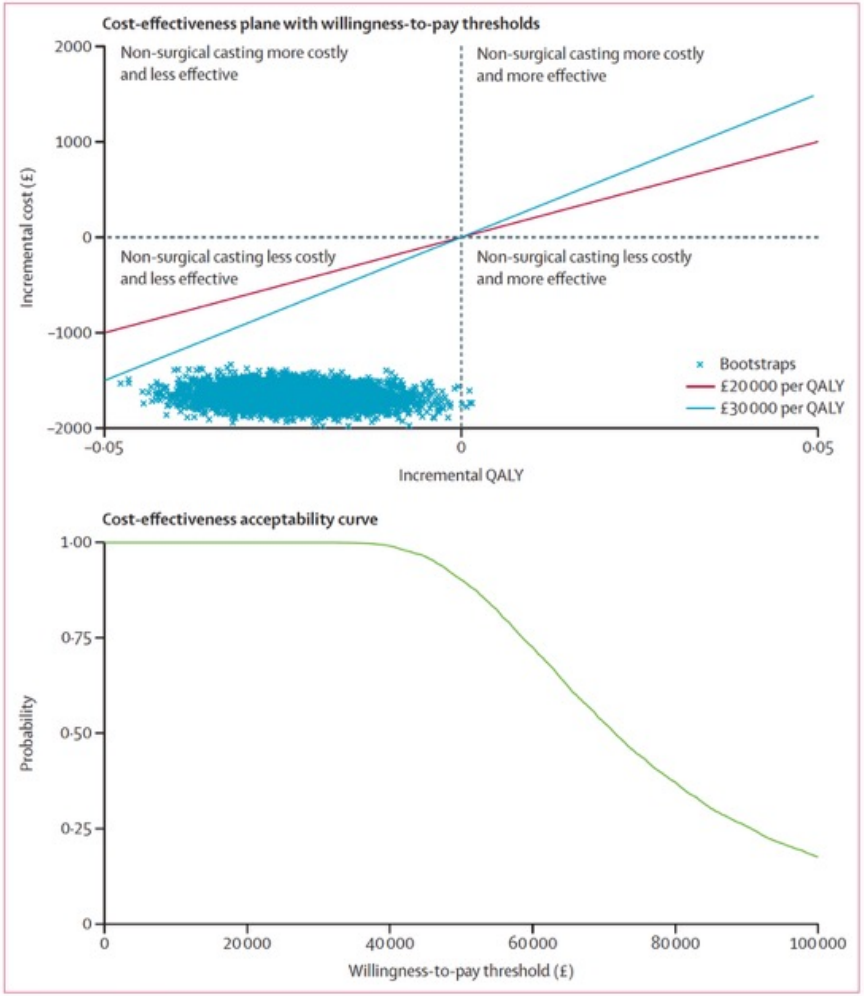


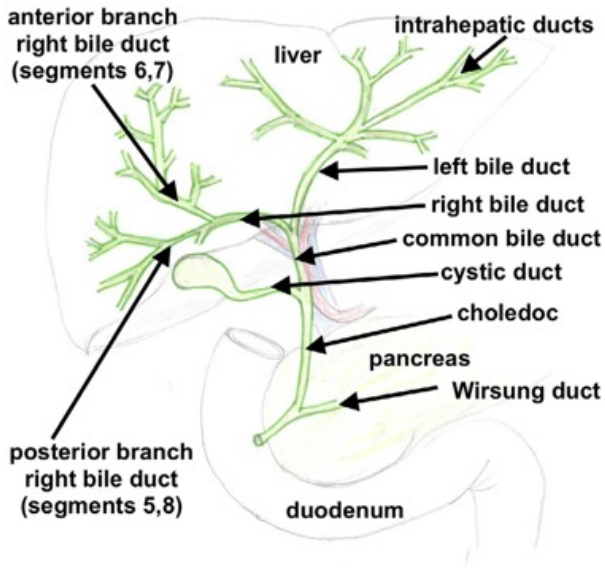
Figure 4: **Cost-effectiveness plane and cost-effectiveness acceptability curve**
The cost-effectiveness plane displays the distribution of incremental cost-effectiveness ratios from bootstrapped simulations comparing non-surgical casting with surgical reduction. The cost-effectiveness acceptability curve shows the probability that non-surgical casting is cost-effective across a range of willingness-to-pay thresholds, based on the proportion of simulations falling below each threshold. QALY=quality-adjusted life-years.

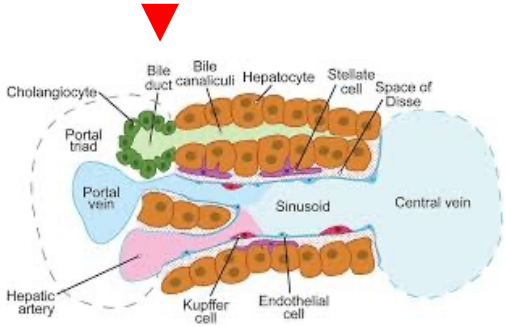
Implications of all the available evidence

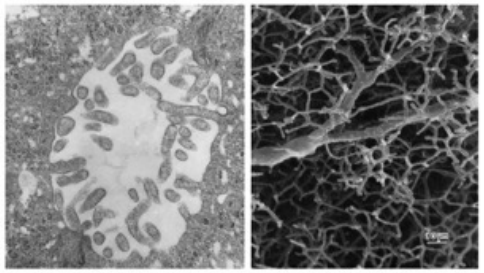
The CRAFFT trial provides the most robust evidence to date for the treatment of these injuries, adding to previous case series and an earlier small, randomised trial. This is a topic not addressed in any international guidelines. Although surgical reduction offered small early advantages, these fell below thresholds families considered clinically meaningful and did not persist. Given the higher costs and avoidable risks associated with surgical reduction, the findings support a cast-first strategy as the preferred initial approach for most children with severely displaced distal radial fractures.

THE LANCET

Die Mikroanatomie des Gallengangsystems (biliärer Baum) beschreibt den strukturellen Aufbau von den kleinsten Kanälen innerhalb der Leber bis hin zu den großen abführenden Gängen.







Microvilli in the biliary canaliculi (Arterburn et al, 1995)

A cast of the biliary canalicular network (Yamamoto et al, 1990)

Primär sklerosierende Cholangitis (PSC) und **Primär biliäre Cholangitis (PBC)** – die früher **Primär biliäre Zirrhose** genannt wurde – sind zwei unterschiedliche Autoimmunerkrankungen der Leber. Obwohl beide die Gallengänge schädigen und im Endstadium zu einer Leberzirrhose führen können, unterscheiden sie sich in ihren Merkmalen, den betroffenen Gängen und der typischen Patientengruppe deutlich.

Primary sclerosing cholangitis

Primary sclerosing cholangitis is a rare, chronic cholestatic liver disease characterised by biliary inflammation and fibrosis. Inflammatory bowel disease co-occurs in 50–80% of individuals with primary sclerosing cholangitis and there is an increased risk for hepatobiliary and colorectal cancers. Primary sclerosing cholangitis presentation is highly variable but there is usually a slowly progressive fibrosis of the bile ducts with strictures, development of liver fibrosis and cirrhosis, and eventually a need for liver transplantation, after which primary sclerosing cholangitis can reoccur. Primary sclerosing cholangitis is diagnosed mostly at the asymptomatic stage but, as the disease advances, people often have itching, fatigue, upper right abdominal pain, recurrent cholangitis, or complications related to portal hypertension. There are few treatment options and its exact cause and pathogenesis remain unclear. It is widely believed that both genetic and environmental factors are important, with the intestinal microbiome increasingly recognised as crucial to disease development, progression, and outcomes. This Seminar explores the clinical features of primary sclerosing cholangitis, summarises the current understanding of its pathogenesis, and gives insights into the challenges and opportunities in managing the disease.

Die genaue Ursache der Primär Sklerosierenden Cholangitis (PSC) ist medizinisch noch **nicht vollständig geklärt**. Es wird jedoch allgemein davon ausgegangen, dass die Erkrankung **multifaktoriell** ist, also durch ein Zusammenspiel verschiedener Einflüsse entsteht.

PSC gilt als eine **immunvermittelte Erkrankung**. Das bedeutet, dass das Immunsystem fälschlicherweise körpereigenes Gewebe – in diesem Fall die Zellen der **Gallengänge** – angreift.

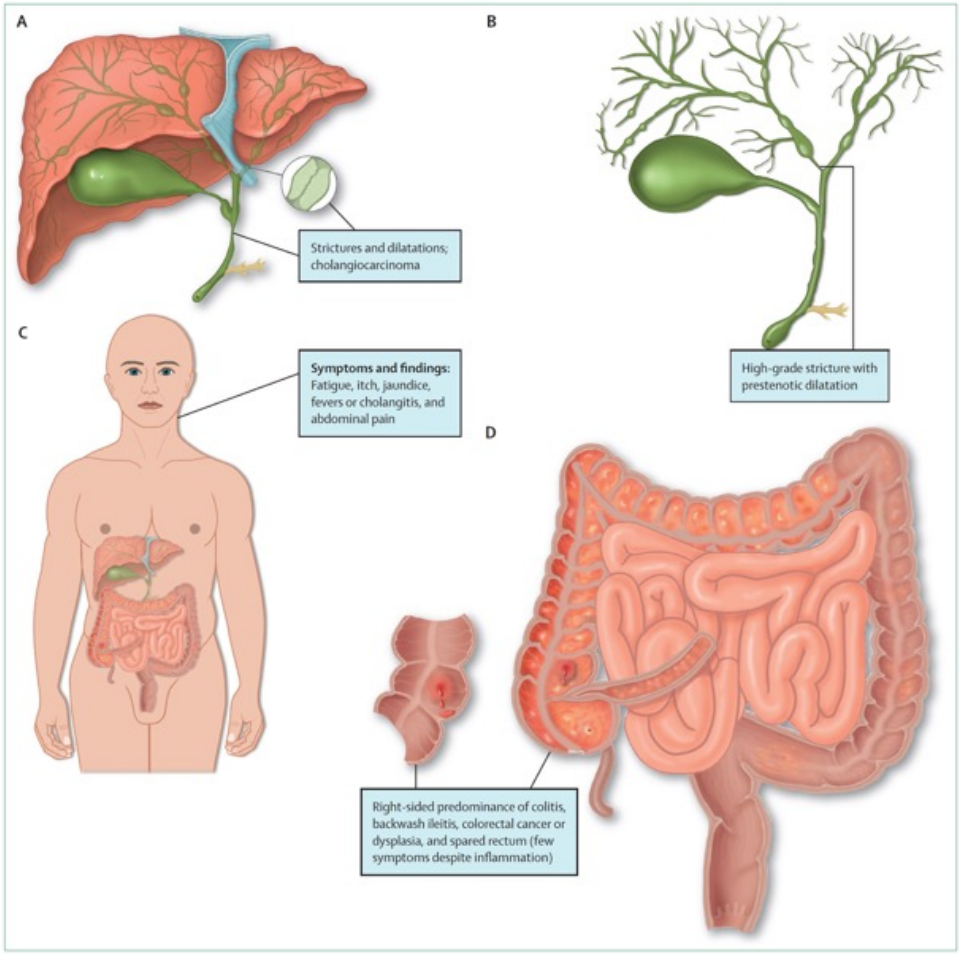


Figure 1: **Clinical characteristics of primary sclerosing cholangitis**
(A) The disease affects the biliary tree through inflammation and fibrosis, which results in multifocal biliary strictures and a high risk of cholangiocarcinoma.[3,5,6–11,31] (B) When the disease progresses, high-grade strictures, often with prestenotic dilatation, can develop, leading to biliary obstruction and clinical symptoms.[1,6,10,11,14,15,16] (C) Fatigue, itching, jaundice, bacterial cholangitis, and intermittent or persistent right upper-quadrant abdominal pain are common symptoms and signs in primary sclerosing cholangitis.[15,16,19,40] Primary sclerosing cholangitis is associated with inflammatory bowel disease and 50–80% of affected individuals have concomitant inflammatory bowel disease. Primary sclerosing cholangitis inflammatory bowel disease shows distinct features from classic isolated inflammatory bowel disease, often with extensive colitis, a patchy inflammatory distribution that shows dominance of inflammation in the ascending colon, rectal sparing, and an increased risk of colorectal dysplasia compared with colitis without primary sclerosing cholangitis. (D) The inflammation almost always involves the colon and isolated ileal disease is rare.[22–24,59–62] Reproduced with permission from Kari C Toverud.

How to make the diagnosis

	Diagnostic means	Clinical advice at diagnosis or causes of disease
Forms of primary sclerosing cholangitis		
Large-duct primary sclerosing cholangitis	MR cholangiography–MRI	Rule out secondary causes; check for associated diseases (inflammatory bowel disease) and rule out cholangiocarcinoma
Small-duct primary sclerosing cholangitis	Liver biopsy and MR cholangiography (normal)	Histology is often unspecific; confirm that other typical diagnostic characteristics are present (inflammatory bowel disease required) and rule out other causes
Primary sclerosing cholangitis with features of autoimmune hepatitis	Antinuclear antibody, antismooth muscle antibody, antiliver kidney microsomal antibody, and antisoluble liver antigen–liver pancreas antibody; IgG; liver biopsy; MR cholangiography (normal or typical large-duct changes)	Autoantibodies typical of autoimmune hepatitis and moderately elevated IgG concentrations are common in large-duct primary sclerosing cholangitis without autoimmune hepatitis; consider the risk of overdiagnosis and treatment side-effects
Differential diagnosis		
IgG4-related cholangitis	Use the HISORt criteria*	Check IgG4 concentrations at diagnosis: mild elevation is common in advanced large-duct primary sclerosing cholangitis
Cholangiocarcinoma	CT, endoscopic ultrasound, and endoscopic retrograde cholangiography with cytology and histology	..
Genetic variants in *ABCB4*	Genetic testing	Consider genetic testing in unclear cases with suspected small-duct primary sclerosing cholangitis
Examples of secondary sclerosing cholangitis (not exhaustive)		
Bile duct injury	History, imaging, and relevant serology	Postoperative complications
Choledocholithiasis	History, imaging, and relevant serology	Bile duct stones
Infections	History, imaging, and relevant serology	HIV, recurrent bacterial infections, and liver fluke or ascaris infestation
Ischaemic injury	History, imaging, and relevant serology	Critical illness and trauma
Pancreatic disease	History, imaging, and relevant serology	Chronic pancreatitis and pancreatic cancer
Congenital disease	History, imaging, and relevant serology	Choledochal cysts and biliary atresia

*A diagnostic framework used in IgG4-related cholangitis (histology, imaging, serology, other organ involvement, and responsiveness to corticosteroids).

Table 1: **Diagnosis of primary and secondary sclerosing cholangitis, its variant forms, and differential diagnoses**

Das ABCB4-Gen kodiert für ein Protein (MDR3), das Phospholipide in die Galle transportiert. Mutationen führen zu einer ABCB4-Defizienz, die Gallengänge schädigt und zu Lebererkrankungen wie LPAC-Syndrom, PFIC Typ 3 oder Schwangerschaftscholestase führt. Typisch sind ein niedriger Phospholipidgehalt der Galle und eine erhöhte GGT.

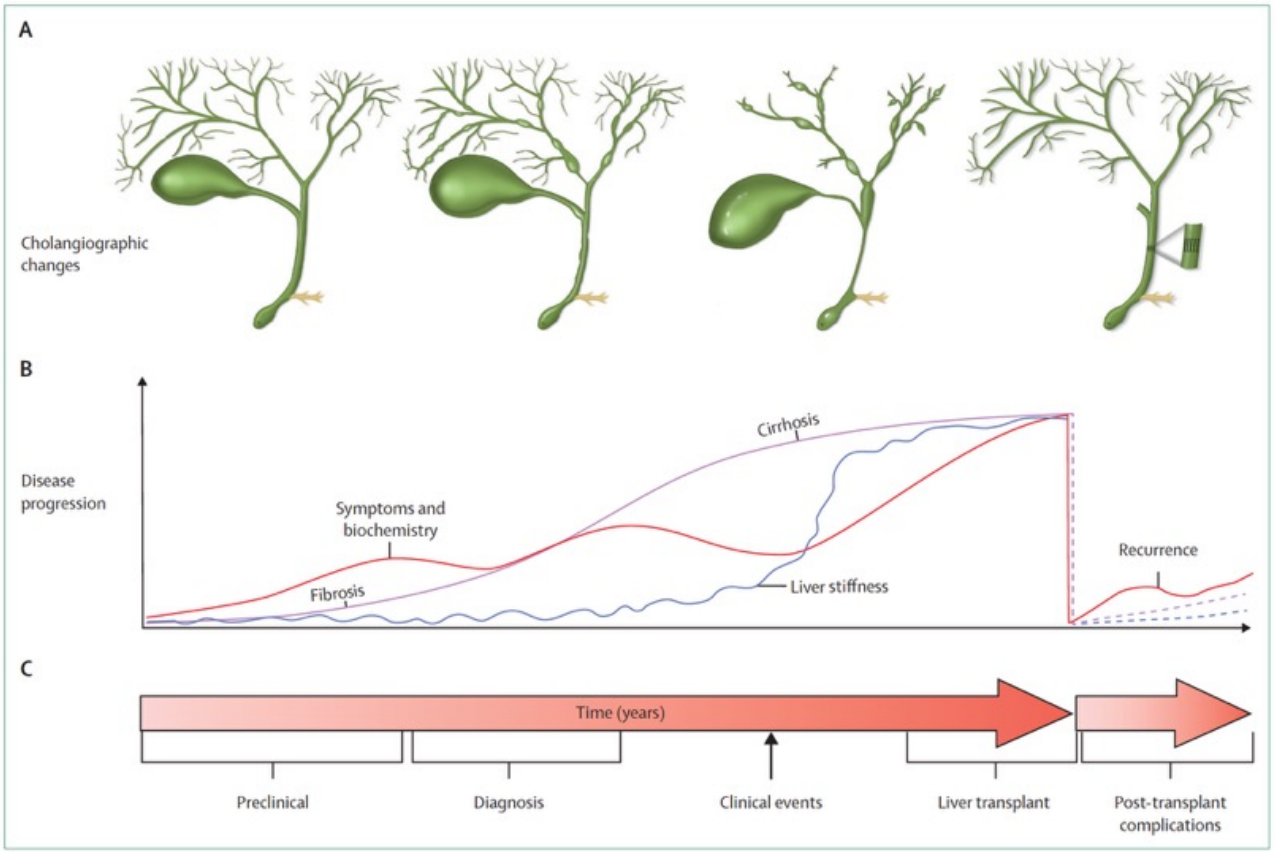


***Figure 2*: Natural history of primary sclerosing cholangitis**

(A) The disease is generally progressive, with cholangiographic changes becoming more extensive throughout disease course. (B) Assessing severity and prognosis is challenging due to the scarcity of widely validated biomarkers, but serum fibrosis tests and liver elastography are increasingly used. There is a long preclinical phase in the disease, which is often asymptomatic with normal or fluctuating liver blood tests. Disease progression is mostly very slow, with a median time to need for liver transplantation of approximately 18–21 years.[1,2] (C) With time, there is increasing biliary and liver fibrosis and cholestasis, leading to a need for liver transplantation. After liver transplantation, primary sclerosing cholangitis can reoccur in up to 30% of individuals. Reproduced with permission from Kari C Toverud.

	Description and references
Clinical variables	
Age	Younger age at diagnosis is associated with longer transplant-free survival[31,33,38,79,89-93]
Sex	Female sex is a protective factor associated with lower risk of cholangiocarcinoma and longer transplant-free survival[33]
IBD	No inflammatory bowel disease and no Crohn's disease is associated with a longer transplant-free survival[33]
Primary sclerosing cholangitis phenotype	
Small-duct primary sclerosing cholangitis	Associated with better prognosis and lower risk of cholangiocarcinoma; risk of progression to large-duct primary sclerosing cholangitis is frequent (23% over 7·4 years)[33,84]
Features of autoimmune hepatitis	Concomitant features of autoimmune hepatitis in primary sclerosing cholangitis have a similar outcome to primary sclerosing cholangitis alone[36,94]
Alkaline phosphatase	Elevated concentrations are associated with worse outcome; difficult to use due to fluctuations during the disease course[30,48,52,58,90,95-98]
Bilirubin	Continuously elevated concentrations indicate worse prognosis but are usually applicable only in late-stage disease; normal or fluctuating values (eg, cholangitis or extrahepatic high-grade strictures) occur in early disease[31,38,79,89-93,99]
Measures of fibrosis	
Histology	Associated with liver transplantation and liver-associated death; not used in clinical practice due to its invasiveness[30,48,100-102]
VCTE	Liver stiffness measured by VCTE is strongly associated with fibrosis degree and clinical outcomes; cutoff values for risk stratification are still to be evaluated; values have been suggested for low-risk (<6·5 kPa) and high-risk (>9·9 kPa) clinical events; single increased values should be interpreted with caution due to high variability and put into clinical context[103-106]
MR elastography	Liver stiffness measured by MR elastography is associated with fibrosis degree and clinical outcomes but is less evaluated and less available in clinical practice than VCTE[107-109]
Enhanced liver fibrosis test	Serum test calculated from concentrations of TIMP-1, hyaluronic acid, and intact N-terminal PIIINP; is associated with liver fibrosis and transplant-free survival at 4–6 years; score >10·6 has been suggested to identify individuals at higher risk for liver transplantation or death; not widely available[30,110-114]
Imaging	
Spleen size >12 cm	Associated with transplant and liver decompensation-free survival[106,115]
Anali score	Risk score based on MRI and MR cholangiopancreatography with or without contrast; includes assessment of intrahepatic bile duct dilatation, hepatic dysmorphia, parenchymal enhancement, and portal hypertension; predicts adverse-free (hepatic decompensation), transplant-free survival[37,116,117]
DiStrict score	MR cholangiopancreatography-based score of intrahepatic and extrahepatic bile duct strictures and dilatations; predicts risk of liver transplantation and liver-related death[118]
Primary sclerosing cholangitis-specific prognostic scores	
Revised Mayo score	Used to estimate the overall survival probability over a time horizon of up to 4 years; based on factors that are affected in advanced disease and are applicable in in late-stage disease[92]
PREsTo	Predicts hepatic decompensation (ie, encephalopathy, ascites, and variceal bleeding) within 5 years; risk score derived from nine variables: bilirubin, albumin, alkaline phosphatase, platelets, aspartate aminotransferase, haemoglobin, sodium, patient age, and disease duration[90]
Amsterdam–Oxford model	Calculates the probability of transplant-free survival after 5, 10, and 15 years; based on seven clinical variables: age at diagnosis, primary sclerosing cholangitis phenotype (large duct or small duct), aspartate aminotransferase, alkaline phosphatase, bilirubin, albumin, and platelets[89]
UK-PSC Risk Score	The short-term score estimates the 2-year transplant-free survival at diagnosis using bilirubin, albumin, haemoglobin, and platelets; 2 years after diagnosis, the long-term score can be applied (based on age at diagnosis, bilirubin, alkaline phosphatase, albumin, platelets, variceal haemorrhage, and presence of extrahepatic biliary disease at diagnosis) to estimate the transplant-free survival during the following 8 years[91]

VCTE=vibration-controlled transient elastography.

Table 2: **Risk factors for liver-related complications and mortality in individuals with primary sclerosing cholangitis**

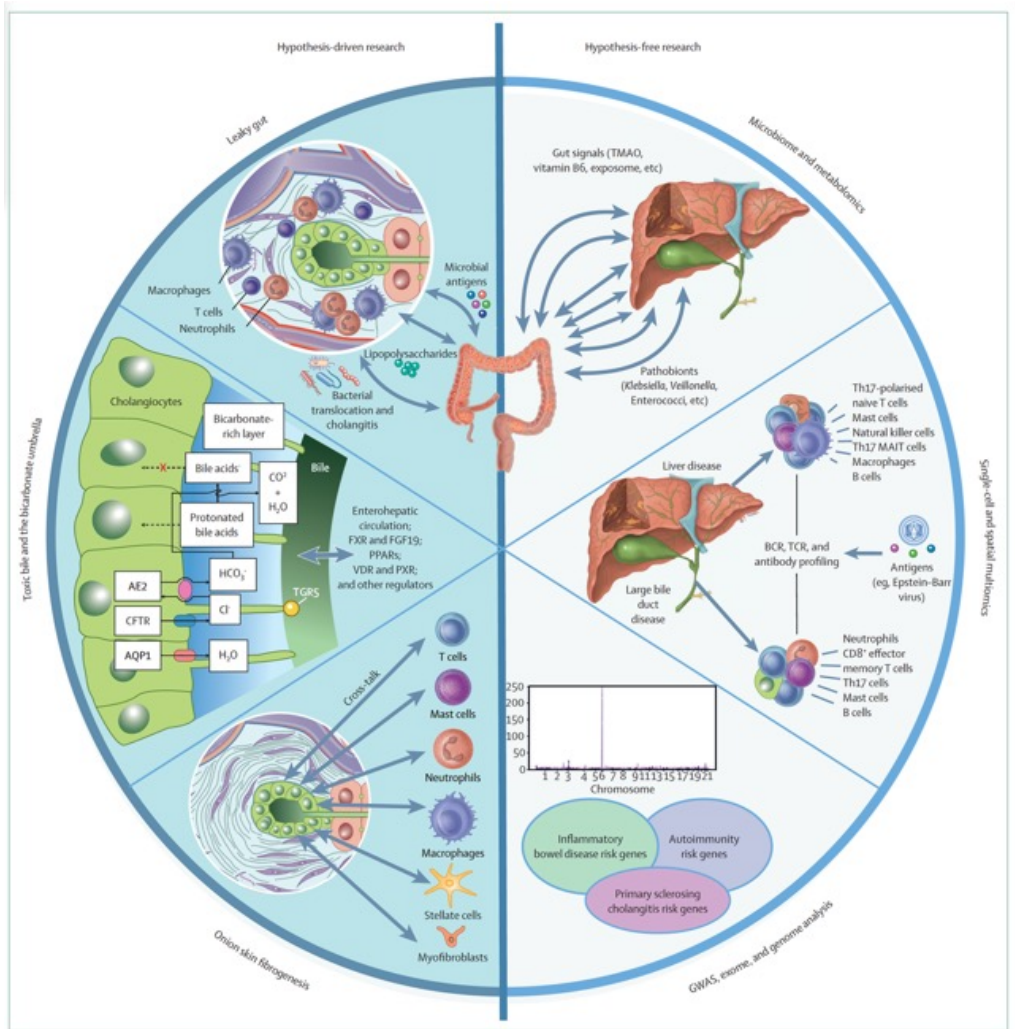


Figure 3: **Important concepts on the pathophysiology of primary sclerosing cholangitis**

Important concepts are those of a leaky gut (based on the relationship with inflammatory bowel disease), toxic bile (related to potential deficits in protection against bile acids), and onion skin fibrosis (driven by cross-talk between cholangiocytes and immune cells and stromal cells involved in immune-mediated injury and the generation of peribiliary scarring). With the development of omics technologies over the past 25 years (eg, genomics and transcriptomics along with spatial information, metabolomics, and associated microbiome analysis) hypothesis-driven research in primary sclerosing cholangitis has been replaced and expanded by the application of hypothesis-free approaches. PPARs=peroxisome proliferator-activated receptors. MAIT=mucosal-associated invariant T cells. TMAO=trimethylamine N-oxide. GWAS=genome-wide association studies. Reproduced with permission from Kari C Toverud.

Clinical trials of various agents

	Description or mechanism of action	Study descriptor	Primary endpoint	Status	Outcome
Ursodeoxycholic acid derivatives					
Norucholic acid	Homologue of ursodeoxycholic acid with a shortened side-chain; induces bicarbonate-rich hypercholeresis, protects cholangiocytes, and has direct anti-inflammatory and immunomodulatory effects	Phase 2 RCT (N=161)	Change in ALP at week 12	Completed[162]	Significant reduction of ALP; no safety concerns
Norucholic acid	Homologue of ursodeoxycholic acid with a shortened side-chain; induces bicarbonate-rich hypercholeresis, protects cholangiocytes, and has direct anti-inflammatory and immunomodulatory effects	Phase 3 RCT (N=302)	Prevention of disease progression by stable histology and ALP <1·5 × ULN at 2 years	Completed[163]	Significantly superior to placebo: 15·1% vs 4·2% reached primary endpoint; well tolerated
Berberine ursodeoxychlolate (HTD1801)	Ionic salt of berberine and ursodeoxycholic acid; improves lipid metabolism and reduces inflammation	Phase 2 RCT (N=55)	Change in ALP at week 6	Completed[164]	Significant reduction of ALP; no safety concerns
FXR agonists					
Obeticholic acid	Steroidal FXR agonist	Phase 2 RCT (N=76)	Change in ALP at week 24	Completed[165]	No significant reduction of ALP; frequent side-effects (pruritus)
Cilofexor	Inhibits bile acid synthesis and promotes choleresis; reduces inflammation and fibrosis	Phase 3 RCT (N=160)	Proportion of patients with histological progression of liver fibrosis	Terminated[166]	Terminated early: low probability (6-8%) of achieving primary endpoint
FGF-19					
NGM282 (Aldafermin)	Non-tumourigenic analogue of FGF-19; inhibits bile acid synthesis by inhibiting CYP7A1 in the liver and reduces inflammation and fibrosis	Phase 2 RCT (N=62)	Change in ALP at week 12	Completed[167]	No significant reduction of ALP; no safety concerns
PPAR agonists					
Bezafibrate (pan-PPAR/PXR agonist)	PPAR-agonist signal through specific intranuclear receptors to control diverse metabolic processes, including lipid and bile acid metabolism	Phase 3 RCT (N=104)	ALP <1·5 × ULN and a reduction of ≥15%; bilirubin ≤ULN; no increase in liver stiffness	Recruiting	NA
Seladelpar (PPAR-δ agonist)	PPAR-agonist signal through specific intranuclear receptors to control diverse metabolic processes, including lipid and bile acid metabolism	Phase 2 RCT (N=100)	Change in ALP at week 24	Terminated	NA
Elafibranor (PPAR-α/δd agonist)	PPAR-agonist signal through specific intranuclear receptors to control diverse metabolic processes, including lipid and bile acid metabolism	Phase 2 RCT (N=68)	Treatment-emergent adverse events	Completed[168]	35·3–57·7% dose-dependent reduction of ALP; no safety concerns
Statins					
Simvastatin	Reduces the production of cholesterol, has pleiotropic effects, improves endothelial function, and reduces inflammation	Phase 3 RCT (N=560)	Time-to-death, liver transplantation listing, variceal bleeding, or the development of hepatobiliary cancer	Recruiting[169]	NA
Biologics and inflammatory pathway blocking agents					
VAP-1 antibody	VAP-1 blockade	Phase 2 observational study (N=23)	Change in ALP at day 99	Completed[170]	No significant reduction of ALP; no safety concerns
Cenicriviroc	Dual antagonist of CCR2 and CCR5	Phase 2 observational study (N=24)	Change in ALP over 24 weeks	Completed[171]	No significant reduction of ALP; no safety concerns
CM-101	CCL24 blockade	Phase 2 RCT (N=68)	Treatment-emergent adverse events	Completed[172]	Significant reduction in liver stiffness measurement in moderate and advanced fibrosis; no safety concerns
Aspirin	Acetylsalicylic acid	Phase 3 RCT (N=968)	Occurrence of primary sclerosing cholangitis-related cancers and need for liver transplantation	Recruiting	NA

(Table 3 continues on next page)

	Description or mechanism of action	Study descriptor	Primary endpoint	Status	Outcome
(Continued from previous page)					
Antifibrotic agents					
Simtuzumab	Monoclonal antibody against LOXL2	Phase 2 RCT (N=234)	Change in hepatic collagen content on liver biopsy at week 96	Completed[16]	No significant reductions in Ishak fibrosis stage; no safety concerns
Bexotegrast (PLN-74809)	Dual-selective inhibitor of $\alpha_v\beta_6$ and $\alpha_v\beta_1$ integrins	Phase 2 RCT (N=121)	Treatment-emergent adverse events	Completed[173]	No safety concerns
Microbial manipulations					
Vancomycin	Oral glycopeptide antibiotics	Phase 3 RCT (N=102)	Change in ALP at 6 months	Active, not recruiting	NA
Faecal microbiota transplantation	Restores gut microbiota diversity	Phase 2 RCT (N=58)	Change in ALP at week 48	Recruiting[174]	NA
Other compounds					
Pyridoxin	Vitamin B6 restores deficiency to improve metabolic and immune functions	Phase 2 RCT	Change in ALP at week 12	Recruiting	NA
Curcumin	Naturally occurring compound with anti-inflammatory effects	Phase 1/2 open-label, single-arm study (N=15)	Change in ALP at week 12	Completed[175]	No significant reduction of ALP; no safety concerns
Vidofludimus Calcium	Dihydroorotate dehydrogenase inhibitor	Phase 2 open-label, single-arm study (N=18)	Change in ALP at week 6 months	Completed[176]	No significant reduction of ALP; no safety concerns
HK-6605	β-Lapachone, anti-inflammatory and antifibrotic effects	Phase 2 RCT (N=21)	Change in ALP at week 12, improvements in primary sclerosing cholangitis severity (MR cholangiography with the Anali score)	Completed[177]	No significant reduction of ALP; no safety concerns
Treatment for itch					
Bezafibrate (included primary sclerosing cholangitis, primary biliary cholangitis, and secondary sclerosing cholangitis)	Pan-PPAR	Phase 3 RCT (N=76)	≥50% reduction of pruritus (visual analogue scale) at day 21	Completed[166]	Bezafibrate superior to placebo: 41% vs 11% reached endpoint
Maralixibat	IBAT inhibitors interrupt the enterohepatic circulation of bile acids and reduce the bile acid pool through inhibition of the apical sodium-dependent bile acid transporter in the terminal ileum	Phase 2 open-label, single-arm study (N=27)	Treatment-emergent adverse events, change in bile acids at week 14 and change in pruritus (secondary endpoint)	Completed[178]	Treatment-emergent adverse event in 85%; itch improved in 8–70%, most in severe pruritus
Ritivixibat (A3907)	IBAT inhibitors interrupt the enterohepatic circulation of bile acids and reduce the bile acid pool through inhibition of the apical sodium-dependent bile acid transporter in the terminal ileum	Phase 2 open-label, single-arm study	Treatment-emergent adverse events	Recruiting	NA
Volixibat	IBAT inhibitors interrupt the enterohepatic circulation of bile acids and reduce the bile acid pool through inhibition of the apical sodium-dependent bile acid transporter in the terminal ileum	Phase 2 RCT	Mean change in daily itch NRS for 28 weeks	Recruiting	NA
EP547 (included primary sclerosing cholangitis and primary biliary cholangitis)	MRGPRX4 inverse agonist; blocking pruritogenic activity prevents the activation of MRGPRX4 and subsequent itch sensation	Phase 2 RCT	Change in worst itch NRS for 6 weeks	Completed	NA

More recently published studies were included when relevant. ALP=alkaline phosphatase. FXR=farnesoid X receptor. IBAT=ileal bile acid transporter. NA=not assessable. NRS=Numeric Rating Scale. PPAR=peroxisome proliferator-activated receptor. RCT=randomised controlled trial. ULN=upper limit of normal. *According to ClinicalTrials.gov (accessed Dec 25, 2024).

Table 3: **Overview of key clinical trials for potential medical therapies in primary sclerosing cholangitis**

Future directions

Despite its rarity, primary sclerosing cholangitis remains a significant health problem through high medical costs, cancer-related mortality, and loss of QALYs.[1,283] Key research priorities include early diagnosis of primary sclerosing cholangitis and cholangiocarcinoma detection, identification of valid surrogate endpoints for clinical trials, and elucidation of pathophysiology to discover potential drug targets.[10] Increasing numbers of clinical trials with promising early-phase results indicate an imminent shift in the clinical management of primary sclerosing cholangitis from therapeutic nihilism and observational strategies towards effective interventions and proactive complication management to slow disease progression, reduce mortality, and minimise symptom burden in people with primary sclerosing cholangitis.[129]

An uncommon cause of recurrent deep vein thrombosis and pulmonary embolism in a young athlete: an osteochondroma compressing the popliteal vein

Lessons for practice

- In a young, athletic patient in whom thrombophilia has been ruled out as the cause of deep vein thrombosis, local causes such as entrapment syndromes should be considered before the event is labelled as unprovoked.
- Recurrence in the same limb after ruling out residual venous insufficiency should strongly suggest a structural abnormality.
- Phlebography-CT or MRI should be considered as useful complementary studies when ultrasound does not detect abnormalities and there is a high suspicion of venous entrapment syndrome.
- Early multidisciplinary intervention, such as vascular and orthopaedic surgery, can shorten the diagnostic delay and improve outcomes.

Learning points

- Recurrent DVT in young patients without identifiable risk factors after thrombophilia and venous insufficiency are ruled out warrants investigation for local anatomical causes.
- Specific cross-sectional images (CT or MRI venography) should be considered in a DVT in a young healthy patient.
- Osteochondroma can rarely compress the popliteal vein and cause DVT and pulmonary embolism.

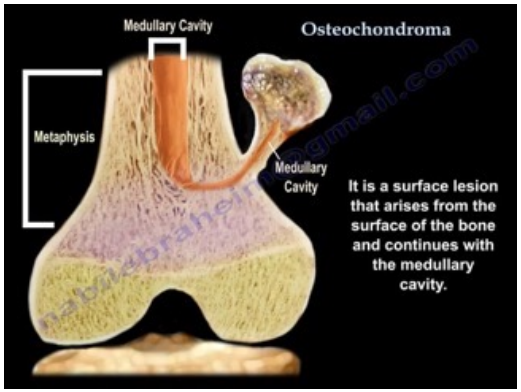
DVT=deep vein thrombosis.

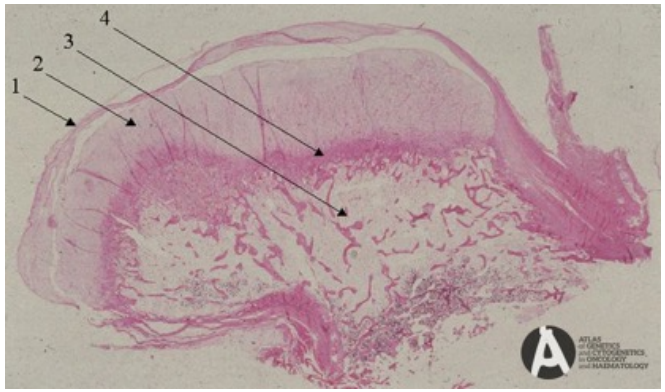
Ein Osteochondrom ist der häufigste gutartige Knochentumor, der meist im Kindes- und Jugendalter (10–25 Jahre) als knöcherner Auswuchs in der Nähe von Wachstumsfugen entsteht. Es besteht aus Knochen und Knorpel, wächst oft gestielt vom gelenknahen Knochen weg und stoppt das Wachstum meist mit Abschluss des Skelettwachstums.

Case presentation

A previously healthy and competitive tennis player (male, aged 20 years), who also trained in weightlifting, presented with acute pain and swelling of the right calf. He had no history of trauma, immobilisation, recent travel, surgery, smoking, use of supplemental hormones for athletic activities, or family history of thrombosis. Doppler ultrasound confirmed an occlusive thrombosis of the popliteal vein with extension to the superficial femoral vein, involving the saphenopopliteal junction and the distal segment of the small saphenous vein.

Laboratory test results, including complete thrombophilia screening (antithrombin, protein C, protein S, factor V Leiden, prothrombin gene mutation, antiphospholipid antibodies, and homocysteine), were within normal range. In the absence of provoking factors, the event was classified as unprovoked. The patient was treated with rivaroxaban for 6 months (15 mg twice a day for 3 weeks, and then 20 mg once a day), and a follow-up doppler ultrasound showed no residual thrombosis or venous insufficiency, confirming complete resolution.





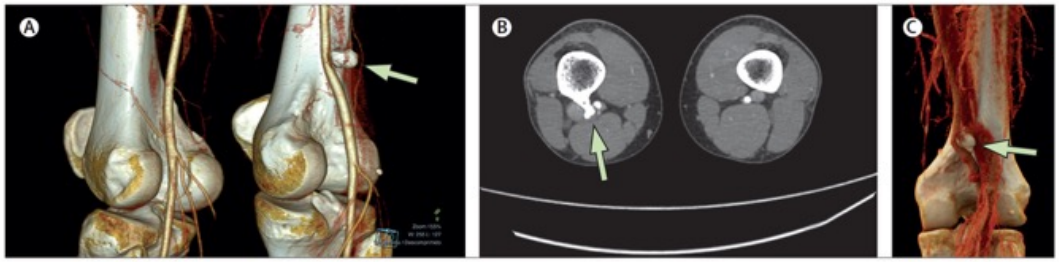


Figure 1: **CT venography**
There is a bony prominence from the distal third of the right femoral shaft that compressed the popliteal vein (A, B), which had an associated intraluminal hypodense band extending cranially, suggestive of subacute or chronic thrombosis. (C) The lesion also compressed the popliteal artery.

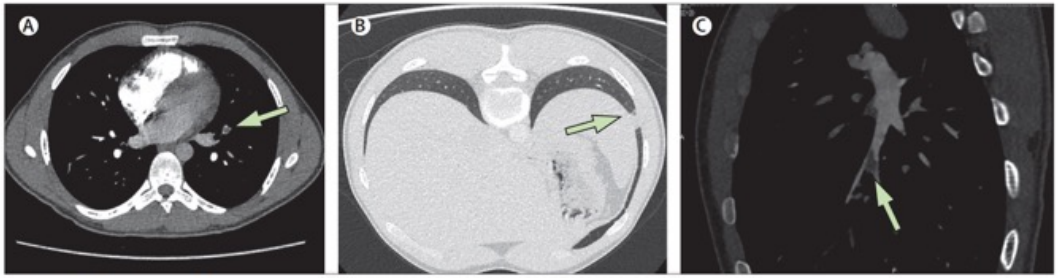


Figure 2: **Chest CT angiography**
(A) Acute and subacute pulmonary embolism in the lateral segmental branch of the left lower lobe. (B) A subpleural opacity suggestive of a small pulmonary infarct. (C) Chronic band-like embolism in the posterior basal segment of the right lower lobe.

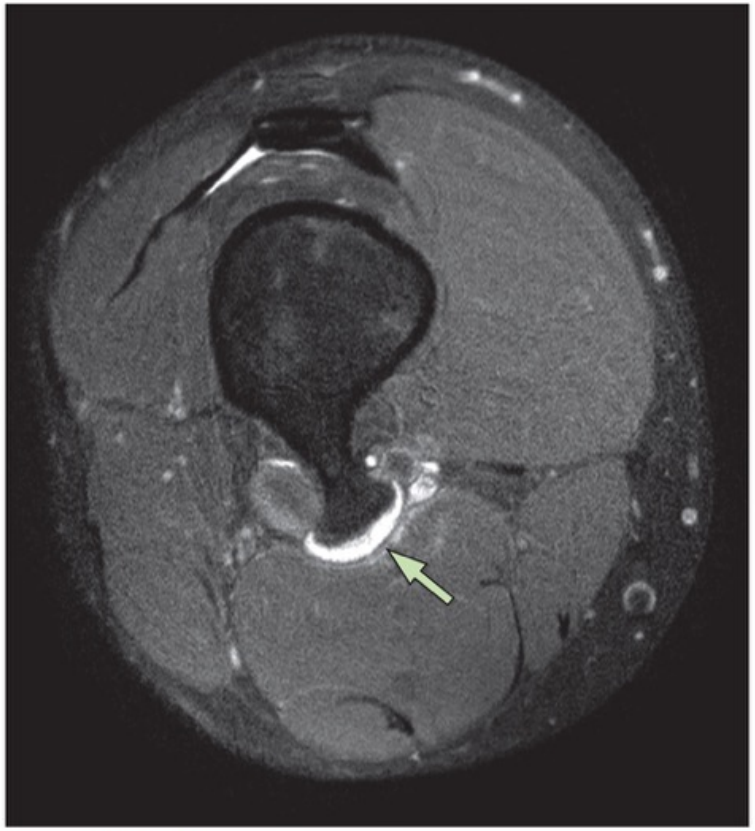


Figure 3: **Right leg MRI**
Focal lesion consistent with osteochondroma of the proximal right tibia, projecting into the popliteal fossa and indenting both the artery and vein.

Discussion

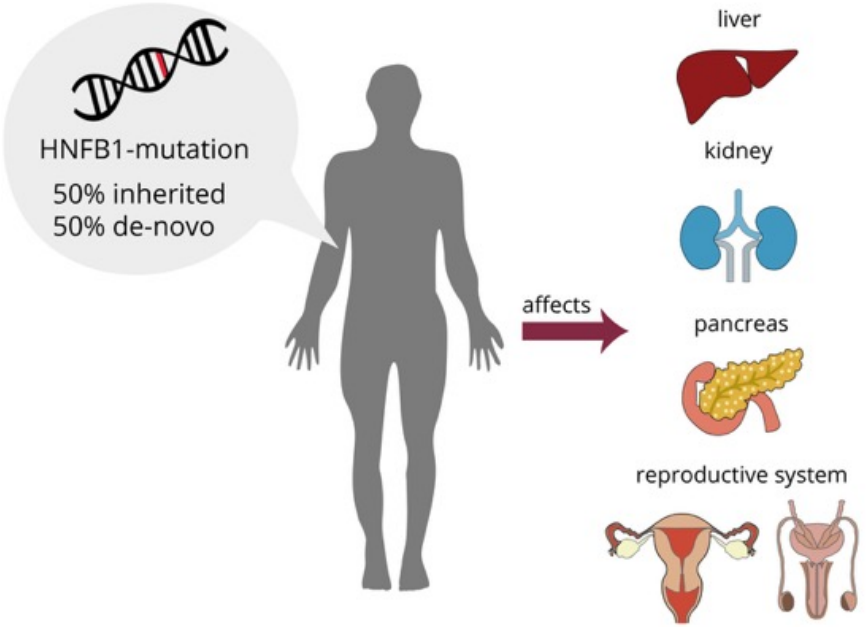
DVT and pulmonary embolism are uncommon in young adults without recognised risk factors, and recurrence should raise suspicion of overlooked underlying causes. In such cases, the diagnostic tests usually expand to rare thrombophilias or occult malignancy.[3]

However, local anatomical causes might be missed if vascular imaging is limited to ultrasound. Popliteal entrapment syndromes and local tumours are rare but important causes of DVT in young athletes,[4,5] mainly runners, cyclists, basketball players, martial artists, and tennis players as a result of repetitive knee movements, flexo-extension, and muscle and ligament hypertrophy common in these sports.

Osteochondroma, although common among benign bone tumours, seldom causes venous complications. Most cases are discovered incidentally or present with orthopaedic symptoms such as pain, deformity, or mechanical irritation. Vascular complications are rare and usually due to arterial compression (pseudoaneurysm, arterial thrombosis, or ischaemia due to repetitive trauma). Venous complications are even less frequent, with only isolated cases of compression-related DVT reported.

HNF1B (Hepatocyte Nuclear Factor 1-Beta) ist ein Gen, das Anweisungen für die Herstellung eines Proteins namens **Transkriptionsfaktor 2** gibt. Dieses Protein fungiert als "Hauptschalter", der die Entwicklung und Funktion wichtiger Organe wie Nieren, Bauchspeicheldrüse und Leber steuert. Mutationen oder das Fehlen dieses Gens (Deletion) führen zu einem breiten Spektrum an Symptomen, das oft als **HNF1B-**

Mangel-Syndrom bezeichnet wird.
Die wichtigsten Auswirkungen
•**Nieren (HNF1B-Nephropathie):** Die häufigste Manifestation. Es kommt oft zu Nierenzysten, Fehlbildungen (z. B. nur eine Niere) oder einer chronischen Nierenerkrankung (ADTKD), die langsam fortschreiten kann.
•**Diabetes (MODY 5):** Betroffene entwickeln häufig vor dem 30. Lebensjahr eine spezielle Form des Diabetes (Maturity-Onset Diabetes of the Young, Typ 5), da die Bauchspeicheldrüse nicht genügend Insulin produziert.
•**Kombination (RCAD-Syndrom):** Treten Nierenzysten und Diabetes zusammen auf, spricht man vom **Renal Cysts and Diabetes** Syndrom.



•**Identifikation (vor über 30 Jahren):** Forscher entdeckten Proteine in Kernextrakten der Leber, die spezifisch an DNA-Sequenzen leberspezifischer Gene banden. Einer der prominentesten war **HNF-4α**, der heute als "Master-Regulator" der Lebertranskription gilt.

HNF1B integrates signals in a feed-forward loop driving kidney disease progression

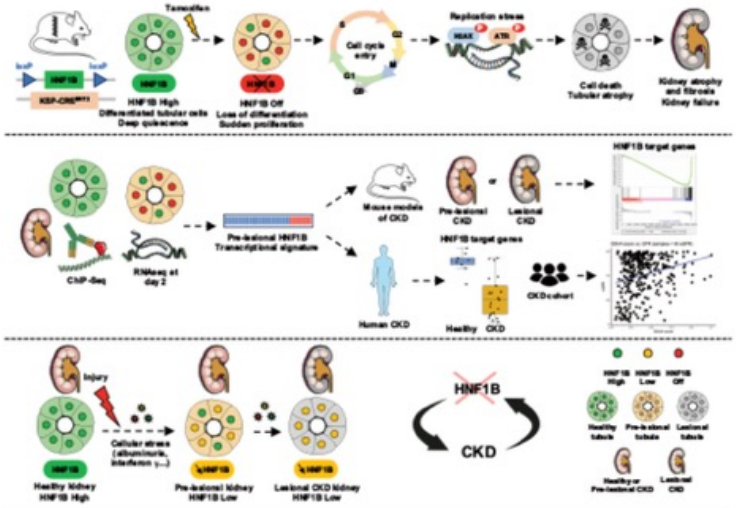
INTRODUCTION: Chronic kidney disease (CKD) affects more than 10% of the global population and is characterized by an inexorable decline in renal function, regardless of the triggering insult. A defining feature of CKD is its self-perpetuating nature: Once established, kidney injury progresses even when the original trigger has resolved. Identifying the molecular circuits that maintain this pathological state is essential to understand disease progression and to design effective therapeutic strategies.

RATIONALE: HNF1B is a transcription factor essential for renal development. Heterozygous loss-of-function mutations in HNF1B cause autosomal dominant tubulointerstitial kidney disease, a rare monogenic disorder whose renal histopathology phenocopies that of common CKD. This phenotypic convergence suggested that HNF1B dysfunction might represent a shared mechanism linking rare genetic kidney diseases to more prevalent, multifactorial CKD. We hypothesized that HNF1B activity may be progressively suppressed during CKD, creating a feed-forward loop that may drive disease progression.

RESULTS: Using a mouse model, we found that postnatal inactivation of *Hnf1b* in renal tubular epithelial cells led to very rapid and severe CKD, characterized by tubular atrophy, interstitial fibrosis, inflammation, and progressive renal failure. Loss of *Hnf1b* disrupted epithelial differentiation and triggered abrupt cell cycle reentry in normally quiescent tubular cells. This unscheduled proliferation caused replication stress, DNA damage, apoptosis, and senescence, leading to CKD. Pharmacological inhibition of aberrant cell cycle entry using the CDK4/6 inhibitor palbociclib slightly mitigated tubular injury and fibrosis in *Hnf1b*-deficient mice, demonstrating that replication stress participates in the progression of the disease downstream of HNF1B loss.

To identify the earliest molecular consequences of HNF1B loss, we defined the transcriptional signature of HNF1B, before the onset of renal lesions. This signature was markedly reduced in multiple preclinical models of CKD initiated by HNF1B-independent insults, including subtotal nephrectomy, Alport syndrome, ischemia-reperfusion injury, nephrotic syndrome, and unilateral ureteral obstruction. Notably, the suppression of HNF1B activity occurred before the appearance of any overt histological damage and was correlated with failed epithelial repair following acute kidney injury.

Palbociclib (Handelsname Ibrance) ist ein zielgerichteter CDK4/6-Inhibitor zur Behandlung von HR+/HER2- metastasiertem Brustkrebs, meist in Kombination mit einer endokrinen Therapie. Es verlangsamt das Tumorwachstum, indem es den Zellzyklus blockiert, und verbessert das progressionsfreie Überleben. Die übliche Dosierung beträgt 125 mg täglich für 21 Tage, gefolgt von 7 Tagen Pause (28-Tage-Zyklus)



Epigenetic repression of HNF1B, induced by renal tubular stress, drives CKD progression. Inactivation of *Hnf1b* in quiescent renal tubular epithelial cells induces rapid dedifferentiation and abrupt cell cycle re entry, leading to replication stress, cell death, and ultimately, severe chronic kidney disease (CKD). To capture the earliest molecular events preceding tissue damage, we combined ChIP-seq and transcriptomic analyses in kidneys from *Hnf1b* mutant mice 2 days after gene inactivation, before the appearance of histological lesions. This analysis identified a prelesional HNF1B transcriptional signature, which was markedly reduced in multiple mouse models of CKD as well as in human CKD even before lesion development. Analysis of a cohort of ~900 patients revealed that reduced expression of this signature strongly correlates with renal function decline. CKD-associated stresses, including albuminuria and interferon-γ, diminished HNF1B transcriptional activity in renal tubular cells. Together, these findings uncover a feed-forward pathogenic loop in which HNF1B deficiency promotes CKD progression, whereas CKD-associated stresses further suppress HNF1B activity through epigenetic mechanisms.

Mechanistically, we found that common CKD-associated stresses, including albuminuria and interferon-γ, reduced HNF1B transcriptional activity in renal tubular cells. Single-cell transcriptomic and chromatin accessibility analyses revealed that injured and maladaptively repairing tubular cells exhibited decreased accessibility at HNF1B binding sites, linking epithelial stress to epigenetic repression of HNF1B function.

Finally, analysis of human kidney transcriptomic datasets, including nearly 900 biopsies spanning a wide range of CKD severity, revealed that reduced HNF1B target gene expression strongly correlated with declining kidney function, tubular atrophy, and fibrosis. These findings establish HNF1B activity as a molecular determinant of CKD severity in humans.

CONCLUSION: Our results demonstrate that HNF1B is a gatekeeper of renal tubular homeostasis whose loss initiates and perpetuates CKD. We uncover a self-reinforcing feed-forward loop in which HNF1B deficiency drives CKD, whereas CKD-associated stresses epigenetically suppress HNF1B activity. This mechanism bridges rare monogenic kidney disorders and common forms of CKD and provides a conceptual framework for understanding the relentless nature of CKD. Restoring HNF1B activity may represent a therapeutic strategy to alter the trajectory of CKD.

HNF1B (Hepatocyte Nuclear Factor 1 Beta) ist ein **essenzieller Transkriptionsfaktor**, der maßgeblich die **renale Homöostase** steuert. Er fungiert als zentraler Regulator sowohl während der Organentwicklung (Nephrogenese) als auch in der funktionellen Aufrechterhaltung der erwachsenen Niere.

•**Elektrolythaushalt & Transport:** Es reguliert Gene für den Ionentransport (z.B. *FXYD2*, *UMOD*, *SLC12A1*), deren Fehlfunktion zu Hypomagnesiämie, Hypokaliämie und Hyperurikämie führt.

•**Zelluläre Struktur:** HNF1B ist entscheidend für die **apiko-basale Polarität**, die Bildung von **Tight Junctions** und die Entwicklung von **Primärzilien**. Ein Verlust führt häufig zu renalen Zysten.

•**Energiestoffwechsel:** Es steuert die mitochondriale Biogenese und Atmung über den *PPARGC1A*-Signalweg. Ein Defekt führt zu einem "vicious cycle" (Teufelskreis), bei dem die Zelle auf Glykolyse umschaltet, was Fibrose und das Fortschreiten chronischer Nierenerkrankungen (CKD) fördert.

•**Gewebeintegrität:** HNF1B unterdrückt die epitheliale-mesenchymale Transition (EMT). Ein Mangel aktiviert pro-fibrotische Gene wie *TWIST2*, was zu interstitieller Fibrose führt.

Amid wellness craze, FDA weighs lifting peptide restrictions

The Food and Drug Administration is taking the first step toward potentially allowing compounding pharmacies to produce seven peptides that are currently restricted because of the agency's previous warning over safety concerns.

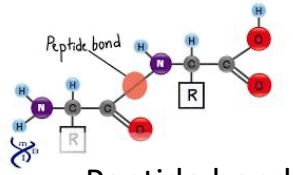
The agency's expert advisory panel on pharmacy compounding is scheduled to discuss whether the peptides should be used in compounding for purposes for ulcerative colitis, wound healing, inflammatory conditions, obesity, insomnia and more, according to a Federal Register notice posted Wednesday announcing a late-July meeting.

Health and Human Services Secretary Robert F. Kennedy Jr. is a self-professed "big fan" of peptides and has said he wants to make them more broadly available. He posted on social media Wednesday that several peptides under consideration would be removed from a restricted category and discussed at upcoming FDA meetings.

"This action begins to restore regulated access and will immediately begin shifting demand away from the black market," he wrote.

The chains of amino acids have grown increasingly popular and have been increasingly marketed for antiaging and health benefits. But many of the claims are untested and some forms of peptides have not undergone clinical trials for their safety or efficacy, public health experts say. Influencers and telehealth companies have also pushed combinations of these smaller versions of proteins in a practice known as "peptide stacking" — a practice that is also largely untested.

Robert F. Kennedy Jr. (RFK Jr.) setzt sich für den freien Zugang zu einer Gruppe von etwa **14 bis 19 Peptiden** ein, die er als "unterdrückt" betrachtet. Dabei handelt es sich um kurzkettige Aminosäuren, die in der Wellness- und "Biohacking"-Szene für die Regeneration von Gewebe, den Muskelaufbau und Anti-Aging beworben werden.
Als US-Gesundheitsminister plant Kennedy, die Beschränkungen der **FDA (Food and Drug Administration)** für diese Substanzen zu lockern, damit sie wieder legal von Apotheken hergestellt ("compounding") werden können.
Die wichtigsten Peptiden im Fokus die von RFK Jr. am häufigsten genannten oder durch seine Initiative betroffenen Peptide sind:
•**BPC-157:** Oft als "Wolverine-Peptid" bezeichnet; es wird für die Heilung von Sehnen-, Muskel- und Magen-Darm-Verletzungen beworben.
•**TB-500 (Thymosin Beta-4):** Bekannt für seine vermeintlichen regenerativen Eigenschaften und die Förderung der Durchblutung.
•**CJC-1295 & Ipamorelin:** Diese Peptide stimulieren die Freisetzung von Wachstumshormonen und werden für Muskelaufbau und Anti-Aging genutzt.
•**GHK-Cu (Kupfer-Peptid):** Wird primär für die Wundheilung, Kollagenproduktion und Hautverjüngung eingesetzt.
•**Thymosin Alpha-1:** Ein Peptid zur Stärkung des Immunsystems.



Peptide bond