

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

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

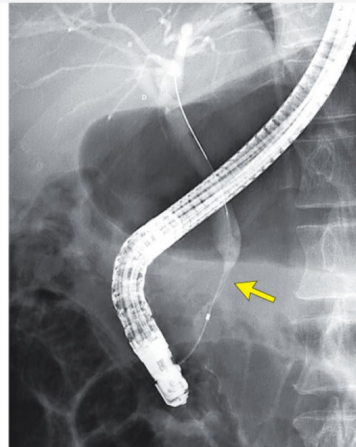
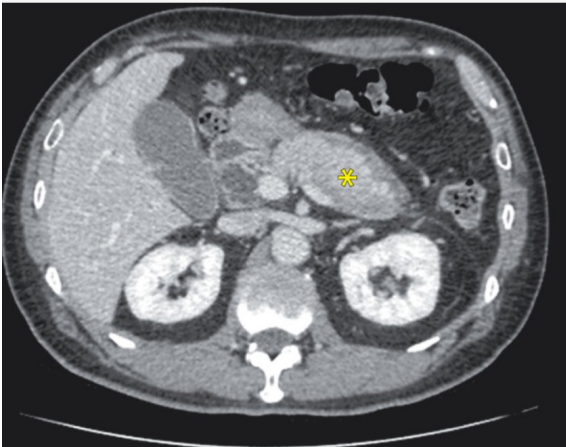
Usually every Wednesday 17:00 - 18:00



Klinische Forschung

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

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



A 60-year-old man presented with a 1-month history of **postprandial epigastric pain**. The physical examination was normal, with no jaundice or abdominal tenderness observed. Laboratory testing showed **mild elevations in levels of alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase**. CT of the abdomen with contrast showed a diffusely **enlarged pancreas with a capsule-like rim of low attenuation**. The **serum IgG4** level was elevated. Endoscopic retrograde cholangiopancreatography identified an intrapancreatic distal bile-duct stricture. Histopathological analysis of a fine-needle aspiration biopsy specimen from the pancreas was limited by crush artifact but showed **lymphoplasmacytic infiltration, fibrosis, chronic inflammation**, and no cancer. Which of the following is the most appropriate next step in management?

On the basis of the typical imaging findings (a “sausage-shaped” pancreas) and an elevated serum IgG4 level, a diagnosis of type 1 autoimmune pancreatitis was made. Type 1 autoimmune pancreatitis is the pancreatic manifestation of IgG4-related disease. It can occur as an isolated disorder or with the involvement of multiple organs. Treatment with a tapering dose of prednisolone was initiated.



Begin glucocorticoid therapy with a gradual taper

Initiate pancreatic enzyme replacement therapy

Observe with repeat imaging in 6 months

Schedule pancreaticoduodenectomy

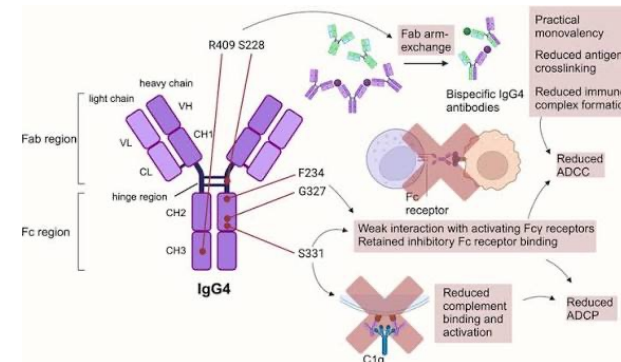
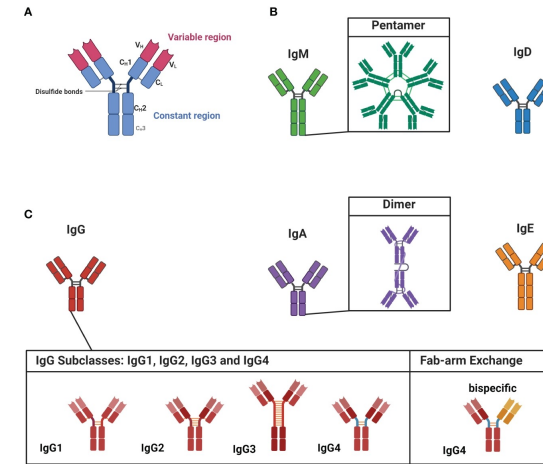
Treat with intravenous immunoglobulin

IgG4-Antikörper sind die seltenste Unterklasse der Immunglobuline G. Ihre normale Aufgabe im Immunsystem ist es, als regulatorischer Puffer zu wirken, überschießende Entzündungen zu dämpfen und bei chronischem Kontakt (wie Allerg Desensibilisierung oder Parasiten) schädliche Immunreaktionen zu blockieren.

Normale Funktionen

Toleranzbildung: Sie fangen Allergene ab, ohne eine heftige allergische Entzündung auszulösen (wichtig z. B. nach einer erfolgreichen Hyposensibilisierung).

Entzündungshemmung: Sie aktivieren das Komplementsystem kaum und binden nur schwach an Fcγ-Rezeptoren. Sie gelten daher als weitgehend „immunologisch inert“.



Die IgG4-assoziierte Erkrankung (IgG4-RD) ist eine seltene, chronisch-entzündliche Systemerkrankung. Sie führt zu Gewebeswellungen, tumorartigen Verhärtungen (Fibrosen) und kann nahezu jedes Organsystem im Körper betreffen, darunter die Bauchspeicheldrüse, Speicheldrüsen, Gallengänge und Nieren.

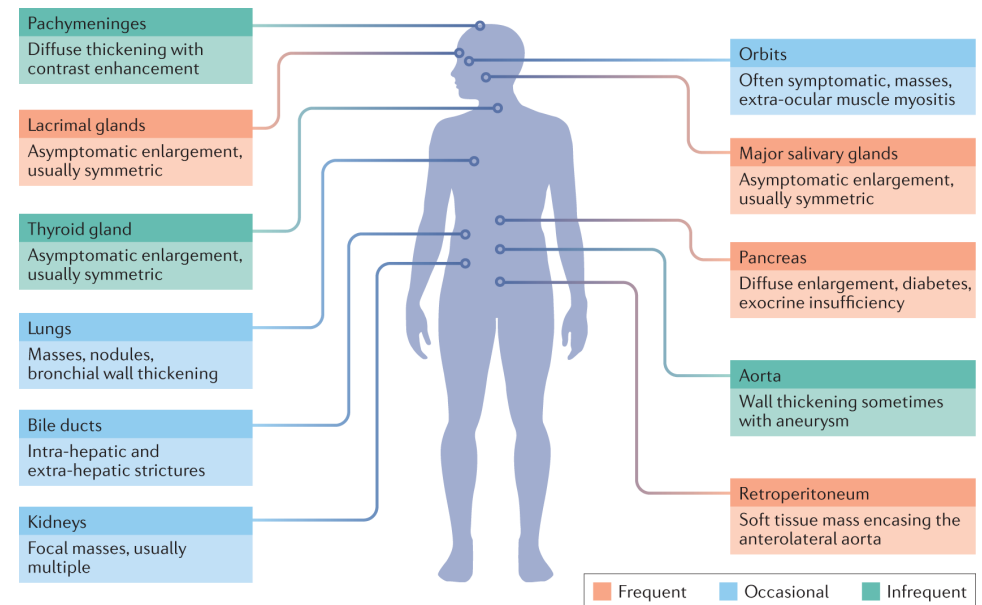
Häufig betroffene Organe und Symptome

Bauchspeicheldrüse (Pankreas): Kann zu autoimmuner Pankreatitis, Gelbsucht oder Gewichtsverlust führen.

Drüsen: Schwellungen der Tränen-, Speichel- oder Schilddrüsen.

Bauchraum und Retroperitoneum: Kann zu einer Retroperitonealfibrose (Morbus Ormond) führen.

Weitere Organe: Häufig auch Lunge, Nieren, Lymphknoten oder Blutgefäße



IgG4 syndrome features **oligoclonal or restricted clonal expansions** of adaptive immune cells reacting to persistent stimuli.

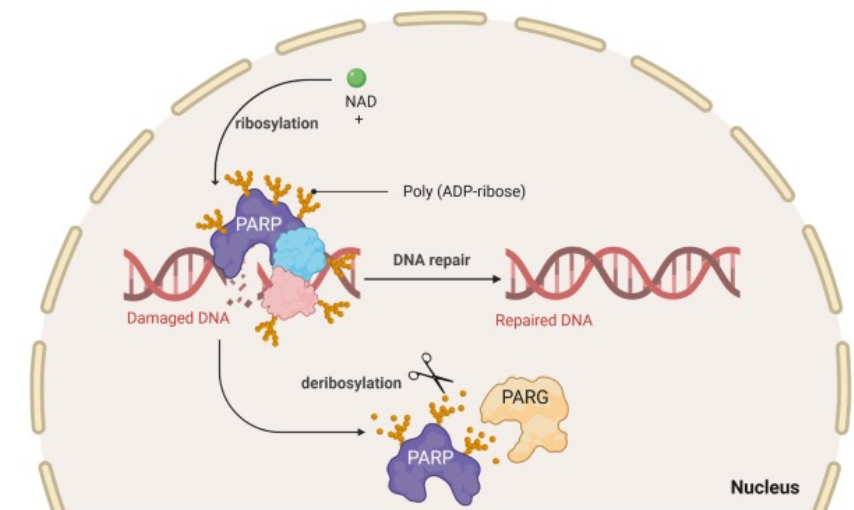
PARP-Inhibitoren (Poly-ADP-Ribose Polymerase; PARP-Hemmer) sind eine moderne Form der zielgerichteten Krebstherapie, die beim **fortgeschrittenen Prostatakarzinom** eingesetzt werden, wenn bestimmte Genmutationen vorliegen. Sie blockieren das Enzym PARP, welches für die Reparatur von DNA-Schäden in Zellen zuständig ist.

Das Wirkprinzip (Synthetische Letalität)

Gesunde Zellen besitzen mehrere Mechanismen, um Schäden an ihrer Erbsubstanz (DNA) zu reparieren. Tumorzellen mit bestimmten Mutationen haben bereits einen defekten Reparaturweg.

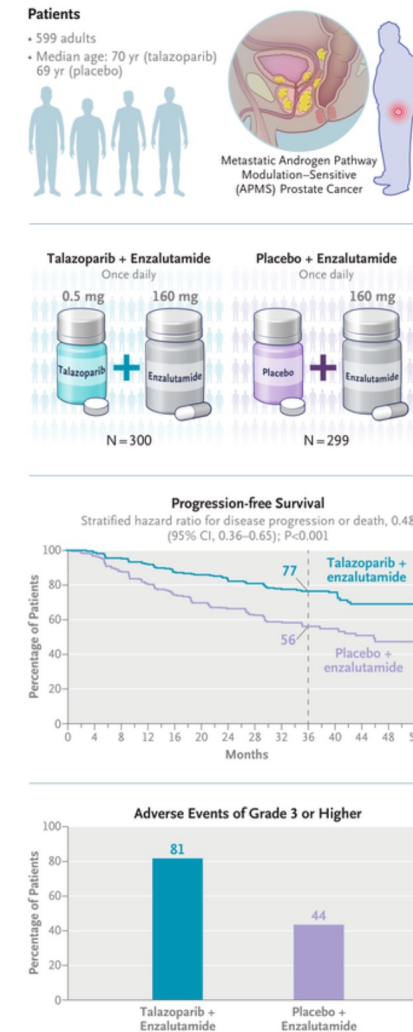
- Die Blockade:** Der PARP-Inhibitor legt den verbleibenden Rettungsweg für die DNA-Reparatur lahm.
- Das Ergebnis:** Die Krebszelle kann ihre DNA-Schäden nicht mehr reparieren und stirbt ab (Zelltod).
- Der Schutz:** Gesunde Zellen überleben, da sie alternative Reparaturwege nutzen können

PARP steht für **Poly(ADP-ribose)-Polymerase**, eine Familie von Enzymen, die wichtig für die Reparatur von DNA-Schäden im Körper sind. Bekannt ist der Begriff vor allem durch [PARP-Inhibitoren](#), die als zielgerichtete Medikamente in der Krebstherapie eingesetzt werden.



PARP and Androgen-Signaling Inhibition plus ADT in Metastatic Prostate Cancer

A previous trial involving patients with metastatic prostate cancer that was resistant to **androgen pathway modulation** (formerly referred to as **castration-resistant**) showed that adding talazoparib to enzalutamide significantly improved imaging-based progression-free survival and overall survival, with the greatest benefit observed in the cohort with **alterations in homologous recombination repair genes**. In this ongoing, phase 3, double-blind trial assessing **talazoparib** in patients with metastatic androgen pathway modulation–sensitive [APMS] prostate cancer harboring alterations in homologous recombination repair genes, we randomly assigned patients in a 1:1 ratio to receive talazoparib at a dose of 0.5 mg plus enzalutamide at a dose of 160 mg once daily (talazoparib group) or placebo plus enzalutamide at a dose of 160 mg once daily (control group). Randomization was stratified according to disease status (new or relapsed), disease volume (high or low), and **BRCA (vs. non-BRCA) mutation status**. The primary end point was investigator-assessed **imaging-based progression-free survival**. The key secondary end point was overall survival.



Recent evidence suggests that alterations in homologous recombination repair genes, reported in 29% of patients with metastatic APMS prostate cancer, are associated with worse outcomes, regardless of disease volume or treatment regimen.

In the phase 3 TALAPRO-2 trial, the addition of the poly(ADP-ribose) polymerase (PARP) inhibitor talazoparib to enzalutamide significantly improved imaging-based progression-free survival and overall survival in patients with metastatic androgen pathway modulation-resistant prostate cancer (i.e., patients with disease progression despite low serum testosterone levels [<50 ng per deciliter]), with the greatest benefit observed in the cohort with alterations in homologous recombination repair genes. The phase 3 TALAPRO-3 trial was designed to investigate the efficacy and safety of talazoparib plus enzalutamide as compared with placebo plus enzalutamide in patients with alterations in homologous recombination repair genes in the earlier clinical context of metastatic APMS prostate cancer.

Here, we report the results of the TALAPRO-3 trial at the time of the final analysis of the primary end point, imaging-based progression-free survival.

Eligibility criteria included metastatic androgen-deprivation positive (MADP) disease documented by a positive bone scan for bone disease or computed tomography or magnetic resonance imaging (MRI) for soft-tissue disease and an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (on a scale of 0 to 5, with higher scores indicating greater disability). Patients with metastatic APMS prostate cancer could have received up to 3 months of androgen-deprivation therapy with or without an approved androgen-receptor pathway inhibitor. After a protocol amendment in September 2021, patients who had received previous docetaxel therapy could not enroll. Patients who had not undergone bilateral orchiectomy must have been receiving ongoing androgen-deprivation therapy with a gonadotropin-releasing hormone agonist or antagonist. All the patients provided written informed consent.

We obtained blood or tumor samples (archived or new) at prescreening or screening and tested them for homologous recombination repair gene alterations on the basis of a 12-gene panel (*ATM, ATR, BRCA1, BRCA2, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, and RAD51C*).

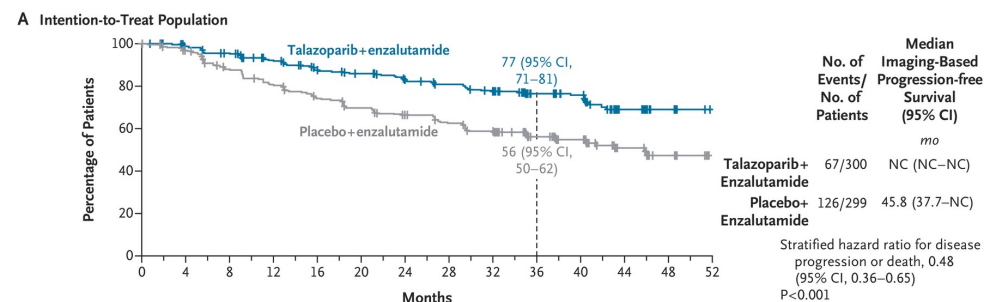
End Points

The primary end point was investigator-assessed imaging-based progression-free survival.

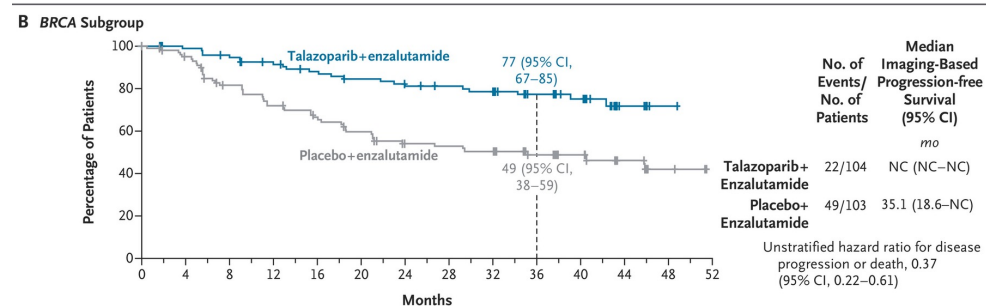
Characteristic	Talazoparib + Enzalutamide (N = 300)	Placebo + Enzalutamide (N = 299)
Median age (range) — yr	70 (45–89)	69 (44–86)
Race or ethnic group — no. (%)†		
White	167 (56)	172 (58)
Asian	115 (38)	116 (39)
Black or African American	6 (2)	3 (1)
American Indian or Alaska Native	4 (1)	2 (1)
Not reported	8 (3)	6 (2)
Geographic region — no. (%)		
Europe	132 (44)	142 (47)
Asia	113 (38)	116 (39)
North America	38 (13)	27 (9)
Rest of the world	17 (6)	14 (5)
Median serum PSA (range) — ng/ml	3.6 (0–1483)	3.6 (0–2282)
Gleason score — no. (%)‡		
<8	45 (15)	49 (16)
≥8	245 (82)	245 (82)
Disease localization at screening — no. (%)§		
Bone only	86 (29)	96 (32)
Soft tissue only	38 (13)	27 (9)
Both bone and soft tissue	176 (59)	173 (58)
ECOG performance-status score — no. (%)¶		
0	199 (66)	208 (70)
1	101 (34)	91 (30)
Disease status — no. (%)		
New	252 (84)	254 (85)
Relapsed	48 (16)	45 (15)
Disease volume — no. (%)		
High	211 (70)	212 (71)
Low	89 (30)	87 (29)
HRR gene alteration — no. (%)		
BRCA1 or BRCA2	104 (35)	103 (34)
Other	196 (65)	196 (66)
Source for HRR gene alteration testing — no. (%)		
Tumor tissue only	39 (13)	45 (15)
Blood only	58 (19)	41 (14)
Tumor tissue and blood	203 (68)	213 (71)
HRR gene with ≥1 alteration — no. (%)		
BRCA2	86 (29)	92 (31)
ATM	87 (29)	80 (27)
CDK12	55 (18)	60 (20)
CHEK2	44 (15)	44 (15)
ATR	23 (8)	18 (6)
BRCA1	16 (5)	11 (4)
PALB2	11 (4)	7 (2)
FANCA	10 (3)	6 (2)
NBN	6 (2)	6 (2)
MRE11A	3 (1)	2 (1)
RAD51C	0	4 (1)
MLH1	1 (<1)	1 (<1)

Adverse Events

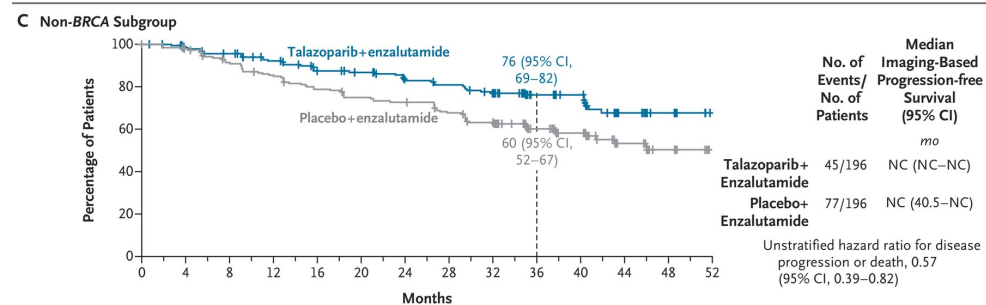
Adverse Event	Talazoparib + Enzalutamide (N = 299)		Placebo + Enzalutamide (N = 295)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	<i>number of patients (percent)</i>			
Any event	297 (99)	243 (81)	286 (97)	130 (44)
Treatment-related event	277 (93)	216 (72)	213 (72)	42 (14)
Serious event	126 (42)	111 (37)	93 (32)	80 (27)
Resulting in dose interruption				
Talazoparib or placebo†	207 (69)	NA	90 (31)	NA
Enzalutamide‡	140 (47)	NA	85 (29)	NA
Resulting in dose reduction				
Talazoparib or placebo†	178 (60)	NA	22 (7)	NA
Enzalutamide‡	53 (18)	NA	25 (8)	NA
Resulting in permanent discontinuation				
Talazoparib or placebo†	56 (19)	NA	29 (10)	NA
Enzalutamide‡	32 (11)	NA	26 (9)	NA
Grade 5	NA	8 (3)§	NA	9 (3)§
Event of any grade occurring in ≥10% of patients¶				
Anemia	213 (71)	152 (51)	64 (22)	8 (3)
Fatigue	85 (28)	9 (3)	45 (15)	1 (<1)
Neutrophil count decreased	81 (27)	34 (11)	16 (5)	3 (1)
Neutropenia	66 (22)	26 (9)	8 (3)	4 (1)
Asthenia	64 (21)	17 (6)	39 (13)	2 (1)
White-cell count decreased	64 (21)	17 (6)	12 (4)	1 (<1)
Hot flash	60 (20)	0	67 (23)	0
Decreased appetite	59 (20)	6 (2)	30 (10)	3 (1)
Back pain	56 (19)	4 (1)	58 (20)	3 (1)
Constipation	54 (18)	0	36 (12)	1 (<1)
Nausea	51 (17)	0	24 (8)	0
Platelet count decreased	49 (16)	14 (5)	10 (3)	1 (<1)
Arthralgia	45 (15)	0	68 (23)	2 (1)
Diarrhea	40 (13)	5 (2)	31 (11)	3 (1)
Fall	40 (13)	1 (<1)	46 (16)	2 (1)
Coronavirus disease 2019	39 (13)	1 (<1)	44 (15)	0
Hypertension	37 (12)	13 (4)	66 (22)	15 (5)
Thrombocytopenia	37 (12)	14 (5)	9 (3)	0
Dysgeusia	33 (11)	0	20 (7)	0
Insomnia	33 (11)	2 (1)	20 (7)	0
Urinary tract infection	32 (11)	6 (2)	19 (6)	2 (1)
Dizziness	31 (10)	0	25 (8)	2 (1)
Lymphocyte count decreased	30 (10)	8 (3)	14 (5)	3 (1)
Weight decreased	30 (10)	2 (1)	16 (5)	1 (<1)
Pain in extremity	28 (9)	1 (<1)	31 (11)	1 (<1)



No. at Risk	300	271	260	241	222	213	196	189	178	126	96	32	14	0
Talazoparib+ enzalutamide														
Placebo+ enzalutamide	299	276	243	222	203	188	175	163	151	98	74	32	12	0



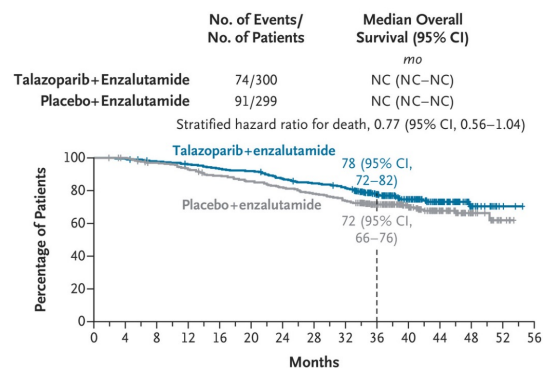
No. at Risk	104	93	89	82	77	73	69	66	64	46	35	10	4	0
Talazoparib+ enzalutamide														
Placebo+ enzalutamide	103	93	76	67	60	53	44	43	41	29	23	12	4	0



Imaging-Based Progression-free Survival.

Shown are Kaplan–Meier estimates of investigator-assessed imaging-based progression-free survival in the intention-to-treat population, the subgroup of patients with *BRCA* alterations, and the subgroup of patients with non-*BRCA* alterations. The widths of the confidence intervals for the *BRCA* and non-*BRCA* subgroups have not been adjusted for multiplicity and cannot be used to infer treatment effects. These subgroups were determined at the time of randomization. NC denotes not calculable.

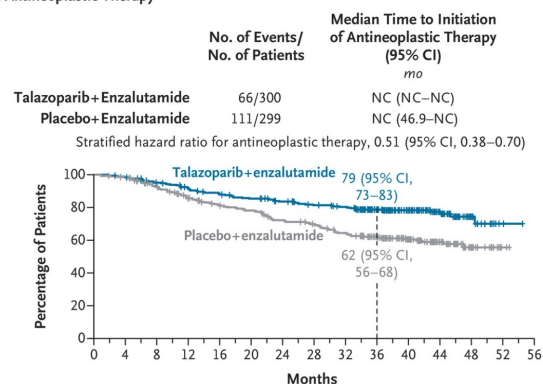
A Overall Survival



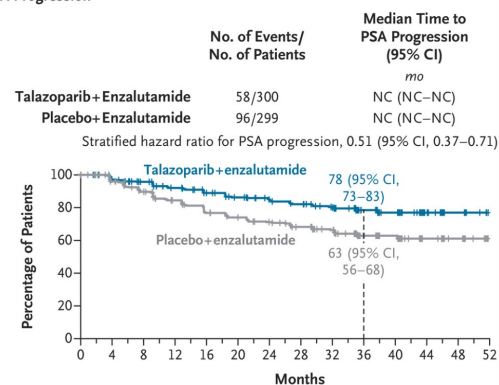
No. at Risk

Talazoparib+enzalutamide	300	299	290	284	276	272	257	248	239	183	121	69	24	3	0
Placebo+enzalutamide	299	297	285	273	260	250	239	228	215	166	113	64	21	5	0

C Subsequent Antineoplastic Therapy



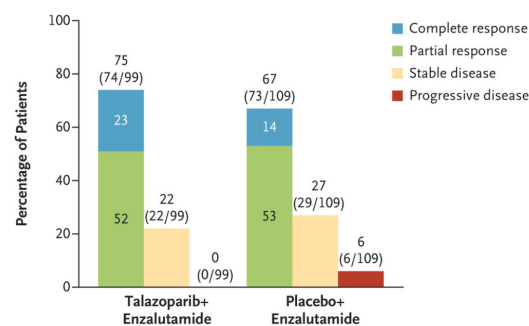
B Confirmed PSA Progression



No. at Risk

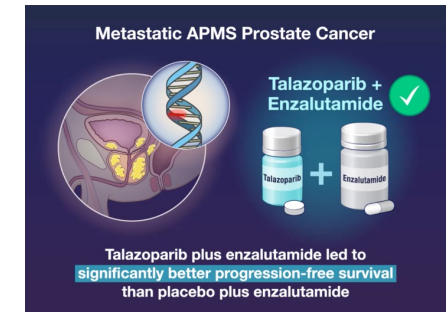
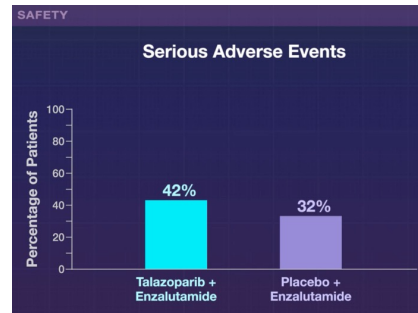
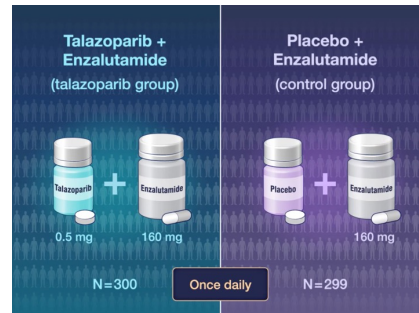
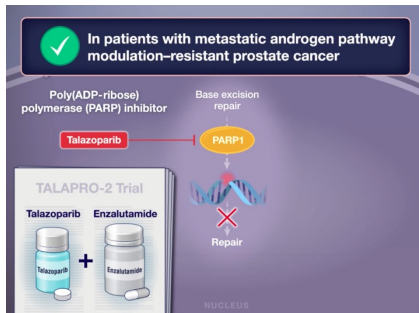
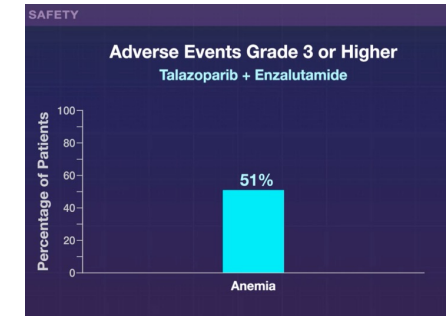
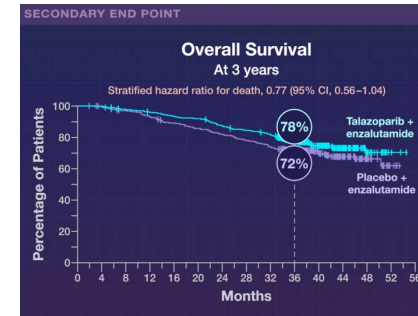
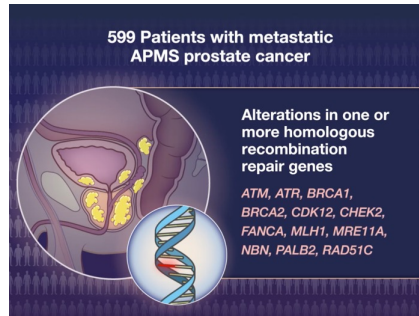
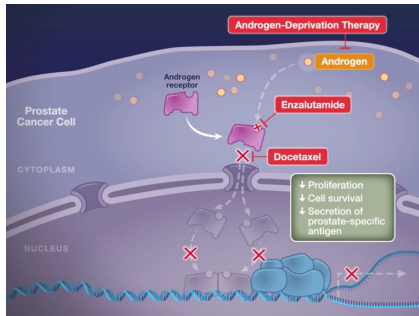
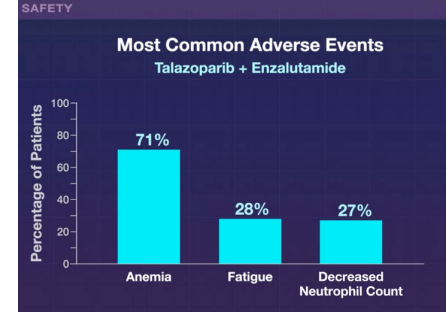
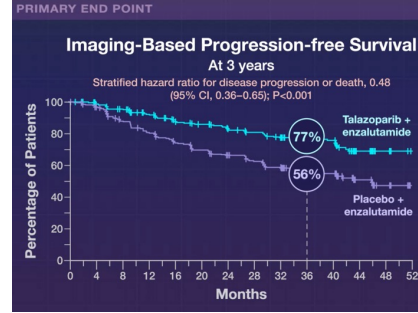
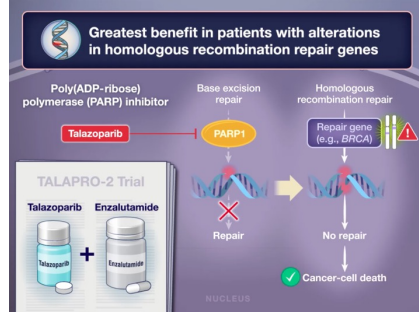
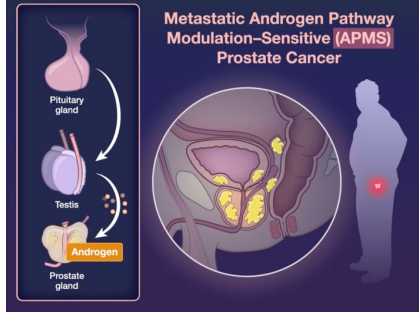
Talazoparib+enzalutamide	300	278	263	246	231	218	205	197	185	121	88	32	12	0
Placebo+enzalutamide	299	266	240	215	192	182	171	158	147	97	73	33	13	0

D Objective Response



Secondary Efficacy End Points.

Panel A shows Kaplan–Meier estimates (time-to-event analysis) of overall survival at the interim analysis. Panel B shows Kaplan–Meier estimates (time-to-event analysis) of confirmed prostate-specific antigen (PSA) progression (defined as a $\geq 25\%$ increase in PSA with an absolute increase of ≥ 2 ng per milliliter above the nadir), and Panel C shows Kaplan–Meier estimates (time-to-event analysis) of initiation of antineoplastic therapy in the intention-to-treat population. The analyses in Panels A, B, and C were performed in the intention-to-treat population. Panel D shows the percentage of patients with an objective response among those in the intention-to-treat population who had measurable soft-tissue disease at baseline. The widths of the confidence intervals have not been adjusted for multiplicity and cannot be used to infer treatment effects. Three of 99 patients in the talazoparib group and 1 of 109 patients in the control group could not be evaluated for objective response.



Teclistamab ist ein moderner, hochwirksamer bispezifischer Antikörper zur Behandlung des Multiplen Myeloms (Knochenmarkkrebs). Er gehört zu einer neuen Klasse von Immuntherapien, den sogenannten T-Zell-Engagern. Er fungiert als molekulare Brücke: **Eine Seite bindet an das Protein BCMA** auf den Myelomzellen, **die andere an CD3 auf den körpereigenen T-Zellen.** Dadurch wird das Immunsystem gezwungen, die Krebszellen direkt zu vernichten.

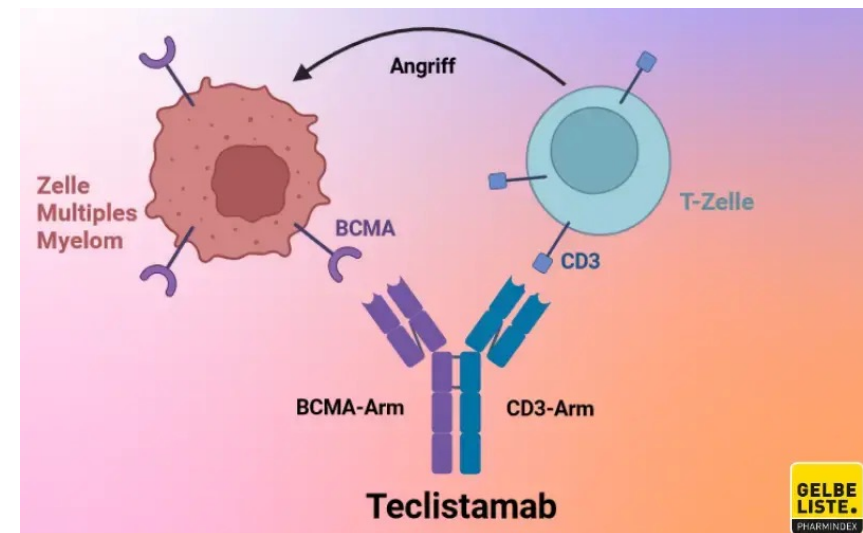
Zulassung und Einsatzbereich

- Spätlinien-Therapie:** Regulär zugelassen als Monotherapie für Erwachsene mit rezidiviertem (wiedergekehrtem) oder refraktärem (therapieresistentem) Multiplen Myelom.

- Voraussetzung:** Patienten müssen mindestens drei Vortherapien erhalten haben. Dazu gehören ein immunmodulierender Wirkstoff (IMiD), ein Proteasom-Inhibitor und ein Anti-CD38-Antikörper.

- Frühzeitiger Einsatz:** Neueste klinische Studien prüfen den [Einsatz bereits in der Erstlinie](#) in Kombination mit Standardtherapien vor einer Stammzelltransplantation

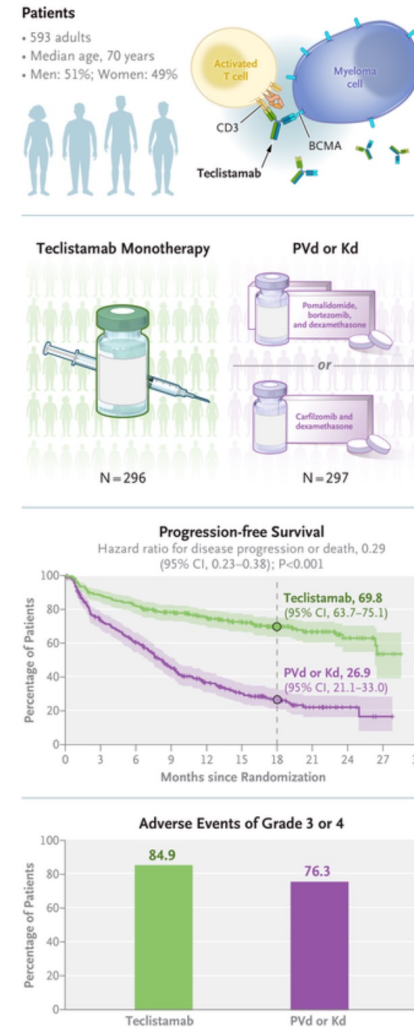
BCMA steht für **B-cell maturation antigen** (B-Zell-Reifungsantigen). Es handelt sich dabei um ein Eiweiß auf der Oberfläche von bestimmten Immunzellen (Plasmazellen), das auch auf den Krebszellen beim **Multiplen Myelom** (einer Art von Knochenmarkkrebs) in großer Menge vorkommt



Teclistamab in Multiple Myeloma with One to Three Previous Lines of Therapy

The efficacy of teclistamab, a bispecific antibody targeting B-cell maturation antigen and CD3, as early-line monotherapy in relapsed or refractory multiple myeloma is unclear.

We randomly assigned patients with relapsed or refractory multiple myeloma who had previously received one, two, or three lines of therapy, including an anti-CD38 monoclonal antibody and lenalidomide, to receive teclistamab or the investigator's choice of pomalidomide, bortezomib, and dexamethasone (PVD) or carfilzomib and dexamethasone (Kd). Antimicrobial prophylaxis and immune globulin replacement were recommended. The primary end point was progression-free survival as assessed by an independent review committee.



In patients with **newly diagnosed multiple myeloma**, outcomes have improved with standard three- and four-drug regimens, which include **proteasome inhibitors, immunomodulatory agents, and anti-CD38 monoclonal antibodies**.

In the earlier phase 3 MajesTEC-3 trial, the synergistic and glucocorticoid-sparing combination of teclistamab, a bispecific antibody targeting CD3 on T-cell surfaces and BCMA on myeloma and B cells, and daratumumab led to significant improvements in progression-free and overall survival as early as **second-line treatment** in patients who had previously received one, two, or three lines of therapy including a proteasome inhibitor and lenalidomide; the safety profile was consistent with each individual component. Results built on findings of the phase 1–2 MajesTEC-1 study, in which **teclistamab monotherapy** led to deep, durable responses in patients with heavily pretreated relapsed or refractory multiple myeloma.

The MajesTEC-9 trial was a phase 3 trial of teclistamab monotherapy, a fully immune-based and glucocorticoid-sparing regimen, in patients with **relapsed or refractory multiple myeloma** who **had previously received one, two, or three lines of therapy including an anti-CD38 monoclonal antibody and lenalidomide**. This patient population has been underrepresented in clinical trials to date. Here, we present efficacy and safety findings from the interim analysis of this trial that compared **teclistamab** with the investigator's choice of **pomalidomide, bortezomib, and dexamethasone (PVd) or carfilzomib and dexamethasone (Kd)**.

Patients

Eligible patients had previously received one, two, or three lines of antimyeloma therapy, including an anti-CD38 monoclonal antibody and lenalidomide, and had documented disease progression or did not have a response to their last regimen. A key exclusion criterion was previous receipt of BCMA-directed therapy. Patients who had received pomalidomide previously or who did not meet the criteria for bortezomib retreatment could not receive PVd; patients who had received carfilzomib previously could not receive Kd. Full eligibility criteria are provided in the protocol.

Trial Treatments

Patients were randomly assigned in 1:1 ratio to receive either **teclistamab monotherapy** (the teclistamab group) or the **investigator's choice of PVd or Kd (the PVd or Kd group)**. Randomization was stratified according to the investigator's choice of PVd or Kd, International Staging System (ISS) disease stage at screening (I vs. II or III), anti-CD38 therapy–refractory status (yes vs. no), and the number of previous lines of therapy (one vs. two or three).

Patients in the teclistamab group received 28-day cycles of subcutaneous teclistamab administered as two step-up doses (0.06 mg per kilogram of body weight and 0.3 mg per kilogram), followed by weekly doses of 1.5 mg per kilogram in cycles one and two, 3 mg per kilogram every 2 weeks in cycles three through six, and 3 mg per kilogram every 4 weeks from cycle 7 onward.

Characteristic	Teclistamab (N =296)	PVd or Kd (N =297)	Total (N =593)
Age			
Median (range) — yr	70 (34–85)	70 (36–86)	70 (34–86)
Distribution — no. (%)			
<65 yr	100 (33.8)	92 (31.0)	192 (32.4)
65 to <75 yr	112 (37.8)	116 (39.1)	228 (38.4)
≥75 yr	84 (28.4)	89 (30.0)	173 (29.2)
Sex — no. (%)			
Male	150 (50.7)	153 (51.5)	303 (51.1)
Female	146 (49.3)	144 (48.5)	290 (48.9)
Race or ethnic group — no. (%) †			
White	190 (64.2)	198 (66.7)	388 (65.4)
Asian	62 (20.9)	56 (18.9)	118 (19.9)
Black	10 (3.4)	10 (3.4)	20 (3.4)
Other‡	34 (11.5)	33 (11.1)	67 (11.3)
Hispanic or Latino ethnic group — no. (%) †			
Yes	37 (12.5)	34 (11.4)	71 (12.0)
No	229 (77.4)	233 (78.5)	462 (77.9)
Not reported or unknown	30 (10.1)	30 (10.1)	60 (10.1)
ECOG performance-status score — no. (%)§			
0	156 (52.7)	135 (45.5)	291 (49.1)
1	121 (40.9)	137 (46.1)	258 (43.5)
2	19 (6.4)	24 (8.1)	43 (7.3)
3	0	1 (0.3)	1 (0.2)
ISS disease stage — no. (%) ¶			
I	168 (56.8)	170 (57.2)	338 (57.0)
II	86 (29.1)	82 (27.6)	168 (28.3)
III	42 (14.2)	45 (15.2)	87 (14.7)
R-ISS disease stage — no./total no. (%)			
I	57/258 (22.1)	70/259 (27.0)	127/517 (24.6)
II	177/258 (68.6)	161/259 (62.2)	338/517 (65.4)
III	24/258 (9.3)	28/259 (10.8)	52/517 (10.1)
Cytogenetic risk — no./total no. (%) **			
High risk	105/294 (35.7)	104/296 (35.1)	209/590 (35.4)
Standard risk	127/294 (43.2)	127/296 (42.9)	254/590 (43.1)
Undetermined	62/294 (21.1)	65/296 (22.0)	127/590 (21.5)
≥1 Soft-tissue plasmacytoma — no. (%) ††	54 (18.2)	65 (21.9)	119 (20.1)
Extramedullary plasmacytomas	19 (6.4)	22 (7.4)	41 (6.9)
Paraskeletal plasmacytomas	43 (14.5)	52 (17.5)	95 (16.0)
≥60% Bone marrow plasma cells — no./total no. (%) ‡‡	31/292 (10.6)	40/295 (13.6)	71/587 (12.1)
Median time from diagnosis of multiple myeloma to randomization (range) — yr	3.8 (0.3–21.0)	3.5 (0.2–22.1)	3.7 (0.2–22.1)
No. of lines of previous therapy			
Median (range)	2 (1–3)	2 (1–3)	2 (1–3)
1 Line — no. (%)	64 (21.6)	64 (21.5)	128 (21.6)
2 or 3 Lines — no. (%)	232 (78.4)	233 (78.5)	465 (78.4)
Previous therapy exposure — no. (%)			
Proteasome inhibitor	256 (86.5)	254 (85.5)	510 (86.0)
Immunomodulatory drug	296 (100)	297 (100)	593 (100)
Anti-CD38 monoclonal antibody	296 (100)	297 (100)	593 (100)
Refractory status — no. (%)			
Any proteasome inhibitor	122 (41.2)	128 (43.1)	250 (42.2)
Any immunomodulatory drug	245 (82.8)	251 (84.5)	496 (83.6)
Lenalidomide	234 (79.1)	240 (80.8)	474 (79.9)
Any anti-CD38 monoclonal antibody	253 (85.5)	252 (84.8)	505 (85.2)
Daratumumab	229 (77.4)	225 (75.8)	454 (76.6)
Triple-class refractory§§	102 (34.5)	98 (33.0)	200 (33.7)
Anti-CD38 monoclonal antibody and immuno-modulatory drug	218 (73.6)	221 (74.4)	439 (74.0)
Last line of therapy	274 (92.6)	273 (91.9)	547 (92.2)

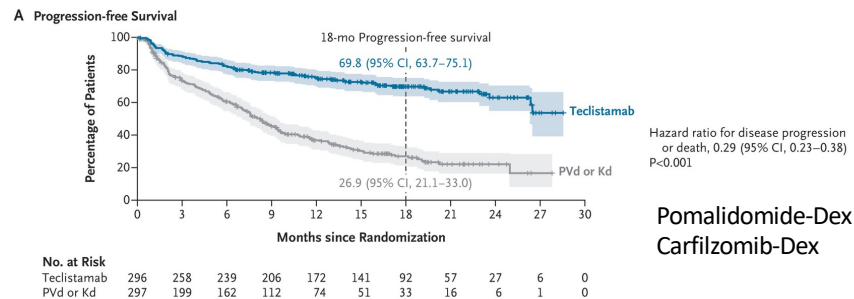
Response

Pomalidomide-Dex
Carfilzomib-Dex

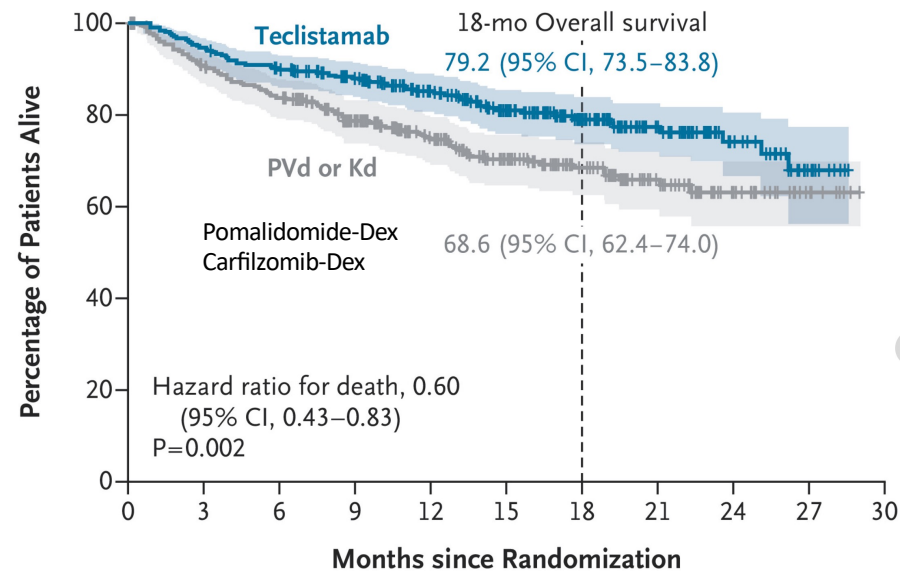
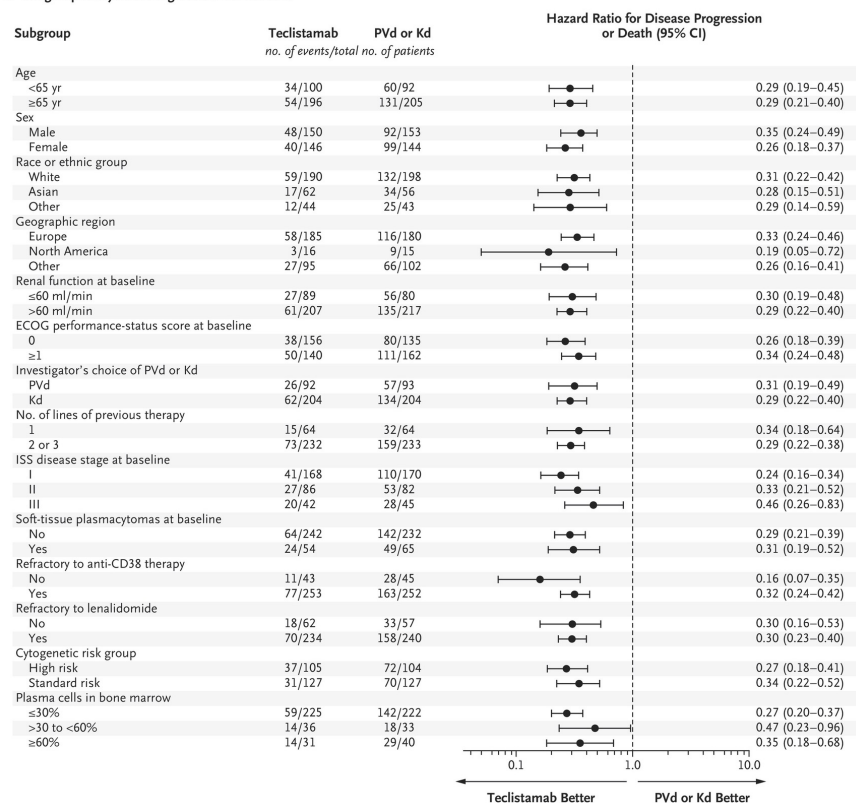
Variable	Teclistamab (N =296)	PVd or Kd (N =297)	Risk Ratio (95% CI) †
Overall response — no. (%) ‡	250 (84.5)	161 (54.2)	1.56 (1.39–1.75)
Response — no. (%) §			
Stringent complete response	159 (53.7)	28 (9.4)	—
Complete response	36 (12.2)	22 (7.4)	—
Very good partial response	42 (14.2)	58 (19.5)	—
Partial response	13 (4.4)	53 (17.8)	—
Minimal response	0	18 (6.1)	—
Stable disease	26 (8.8)	81 (27.3)	—
Progressive disease	13 (4.4)	24 (8.1)	—
Could not be evaluated ¶	7 (2.4)	13 (4.4)	—
Complete response or better — no. (%)	195 (65.9)	50 (16.8)	3.95 (3.03–5.14)
Very good partial response or better — no. (%)	237 (80.1)	108 (36.4)	2.20 (1.88–2.59)
Measure of response			
Median duration of response (95% CI) — mo	NE (25.2–NE)	13.4 (10.4–17.3)	—
Median time to first response (range) — mo	1.2 (0.9–7.9)	1.1 (0.7–11.1)	—
Median time to complete response or better (range) — mo	5.8 (1.0–23.0)	5.6 (0.9–16.3)	—

Adverse

Event	Teclistamab (N =291)		PVd or Kd (N =283)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
<i>number of patients with event (percent)</i>				
Any adverse event	290 (99.7)	247 (84.9)	277 (97.9)	216 (76.3)
Hematologic event				
Neutropenia	182 (62.5)	158 (54.3)	81 (28.6)	63 (22.3)
Anemia	110 (37.8)	52 (17.9)	119 (42.0)	46 (16.3)
Thrombocytopenia	80 (27.5)	31 (10.7)	110 (38.9)	60 (21.2)
Lymphopenia	71 (24.4)	59 (20.3)	49 (17.3)	32 (11.3)
Nonhematologic event				
Cytokine release syndrome	192 (66.0)	2 (0.7)	0	0
Diarrhea	124 (42.6)	15 (5.2)	72 (25.4)	4 (1.4)
Hypogammaglobulinemia †	124 (42.6)	7 (2.4)	46 (16.3)	1 (0.4)
Cough	80 (27.5)	2 (0.7)	39 (13.8)	0
Upper respiratory tract infection	77 (26.5)	7 (2.4)	58 (20.5)	6 (2.1)
Injection-site erythema	71 (24.4)	0	8 (2.8)	0
Pneumonia	64 (22.0)	42 (14.4)	43 (15.2)	30 (10.6)
Hypertension	20 (6.9)	13 (4.5)	51 (18.0)	32 (11.3)

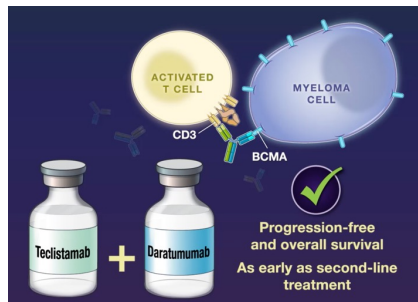


B Subgroup Analysis of Progression-free Survival



Overall Survival.

Shown are Kaplan–Meier estimates of overall survival among patients who had been randomly assigned to the teclistamab group or the PvD or Kd group, in which patients received investigator's choice of PvD or Kd. Tick marks indicate censored data, and shaded areas 95% confidence intervals. At a median follow-up of 17.3 months, the median overall survival was not reached in either trial group. The widths of the confidence intervals have not been adjusted for multiplicity and may not be used in place of hypothesis testing.



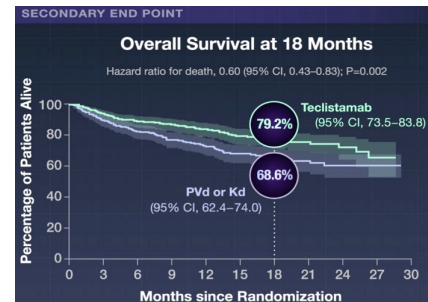
Teclistamab Monotherapy
N=296

Investigator's Choice, N=297

PVd
Pomalidomide, bortezomib, and dexamethasone

OR

Kd
Carfilzomib and dexamethasone

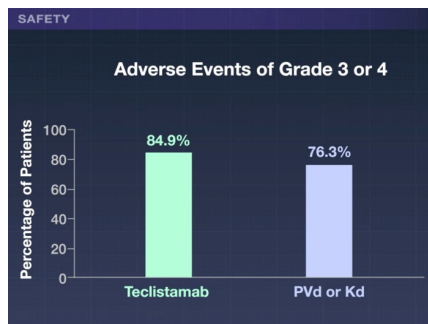
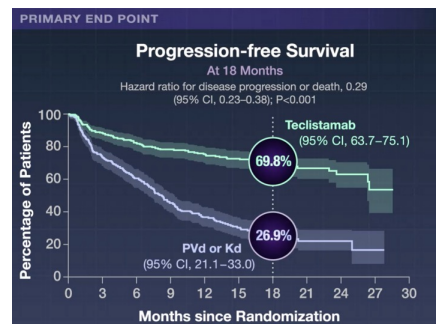


Relapsed or Refractory Multiple Myeloma

Progression-free and overall survival as compared with PVd or Kd

Teclistamab **VS.**

For patients with relapsed or refractory multiple myeloma

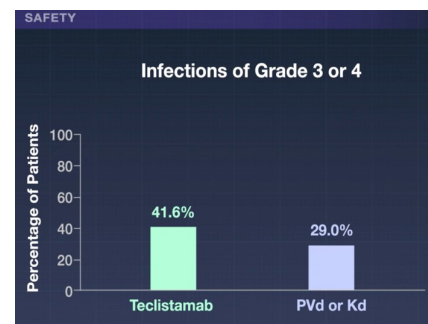
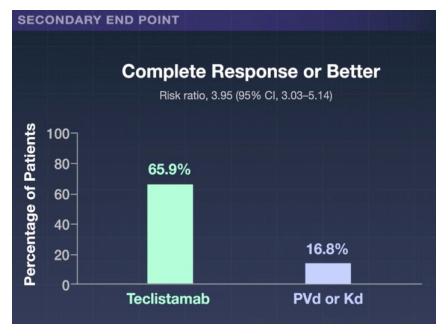


593 Patients

1, 2, or 3 lines of therapy

Anti-CD38 monoclonal antibody

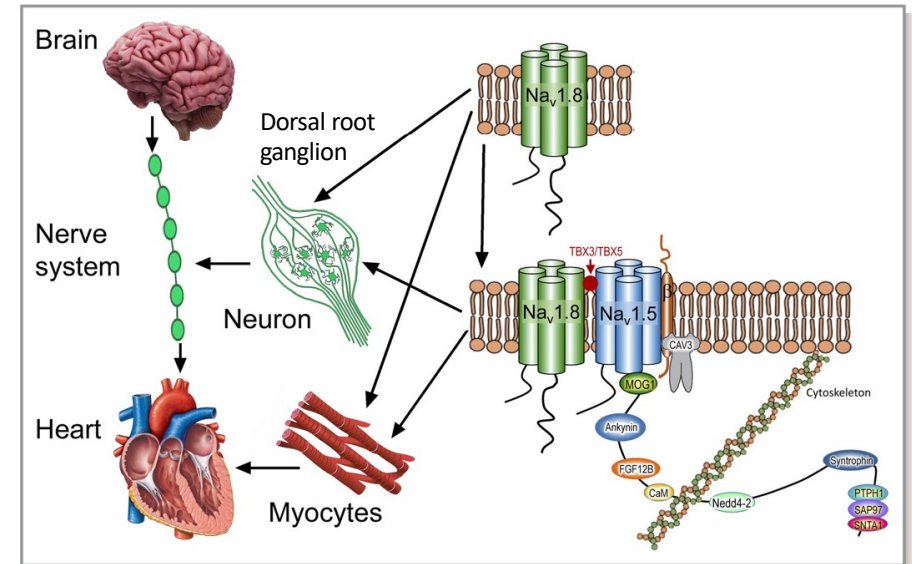
Documented disease progression or did not have a response to their last regimen



Nav1.8 ist ein spannungsgesteuerter Natriumkanal, der hauptsächlich in schmerzleitenden Nervenfasern des peripheren Nervensystems vorkommt. Er spielt eine zentrale Rolle bei der Weiterleitung von chronischen und entzündlichen Schmerzsignalen an das Gehirn.

Wichtige Merkmale und Funktionen

- **Lokalisierung:** Überwiegend in nozizeptiven (schmerzempfindlichen) Neuronen der Spinalganglien ([Dorsal Root Ganglia](#)).
- **Genetische Kodierung:** Wird beim Menschen durch das Gen *SCN10A* auf Chromosom 3 kodiert.
- **Besonderheit:** Er besitzt eine Resistenz gegen das Nervengift Tetrodotoxin (TTX-resistent).
- **Funktion:** Aktiviert sich bei Depolarisation und bleibt auch bei anhaltendem Schmerzreiz aktiv.
- **Medizinische Relevanz:** Ein Blockieren von Nav1.8 gilt als vielversprechender Ansatz für neue Schmerzmittel ohne Suchtpotenzial.



Abdominoplastik

Eine **Abdominoplastik** (umgangssprachlich **Bauchdeckenstraffung**) ist ein chirurgischer Eingriff der plastischen Chirurgie, bei dem überschüssige Haut und Fettgewebe aus dem mittleren und unteren Bauchbereich entfernt werden. In den meisten Fällen werden dabei auch die darunter liegenden Bauchmuskeln (Rektusdiastase) durch innere Nähte gestrafft, um eine flachere und stabilere Bauchwand zu formen.

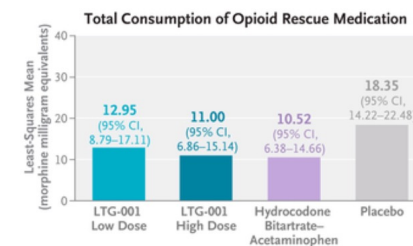
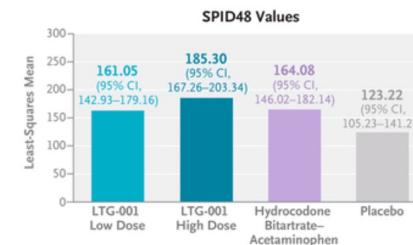
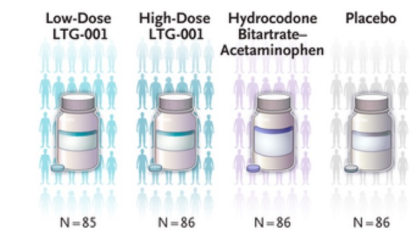
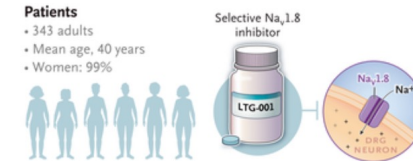
Der Eingriff dient vor allem der Formung des Körpers (Body Contouring) nach einer massiven Gewichtsabnahme, nach Schwangerschaften oder bei altersbedingter Erschlaffung des Gewebes, wenn sich die Haut nicht mehr von selbst zurückbilden kann. Eine Abdominoplastik ist ausdrücklich **keine Methode zur Gewichtsreduktion** und wird in der Regel nur bei Personen mit stabilem Normal- oder leichtem Übergewicht durchgeführt.



Phase 2b Trial of a Na_v1.8 Inhibitor for Acute Pain

Na_v1.8, a voltage-gated sodium channel expressed in the peripheral nervous system, has a critical role in pain signaling. Previous trials of Na_v1.8 inhibitors have shown effectiveness in reducing postoperative pain.

We conducted a phase 2b, double-blind, randomized, placebo-controlled trial to evaluate LTG-001, a selective Na_v1.8 inhibitor, in patients with moderate-to-severe pain after abdominoplasty. Patients were randomly assigned in a 1:1:1:1 ratio to receive a 300-mg loading dose of LTG-001, followed by 150 mg every 12 hours (low-dose group); a 450-mg loading dose of LTG-001, followed by 300 mg every 12 hours (high-dose group); hydrocodone bitartrate–acetaminophen (5 mg of hydrocodone bitartrate and 325 mg of acetaminophen) every 6 hours; or placebo every 6 hours. All doses were administered orally over a 48-hour period. The primary end point was the time-weighted **sum of the pain-intensity difference (SPID) over the 48-hour treatment period (SPID48)**, based on scores on the Numeric Pain Rating Scale (range, 0 to 10, with higher values indicating more severe pain; higher SPID48 values indicate greater pain reduction). Secondary end points included the amount of opioid rescue medication consumed in morphine milligram equivalents (MME) and **no receipt of opioid rescue medication**.



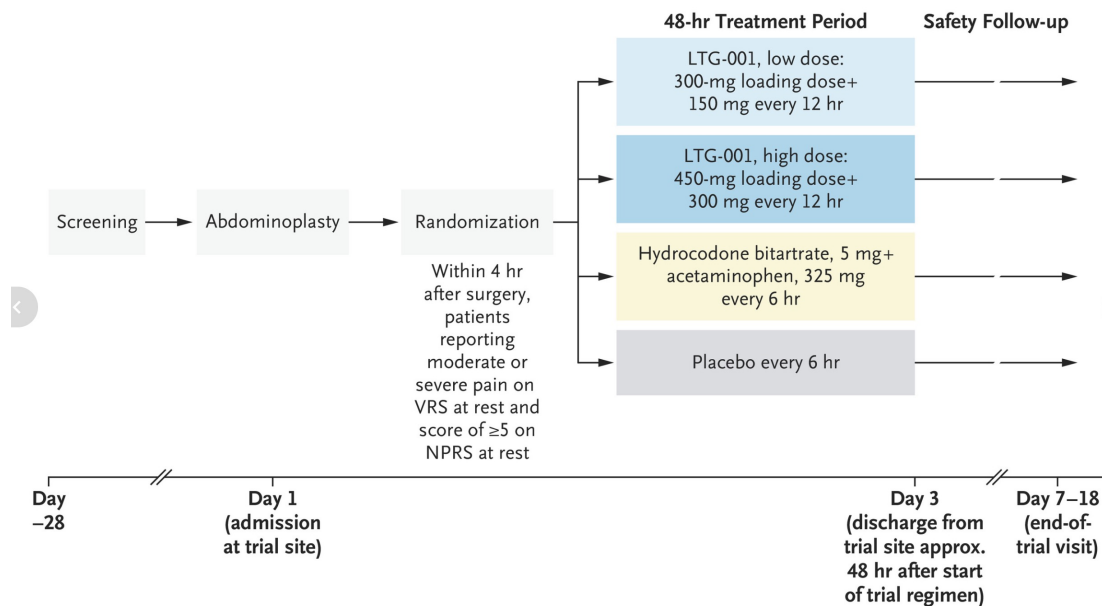
Na_v1.8 is a voltage-gated sodium channel expressed in the peripheral nervous system (preferentially in nociceptors and dorsal-root ganglia). It has a critical role in pain signaling through the transmission of pain signals in peripheral sensory neurons, which makes it an attractive target for the management of acute and chronic pain with little to no risk of addiction.

Suzetrigine showed a relatively modest treatment effect for acute pain as compared with placebo in clinical trials. These findings suggest that modulating just one mechanism of pain transmission (i.e., sodium-channel modulation) may be unlikely to lead to large effects on pain. Furthermore, given the failure of a more-potent suzetrigine follow-on Na_v1.8 inhibitor (VX-993) to provide higher levels of pain relief than placebo in a recently completed trial involving patients who had undergone bunionectomy, it has been suggested that Na_v1.8 inhibitors may have hit an efficacy ceiling for acute pain.

LTG-001 is an oral, nonopioid, potent, selective Na_v1.8 inhibitor designed to deliver opioid-level analgesia. To date, molecules in the Na_v1.8 inhibitor class have been characterized primarily by in vitro assays of potency for blocking the Na_v1.8 channel. However, inhibition of the Na_v1.8 channel in vitro (target inhibition) depends on both potency and the degree of penetration into the target tissue. LTG-001 led to high levels of Na_v1.8 target inhibition owing to both its potency and a high degree of penetration into the peripheral nerve (the site of action). Evaluation of LTG-001 in an **experimental model of pain in humans (the cold pressor test)** confirmed a pharmacodynamic dose response. The primary objective of the LTG-001-010 trial was to **evaluate the efficacy and safety** of low and high doses of LTG-001 in treating acute pain after abdominoplasty.

Patients

Patients 18 to 65 years of age who were scheduled to undergo elective abdominoplasty were enrolled at four sites in the United States. After surgery, patients were eligible for the trial if they had undergone a lower abdominoplasty with rectus plication without other collateral procedures and if, within 4 hours after surgery, **they reported moderate or severe pain at rest on the verbal categorical rating scale** (VRS, a four-level scale ranging from no pain to severe pain) and a pain score of at least 5 on the Numeric Pain Rating Scale (NPRS, an 11-point scale ranging from 0 [no pain] to 10 [worst pain imaginable]). Patients with current or long-term opioid use or a history of chronic pain conditions, depression, anxiety, or other psychiatric disorders that had not been clinically stable for at least 90 days before surgery were not eligible for the trial.



Trial Design.

Patients who were potentially eligible for the trial on screening before surgery were assessed for randomization after surgery with the verbal categorical rating scale (VRS, a four-level scale ranging from no pain to severe pain) and the Numeric Pain Rating Scale (NPRS, an 11-point scale ranging from 0 [no pain] to 10 [worst pain imaginable]). After randomization, all the patients received pills every 6 hours for 48 hours, regardless of trial-group assignment. The LTG-001 groups received placebo at nonactive dose-administration time points to ensure balanced and blinded double-dummy dose administration across all trial groups.

End Points

The primary end point was the time-weighted sum of the pain-intensity difference (SPID), based on NPRS scores, over the course of 48 hours (SPID48). In brief, the SPID48 is a time-weighted average of the difference in pain intensity from baseline at each time point at which pain is assessed. Higher values indicate greater pain reduction from baseline; however, a minimum clinically important difference in acute pain has not been established.

Secondary efficacy end points, hierarchically gated in the following order, were the amount of opioid rescue medication consumed in morphine milligram equivalents (MME), no receipt of opioid rescue treatment, the time to a reduction in the NPRS score of at least 2 points (which represents clinically meaningful pain relief), the time to a reduction in the NPRS score of at least 1 point, nausea or vomiting during the treatment period, the pain-intensity difference at 60 minutes, the SPID over the course of the first 24 hours of the treatment period (SPID24), and a favorable patient global assessment of the trial product (LTG-001, hydrocodone bitartrate–acetaminophen, or placebo) for pain control. Patient global assessments used a five-level scale (poor, fair, good, very good, or excellent). An assessment of good, very good, or excellent was considered to be favorable. The hierarchical structure to adjust for multiplicity for end-point comparisons.

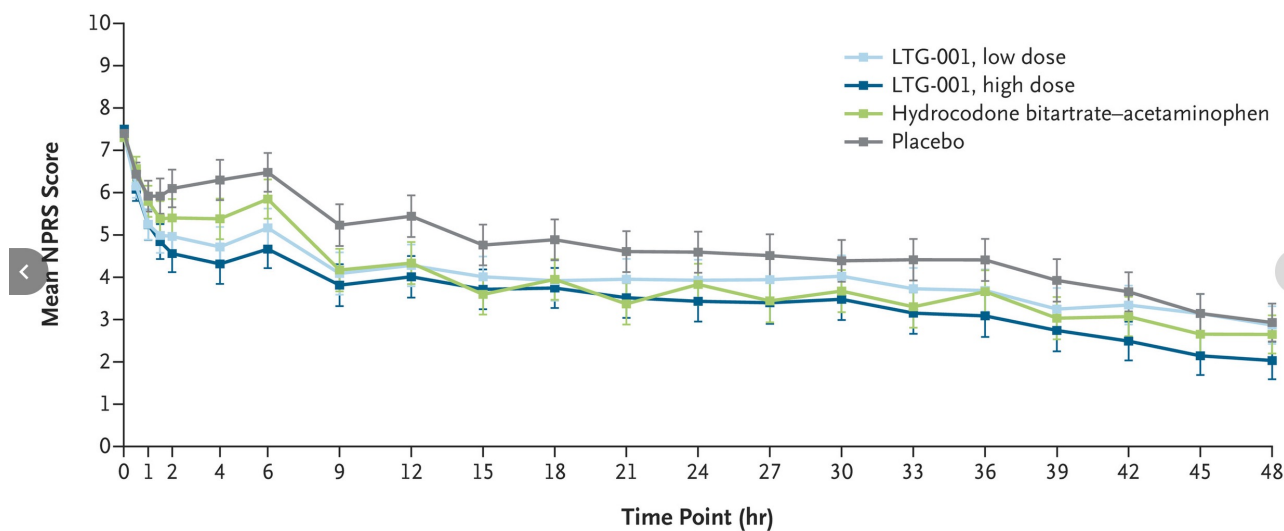
Characteristic	Low-Dose LTG-001 (N=85)	High-Dose LTG-001 (N=86)	Hydrocodone Bitartrate– Acetaminophen (N=86)	Placebo (N=86)
Age — yr	40.5±9.3	40.3±8.6	41.2±8.9	39.9±9.1
Female sex — no. (%)	83 (98)	85 (99)	85 (99)	85 (99)
Race or ethnic group — no. (%)†				
White	58 (68)	60 (70)	55 (64)	60 (70)
Black	22 (26)	18 (21)	27 (31)	21 (24)
Asian	1 (1)	6 (7)	1 (1)	0
Other	4 (5)	2 (2)	3 (3)	5 (6)
Hispanic or Latino ethnic group — no. (%)†	25 (29)	31 (36)	22 (26)	30 (35)
BMI‡	27.0±3.3	27.1±4.2	27.4±3.8	26.7±3.7
VRS category — no. (%)§				
Moderate	44 (52)	41 (48)	50 (58)	37 (43)
Severe	41 (48)	45 (52)	36 (42)	49 (57)
NPRS score¶	7.3±1.3	7.5±1.2	7.3±1.2	7.4±1.3

Outcomes

End Point	Low-Dose LTG-001 (N=85)	High-Dose LTG-001 (N=86)	Hydrocodone Bitartrate– Acetaminophen (N=86)	Placebo (N=86)
Primary end point				
SPID48†				
LSM (95% CI)	161.05 (142.93 to 179.16)	185.30 (167.26 to 203.34)	164.08 (146.02 to 182.14)	123.22 (105.23 to 141.21)
LSM difference vs. placebo (95% CI)	37.82 (12.62 to 63.03)	62.08 (36.95 to 87.21)	40.86 (15.71 to 66.01)	—
P value	0.003	<0.001	—	—
LSM difference vs. hydrocodone bitartrate-acetaminophen (95% CI)	−3.04 (−28.24 to 22.17)	21.22 (−3.95 to 46.39)	—	—
Secondary end points				
Total consumption of opioid rescue medication				
LSM (95% CI) — MME	12.95 (8.79 to 17.11)	11.00 (6.86 to 15.14)	10.52 (6.38 to 14.66)	18.35 (14.22 to 22.48)
LSM difference vs. placebo (95% CI) — MME	−5.40 (−11.19 to 0.39)	−7.35 (−13.12 to −1.58)	−7.83 (−13.61 to −2.06)	—
P value	NS	0.01	—	—
No receipt of opioid rescue medication — no. of patients (%)	42 (49)	45 (52)	43 (50)	19 (22)
Difference vs. placebo (95% CI) — percentage points	28 (15 to 41)	30 (17 to 43)	28 (15 to 41)	—
P value	—	<0.001	—	—
Median time to ≥2-point reduction in NPRS score (95% CI) — min	60.0 (45.0 to 73.5)	51.7 (31.0 to 61.0)	82.8 (60.0 to 121.0)	87.5 (57.0 to 385.6)
Median time to ≥1-point reduction in NPRS score (95% CI) — min	30.0 (29.0 to 35.0)	26.0 (15.5 to 30.0)	34.0 (30.0 to 56.0)	32.0 (28.0 to 55.0)
Nausea or vomiting during treatment period (95% CI) — % of patients	14 (8 to 23)	16 (9 to 26)	31 (22 to 42)	29 (20 to 40)
Difference vs. placebo (95% CI) — percentage points	−16 (−28 to −4)	−13 (−25 to <0)	1 (−12 to 14)	—
Pain-intensity difference at 60 min‡				
LSM (95% CI)	2.2 (1.8 to 2.5)	2.2 (1.8 to 2.5)	1.7 (1.3 to 2.0)	1.4 (1.1 to 1.8)
LSM difference vs. placebo (95% CI)	0.7 (0.2 to 1.2)	0.7 (0.2 to 1.2)	0.2 (−0.3 to 0.7)	—
SPID24‡				
LSM (95% CI)	70.56 (61.72 to 79.40)	79.31 (70.51 to 88.12)	68.88 (60.06 to 77.69)	45.48 (36.70 to 54.27)
LSM difference vs. placebo (95% CI)	25.07 (12.77 to 37.38)	33.83 (21.56 to 46.09)	23.39 (11.12 to 35.67)	—
Favorable PGA (95% CI) — % of patients¶	81 (71 to 89)	81 (72 to 89)	87 (78 to 93)	73 (63 to 82)
Difference vs. placebo (95% CI) — percentage points	9 (−4 to 22)	8 (−4 to 21)	15 (3 to 27)	—

Adverse events

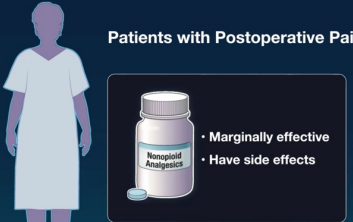
Event	Low-Dose LTG-001 (N=85)	High-Dose LTG-001 (N=86)	Hydrocodone Bitartrate– Acetaminophen (N=86)	Placebo (N=86)
<i>number of patients (percent)</i>				
Any adverse event	53 (62)	43 (50)	54 (63)	56 (65)
Any severe (grade ≥3) adverse event	3 (4)	3 (3)	6 (7)	3 (3)
Any trial-related adverse event†	15 (18)	20 (23)	31 (36)	20 (23)
Any serious adverse event	1 (1)	1 (1)	1 (1)	1 (1)
Any trial-related serious adverse event‡	0	0	0	0
Adverse event leading to discontinuation of trial regimen	0	0	4 (5)	0
Adverse event leading to discontinuation of trial	0	0	2 (2)	0
Adverse events occurring in ≥5% of patients in any group				
Nausea	16 (19)	17 (20)	28 (33)	32 (37)
Headache	21 (25)	15 (17)	16 (19)	20 (23)
Dizziness	5 (6)	5 (6)	9 (10)	9 (10)
Constipation	5 (6)	2 (2)	5 (6)	8 (9)
Vomiting	1 (1)	1 (1)	6 (7)	5 (6)
Pyrexia	2 (2)	6 (7)	1 (1)	2 (2)
Syncope	1 (1)	1 (1)	4 (5)	3 (3)
Presyncope	0	5 (6)	1 (1)	1 (1)
Serious adverse events‡				
Abdominal-wall abscess	1 (1)	0	0	0
Cellulitis	1 (1)	0	0	0
Sepsis	1 (1)	0	0	0
Postprocedural hemorrhage	0	0	1 (1)	0
Abnormal liver-function test results	0	0	0	1 (1)
Pulmonary embolism	0	1 (1)	0	0



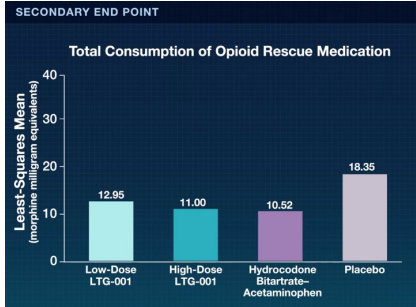
Mean NPRS Scores over the Treatment Period (Full Analysis Population).

The full analysis population included all the patients who had undergone randomization and received at least one dose of LTG-001, hydrocodone bitartrate-acetaminophen, or placebo. Scores on the NPRS were recorded at baseline and at 20 subsequent time points: 0.5, 1, 1.5, 2, 4, and 6 hours after the first dose and then every 3 hours until the end of the 48-hour treatment period. I bars indicate 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity.

Patients with Postoperative Pain



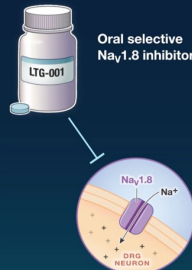
- Marginally effective
- Have side effects



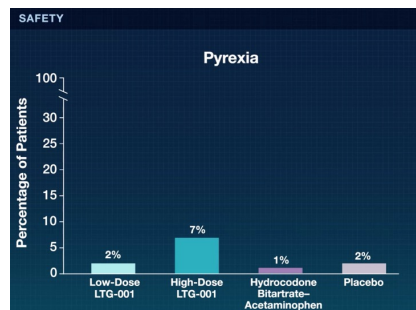
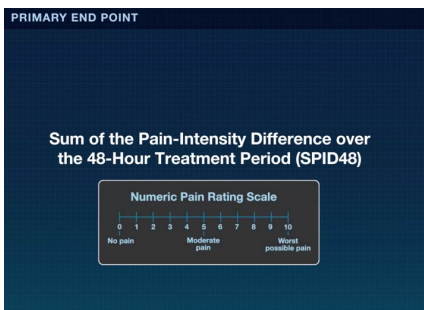

LTG-001 led to significantly greater reductions in moderate-to-severe pain than placebo

LTG-001-010 Trial

Efficacy and Safety



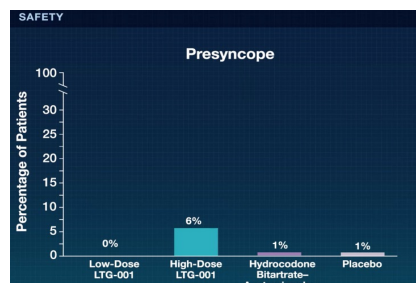
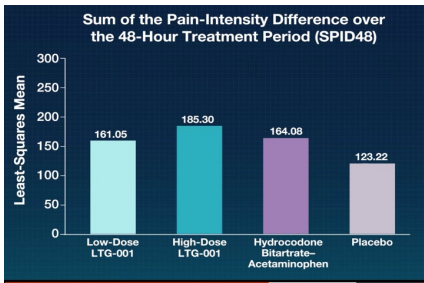
Oral selective $\text{Na}_v1.8$ inhibitor



LTG-001-010 Trial

- Multicenter
- Phase 2b
- Randomized
- Placebo-controlled
- Double-blind

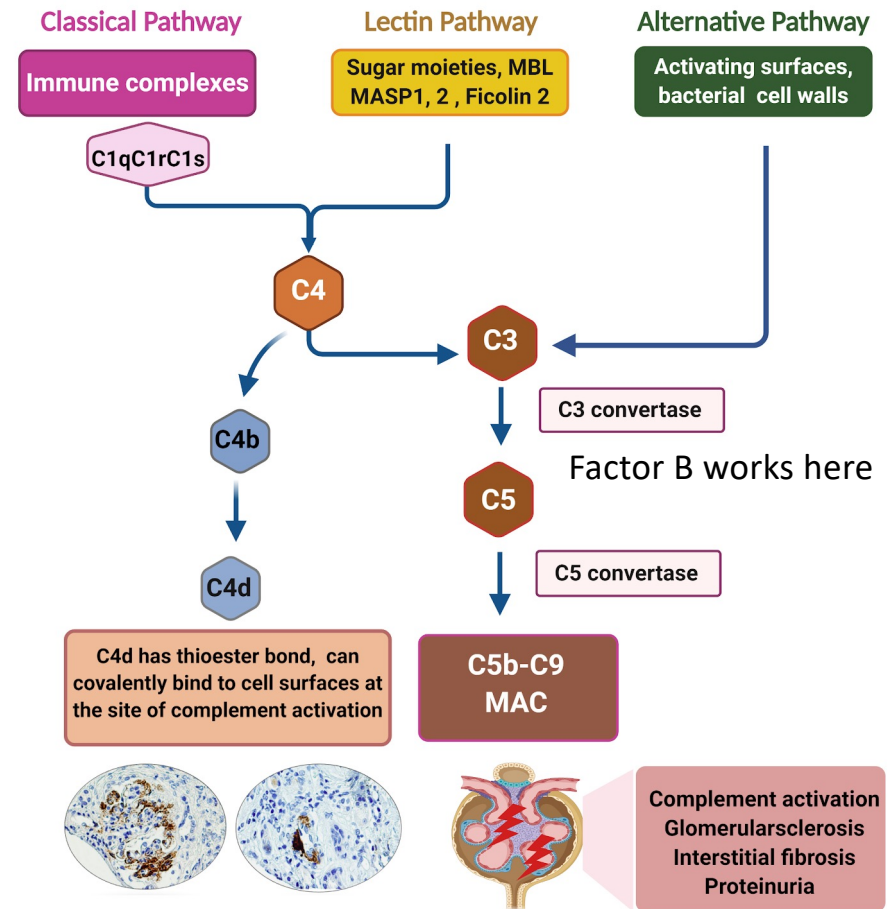
- 343 Patients
- Moderate-to-severe pain after abdominoplasty



Das Komplementsystem spielt eine **zentrale Rolle bei der Entstehung und dem Fortschreiten der IgA-Nephropathie (IgAN)**. Während die Erkrankung durch die Ablagerung von Immunkomplexen in den Nierenkörperchen (Glomeruli) ausgelöst wird, ist es vor allem die nachfolgende Aktivierung des Komplementsystems, die die chronische Entzündung und letztlich den Gewebeschaden vorantreibt.

Die IgA-Nephropathie läuft klassischerweise in vier Schritten ab:

1. Der Körper bildet vermehrt eine veränderte Form von Immunglobulin A1 (galaktosedefizientes IgA1 oder **Gd-IgA1**).
2. Das Immunsystem bildet **Autoantikörper** gegen dieses fehlerhafte IgA1.
3. Gd-IgA1 und die Antikörper binden aneinander und formen **Immunkomplexe** im Blut.
4. Diese Komplexe **lagern sich im Mesangium** (dem Bindegewebe der Nierenfilter) ab.



Iptacopan ist ein oral verfügbarer, proximaler Komplementinhibitor, der spezifisch an den Faktor B des Komplementsystems bindet. Es wird vor allem zur Behandlung der paroxysmalen nächtlichen Hämoglobinurie (PNH) eingesetzt.

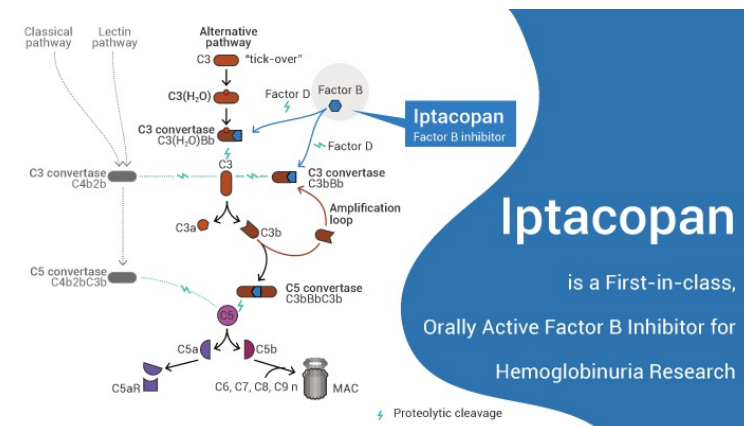
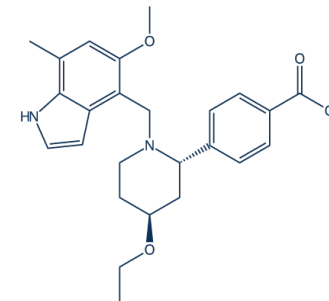
Anwendungsgebiet und Wirkung

Indikation: Behandlung von erwachsenen Patienten mit paroxysmaler nächtlicher Hämoglobinurie (PNH) und hämolytischer Anämie.

Wirkmechanismus: Hemmung des Faktors B im alternativen Komplementweg zur Verhinderung der C3-Aktivierung und der Blutkörperchenzerstörung (Hämolyse).

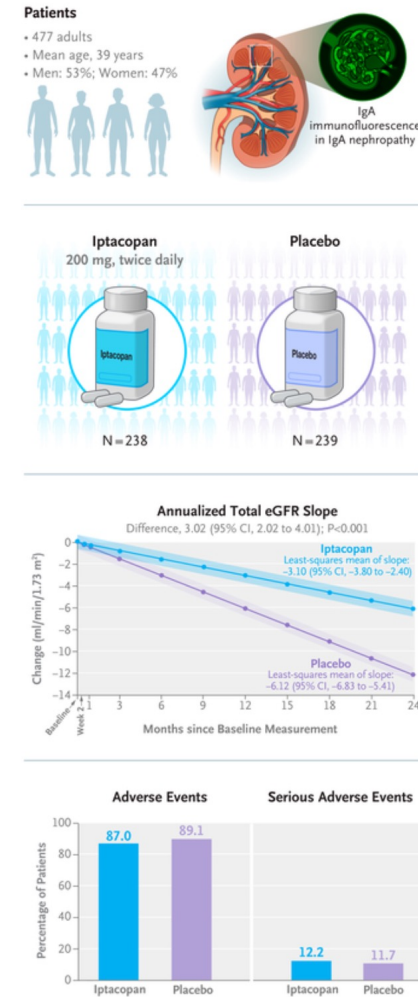
Darreichungsform: Als orale Monotherapie (Kapseln) eingenommen.

Faktor B bindet an das Protein C3b und wird danach vom Enzym Faktor D in die Fragmente *Ba* und *Bb* gespalten. Das Fragment Bb bildet zusammen mit C3b eine Konvertase, die für die Abwehr von Bakterien entscheidend ist



Iptacopan in IgA Nephropathy — Final 24-Month Data

Overactivation of the alternative complement pathway contributes to IgA nephropathy and glomerular inflammation. In the 9-month interim analysis of this phase 3 trial, iptacopan, a complement factor B inhibitor, led to a significant reduction of 38.3% in the 24-hour urinary protein-to-creatinine ratio as compared with placebo and had an acceptable safety profile. In this phase 3 trial, we enrolled adults who had IgA nephropathy, an estimated glomerular filtration rate (eGFR) of at least 30 ml per minute per 1.73 m² of body-surface area, and a 24-hour urinary protein-to-creatinine ratio of 1 or higher (with protein and creatinine both measured in grams) despite supportive care. Patients were randomly assigned, in a 1:1 ratio, to receive oral iptacopan (200 mg) or placebo twice daily. The primary end point for the final analysis was the annualized total eGFR slope as estimated over a 24-month period. Secondary end points included a composite kidney-failure end point (i.e., a sustained decline in eGFR of ≥30%, a sustained eGFR of <15 ml per minute per 1.73 m², the initiation of maintenance dialysis, receipt of kidney transplant, or death from kidney failure), assessed in a time-to-event analysis. Safety was also assessed.



Iptacopan is an oral, highly potent complement inhibitor that targets complement factor B of the alternative pathway. **Inhibition of factor B blocks alternative pathway**–mediated C3 cleavage and activation of the amplification loop, which subsequently prevents downstream generation of the membrane attack complex. Iptacopan has improved clinical outcomes in C3 glomerulopathy and paroxysmal nocturnal hemoglobinuria, diseases that are characteristically associated with dysregulated alternative pathway activation.

Results from a phase 2 trial and the month 9 interim analysis of the present phase 3 trial indicated that iptacopan was effective in patients with IgA nephropathy who were at high risk for rapid disease progression. The interim analysis of the present trial showed that iptacopan therapy led to a significant reduction of 38.3% (95% confidence interval [CI], 26.0 to 48.6) in the 24-hour urinary protein-to-creatinine ratio as compared with placebo ($P < 0.001$), with an acceptable safety profile. On the basis of these results, iptacopan received accelerated approval from the Food and Drug Administration for the treatment of primary IgA nephropathy. Here, we report the **final 24-month results** of this phase 3 trial, APPLAUSE-IgAN (A Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase III Study to Evaluate the Efficacy and Safety of LNP023 in Primary IgA Nephropathy Patients).

Patients

Eligible patients were 18 years of age or older and had biopsy-confirmed IgA nephropathy, an eGFR of at least 30 ml per minute per 1.73 m², and a 24-hour urinary protein-to-creatinine ratio of 1 or higher, despite a maximum and stable dose of an angiotensin-converting–enzyme inhibitor or angiotensin II–receptor blocker for at least 90 days before the receipt of iptacopan or placebo, with or without the use of sodium–glucose cotransporter 2 (SGLT2) inhibitors. If the eGFR was at least 45 ml per minute per 1.73 m², a qualifying biopsy had to have been performed within 5 years before screening; if the eGFR was 30 to less than 45 ml per minute per 1.73 m², the biopsy had to have been performed within 2 years before screening and had to have shown less than 50% tubulointerstitial fibrosis. Vaccination against *Neisseria meningitidis* and *Streptococcus pneumoniae* was required, and *Haemophilus influenzae* type B vaccination was recommended according to local availability and regulations.

Trial Assessments and Analyses

The primary end point for the final analysis was the annualized total eGFR slope estimated over a period of 24 months. Secondary end points were a 24-hour urinary protein-to-creatinine ratio of less than 1 at 9 months without the receipt of alternative or rescue medication or kidney-replacement therapy; a composite kidney-failure end point (defined as a sustained decline in the eGFR of ≥30% from baseline for ≥4 weeks, a sustained eGFR of <15 ml per minute per 1.73 m² for ≥4 weeks, initiation of maintenance dialysis).

Characteristic	Iptacopan (N = 238)	Placebo (N = 239)
Age — yr	39.7±11.6	39.2±12.5
Male sex — no. (%)	134 (56.3)	121 (50.6)
Race or ethnic group — no. (%)†		
White	110 (46.2)	111 (46.4)
Black	0	3 (1.3)
Asian	125 (52.5)	122 (51.0)
Native Hawaiian or other Pacific Islander	1 (0.4)	1 (0.4)
American Indian or Alaska Native	2 (0.8)	2 (0.8)
Median time since kidney biopsy (IQR) — yr	1.1 (0.5–2.5)	0.7 (0.3–2.3)
Oxford Classification MEST-C score — no. (%)‡		
M score		
M1	146 (61.3)	146 (61.1)
M0	79 (33.2)	75 (31.4)
E score		
E1	72 (30.3)	70 (29.3)
E0	150 (63.0)	146 (61.1)
S score		
S1	169 (71.0)	173 (72.4)
S0	54 (22.7)	48 (20.1)
T score		
T2	12 (5.0)	3 (1.3)
T1	80 (33.6)	95 (39.7)
T0	134 (56.3)	124 (51.9)
C score		
C2	5 (2.1)	2 (0.8)
C1	60 (25.2)	47 (19.7)
C0	150 (63.0)	158 (66.1)
24-Hr urinary protein-to-creatinine ratio§		
Median (interquartile range)	1.7 (1.3–2.4)	1.8 (1.5–2.6)
Distribution — no. (%)		
<2	143 (60.1)	139 (58.2)
≥2	95 (39.9)	100 (41.8)
Estimated glomerular filtration rate		
Mean — ml/min/1.73 m²	63.4±25.5	65.6±26.5
Distribution — no. (%)		
30 to <45 ml/min/1.73 m²	64 (26.9)	65 (27.2)
45 to <60 ml/min/1.73 m²	60 (25.2)	49 (20.5)
60 to <90 ml/min/1.73 m²	72 (30.3)	80 (33.5)
≥90 ml/min/1.73 m²	42 (17.6)	45 (18.8)
ACE inhibitor or ARB use at baseline — no. (%)	238 (100)	235 (98.3)
SGLT2 inhibitor use at baseline — no. (%)	51 (21.4)	41 (17.2)
Blood pressure — mm Hg¶		
Systolic	121.0±11.4	122.1±11.7
Diastolic	77.9±7.9	78.1±8.4
Hematuria at baseline — no. (%)	178 (74.8)	178 (74.5)
Previous treatment for IgA nephropathy — no. (%)		
Glucocorticoids	70 (29.4)	62 (25.9)
Other immunosuppressant	41 (17.2)	17 (7.1)
FACIT-Fatigue score**	42.6±7.8	42.6±8.0

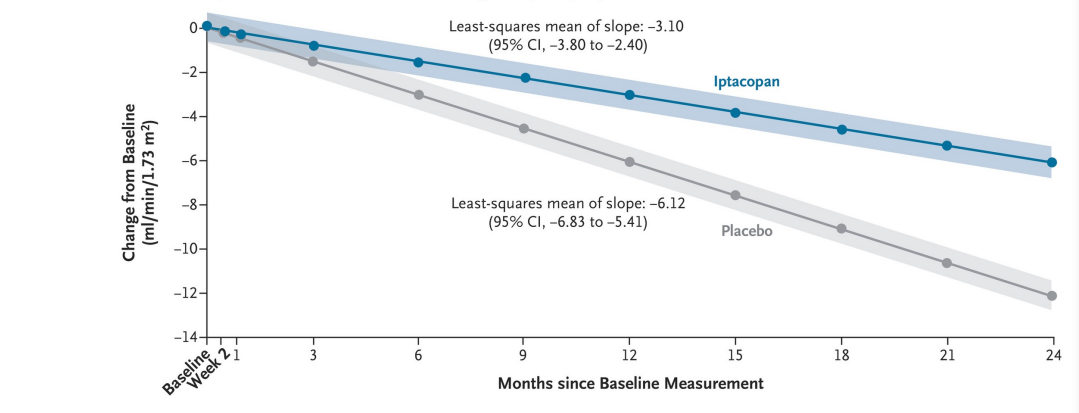
Outcomes

End Point	Iptacopan (N = 238)	Placebo (N = 239)	Effect Estimate (95% CI)†	P Value
Primary end point				
Primary end point: annualized total eGFR slope estimated over 24-mo period (95% CI) — ml/min/1.73 m²/yr	–3.10 (–3.80 to –2.40)	–6.12 (–6.83 to –5.41)	Difference: 3.02 (2.02 to 4.01)	<0.001
Supplementary analysis: mean change in eGFR from baseline to 24 mo				
No. of patients with data	197	171		
Value (95% CI) — ml/min/1.73 m²	–5.62 (–7.17 to –4.06)	–10.64 (–12.28 to –9.00)	Difference: 5.02 (2.80 to 7.25)	
Secondary end points				
24-Hr UPCR <1 at 9 mo (95% CI) — % of patients‡	43.9 (38.0 to 49.8)	17.5 (12.7 to 22.4)	Difference: 26.4 (18.7 to 34.0); odds ratio: 4.45 (2.79 to 7.09)	<0.001§
Composite kidney-failure end point — % of patients¶	21.4	33.5	Hazard ratio: 0.57 (0.40 to 0.81)	0.003
FACIT-Fatigue score				
No. of patients with data	213	207		
Mean change from baseline to 9 mo (95% CI)	1.07 (0.23 to 1.91)	0.31 (–0.54 to 1.16)	Difference: 0.76 (–0.43 to 1.95)	—
Exploratory end points				
24-Hr UPCR <1 at 24 mo (95% CI) — % of patients‡	40.7 (34.8 to 46.6)	23.7 (18.2 to 29.1)	Difference: 17.0 (9.0 to 25.1)	
Adjusted GMR to baseline in 24-hr UPCR				
At 9 mo				
No. of patients with data	226	211		
Ratio (95% CI)	0.56 (0.51 to 0.61)	0.92 (0.84 to 1.0)	GMR: 0.61 (0.54 to 0.69)	
At 24 mo				
No. of patients with data	198	165		
Ratio (95% CI)	0.57 (0.52 to 0.63)	0.91 (0.81 to 1.01)	GMR: 0.63 (0.54 to 0.73)	
Adjusted GMR to baseline in UPCR from first morning urine sample				
At 9 mo				
No. of patients with data	220	202		
Ratio (95% CI)	0.57 (0.52 to 0.62)	0.92 (0.84 to 1.01)	GMR: 0.62 (0.55 to 0.70)	
At 24 mo				
No. of patients with data	193	158		
Ratio (95% CI)	0.59 (0.53 to 0.67)	0.98 (0.87 to 1.10)	GMR: 0.61 (0.51 to 0.72)	

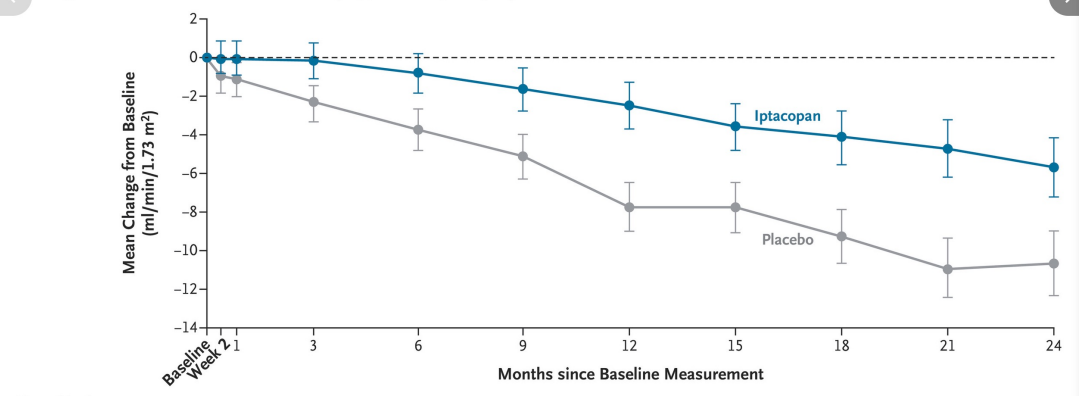
Adversity

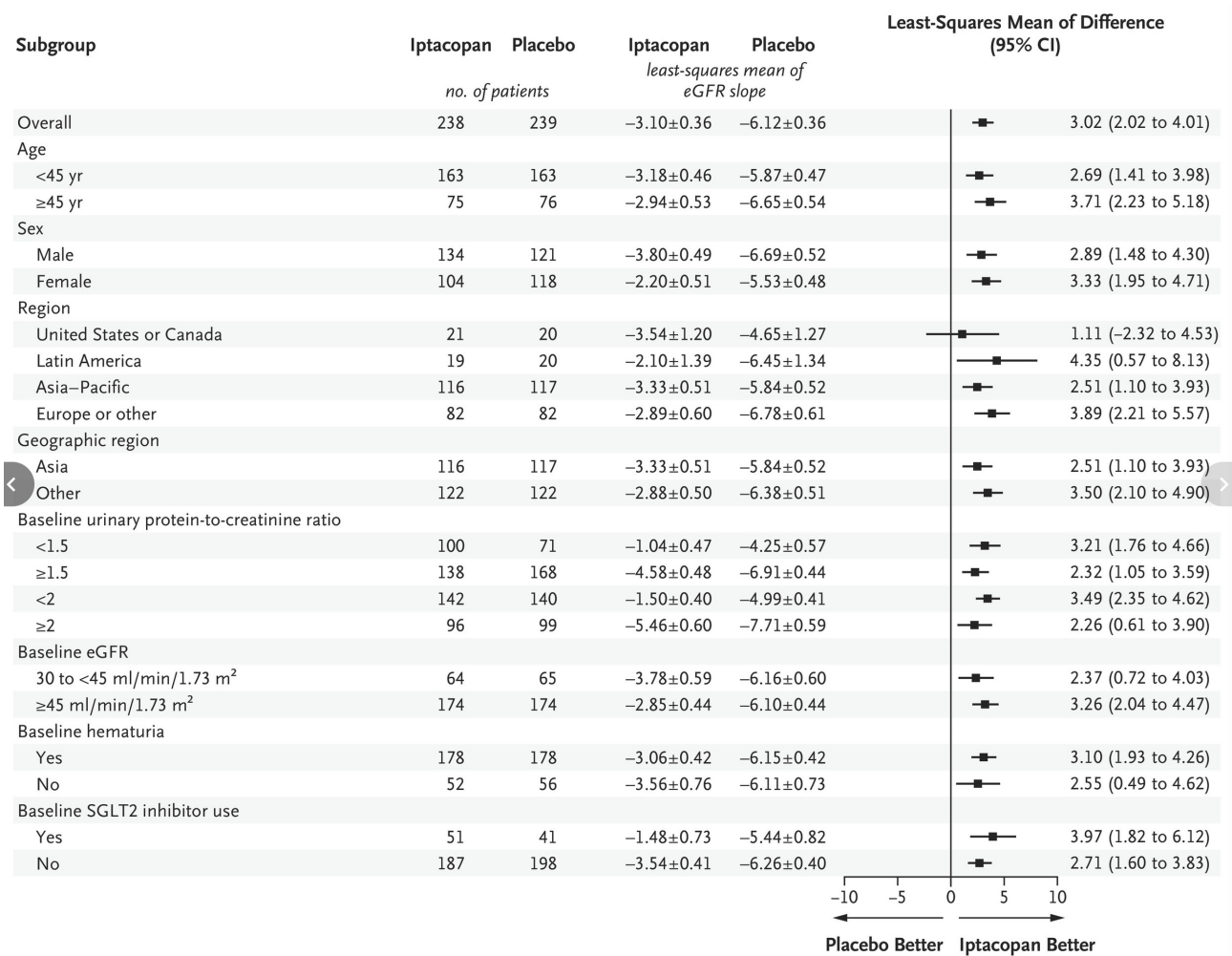
Variable	Iptacopan (N = 238)	Placebo (N = 239)	Difference (95% CI)†
	number (percent)		percentage points
Any adverse event	207 (87.0)	213 (89.1)	-2.2 (-8.0 to 3.7)
Adverse events occurring in ≥5% of the patients in either group‡			
Covid-19	50 (21.0)	47 (19.7)	1.3 (-5.9 to 8.6)
Upper respiratory tract infection	38 (16.0)	38 (15.9)	0.1 (-6.5 to 6.7)
Nasopharyngitis	24 (10.1)	29 (12.1)	-2.1 (-7.7 to 3.7)
Headache	15 (6.3)	21 (8.8)	-2.5 (-7.3 to 2.4)
Diarrhea	14 (5.9)	13 (5.4)	0.4 (-3.8 to 4.7)
Hyperlipidemia	13 (5.5)	16 (6.7)	-1.2 (-5.6 to 3.2)
Pyrexia	13 (5.5)	15 (6.3)	-0.8 (-5.1 to 3.5)
Cough	12 (5.0)	11 (4.6)	0.4 (-3.5 to 4.4)
Dizziness	12 (5.0)	6 (2.5)	2.5 (-1.1 to 6.1)
Influenza	12 (5.0)	10 (4.2)	0.9 (-3.0 to 4.7)
Back pain	11 (4.6)	13 (5.4)	-0.8 (-4.9 to 3.2)
Hyperuricemia	11 (4.6)	13 (5.4)	-0.8 (-4.9 to 3.2)
Hyperkalemia	10 (4.2)	18 (7.5)	-3.3 (-7.6 to 1.0)
Gastroenteritis	8 (3.4)	13 (5.4)	-2.1 (-5.9 to 1.8)
Hypertension	6 (2.5)	24 (10.0)	-7.5 (-11.9 to -3.1)
Serious adverse event	29 (12.2)	28 (11.7)	0.5 (-5.4 to 6.3)
Fatal serious adverse event	0	0	—
Severity of adverse event			
Mild	111 (46.6)	103 (43.1)	3.5 (-5.4 to 12.4)
Moderate	81 (34.0)	92 (38.5)	-4.5 (-13.0 to 4.2)
Severe	15 (6.3)	18 (7.5)	-1.2 (-5.9 to 3.4)
Adverse event suspected to be related to iptacopan or placebo	48 (20.2)	49 (20.5)	-0.3 (-7.6 to 6.9)
Adverse event leading to discontinuation of iptacopan or placebo	11 (4.6)	11 (4.6)	0.0 (-3.9 to 3.9)

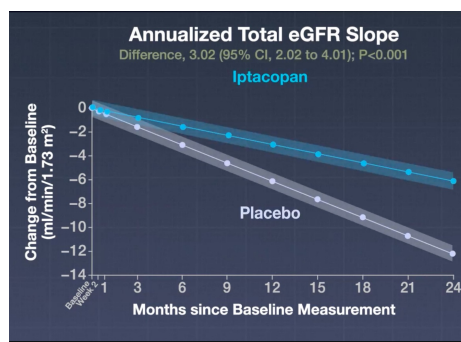
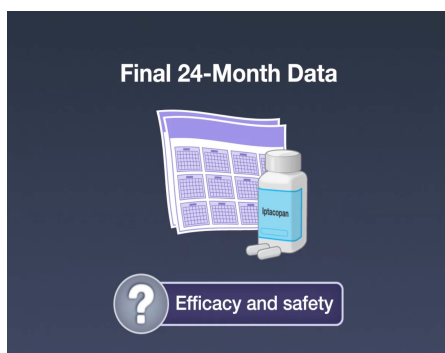
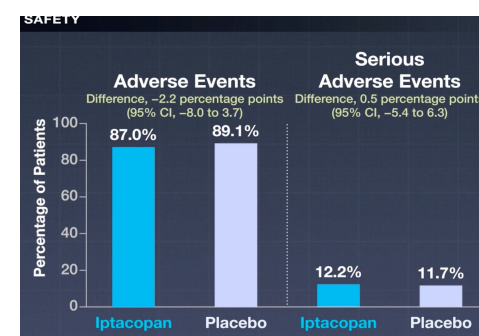
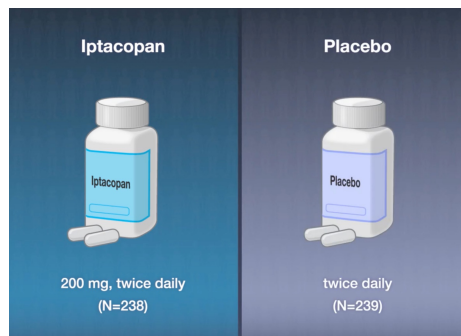
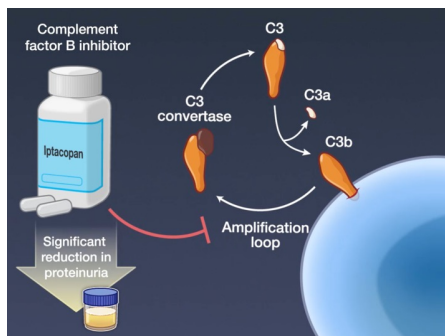
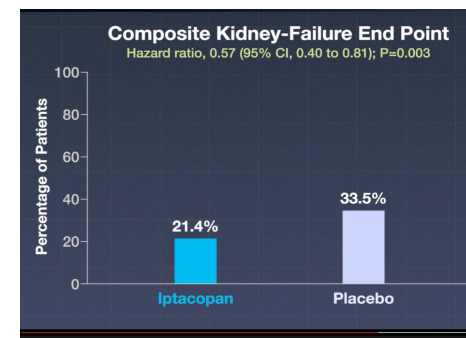
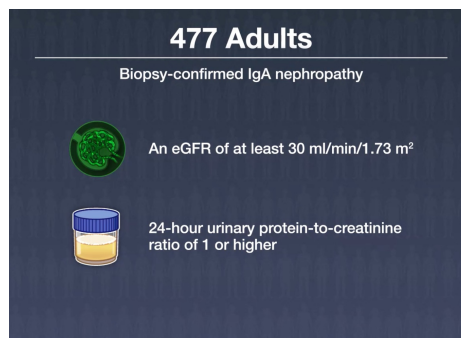
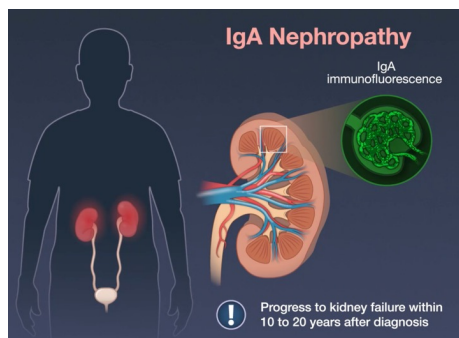
A Annualized Total eGFR Slope Estimated over 24-Month Period (primary analysis)



B Change in the eGFR over 24-Month Period (supplementary analysis)







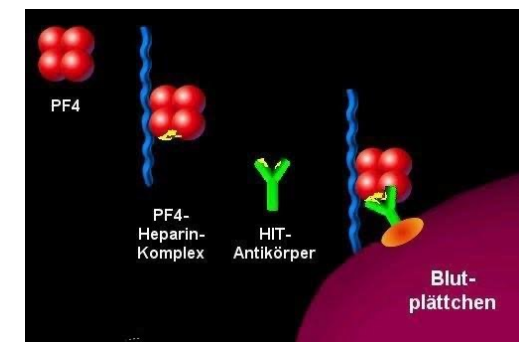
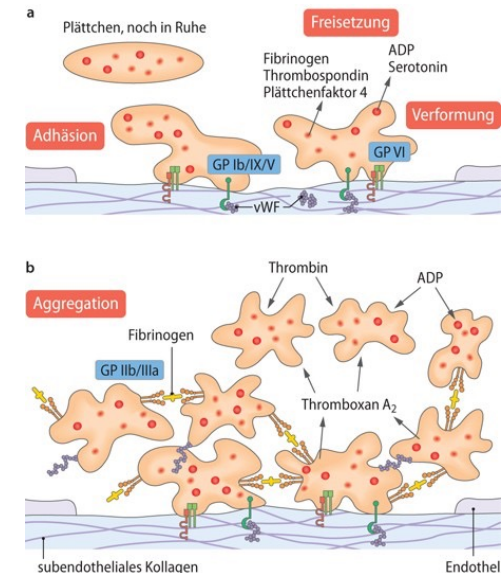
„**Plättchenfaktor 4**“ (kurz **PF4**) ist ein Protein, das von Blutplättchen (Thrombozyten) freigesetzt wird. Es spielt die zentrale Rolle bei der gefährlichen **Heparin-induzierten Thrombozytopenie (HIT)** sowie der sogenannten **VITT** (Impfstoff-induzierte Immunthrombozytopenie und Thrombose).

Die "4" in Plättchenfaktor 4 bezeichnet keine medizinische Stufe (wie z.B. bei Fatigue-Graden). Vielmehr verweist die Zahl auf den Namen des Proteins selbst: Es handelt sich um ein kleines Protein (ein Chemokin) mit der **offiziellen Bezeichnung CXCL4**, das von den Blutplättchen ausgeschüttet wird, um Immunzellen zu aktivieren.

Im medizinischen Kontext meint man mit PF4 meist das Risiko von immunvermittelten Thrombosen:

Heparin-induzierte Thrombozytopenie (HIT II): Bei manchen Patienten bilden sich Antikörper, die den Plättchenfaktor 4 zusammen mit Heparin angreifen. Dies führt paradoxerweise zu einer schnellen Aktivierung der Blutplättchen und schweren, lebensbedrohlichen Gefäßverschlüssen.

4 T-Score: Wenn der Verdacht auf eine solche Autoimmunreaktion besteht, nutzen Ärzte das klinische Bewertungssystem der „4 T's“ (Thrombozytopenie, Timing, Thrombosis, Absence of other explanations), um die Wahrscheinlichkeit für das Vorliegen einer HIT abzuschätzen. Bei einem Wert von unter 4 Punkten gilt eine HIT als sehr unwahrscheinlich



Platelet-Activating Anti–Platelet Factor 4 Disorders

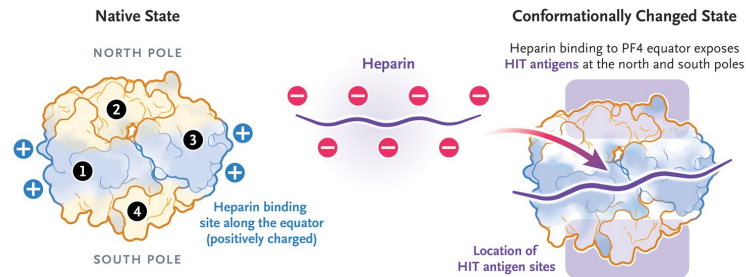
Summary

Platelet-activating antibodies against platelet factor 4 (PF4) cause highly prothrombotic disorders with reduced platelet counts. In heparin-induced thrombocytopenia (HIT), these antibodies bind PF4–heparin complexes, causing heparin-dependent platelet activation. Less common autoimmune and spontaneous HIT variants that are triggered by heparin and nonpharmacologic polyanions, respectively, have atypical clinical features and antibodies with additional heparin-independent platelet-activating properties. Vaccine-induced immune thrombocytopenia and thrombosis (VITT) antibodies directly target PF4. Initially, VITT was linked to adenoviral vector–based coronavirus disease 2019 vaccines, but in rare cases, an immune thrombocytopenia and thrombosis disorder that is clinically nearly identical to VITT can be caused by infection resulting from natural exposure to viruses, especially adenovirus. In persons with the *IGLV3-21*02/*03* gene, anti–adenovirus protein VII antibody specificity shifts to PF4 by way of a specific somatic hypermutation (K31E) that creates VITT antibodies. In VITT-like monoclonal gammopathy of thrombotic significance, monoclonal anti-PF4 antibodies cause chronic prothrombotic conditions. Accurate diagnosis relies on distinct assays for HIT and VITT antibodies. Beyond anticoagulation, inhibition of FcγIIa receptor–mediated platelet activation may be needed for anti-PF4 disorders with heparin-independent reactivity (e.g., high-dose immune globulin in acute disease manifestations and Bruton’s tyrosine kinase inhibitors in chronic manifestations).

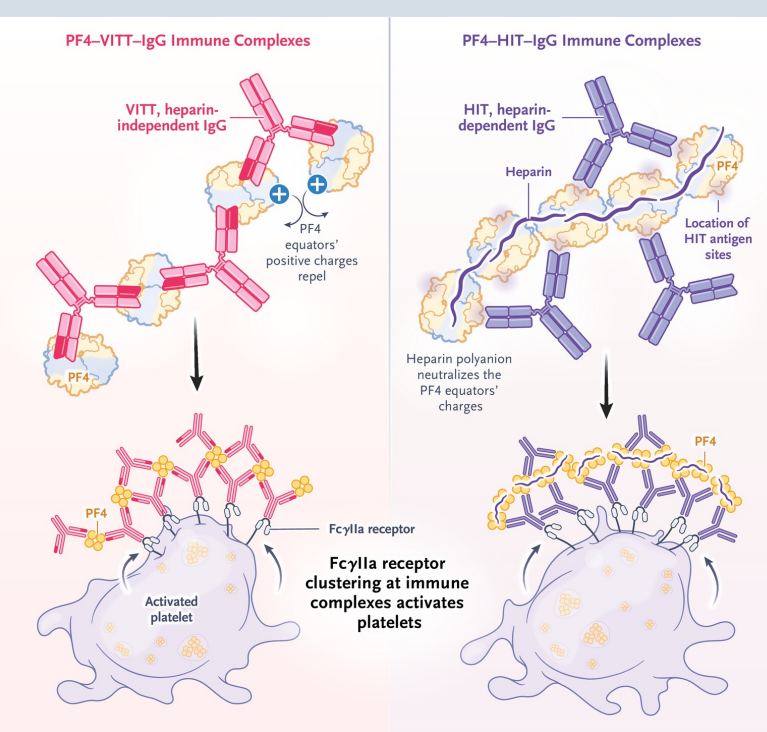
Platelet-Activating Anti-Platelet Factor 4 Disorders

- Heparin-induced thrombocytopenia (HIT) may be considered when thrombosis, thrombocytopenia (or decreasing platelet count), or both occur 5 or more days after heparin therapy is initiated; onset can occur even after heparin therapy is stopped.
- Only a subset of anti-PF4–polyanion antibodies detected by immunoassay can activate platelets through platelet FcγIIa receptors and cause HIT; therefore, platelet-activation assays are more specific than immunoassays for the diagnosis of HIT.
- Autoimmune HIT indicates the presence of highly pathologic antibodies triggered by heparin that have both heparin-dependent and heparin-independent platelet-activating properties, resulting in atypical clinical and laboratory features.
- ▶ • Vaccine-induced immune thrombocytopenia and thrombosis (VITT) — as well as immune thrombocytopenia and thrombosis caused by natural exposure to adenovirus — and VITT-like monoclonal gammopathy of thrombotic significance (MGTS) feature distinct platelet-activating anti-PF4 antibodies that warrant different laboratory diagnostic pathways.
- Anti-PF4 disorder variants other than classic HIT — autoimmune HIT, spontaneous
- ▶ HIT (indicating a nonheparin trigger), VITT, and VITT-like MGTS — involve anti-PF4 antibodies with heparin-independent platelet-activating properties, a factor
- ▶ that necessitates anticoagulation as well as adjunctive treatment such as Fc-
- ▶ receptor blockade with high-dose intravenous immune globulin (in acute disease) or Bruton's tyrosine kinase inhibitors (in chronic disease).

A Platelet Factor 4 (PF4) Tetramer

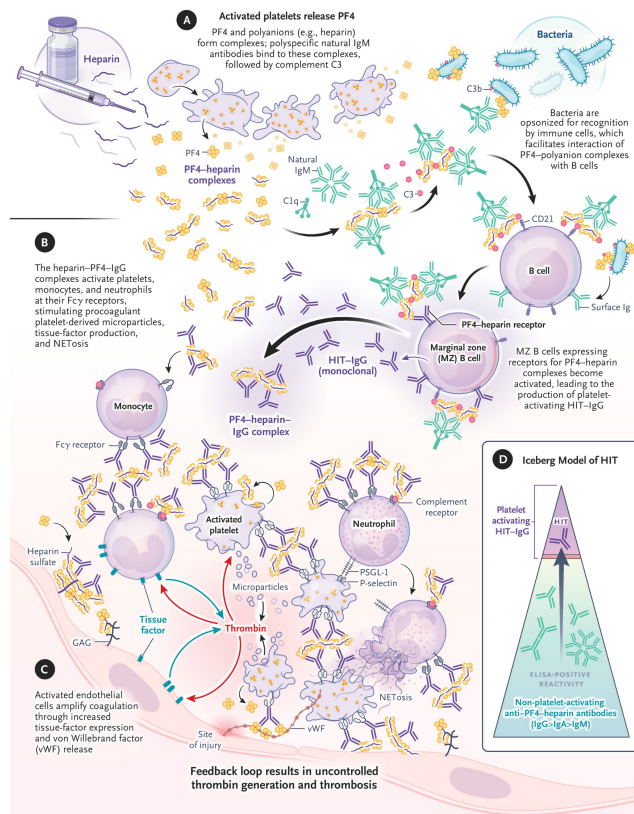


B Immune Complex Formation



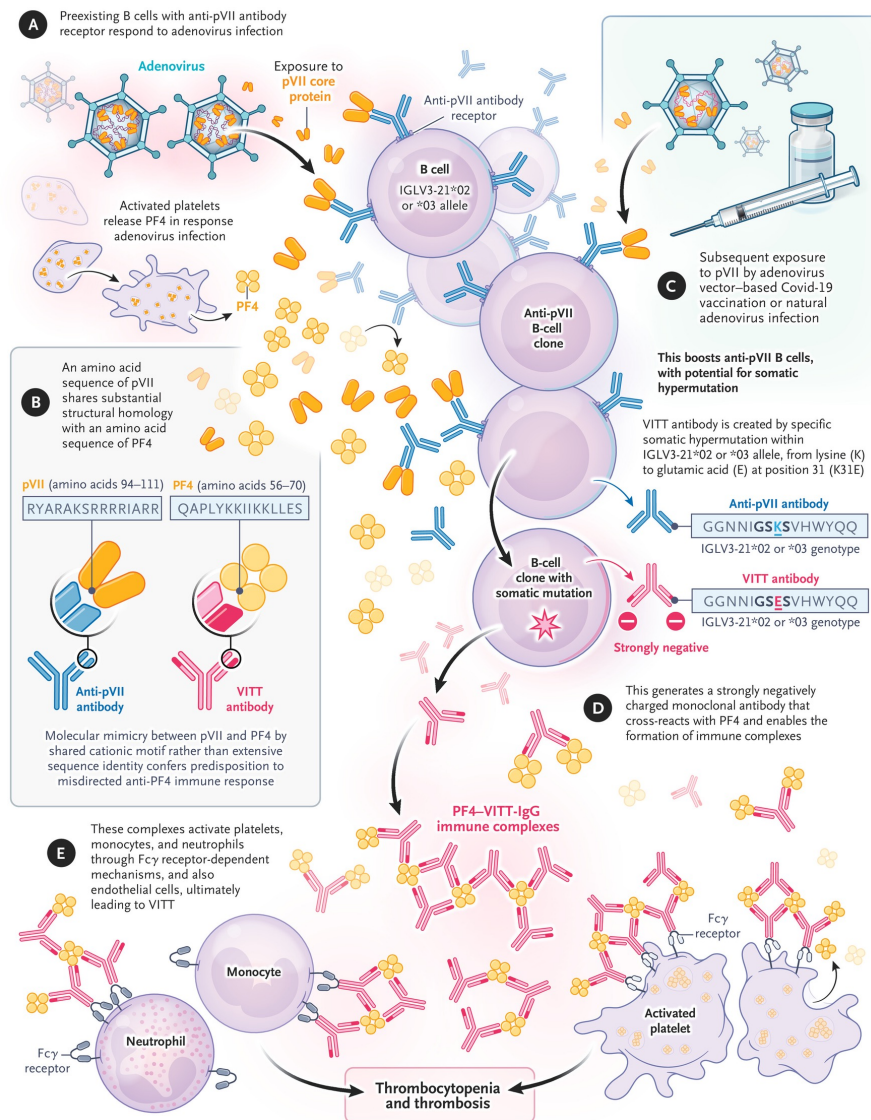
PF4 Structure, Immune-Complex Formation, and Platelet Activation in HIT and VITT.

As shown in Panel A, platelet factor 4 (PF4) is a tetrameric protein (denoted by the numerals 1, 2, 3, and 4; Protein Data Bank number, [1RHP](#)) that expresses a ring of positively charged amino acids (an “equator”) to which polyanion heparin binds, forming heparin-dependent antigen. As shown in Panel B, in heparin-induced thrombocytopenia (HIT) as well as in vaccine-induced immune thrombocytopenia and thrombosis (VITT) and immune thrombocytopenia and thrombosis caused by natural exposure to adenovirus, antibodies bind to PF4, forming immune complexes that activate platelets through cross-linking of FcγIIa receptors. PF4 tetramers normally repel each other owing to their strong positive charge, creating a distance greater than the span of two antibody-binding sites. Consequently, a single IgG molecule usually cannot cross-link two PF4 tetramers. In HIT, heparin binding induces conformational changes in PF4, exposing cryptic epitopes, or neoepitopes, at the north and south poles of the tetramer, and reducing the positive charge, allowing tetramer approximation and cross-linking by IgG. In VITT, antibodies bind directly to PF4, neutralizing its positive charge and enabling tetramer cross-linking without the need for polyanions. These resulting immune complexes then cross-link FcγIIa receptors on platelets, leading to platelet activation.



HIT Immunopathogenesis and the Iceberg Model.

The pathogenesis of HIT involves both innate and adaptive immunity as well as hemostasis. **Initially, PF4 and polyanions (e.g., heparin) form complexes.** Natural IgM antibodies then bind to these complexes, followed by complement C3. This process opsonizes bacteria for recognition by immune cells; however, in HIT, this process facilitates the interaction of PF4–heparin complexes with B cells through the complement receptor CD21. Specifically, marginal-zone B cells expressing receptors for PF4–heparin complexes become activated. Resulting B-cell activation leads to the production of platelet-activating HIT IgG by plasma cells (not shown). The HIT IgG forms multimolecular immune complexes with PF4–heparin, which then signal through the Fcγ1a receptors, strongly activating platelets and forming procoagulant platelet-derived microparticles. Cellular myeloproliferative leukemia protein (c-Mpl, the product of a proto-oncogene that acts as a cellular receptor for thrombopoietin) and platelet glycoprotein VI are also involved in binding of PF4–heparin–IgG immune complexes to platelet surfaces (not shown). Formation of PF4–heparin–IgG immune complexes also activates monocytes and neutrophils through their Fcγ receptors, stimulating tissue-factor production and the release of neutrophil extracellular traps (NETosis), respectively. Activated endothelial cells further amplify coagulation through tissue-factor expression and the release of von Willebrand factor. Resulting pancellular activation creates self-enhancing feedback loops that result in uncontrolled thrombin generation and thrombosis. Notably, most anti-PF4–heparin antibodies do not produce cellular activation; the iceberg model refers to the concept that only a minority of antibodies of the IgG class are able to activate platelets and thereby cause HIT (the tip of the iceberg). Many patients who are exposed to heparin generate non-platelet-activating — and nonpathogenic — antibodies of any one or more of the three major immunoglobulin classes, and in the following descending order of frequency: IgG, IgA, and IgM. Another characteristic feature of anti-PF4–heparin antibody formation is that when two or three different immunoglobulin classes are formed, they develop at approximately the same time (median, 4–5 days after receipt of heparin or another polyanion), and without IgM class precedence. High-affinity anti-PF4–heparin IgG antibodies result from B-cell gene rearrangements induced by the highly mutagenic cytidine deaminase. Resulting B cells with higher affinity are selected to survive and to secrete high-affinity anti-PF4–polyanion IgG. The reason that these B cells are short-lived, with antibody titers rapidly declining after acute HIT, is currently unknown. In the atypical HIT variants, autoimmune HIT and spontaneous HIT, the affinity-matured B-cell clones produce high-affinity anti-PF4 IgG antibodies that bind to PF4 even in the absence of heparin.

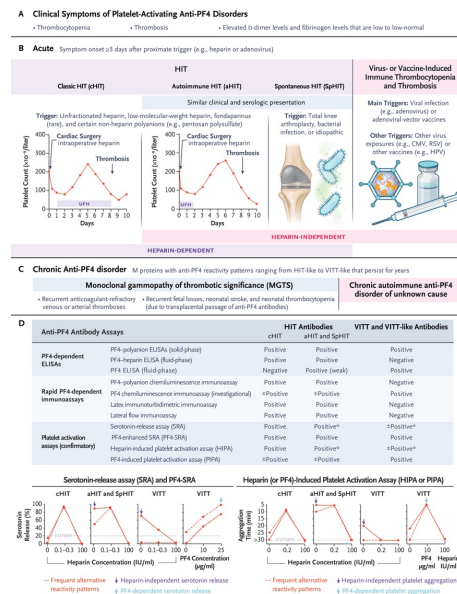


VITT Immunopathogenesis.

VITT is a misdirected immune response. Our current understanding is that the **initiating trigger is the adenovirus core protein VII (pVII)**. Amino acid sequence 94–111 of pVII shares substantial structural homology with amino acid sequence 56–70 of PF4 (despite differences in sequence). The rapid appearance of high-titer IgG antibodies as early as day 5 suggests that **VITT represents a secondary immune response after earlier primary immunization against pVII**. Subsequent exposure to adenovirus — either through vaccination (adenoviral-vector vaccine) or natural infection — boosts anti-pVII B cells, inducing somatic hypermutation. In persons who carry the genetic haplotype for the IgG light-chain (IGLV3) 21*02 or *03, a rare somatic hypermutation at position 31 of the light chain can occur, substituting the positively charged germline amino acid lysine (K) with the negatively charged glutamic acid (E) — that is, a K31E mutation. This process generates a strongly negatively charged antibody (VITT antibody) that cross-reacts with PF4, neutralizing its charge and enabling the formation of PF4-VITT-IgG immune complexes. These complexes activate platelets, monocytes, and neutrophils by means of Fcγ receptor-dependent mechanisms, ultimately leading to VITT. Rarely, nonadenoviral antigens trigger acute VITT-mimicking disorders through distinct pathways; there have been single reports to date describing acute **VITT-like disorder after cytomegalovirus (CMV) infection, respiratory syncytial virus (RSV) infection, or human papilloma virus (HPV) vaccination**. The underlying mechanisms probably differ from those in adenovirus-induced VITT: where assessed, the IGLV3 haplotype was different.

Spectrum of Anti-PF4 Disorders.

Platelet-activating anti-PF4 disorders share the following clinical features: thrombocytopenia, high frequency of thrombosis, and hypercoagulability, with elevated d-dimer levels and fibrinogen levels that are low to low-normal (Panel A); moreover, the key pathological finding is that **platelet-activating anti-PF4 antibodies are detectable in patient serum or plasma**, usually by both PF4-dependent immunoassay and by platelet-activation assay (anti-PF4 antibody assays). Anti-PF4 disorders are categorized as acute, usually developing between 5 and 10 days post-trigger (although clinical symptoms may not be evident until up to approximately 30 days postexposure, especially in outpatients) (Panel B), or chronic (Panel C). The most **common acute anti-PF4 disorder is HIT, which typically occurs after unfractionated heparin administration** in the context of surgical procedures. Antibody affinity maturation can allow heparin-triggered antibodies to bind PF4 and activate platelets even without ongoing heparin exposure, with both heparin-dependent and heparin-independent platelet-activating properties (autoimmune HIT). **Rarely, such antibodies can occur with nonpharmacologic triggers, such as following knee arthroplasty surgery or bacterial infection (spontaneous HIT)**; potential triggers include DNA or RNA (released during knee arthroplasty) or bacterial surfaces. PF4–polyanion complexes activate the cognate B cells; when — through affinity maturation — anti-PF4 IgG antibodies with very high affinity to PF4 are generated, the patient presents clinically with spontaneous HIT. **VITT is rarely triggered by adenovirus, either in adenoviral-vector vaccines or through natural adenovirus infection. VITT-like disorders may also be acutely triggered by other vaccines, such as the HPV vaccine, or by viral infections like CMV or RSV infection.** Chronic anti-PF4 disorders feature VITT-like or HIT-like antibodies and have been reported in a subgroup of patients with **monoclonal gammopathy of thrombotic significance (MGTS)** such as VITT-like MGTS, a disorder that can occur even in young patients. In women with chronic VITT-like MGTS, fetomaternal complications can occur (e.g., recurrent miscarriages, neonatal thrombocytopenia, and thrombosis). Chronic anti-PF4 disorder of apparent autoimmune origin (without detectable MGTS) has also been reported. As the number of patients identified remains limited, it is possible that some patients with chronic anti-PF4 disorders might have reactivity profiles more in keeping with HIT or autoimmune-HIT antibodies than with VITT or VITT-like antibodies; some antibodies are reactive only in platelet-activation assays. **Therefore, an assay detecting anti-PF4–heparin antibodies and an assay detecting anti-PF4 antibodies should be performed if a chronic anti-PF4 disorder is suspected.** Reactivity profiles of various anti-PF4 disorders are shown for the following assays (Panel D): PF4–polyanion enzyme-linked immunosorbent assays (ELISAs, solid-phase and fluid-phase), rapid PF4-dependent immunoassays (chemiluminescence, latex immunoturbidimetric, and lateral flow), and platelet activation assays using washed platelets (serotonin-release assay [SRA], PF4-enhanced SRA, heparin-induced platelet-activation assay [HIPA], and PF4-induced activation assay [PIPA]). An asterisk indicates a heparin-independent platelet-activation profile, and a plus-minus sign indicates that the reaction is negative in more than 20% of serum specimens from patients with HIT or VITT.



Characteristics	Comments and Recommendations
Pathophysiological factors	
Anti-PF4 disorders (immune-mediated and transient)	Symptoms typically appear ≥ 5 days after an immunizing heparin exposure, adenoviral-vector vaccine, or adenovirus infection. ^{8,11,41} Reexposure to heparin may be appropriate in some situations (e.g., cardiac surgery) ^{36,71} despite previous HIT.
Variable but high frequency of anti-PF4–heparin antibody formation	Unexplained thrombocytopenia or thrombosis 1–4 weeks after heparin exposure may indicate HIT or autoimmune HIT. ^{3,8,11,26} HIT frequency with LMWH is as much as 10 times lower than that with UFH ¹⁰ and is rare with fondaparinux.
Inflammation and anti-PF4 response	HIT is more common in postsurgical patients than in medical patients and rare in pregnancy. The incidence of HIT increases with proinflammatory signals (e.g., 4% incidence of HIT with G-CSF for stem-cell apheresis with use of heparin flushes). ²⁷
Relative decrease in platelet count (consistent with platelet activation)	Focus on decrease in platelet counts even if absolute platelet counts are within the normal range. Platelet-count decrease in chronic anti-PF4 disorder (VITT-like MGTS) can indicate acute exacerbation with thrombosis. ⁶¹
Hypercoagulability and high risk of thrombosis	Heparin cessation alone is insufficient treatment. Monitor coagulation tests (INR, PTT, fibrinogen, D-dimer). Be aware of PTT confounding when using DTIs. ^{26,72*} Screen for DVT with strong clinical suspicion of HIT. ⁷¹ Avoid intravascular devices when possible (nidus for thrombosis). Consider pre-VITT with severe headache, thrombocytopenia, and high D-dimer level. ⁴⁰
Microthrombosis and natural anti-coagulant (protein C) depletion	Reverse vitamin K deficiency or antagonism if present. ^{15,71} Theoretically, anticoagulants with anti-factor Xa activity (fondaparinux, Xa DOACs) may have advantages over DTIs (e.g., no interference with thrombin-induced protein C activation). ^{3,72-74†}
Heparin-independent platelet activation	Consider high-dose IVIG therapy for atypical presentations of HIT (e.g., thrombocytopenia after stopping heparin or after knee arthroplasty) or postviral or postvaccine VITT. ^{3,30} Consider therapeutic plasma exchange for severe refractory HIT ⁷⁵ or VITT. ⁷⁶
VITT immunopathogenesis	Lessons learned from postvaccine VITT apply to sporadic postviral VITT (near-identical immunopathogenesis). ⁷

Diagnostic factors	
Antibody heterogeneity and pathogenicity (iceberg model)	Functional assays (SRA, HIPA) detect pathogenic anti-PF4 antibodies (adding heparin for HIT antibodies, adding PF4 for VITT or VITT-like antibodies) and can also indicate heparin-independent platelet activation. Greater PF4–polyanion immunoassay reactivity indicates higher probability of positive platelet-activation test. ⁶⁶⁻⁶⁹
Fc γ receptor–mediated activation	Obtain samples for functional tests before administering high-dose IVIG (treatment for anti-PF4 disorders with heparin-independent platelet-activating properties). ^{20,70} Bruton's tyrosine kinase inhibitors (e.g., ibrutinib) are potential therapy for chronic VITT-like disorders. ^{20,61,62,65}
Antigen specificity and assay limitations	Microtiter ELISAs detect HIT and VITT antibodies. ⁶⁶ Rapid immunoassays detect HIT but not VITT antibodies. ^{43,66,67} Addition of PF4 enhances sensitivity for VITT platelet-activation assays. ^{35,66} Heparin can cause false negative results in VITT antibody tests. ³⁵
Chronic anti-PF4 disorders (e.g., VITT-like MGTS)	Consider serum protein electrophoresis–immunoelectrophoresis in unexplained chronic or recurrent thrombocytopenia, including treatment-refractory thrombosis ^{60,61} ; however, VITT-like M-protein levels may be lower than detectable by SPEP–IEP. ^{64,77}
Background prevalence	Be aware of low-titer anti-PF4 antibodies in the healthy population (approximately 3–5% of persons).

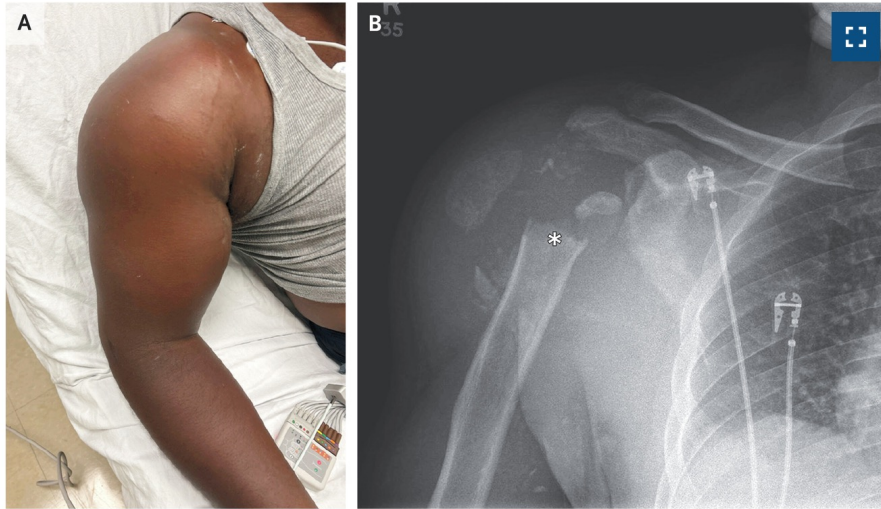
Patients with heparin-induced thrombocytopenia (HIT) or vaccine-induced immune thrombotic thrombocytopenia (VITT) must be treated immediately using non-heparin, HIT-safe anticoagulants, specifically **non-heparin parenteral direct thrombin inhibitors, fondaparinux, or direct oral anticoagulants (DOACs)**, while completely avoiding all forms of heparin and avoiding vitamin K antagonists or platelet transfusions

Diagnostic and Treatment Implications

The spectrum of anti-PF4 disorders and representative diagnostic assays are summarized. The combination of thrombocytopenia and thrombosis may prompt consideration of an anti-PF4 disorder, **especially in an appropriate clinical context (e.g., recent or concurrent heparin treatment, bacterial or viral infection, or knee-replacement surgery)**. Clinicians need to be aware of the locally available screening tests for anti-PF4 antibodies, in light of the differences in test sensitivity for HIT and VITT antibodies.

Apart from classic HIT, which features predominantly heparin-dependent platelet-activating antibodies, the other entities feature predominant or exclusive heparin-independent platelet-activating properties. Many cases of such heparin-independent anti-PF4 disorders warrant a treatment approach that inhibits Fc-receptor–dependent platelet activation in addition to a **nonheparin anticoagulant (e.g., high-dose IVIG or ibrutinib)**. Several diagnostic and treatment implications arising from the pathophysiological concepts discussed here are summarized. Treatment of chronic anti-PF4 disorders is challenging, because anticoagulation alone is insufficient. **Eradication of the paraprotein producing B-cell clone and inhibition of the FcγRIIIa signaling pathway by a Bruton's tyrosine-kinase inhibitor (e.g., ibrutinib or pirtobrutinib) are rational treatment approaches.**

Milwaukee Shoulder Syndrome



A 45-year-old man presented to the emergency department with a 2-month history of worsening pain and swelling in his right shoulder. He worked in construction and had chronic intermittent pain in the joint. Physical examination was notable for swelling of the right shoulder (Panel A) and decreased active range of motion. Radiography of the right shoulder showed destruction of the humeral head with a free-floating humeral diaphysis (Panel B, asterisk). Magnetic resonance imaging showed destructive arthropathy of the glenohumeral joint associated with a large effusion and free-floating calcific fragments. Full-thickness tears were seen in the supraspinatus, infraspinatus, and subscapularis tendons. Analysis of the synovial fluid revealed hemorrhagic, noninflammatory fluid with negative cultures and no visible crystals. A diagnosis of Milwaukee shoulder syndrome was made. This destructive arthropathy is characterized by the deposition of hydroxyapatite crystals (which are not visible on light microscopy), humeral head destruction, and severe rotator-cuff damage. Although this condition is most commonly seen in women over the age of 65 years, the patient was thought to be at increased risk because of his repetitive use of the shoulder in his work and a possible preexisting rotator-cuff injury. Treatment with celecoxib and acetaminophen was provided, and he was referred for evaluation for shoulder replacement.

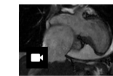
Pulsatile Liver in Severe Tricuspid Regurgitation



A 51-year-old woman with right heart failure of unknown cause that was complicated by cardiac cirrhosis presented to the cardiology clinic with several years of worsening abdominal distention and leg swelling. The patient had faced socioeconomic barriers to accessing regular health care. Physical examination

was notable for ascites, severe leg edema, giant venous pulsations in the neck, and a grade 4/6 holosystolic murmur at the lower left sternal border that augmented with inspiration. The liver was enlarged and pulsatile (Video 1A) — a late finding in chronic, severe tricuspid regurgitation. Transthoracic echocardiography revealed right cardiac-chamber enlargement, right ventricular hypokinesis, and massive tricuspid regurgitation with normal left ventricular size and function. Subsequent cardiac magnetic resonance imaging revealed marked dilatation of the right atrium and ventricle and severe tricuspid regurgitation. The liver was pulsatile owing to anterograde flow into the right atrium during diastole and retrograde flow into the inferior vena cava and hepatic veins during systole (Video 1B, coronal view, acquired during breath hold). A circumferential pericardial effusion and probable thrombus in the right atrial appendage were also present. Appropriate medical therapy was initiated, and the patient was listed for heart transplantation. Two years after starting treatment, she died of advanced heart failure and sepsis.

VIDEO



Examination of the Liver 0m 26s

Case 22-2026: A 37-Year-Old Woman with Persistent Nasal Ulceration

Seventeen years before the current presentation, the patient noticed a painful bump inside the right naris. Associated scabbing was present. The patient removed a scab from the lesion multiple times each week, and there was intermittent bleeding from the lesion. She used an unknown nasal spray daily, with no decrease in symptoms.

Ten years before the current presentation, the patient was evaluated at an otolaryngology clinic affiliated with another hospital. Examination reportedly revealed severe irritation of the right inferior turbinate, along with crusting that was thought to be related to the long-term use of nasal spray. She was instructed to avoid nasal sprays and nose blowing. An examination 1 month later reportedly showed a decrease in the turbinate irritation, and treatment with mupirocin ointment was started, with plans to evaluate 1 month later for resolution. However, the patient did not return to the clinic for additional evaluation.

Three weeks before the current presentation, the patient was evaluated in the otolaryngology clinic. She reported that she had stopped using the nasal spray 10 years earlier. She had no history of fever, chills, weight loss, joint pain, rash, diarrhea, abdominal pain, hemoptysis, cough, dyspnea, or chest pain. She noted that she did not pluck her nasal hairs or insert her fingers into her nose, aside from removing crusts from the nasal lesion. Her medical history included childhood asthma, varicose veins in the legs, and nephrolithiasis. She had moved to Massachusetts from Honduras 15 years earlier. As a child in Honduras, she had had a nonhealing skin lesion that eventually resolved after treatment with what the patient described as “hot metal.” Her last contact with the medical system before the evaluation by her primary care physician had been 5 years earlier, for the birth of her second child. The patient took no medications and had no known drug allergies. She was married and lived with her husband and two small children in Massachusetts. She did not use alcohol, tobacco, or illicit drugs, including intranasal drugs. Her mother had had a similar recurrent lesion in her nose, for which she had received prescribed medications in Honduras, with improvement in the lesion.

On examination, the temporal temperature was 36.6°C, the blood pressure 114/67 mm Hg, the heart rate 65 beats per minute, the respiratory rate 16 breaths per minute, and the oxygen saturation 100% while the patient was breathing ambient air. She appeared well. Anterior rhinoscopy showed an area of debris and ulceration of the anterior inferior turbinate of the right nasal cavity; the turbinate was touching the septum. In the left nasal cavity, the mucous membranes were moist, without polyps, purulent discharge, or bleeding. The septum was deviated to the right. The buccal mucosa, tongue, and soft palate were normal, as were the oropharynx and tonsils. A well-healed scar that measured 4 cm in diameter was noted on the left arm. The remainder of the examination was normal. Treatment with intranasal mupirocin was started, and the patient was referred to the rhinology clinic affiliated with this hospital.

At the current presentation, 3 weeks later, the patient was evaluated in the rhinology clinic. She reported that after starting treatment with mupirocin ointment, the crusting had abated and no additional episodes of epistaxis had occurred. **Nasal endoscopy showed copious crusting in the right naris that was débrided with no bleeding**; the underlying mucosa of the inferior turbinate and septum was erythematous with mild edema, but no discrete mass lesion or ulceration was seen. Treatment with mupirocin was continued.

Common Causes

- Nasal vestibulitis
- Chronic digital manipulation
- History of nasal surgery, trauma, or cautery
- Intranasal medication use
 - Glucocorticoid nasal sprays
- Intranasal drug use
 - Cocaine
 - Opioids

Uncommon Causes

- Neoplasms
 - Natural killer T-cell lymphoma
- Immune-mediated processes
 - Granulomatosis with polyangiitis
 - IgG4-related disease
 - Sarcoidosis
 - Rosai–Dorfman disease
- Infectious diseases
 - Invasive fungal disease
 - Rhinoscleroma
 - Rhinosporidiosis
 - Leprosy
 - Tuberculosis
 - Syphilis
 - Leishmaniasis
 - Paracoccidioidomycosis

Cancer

The most common sinonasal cancer is **squamous-cell carcinoma**, which may be associated with human papillomavirus (HPV) and can arise from a preexisting inverted papilloma. Other notable but less common cancers include adenocarcinoma, sinonasal melanoma, olfactory neuroblastoma, lymphoma, adenoid cystic carcinoma, sinonasal undifferentiated carcinoma, and metastatic disease.

Granulomatosis with Polyangiitis

Granulomatosis with polyangiitis (GPA) is an antineutrophil cytoplasmic antibody (ANCA)–associated necrotizing granulomatous vasculitis that often involves the sinonasal tract. Common manifestations include nasal crusting, epistaxis, and facial pain. Although systemic involvement of the upper airway, lungs, and kidneys may occur, isolated sinonasal disease is not uncommon. Septal perforation and sinus involvement may develop over time when GPA is untreated; however, early disease may manifest solely with nasal crusting and ulceration. Initial evaluation includes assessment of inflammatory markers (erythrocyte sedimentation rate, C-reactive protein level) and ANCA testing, despite the fact that results may be negative in patients with localized disease.

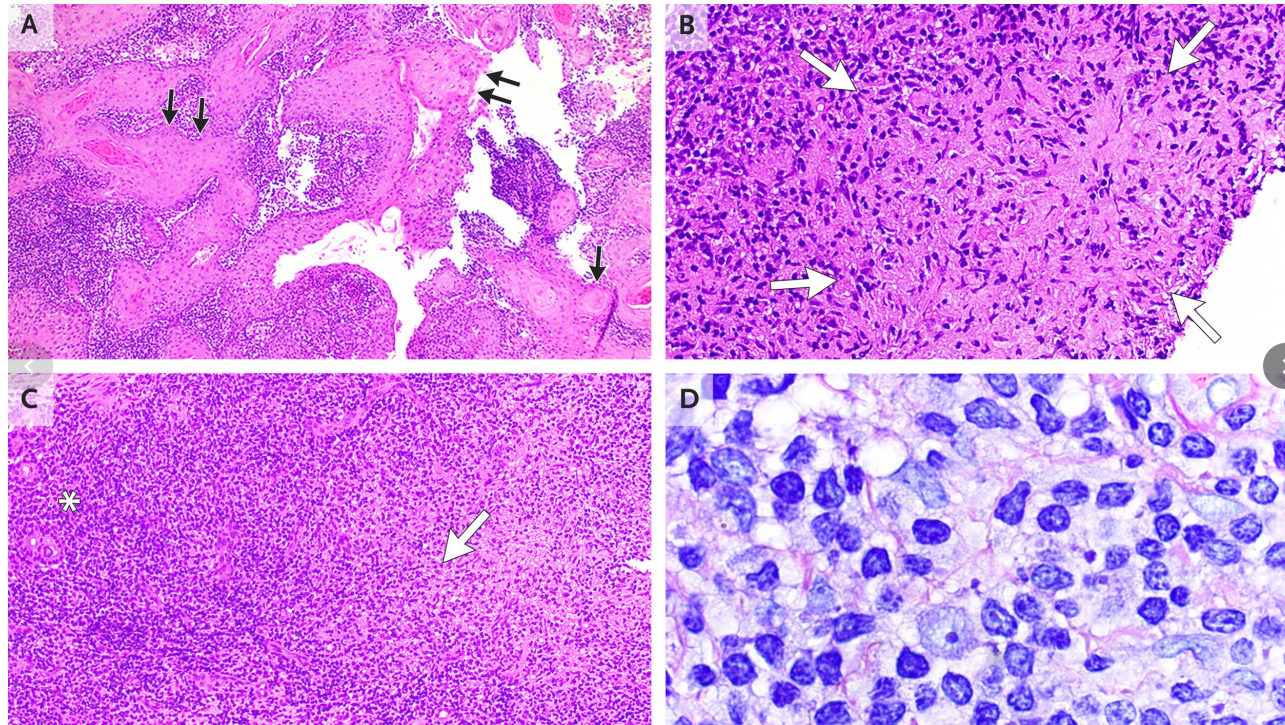
IgG4-Related Disease

IgG4-related disease is a fibroinflammatory condition that is typically characterized by mass-forming lesions. It may involve multiple organ systems, including the pancreas, retroperitoneum, and lacrimal and salivary glands. Isolated sinonasal involvement is uncommon but can manifest with nasal congestion, crusting, and epistaxis.

Infection

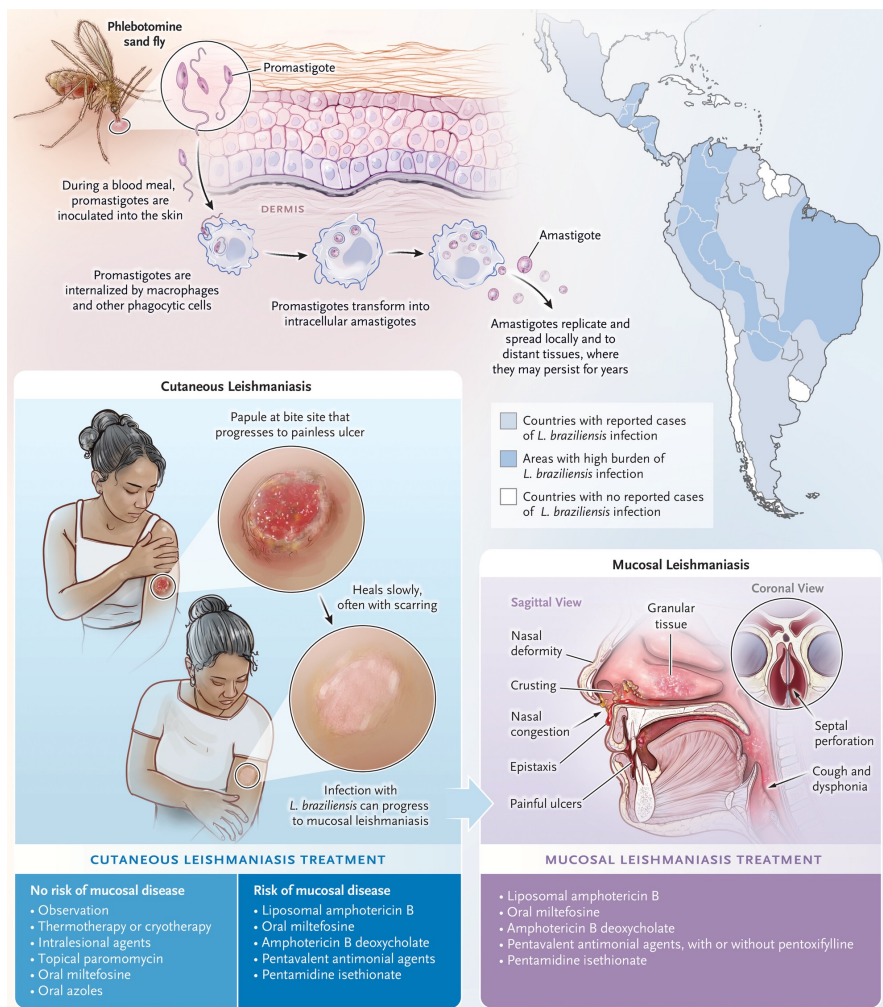
The prolonged time course of this patient's condition suggests a chronic rather than an acute infection. However, one critical condition to rule out is **invasive fungal disease**, which is typically caused by molds in the order **mucorales**. Acute invasive fungal sinusitis is a severe, life-threatening infection that is most commonly seen in patients with poorly controlled diabetes mellitus (especially in the context of diabetic ketoacidosis), immunocompromise, or long-term glucocorticoid use. Patients usually present with fever and facial pain and pressure; symptoms may rapidly progress to cranial neuropathies and orbital complications, including vision loss, ophthalmoplegia, and proptosis. **Early recognition, prompt biopsy**, and treatment with surgical débridement and systemic antifungal therapy are essential in patients with invasive fungal disease, given that this condition is associated with high morbidity and mortality.

Leprosy, an infection caused by ***Mycobacterium leprae***, often involves the nasal cavity early in the disease course and can lead to crusting, ulceration, septal destruction, and saddle-nose deformity. Tuberculosis and syphilis may also have sinonasal manifestations. Leishmaniasis, a disease caused by the **protozoan parasite leishmania**, is transmitted through the bite of infected sand flies and can occur in visceral, cutaneous, or mucosal forms. Mucosal leishmaniasis may involve the nasal cavity and lead to inflammation, crusting, and epistaxis.



Nasal-Biopsy Specimen.

Hematoxylin and eosin staining of a nasal-biopsy specimen obtained from the septum at low magnification (Panel A) shows prominent surface squamous metaplasia with deep keratinization (arrows), a finding suggestive of a prominent inflammatory process. At higher magnification, hematoxylin and eosin staining shows poorly formed granulomas (Panels B and C, arrows) and entrapped nasal glands (Panel C, asterisk). Giemsa staining (Panel D), which was performed to assess for **intrahistiocytic amastigotes of leishmania, is negative.**



Additional Diagnostic Testing

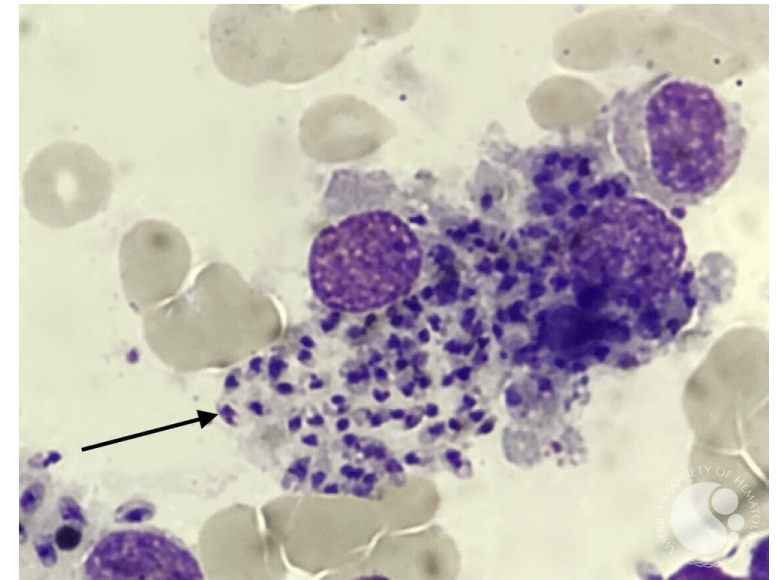
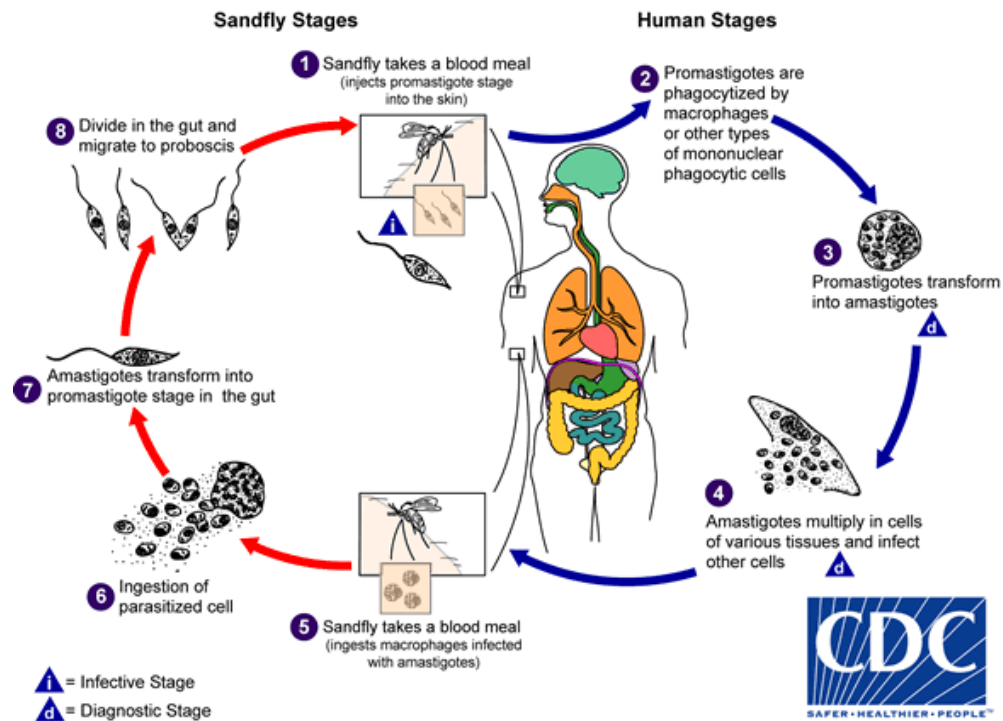
After suspicion for possible leishmaniasis arose, formalin-fixed, paraffin-embedded tissue from the biopsy specimen was sent for molecular testing. A nucleic acid amplification test (mini-exon DNA detection, University of Washington, Seattle) confirmed the presence of *L. (Viannia) braziliensis*. In retrospect, it is notable that subsequent Giemsa staining of the biopsy specimen did not show amastigotes, which are nonmotile bodies of developing organisms that may be seen in the cytoplasm of histiocytes; their absence is indicative of low-volume disease.

Molecular Pathological Diagnosis

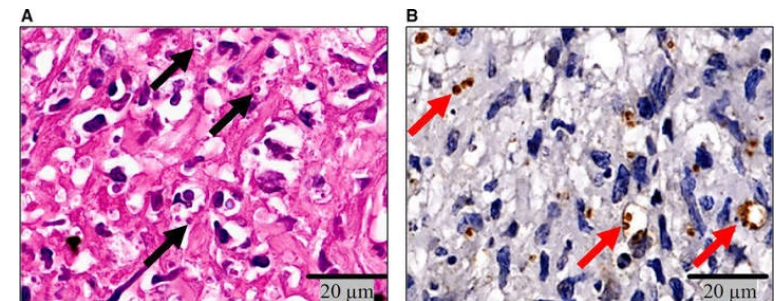
Mucosal leishmaniasis due to *Leishmania braziliensis*.

The patient received intravenous liposomal amphotericin B, as well as premedication with intravenous fluids, acetaminophen, and diphenhydramine. During the first infusion, she had flushing and transient dyspnea, which resolved with additional diphenhydramine, temporary interruption of the infusion, and resumption at a slower rate. Her treatment course was complicated by mild acute kidney injury, hypomagnesemia, and nausea; these conditions abated with fluid and electrolyte repletion and antiemetic agents.

Sir William Boog Leishman (* 6. November 1865 in Glasgow;
 † 2. Juni 1926 ebenda) war ein schottischer Militärarzt,
 Tropenarzt und Pathologe. Er entdeckte um 1900 den Erreger
 des Kala-Azar-Fiebers.



Amastigotes in bone marrow



Amastigotes in tissue

THE LANCET



Eugene Braunwald

Leading cardiologist who changed clinical practice and research. Born on Aug 15, 1929, in Vienna, Austria, he died on April 22, 2026, in Newton, MA, USA, aged 96 years.

Through his research alone Eugene Braunwald “changed the way cardiology is practised”, said Marc Pfeffer, Distinguished Dzaou Professor of Medicine at Harvard Medical School (HMS) and Senior Member of the Cardiovascular Division of Brigham and Women’s Hospital (BWH) in Boston, MA, USA. Yet, that was only one component of a career that saw Braunwald revolutionise how research is done and how medicine is taught, even as he helped identify and train new generations of researchers and physicians. “If you look at academic medicine, an unbelievable number of leaders around the country trained under Dr Braunwald”, said Marc Sabatine, Professor of Medicine at HMS, Chairman of the Thrombolysis in Myocardial Infarction (TIMI) Study Group, and Lewis Dexter, MD, Endowed Chair in Cardiovascular Medicine at BWH. “Many call him the father of modern cardiology and it’s very true”, said Elliott Antman, Professor of Medicine at HMS and Senior Clinician at BWH.

Multidomain lifestyle intervention for the prevention of cognitive decline in at-risk older adults in Latin America (LatAm-FINGERS): a single-blind, multicentre, randomised controlled trial

Summary

Systematic
lifestyle

vs.

Flexible
lifestyle

Can SLI
beat FLI?

Background Latin America faces a high dementia burden, with increased prevalence of factors associated with cognitive decline. Multidomain lifestyle interventions might delay cognitive decline, but populations from Latin America remain under-represented in dementia prevention trials. We aimed to investigate the feasibility of a culturally adapted, multidomain, systematic lifestyle intervention and investigate its effects on global cognitive function in at-risk older adults (aged 60–77 years).

Methods The LatAm-FINGERS Initiative for Cognitive Change (hereafter referred to as LatAm-FINGERS) was a single-blind, multicentre, randomised clinical trial conducted in 11 Latin American countries (Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Dominican Republic, Ecuador, Mexico, Peru, and Uruguay). Individuals aged 60–77 years with high risk of dementia (cardiovascular risk factors, ageing, and dementia risk score ≥ 6), and suboptimal cognitive performance were randomly assigned (1:1) to receive either a 2-year systematic lifestyle intervention (SLI group) or a flexible lifestyle intervention (FLI group). Randomisation was stratified by the study centre to ensure balance and implemented using permuted blocks of eight. Participants and intervention staff were not masked to group assignment, but individuals who assessed outcomes were masked throughout the trial. The SLI provided structured multidomain lifestyle interventions with supervised support and monitoring; FLI offered health advice. Primary outcomes were trial feasibility (evaluated using selected RE-AIM measures: Reach, Implementation, and Maintenance) and the intervention's effects on global cognitive composite trajectories over 2 years (change in the global cognitive composite score over 2 years). This trial is registered at ClinicalTrials.gov (NCT06492967) and has been completed.

Findings Participants were enrolled between Oct 27, 2021, and July 7, 2023; the last participant completed follow-up on Nov 7, 2025. Among 1719 assessed, 1065 participants included in the analytic sample were randomly assigned to the SLI group (n=539) or the FLI group (n=526). Mean age was 67·5 years (SD 4·7), 795 (75%) of 1065 participants were women, and 270 (25%) were men. Self-reported race and ethnicity were: 624 (59%) Mestizo, 288 (27%) White, 72 (7%) Mulatto, 25 (2%) Mixed or other, 18 (2%) Black, 14 (1%) Indigenous, and 24 (2%) did not report race or ethnicity. 877 (82·3%) of 1065 completed the 2-year follow-up. Recruitment effectiveness (Reach) was 62·0%; mean adherence to the SLI group (Implementation) was 71·6% over the entire trial; and frequencies of complete cognitive outcomes data (Maintenance) were 87·9% at 6 months, 85·3% at 12 months, 81·4% at 18 months, and 84·8% at 24 months in the SLI group compared with 86·3% at 6 months, 78·9% at 12 months, 73·4% at 18 months, and 79·8% at 24 months in the FLI group. Dropouts were higher in the FLI group than in the SLI group (20·2% vs 15·2%; $p=0·042$). Global cognitive composite scores increased over time in both groups, with a mean annual change of 0·31 SD (95% CI 0·28–0·34) per year in the SLI group and 0·20 SD (0·17–0·23) per year in the FLI group (mean between-group difference of 0·11 SD per year [0·06–0·15; $p<0·0001$]). Overall, 478 adverse events were reported (412 in the SLI group and 66 in the FLI group). The most common adverse events were musculoskeletal symptoms (113 [21%] in the SLI group, 13 [2%] in the FLI group), upper respiratory infections (50 [9%] in the SLI group, one [$<1\%$] in the FLI group), and COVID-19 infection (31 [6%] events in the SLI group). Serious adverse events occurred in 50 (9%) participants in the SLI group and 24 (5%) participants in the FLI group; none were related to the intervention. There were eight deaths (three in the SLI group and five in the FLI group), and none were related to the intervention.

Interpretation A culturally adapted multidomain lifestyle intervention was feasible across Latin America and resulted in greater cognitive improvements than a flexible health-advice intervention in older adults at risk of cognitive decline. These findings extend the evidence base for multidomain lifestyle interventions to populations historically under-represented in dementia research, supporting their feasibility and scalability as strategies to reduce cognitive decline risk amid the rapidly growing burden of dementia in low-income and middle-income countries.

SLI included supervised physical activity 4 days per week, with aerobic exercise (35 min per session), resistance training (15 min twice a week), coordination and balance training (15 min twice a week), and 5-min warm-up or cool-down periods. Exercise intensity was initially at 55–65% of maximum heart rate, increasing to 70–80% after 6 months.

Dietary counselling was based on the Mediterranean-Dietary Approaches to Stop Hypertension Intervention for Neurodegenerative Delay (MIND) diet²⁵ and included two individualised yearly consultations with a dietitian. Participants completed weekly dietary logs and were regularly contacted by nutritionists.

Cognitive training consisted of four 25-min weekly sessions of computerised exercises delivered through BrainHQ (Posit Science Corporation; San Francisco, CA, USA). Tasks targeted processing speed, attention, memory, and executive function, with difficulty automatically adjusted to performance.

Cardiovascular risk management was addressed by monitoring blood pressure, bodyweight, waist circumference, fasting glucose, glycated haemoglobin, and lipid levels at baseline and every 6 months, with reinforcement of guideline-based targets. Social engagement was incorporated through the 38 in-person team meetings described above, led by an interventionist. Additional details are provided in the trial protocol (appendix 4).

Participants in the FLI group attended four 1-h team meetings over 24 months (one in year 1, three in year 2), receiving oral and written guideline-based recommendations on diet, physical activity, cognitive or social engagement, and cardiovascular risk management. Outcome assessments were also conducted every 6 months in the FLI group.

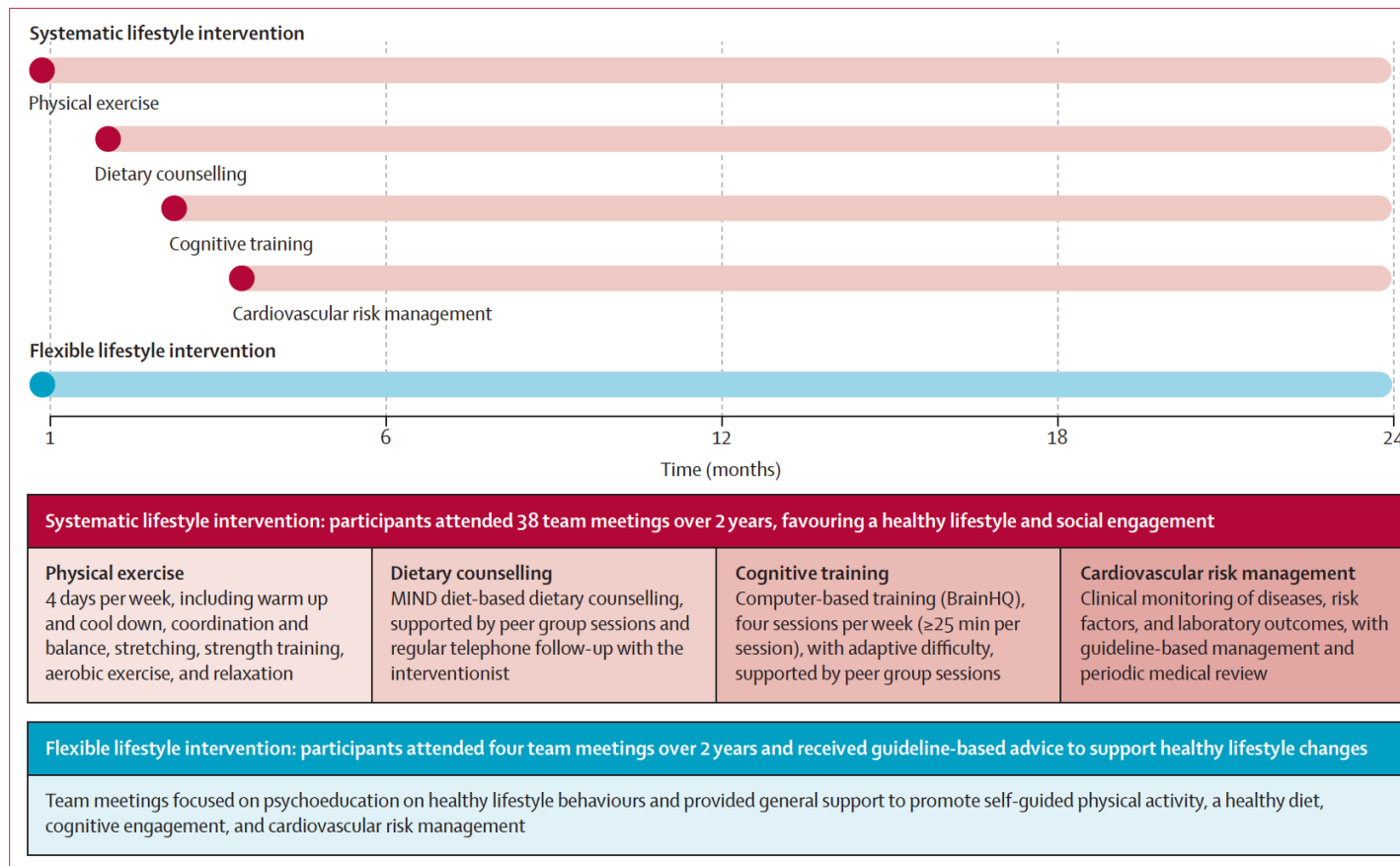


Figure 1: Design and components of the multidomain lifestyle intervention

Intervention timeline and components. Over 24 months, with assessments every 6 months, flexible lifestyle intervention provided general lifestyle guidance, whereas systematic lifestyle intervention delivered a structured multidomain programme including physical exercise, MIND diet counselling, cognitive training (BrainHQ), and cardiovascular risk management. Coloured bars indicate the duration of each component. MIND=Mediterranean-Dietary Approaches to Stop Hypertension Intervention for Neurodegenerative Delay.

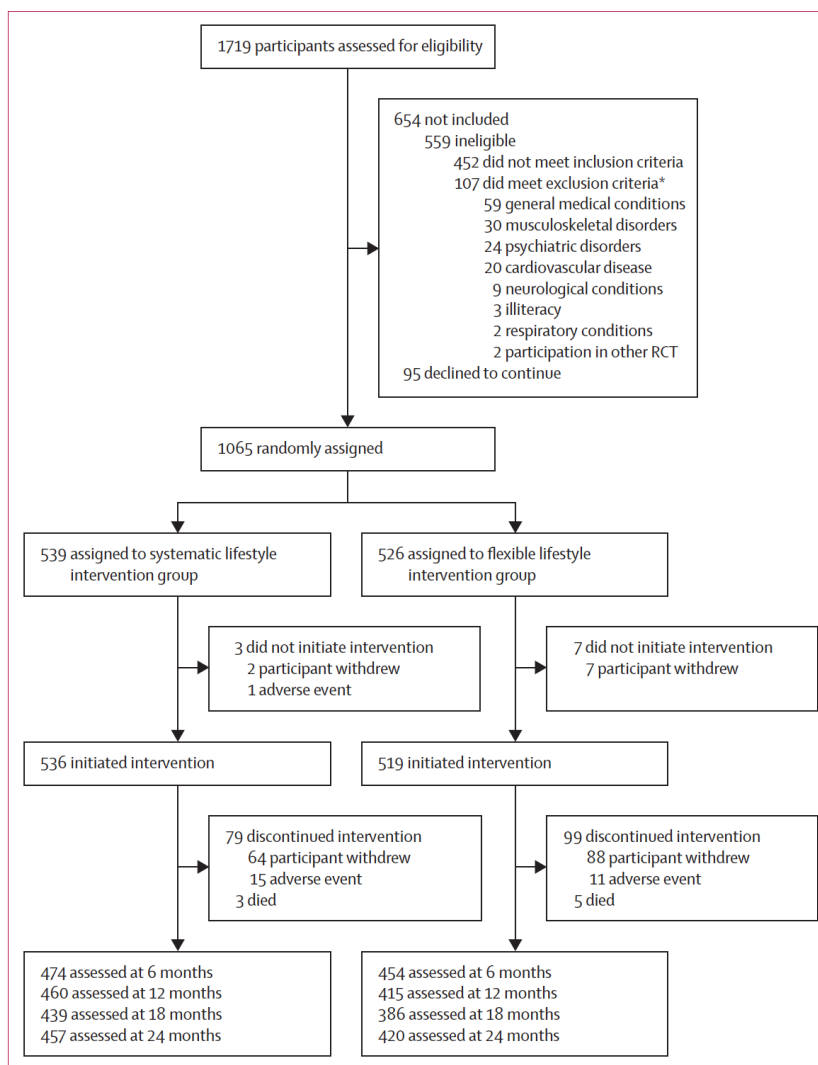


Figure 2: Trial profile

RCT=randomised controlled trial. *Participants could be excluded for more than one reason.

	SLI group (n=539)	FLI group (n=526)
Sociodemographic characteristics		
Age (years)	67.4 (4.6)	67.6 (4.8)
Sex		
Female	397 (74%)	398 (76%)
Male	142 (26%)	128 (24%)
Education*		
High school or less	199 (37%)	202 (38%)
College or more	340 (63%)	324 (62%)
Race and ethnicity		
Mestizo (White-Indigenous mix)	313 (58%)	311 (59%)
White	147 (27%)	141 (27%)
Mulatto (White-Black mix)	39 (7%)	33 (6%)
Indigenous (Native American)	9 (2%)	5 (1%)
Black	7 (1%)	11 (2%)
Mixed or other	13 (2%)	12 (2%)
Preferred not to say	11 (2%)	13 (2%)
Cardiovascular factors		
BMI (kg/m ²)	28.0 (4.6)	27.9 (4.4)
Systolic blood pressure (mm Hg)	129.1 (17.4)	130.2 (17.2)
Haemoglobin (g/dL)	14.3 (1.6)	14.4 (2.0)
Total cholesterol (mg/dL)	200.8 (46.7)	201.4 (42.8)
Haemoglobin A _{1c} (%)	5.8 (0.6)	5.9 (1.0)
Cardiovascular risk†		
Low	60 (11%)	57 (11%)
Medium	452 (84%)	432 (82%)
High	27 (5%)	37 (7%)
Clinical characteristics		
MIND score‡	8.0 (2.2)	7.8 (2.3)
Physical activity level (IPAQ)§		
Sedentary	32 (6%)	35 (7%)
Irregularly active	182 (34%)	184 (36%)
Active	264 (50%)	249 (48%)
Very active	51 (10%)	46 (9%)
Mini-mental state examination	27.4 (1.7)	27.3 (1.7)
Clinical dementia rating¶		
0	414 (78%)	397 (77%)
0-5	114 (22%)	115 (22%)
Geriatric Depression Scale	2.9 (2.9)	2.7 (2.7)
APOE ε4 carrier		
Carrier	106 (22%)	99 (22%)
Non-carrier	376 (78%)	353 (78%)

Data are n (%) or mean (SD). APOE=apolipoprotein E. DASH=dietary approaches to stop hypertension. FLI=flexible lifestyle intervention. IPAQ=International Physical Activity Questionnaire. MIND=Mediterranean-DASH Intervention for Neurodegenerative Delay. SLI=systematic lifestyle intervention. *Education was categorised based on completed years of formal schooling: high school or less (1–12 years) and college or more (≥13 years). †Cardiovascular disease risk was estimated using the Framingham Risk Score to identify low (<10%), medium (10–20%), and high (>20%) risk, based on D'Agostino and colleagues.²⁷ ‡MIND score refers to adherence to the Mediterranean-DASH Intervention for Neurodegenerative Delay diet. §IPAQ is categorised as sedentary, irregularly active, active, or very active. Physical activity data were available for 529 participants in the SLI group and 514 participants in the FLI group; percentages are calculated using these available-data denominators. ¶Clinical dementia rating data were available for 528 participants in the SLI group and 512 participants in the FLI group; percentages are calculated using these available-data denominators. ||APOE ε4 denotes apolipoprotein E ε4 carrier status, indicating the presence of at least one ε4 allele. Genotyping data were available for 482 participants in the SLI group and 452 participants in the FLI group; percentages are calculated using these available-data denominators.

Table 1: Baseline characteristics of participants by intervention group (n=1065)

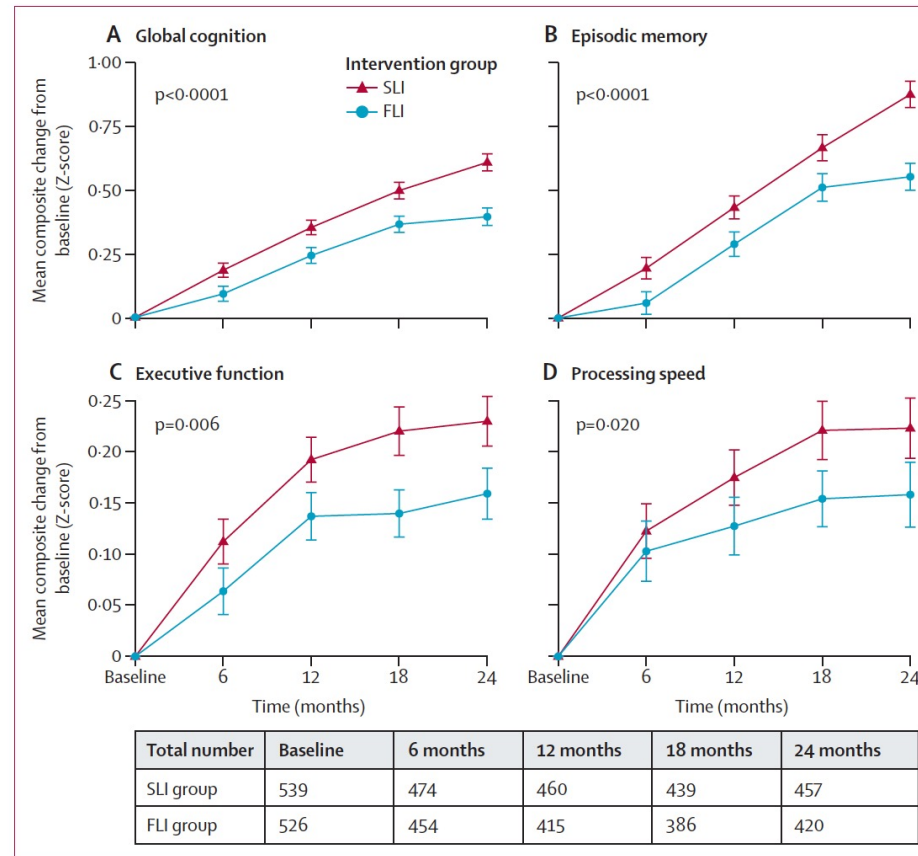


Figure 3: Change from baseline in global and domain-specific cognitive composite scores during the 2 years of interventions

Mean change from baseline for the primary outcome and secondary outcomes was estimated using linear mixed-effects models with random intercept and slopes. Models included fixed effects for the intervention groups, study centre, time, and the group-by-time interaction. The primary effect estimate was the group-by-time interaction, representing the adjusted between-group difference in annualised cognitive change. Cognitive composite Z-scores were standardised to have an SD of 1. Higher values indicate performance improvement relative to baseline. Error bars represent standard errors. FLI=flexible lifestyle intervention. SLI=systematic lifestyle intervention.

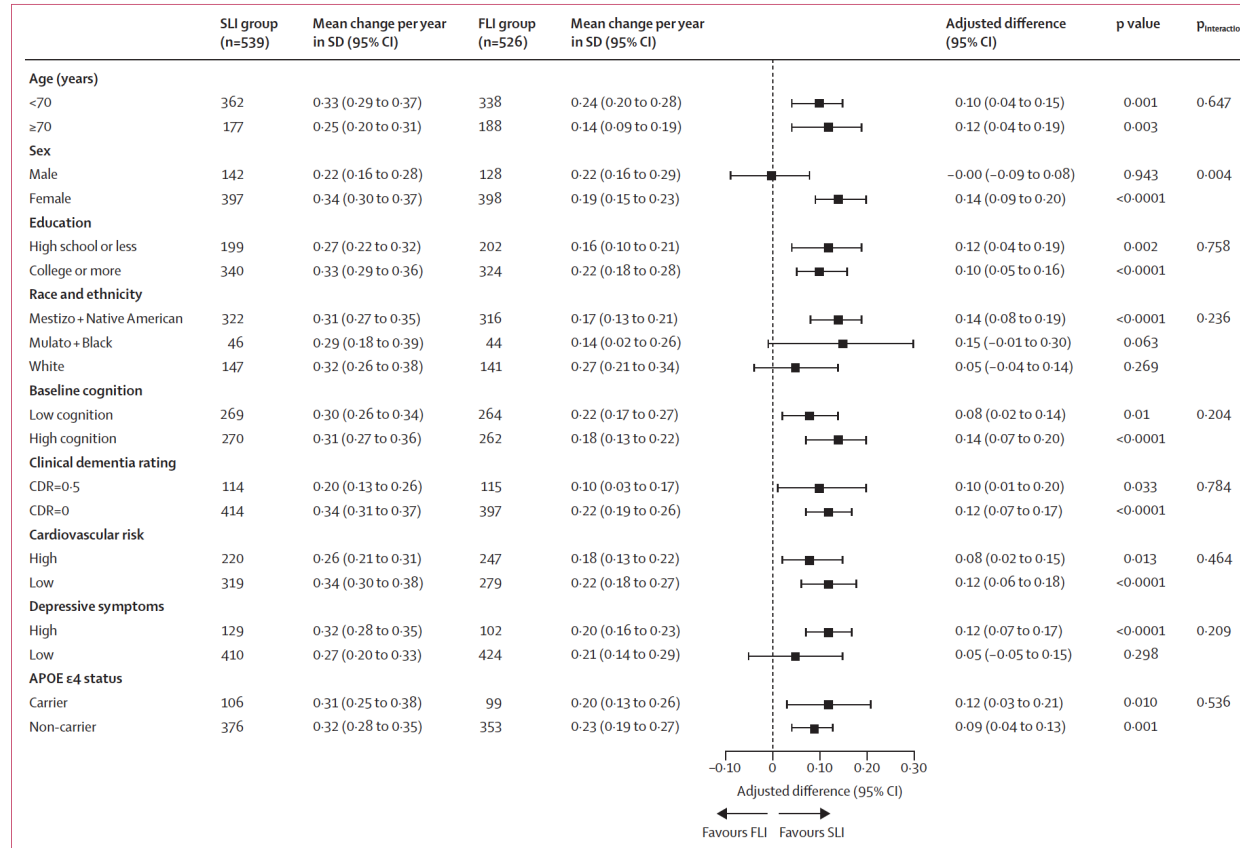


Figure 4: Estimated mean annual changes in the global cognitive function composite in the SLI and FLI groups by subgroups

Values are mean annual changes (with 95% CI) estimated from stratified analyses by prespecified subgroups using linear mixed-effects models with random intercepts and slopes and inverse probability weighting for censoring. p values for the triple interaction were derived from models including subgroup × intervention × time. Cardiovascular risk was estimated with the Framingham Risk Score and categorised as low, medium, or high according to specific thresholds. Depressive symptoms were assessed with the Geriatric Depression Scale (range 0–15); scores of 5 or higher were used to indicate clinically relevant depressive symptoms, consistent with established cutoffs in community-dwelling older populations. APOE ε4 denotes apolipoprotein E ε4 carrier status, indicating the presence of at least one ε4 allele. APOE=apolipoprotein E. CDR=Clinical Dementia Rating. FLI=flexible lifestyle intervention. SLI=systematic lifestyle intervention.

	Total (n=1065)	SLI group (n=539)	FLI group (n=526)	p value
Adverse events*	478	412	66	<0.0001
Participants with ≥1 adverse event	279 (26%)	221 (41%)	58 (11%)	<0.0001
Intervention-related adverse events*	24 (2%)	23 (4%)	1 (<1%)	<0.0001
Most common adverse events*†				
Musculoskeletal symptoms	126 (12%)	113 (21%)	13 (2%)	<0.0001
Upper respiratory infections	51 (5%)	50 (9%)	1 (<1%)	<0.0001
COVID-19 infection	31 (3%)	31 (6%)	0	<0.0001
Cancer	24 (2%)	14 (3%)	10 (2%)	0.44
Bone fracture	23 (2%)	18 (3%)	5 (1%)	0.010
Fall	22 (2%)	16 (3%)	6 (1%)	0.036
Mental disorders	17 (2%)	13 (2%)	4 (1%)	0.048
Gastrointestinal symptoms	16 (2%)	15 (3%)	1 (<1%)	0.0005
Asthma or bronchitis	13 (1%)	13 (2%)	0	0.0002
Inguinal hernia	9 (1%)	8 (1%)	1 (<1%)	0.038
Serious adverse events‡	74 (7%)	50 (9%)	24 (5%)	0.002
Death	8 (1%)	3 (1%)	5 (1%)	0.50
Disability	14 (1%)	9 (2%)	5 (1%)	0.42
Hospitalisation	51 (5%)	38 (7%)	13 (2%)	0.005
Life-threatening	1 (<1%)	0	1 (<1%)	0.49
Intervention-related serious adverse event*	0	0	0	1.00

Data are number of events (%). Percentages were calculated using the number of randomly assigned participants who initiated the interventions in the denominator. p values were calculated using χ^2 test or Fisher's exact test when any observed cell count was ≤5 events. FLI=flexible lifestyle intervention. SLI=systematic lifestyle intervention.

*A participant could have more than one event. †Ten most commonly reported adverse events. ‡Serious adverse events were events that resulted in death, disability, hospitalisation, or were life-threatening.

Table 2: Adverse events during the clinical trial period

Research in context

Evidence before this study

We searched PubMed on May 6, 2026, without language or date restrictions, using the terms (“lifestyle intervention” OR “multidomain intervention” OR “preventive intervention” OR “World-Wide FINGERS”) AND (“cognitive” OR “cognition”). We included randomised controlled trials of multidomain lifestyle interventions in adults aged 60 years or older that reported cognitive outcomes and had an intervention duration of at least 1 year. Previous multidomain lifestyle intervention trials have shown heterogeneous findings regarding the prevention of cognitive decline and dementia. Early large-scale trials such as preDIVA and MAPT did not show significant overall effects on dementia incidence or global cognition. By contrast, the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) demonstrated beneficial effects on global cognition among older adults at increased risk of dementia. Subsequent studies, including US POINTER, have reported cognitive benefits associated with structured multidomain interventions, whereas other trials such as J-MINT and AgeWell.de did not identify significant between-group differences in global cognition after follow-up. Notably, none of these trials were conducted in Latin American populations, leaving a critical gap in evidence for regions with distinct sociodemographic, cultural, and epidemiological contexts that may influence both dementia risk and the feasibility of lifestyle interventions.

Added value of this study

The LatAm-FINGERS study provides large-scale randomised trial evidence from 12 countries in Latin America showing that

a culturally adapted multidomain lifestyle intervention can be implemented across diverse low-income and middle-income countries using harmonised procedures. This trial demonstrated that a 2-year systematic multidomain lifestyle intervention improved global cognition, episodic memory, executive function, and processing speed in older adults at risk of cognitive decline, compared with a flexible lifestyle intervention consisting of regular health advice. These findings extend evidence from previous multidomain prevention trials conducted primarily in high-income countries to populations historically underrepresented in dementia research, including participants with diverse racial, ethnic, educational, and socioeconomic backgrounds.

Implications of all the available evidence

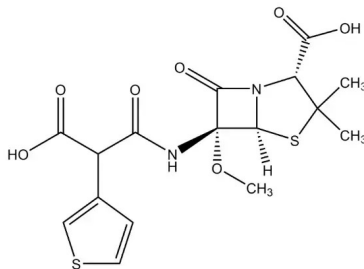
The results suggest that harmonised, non-pharmacological interventions can be implemented across diverse sociocultural settings while maintaining standardisation and producing measurable cognitive benefits in older adults. The feasibility and efficacy findings from LatAm-FINGERS support the potential development of prevention strategies, which are particularly relevant for low-income and middle-income countries, where the burden of dementia is expected to increase substantially. These findings also provide a framework for future public health and implementation strategies aimed at reducing disparities in dementia prevention.

Temocillin ist ein stabiles β -Lactamase-resistentes Penicillin-Antibiotikum, das gezielt gegen gramnegative Bakterien wirkt. Es zeichnet sich durch eine hohe Stabilität gegen β -Lactamasen aus. Aufgrund seiner schmalen Bandbreite ist es besonders wertvoll bei der Bekämpfung multiresistenter gramnegativer Erreger. Zu den typischen Indikationen zählen:

Komplizierte Harnwegsinfektionen (wie Nierenbeckenentzündung)

Infektionen der unteren Atemwege

Bakteriämie (Blutvergiftung)



GELBE
LISTE.
PHARMACEUTICA

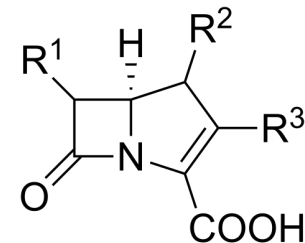
Carbapeneme sind hochwirksame **Reserveantibiotika** aus der **Gruppe der Beta-Lactam-Antibiotika**, die aufgrund ihres extrem breiten Wirkspektrums vor allem bei **schweren, lebensbedrohlichen Infektionen** und **multiresistenten Keimen** eingesetzt werden. Sie kommen in der Regel dann zum Zug, wenn andere Antibiotika versagen

•**Meropenem**: Häufig genutzt bei Sepsis, Lungenentzündungen und Hirnhautentzündungen.

•**Imipenem**: Wird immer mit *Cilastatin* kombiniert, um den Abbau in der Niere zu verhindern.

•**Ertapenem**: Besitzt ein etwas schmaleres Spektrum, hat dafür aber eine längere Halbwertszeit.

•**Doripenem**: Besonders aktiv gegen hartnäckige Krankenhauskeime wie *Pseudomonas*.



Temocillin versus carbapenems for bacteraemia due to third-generation cephalosporin-resistant Enterobacterales in Spain (ASTARTÉ): a multicentre, phase 3, open-label, non-inferiority, randomised clinical trial

Summary

Background Alternatives to carbapenems for the treatment of third-generation cephalosporin-resistant Enterobacterales (3GCR-E) are urgently needed to reduce the selection pressure posed by these drugs. Temocillin is a neglected narrow-spectrum β -lactam. The aim of the trial was to investigate if temocillin is non-inferior to carbapenems for the targeted treatment of bacteraemia due to 3GCR-E.

Methods This multicentre, phase 3, open-label, non-inferiority, randomised, pragmatic, investigator-initiated clinical trial was conducted in 29 Spanish hospitals. We randomly assigned patients with bacteraemia caused by 3GCR-E to receive intravenous temocillin (2 g every 8 h) or meropenem (1 g every 8 h; or ertapenem [1 g per day] if appropriate). Patients aged 18 years or older were eligible if they had monomicrobial bacteraemia due to any 3GCR-E that was susceptible to meropenem and temocillin and treatment for at least 4 days with an active intravenous drug was considered necessary. Randomisation (1:1) was stratified according to previous active drug and to source of infection; no blocks were used. The primary endpoint was clinical success (clinical cure, no need to stop or change the study drug because of adverse event or clinical failure, absence of recurrence, and survival by day 28) in all randomly assigned patients who received at least one dose of a study drug (modified intention-to-treat population [mITT]). Adverse events were assessed in the mITT population. No missing data were reported. A 10% non-inferiority margin was established. The trial was registered in ClinicalTrials.gov (NCT04478721) and is complete and closed to new participants.

Findings 334 eligible patients were enrolled between Dec 15, 2020, and Nov 29, 2024, of whom 328 were included in the mITT population (163 assigned temocillin and 165 assigned carbapenems). In 328 participants, the median age was 72 years (IQR 65–80), 106 (32%) were female, 222 (68%) were male, and the median Charlson Comorbidity Index was 2 (IQR 0–4). In the mITT population, clinical success occurred in 120 (74%) of 163 patients assigned temocillin and 121 (73%) of 165 patients assigned carbapenems (difference 0.3% [95% CI –7.7 to ∞]; non-inferiority $p=0.017$). Serious adverse events were reported in 31 (19%) of 163 patients assigned temocillin and 35 (24%) of 165 patients assigned carbapenems.

Interpretation In patients with bacteraemia caused by 3GCR-E, temocillin was non-inferior to carbapenems as targeted treatment. These findings support the use of temocillin as an effective and safe alternative to carbapenems in this setting.

Temocillin

Vs.

Carbapenems

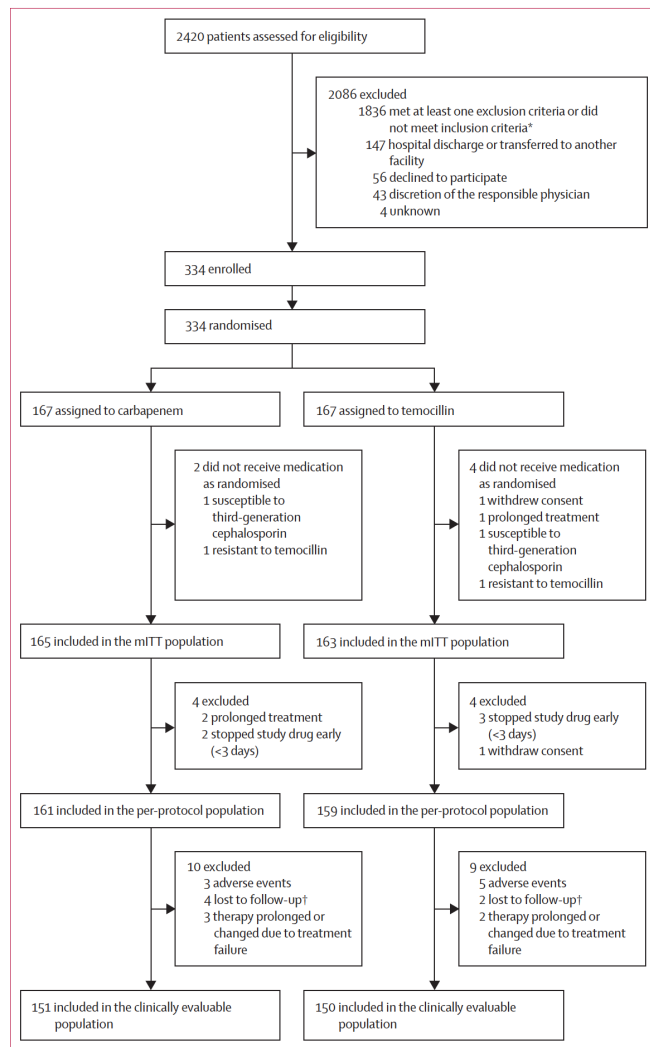


Figure 1: Profile of the ASTARTE trial
mITT=modified intention-to-treat. *More detailed data on exclusion criteria are in appendix 2 (p 2). †All were alive at day 28 but were lost to follow-up because they did not attend at least two consecutive visits for any reason.

	Temocillin (n=163)	Carbapenem* (n=165)
Demographics		
Age, years	74 (65–82)	71 (66–77)
Sex		
Female	59 (36%)	47 (28%)
Male	104 (64%)	118 (72%)
Ethnicity		
Western Europe	146 (90%)	144 (87%)
Latino	15 (9%)	17 (10%)
Other	2 (1%)	4 (2%)
Underlying conditions		
Charlson Comorbidity Index	2 (1–4)	2 (0–3)
Type 1 or type 2 diabetes	55 (34%)	35 (21%)
Chronic heart failure	28 (17%)	30 (18%)
Chronic pulmonary disease	20 (12%)	21 (13%)
Solid cancer	34 (21%)	30 (18%)
Haematological cancer	6 (4%)	6 (4%)
Chronic renal disease, moderate–severe	30 (18%)	27 (16%)
Chronic liver disease, mild–severe	12 (7%)	11 (7%)
Immunosuppressive therapy	40 (25%)	37 (22%)
Fully or partial dependent for basic activities	59 (36%)	51 (31%)
Barthel score (only participants aged 70 years or older)†	65 (30–95)	90 (48–100)
Surgery in past month	26 (16%)	24 (15%)
Invasive procedure in past week	74 (45%)	80 (48%)
Dialysis	2 (1%)	9 (5%)
Infection features		
Nosocomial acquisition	28 (17%)	38 (23%)
Health care-associated acquisition	72 (44%)	68 (41%)
Community acquisition	63 (39%)	59 (36%)
Source of bacteraemia		
Urinary tract	123 (75%)	123 (75%)
Biliary tract	17 (10%)	15 (9%)
Intra-abdominal, no biliary	8 (5%)	9 (5%)
Catheter-related	8 (5%)	6 (4%)
Respiratory tract	2 (1%)	3 (2%)
Unknown	4 (2%)	5 (3%)
Other	1 (1%)	4 (2%)
Pitt score on day of blood culture	1 (0–2)	1 (0–2)
SOFA score on day of blood culture	2 (1–3)	2 (1–3)
Days from blood culture to randomisation‡	3 (2–3)	3 (2–3)

(Table 1 continues in next column)

	Temocillin (n=163)	Carbapenem* (n=165)
(Continued from previous column)		
Cause of infection		
<i>Escherichia coli</i>	118 (72%)	109 (66%)
<i>Klebsiella pneumoniae</i>	33 (20%)	42 (25%)
Other Enterobacterales	12 (7%)	14 (8%)
ESBL-producing bacteria§	148/158 (94%)	145/158 (92%)
AmpC-producing bacteria§	4/158 (3%)	6/158 (4%)
Treatment variables		
First drug administered	103 (63%)	103 (62%)
Carbapenem as first drug administered	61 (37%)	60 (36%)
Any drug administered before randomisation¶	154 (94%)	153 (93%)
Carbapenem, at least one dose	137 (84%)	133 (81%)
Duration of therapy before randomisation, days	2 (1–3)	2 (1–3)
Duration of intravenous treatment with study drug, days	6 (4–8)	6 (4–8)
Duration of oral therapy in patients receiving oral drugs, days	4 (2–6)	4 (2–6)
Total therapy from randomisation, days	8 (6–10)	7 (6–11)
Switched to oral treatment	60 (37%)	64 (39%)
Ciprofloxacin	16 (10%)	17 (10%)
Cotrimoxazole	19 (12%)	22 (13%)
Amoxicillin-clavulanic acid	14 (9%)	22 (13%)
Fosfomycin	11 (7%)	3 (2%)

Data are median (IQR), n (%), or n/N (%). SOFA=Sequential Organ Failure Assessment score. ESBL=extended-spectrum β -lactamase. *99 patients received meropenem and 66 patients received ertapenem. †The limit for recruitment was 2 days after susceptibility results were available; susceptibility results were typically available 1–2 days after blood cultures were drawn. ‡Subset of patients aged 70 years or older: temocillin n=92 and carbapenems n=103. §Five isolates were not available for the characterisation of the resistance mechanisms in the temocillin group and seven isolates were not available in the carbapenem group. ¶Due to use of rapid phenotypic detection of cephalosporin resistance.

Table 1: Baseline and general characteristics in the modified intention-to-treat population

	Temocillin (n=163)	Carbapenem (n=165)	Difference (one- sided 95% CI)	One-sided p value*
Primary outcome				
Clinical success	120 (74%)	121 (73%)	0.3 (-7.7 to ∞)	0.017
Components of the primary outcome and secondary outcomes				
Clinical cure	130 (80%)	135 (82%)	-2.0 (-9.2 to ∞)	0.032
Stop or change study drug for any reason	10 (6%)	8 (5%)	1.3 (-∞ to 5.4)	0.0016
Recurrence until day 28	6 (4%)	10 (6%)	-2.4 (-∞ to 1.5)	<0.0001
Death, any cause at day 28	4 (2%)	6 (4%)	-1.2 (-∞ to 1.9)	<0.0001
Other outcomes				
Microbiological cure (only urinary tract infection) at TOC	37/82 (45%)	35/81 (43%)	1.9 (-10.9 to ∞)	0.063
Changes in SOFA score†	-1.4 (-1.7)	-1.2 (-1.5)	0.2 (-9.1 to ∞)	<0.0001
Reinfection until day 28	2 (1%)	2 (1%)	0.0 (-∞ to 2.0)	<0.0001
Length of hospital stay‡, days	8.9 (8.5)	9.7 (10.6)	-0.8 (-∞ to 9.5)	<0.0001

Data are n (%) or mean (SD), unless otherwise stated. TOC=test of cure. SOFA=Sequential Organ Failure Assessment score. *Non-inferiority p value. †Difference between SOFA score at blood culture day and SOFA score on TOC, data available for 146 patients receiving temocillin and 148 patients receiving carbapenem. ‡Time from inclusion to discharge, data available for 136 patients receiving temocillin and 132 patients receiving carbapenem.

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

	Temocillin (n=163)	Carbapenem (n=165)
Patients with at least one adverse event	83 (51%)	68 (41%)
Patients with at least one serious adverse event	31 (19%)	35 (21%)
Patients with a treatment-related serious adverse event	4 (2%)	1 (1%)
Patients with adverse events of special interest*		
<i>Clostridioides difficile</i> infection	10 (6%)	4 (2%)
Diarrhoea	12 (7%)	9 (5%)
Aspartate aminotransferase or alanine aminotransferase elevation	1 (1%)	1 (1%)
Leukopenia	1 (1%)	0
Vaginal candidiasis	0	1 (1%)
Nausea or vomiting	3 (2%)	2 (1%)
Acute renal failure	2 (1%)	1 (1%)
Rash or pruritus	4 (2%)	2 (1%)

*Individual patients who had at least one occurrence of the event.

Table 3: Adverse events occurring until day 28 of follow-up (modified intention-to-treat population)

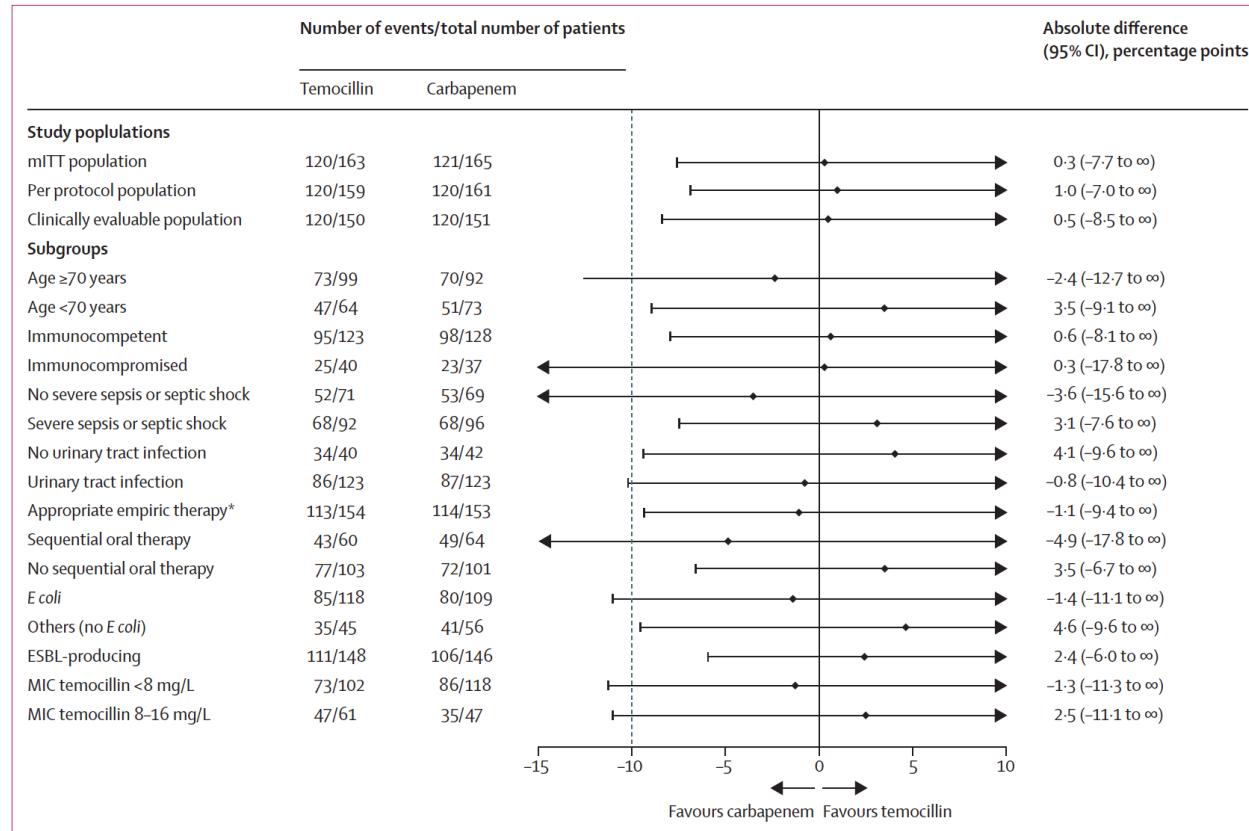


Figure 2: Forest plot of study populations and subgroups for clinical success

Oral therapy subgroups were not pre-planned and were added in the review process. More detailed data is in appendix 2 (p 12). *E coli*=*Escherichia coli*. ESBL=extended-spectrum β -lactamase. mITT=modified intention-to-treat. MIC=minimum inhibitory concentration. *Data on inappropriate empirical therapy is not reported due to the low number of this subgroup; full data are shown in appendix 2 (p 12).

Research in context

Evidence before this study

Global spread of third-generation cephalosporin-resistant Enterobacterales (3GCR-E) has led to a substantial increase in carbapenem consumption, as they are considered the drugs of choice, which is fuelling the spread of carbapenem-resistant organisms. We searched PubMed from Jan 1, 1980, to July 31, 2025, for studies estimating temocillin efficacy in infections caused by 3GCR-E in humans. The search terms used were temocillin AND (ESBL OR cephalosporin-resistant OR AmpC OR cefotaxime-resistant OR ceftriaxone-resistant OR ceftazidime-resistant) AND (outcome OR cure OR failure OR mortality). No language limits were applied. We identified several observational studies evaluating temocillin efficacy in different types of infections caused by 3GCR-E, but no randomised controlled trial for these pathogens. Two previous trials have investigated potential alternatives to carbapenems in invasive infections caused by 3GCR-E, including piperacillin-tazobactam and fosfomycin; both did not show non-inferiority compared with meropenem. Therefore, high-level evidence

supporting appropriate carbapenem-sparing alternatives for bacteraemia due to 3GCR-E are needed. Temocillin, due to its in vitro activity against these bacteria, is a potential candidate.

Added value of this study

This study is the first randomised controlled trial investigating the efficacy and safety of temocillin compared with carbapenems in bacteraemic infections caused by 3GCR-E. Temocillin was shown to be non-inferior in efficacy to carbapenems. No differences were observed in the rate of severe adverse events between the two treatment groups. Therefore, an alternative antibiotic to carbapenems has been shown for the first time in these infections.

Implications of all the available evidence

These results support the use of temocillin as an effective and safe alternative to carbapenems in bacteraemic infections caused by 3GCR-E. As temocillin is a narrow-spectrum agent, its use in these infections instead of carbapenems might contribute to reduce the spread of resistance to carbapenems.

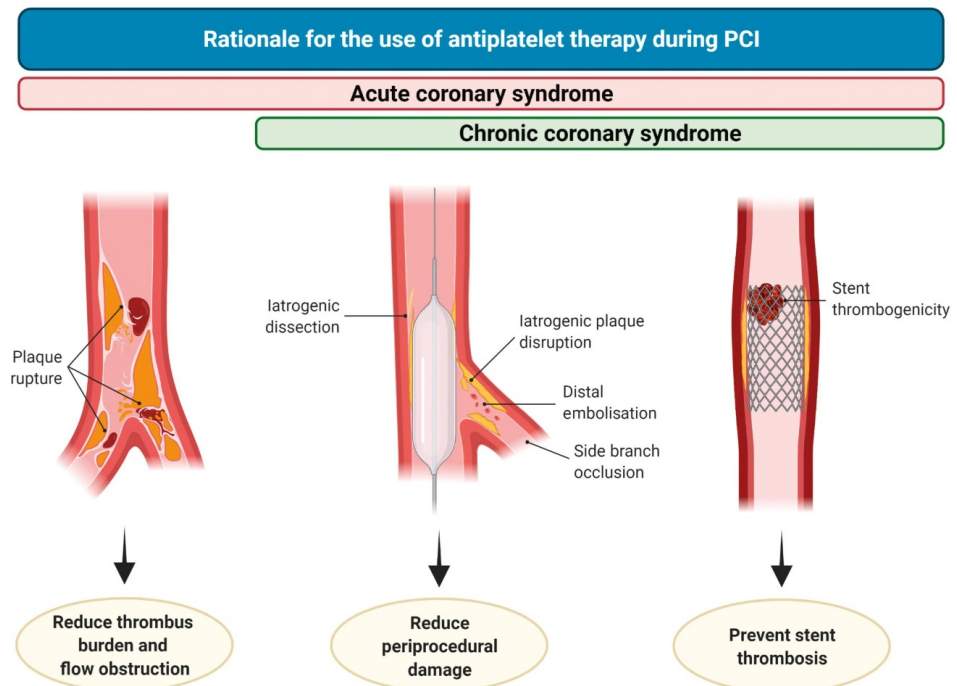
Managing patients with **atrial fibrillation (AF)** who undergo **percutaneous coronary intervention (PCI)** requires balancing clot prevention and bleeding risks through a phased approach: short-term triple therapy (an oral anticoagulant plus dual antiplatelet therapy) for up to one week, followed by double therapy (an anticoagulant plus a single antiplatelet like clopidogrel) up to 12 months, and then anticoagulant monotherapy.

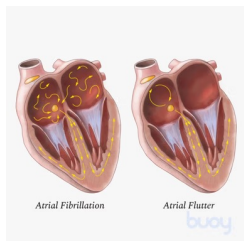
Phased Treatment Plan

Peri-PCI (Up to 1 Week): Short course of triple therapy consisting of an oral anticoagulant (preferably a DOAC like apixaban or rivaroxaban) combined with dual antiplatelet therapy (aspirin plus clopidogrel).

Maintenance Phase (1 Month to 12 Months): Double therapy consisting of the oral anticoagulant plus a single antiplatelet agent (clopidogrel 75 mg daily preferred).

Long-Term Phase (After 12 Months): Discontinuation of antiplatelet therapy; continuation of oral anticoagulant monotherapy for stroke prevention in AF, provided ischemic risk is stable.





Platelet inhibition in
AF patients
undergoing PCI

Is 1 month enough?

1-month versus 12-month dual antithrombotic therapy after percutaneous coronary intervention in patients with atrial fibrillation (OPTIMA-AF): a multicentre, open-label, hybrid non-inferiority and superiority, randomised, controlled trial

Summary

Background The optimal duration of dual antithrombotic therapy after percutaneous coronary intervention (PCI) in patients with atrial fibrillation remains uncertain. We aimed to compare the efficacy and safety of 1-month versus 12-month dual antithrombotic therapy in this population.

Methods OPTIMA-AF was an active-control, randomised, hybrid non-inferiority and superiority trial in which patients with atrial fibrillation undergoing PCI with intravascular imaging guidance were randomly assigned (1:1) to receive 1-month dual antithrombotic therapy (direct oral anticoagulant [DOAC] plus P2Y₁₂ inhibitor) followed by DOAC monotherapy or 12-month dual therapy followed by DOAC monotherapy, across 75 sites in Japan. Eligible patients were aged 20 years or older with non-valvular atrial fibrillation, a CHADS₂ score of 1 or higher, undergoing PCI for native coronary lesions for chronic coronary syndrome or unstable angina, with planned post-PCI treatment with a DOAC. Randomisation used web-based central allocation stratified by trial centre. Investigators and patients were unmasked; clinical events were adjudicated by an independent committee masked to treatment. The primary efficacy endpoint was a composite of all-cause death or thromboembolic events at 12 months; the primary safety endpoint was major or clinically relevant non-major bleeding at 12 months. The trial used a fixed-sequence testing strategy of non-inferiority for efficacy, superiority for safety, and superiority for efficacy. Analyses used the full analysis set including all patients who underwent PCI, were randomly assigned to treatment, received at least one dose of study drugs, and met prespecified analysis-set criteria. This trial is registered with the Japan Registry of Clinical Trials (jRCTs051190053), and is complete.

Findings From Oct 7, 2019, to Sept 3, 2024, 1101 patients were assessed for eligibility; 1088 were randomly assigned to treatment and 1079 were included in the full analysis set (1-month dual therapy n=542; 12-month dual therapy n=537). Median age was 76 years (IQR 70–81). 225 (21%) of 1079 patients were female and 854 (79%) were male. Median CHADS₂ score was 2 (IQR 2–3). Median follow-up was 540 days (IQR 517–559). The primary efficacy endpoint occurred in 29 patients in the 1-month dual therapy group and 23 patients in the 12-month dual therapy group (Kaplan–Meier estimate 5·4% vs 4·3%; absolute difference 1·1 percentage points [95% CI –1·5 to 3·6]; hazard ratio [HR] 1·25 [95% CI 0·73–2·17]). The primary safety endpoint occurred in 24 patients versus 47 patients (Kaplan–Meier estimate 4·5% vs 8·8%; absolute difference –4·4 percentage points [95% CI –7·3 to –1·4]; HR 0·50 [95% CI 0·30–0·81]; p=0·0041 for superiority).

Interpretation Among patients with atrial fibrillation and predominantly chronic coronary syndrome undergoing PCI with intravascular imaging guidance, 1-month dual antithrombotic therapy followed by DOAC monotherapy was non-inferior to 12-month therapy for death or thromboembolic events and reduced major or clinically relevant non-major bleeding at 12 months, suggesting an overall favourable net clinical profile. Efficacy findings should be interpreted with appropriate caution in light of the lower-than-anticipated event rates and fixed absolute non-inferiority margin.

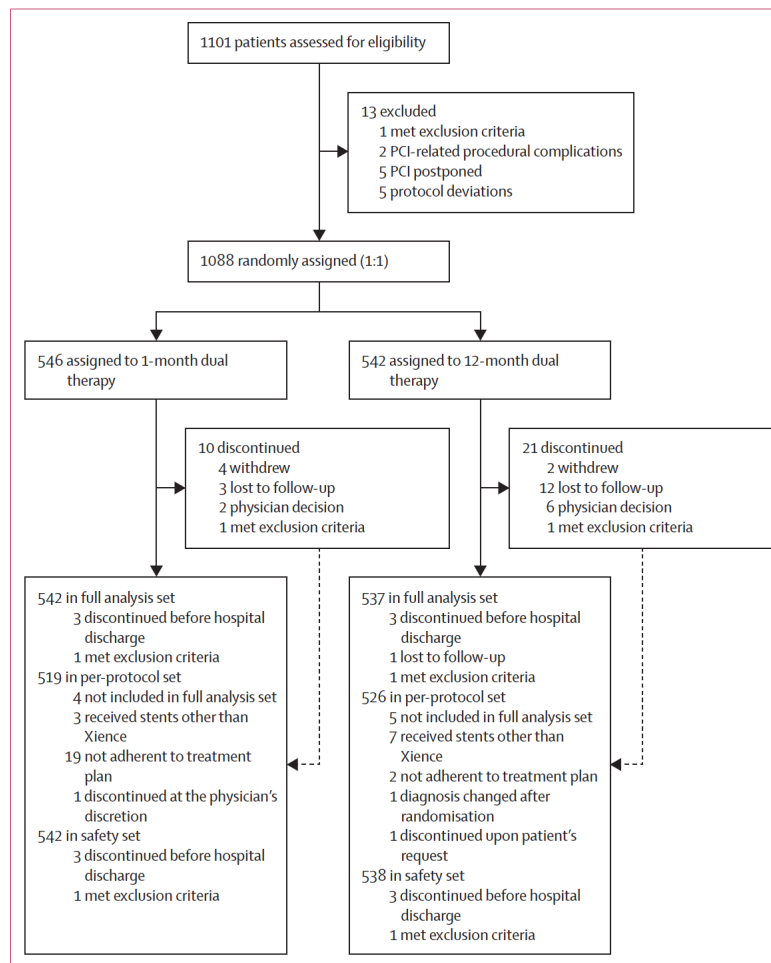


Figure 1: Trial profile

The number assessed for eligibility represents electronic data capture pre-registered patients judged by investigators as likely eligible (per inclusion and exclusion criteria), rather than the total number screened at sites. Patients were randomly assigned in a 1:1 ratio to receive 1-month dual antithrombotic therapy with a DOAC plus a P2Y12 inhibitor (clopidogrel or prasugrel), followed by DOAC monotherapy, or 12-month dual antithrombotic therapy with a DOAC plus a single P2Y12 inhibitor, followed by DOAC monotherapy. DOAC=direct oral anticoagulant. PCI=percutaneous coronary intervention.

	1-month dual therapy (n=542)	12-month dual therapy (n=537)
Age, years	76 (71–82)	76 (70–81)
Sex		
Male	438 (81%)	416 (77%)
Female	104 (19%)	121 (23%)
BMI, kg/m ²	23.8 (21.6–26.6)	24.2 (22.0–26.4)
Diabetes	208 (38%)	216 (40%)
Hypertension	471 (87%)	459 (85%)
Dyslipidaemia	382 (70%)	392 (73%)
Current smoker	49 (9%)	57 (11%)
Chronic coronary syndrome	510 (94%)	508 (95%)
Acute coronary syndrome*	32 (6%)	29 (5%)
Type of atrial fibrillation		
Paroxysmal	252 (46%)	266 (50%)
Persistent	122 (23%)	103 (19%)
Long-standing persistent	159 (29%)	162 (30%)
Unknown	9 (2%)	6 (1%)
History of cerebral infarction	71 (13%)	61 (11%)
Creatinine clearance, mL/min†	56.4 (43.2–73.5)	57.3 (43.1–74.7)
CHADS ₂ score	2 (2–3)	2 (2–3)
CHA ₂ DS ₂ -VASc score	4 (3–5)	4 (3–5)
HAS-BLED score	2 (2–3)	2 (2–3)
Type of antiplatelet agents at hospital discharge		
Clopidogrel	263 (49%)	258 (48%)
Prasugrel	273 (50%)	273 (51%)
Aspirin	24 (4%)	29 (5%)
Others	3 (1%)	1 (<1%)
Type of direct oral anticoagulants at hospital discharge		
Dabigatran	23 (4%)	22 (4%)
Rivaroxaban	126 (23%)	119 (22%)
Aspirin Apixaban	142 (26%)	142 (26%)
Edoxaban	251 (46%)	253 (47%)
Not recorded	0	1 (<1%)

Data are median (IQR) or n (%). Percentages might not sum to 100 due to rounding and potential double counting. CHADS₂ and CHA₂DS₂-VASc scores assess stroke risk in patients with atrial fibrillation; HAS-BLED score assesses bleeding risk in patients receiving anticoagulation—higher scores indicate greater risk. *Acute coronary syndrome in this trial refers to unstable angina only (myocardial infarction was excluded). †Creatinine clearance was assessed with the Cockcroft–Gault formula.

Table 1: Baseline characteristics of the full analysis set

	1-month dual therapy (n=542)		12-month dual therapy (n=537)		Absolute risk difference	Hazard ratio
	Events	Kaplan–Meier	Events	Kaplan–Meier		
Primary outcomes						
All-cause death or thromboembolic events	29 (5%)	5.4 (3.8–7.6)	23 (4%)	4.3 (2.9–6.4)	1.1 (–1.5 to 3.6)	1.25 (0.73–2.17)
Major bleeding or clinically relevant non-major bleeding	24 (4%)	4.5 (3.0–6.6)	47 (9%)	8.8 (6.7–11.6)	–4.4 (–7.3 to –1.4)	0.50 (0.30–0.81)
Secondary outcomes						
All-cause death	22 (4%)	4.1 (2.7–6.1)	15 (3%)	2.8 (1.7–4.6)	1.3 (–0.9 to 3.4)	1.46 (0.76–2.81)
Cardiovascular death	8 (1%)	1.5 (0.7–3.0)	7 (1%)	1.3 (0.6–2.8)	0.2 (–1.2 to 1.6)	1.13 (0.41–3.12)
Non-cardiovascular death	14 (3%)	2.6 (1.6–4.4)	8 (1%)	1.5 (0.8–3.0)	1.1 (–0.6 to 2.8)	1.74 (0.73–4.14)
Myocardial infarction	4 (1%)	0.7 (0.3–2.0)	4 (1%)	0.8 (0.3–2.0)	0.0 (–1.0 to 1.0)	0.99 (0.25–3.96)
Periprocedural myocardial infarction	1 (<1%)	0.2 (0.0–1.3)	2 (<1%)	0.4 (0.1–1.5)	–0.2 (–0.8 to 0.4)	0.50 (0.04–5.46)
Spontaneous myocardial infarction	3 (1%)	0.6 (0.2–1.7)	2 (<1%)	0.4 (0.1–1.5)	0.2 (–0.6 to 1.0)	1.49 (0.25–8.90)
Stent thrombosis (ARC definition)						
Any stent thrombosis	7 (1%)	1.3 (0.6–2.7)	2 (<1%)	0.4 (0.1–1.5)	0.9 (–0.2 to 2.0)	3.46 (0.72–16.65)
Definite stent thrombosis	1 (<1%)	0.2 (0.0–1.3)	1 (<1%)	0.2 (0.0–1.3)	0.0 (–0.5 to 0.5)	0.99 (0.06–15.78)
Probable stent thrombosis	1 (<1%)	0.2 (0.0–1.3)	1 (<1%)	0.2 (0.0–1.3)	0.0 (–0.5 to 0.5)	0.99 (0.06–15.80)
Possible stent thrombosis	5 (1%)	0.9 (0.4–2.2)	0	0.0 (0.0–0.7)	0.9 (0.1 to 1.8)	Not estimable
Stent thrombosis (ARC-2 definition)						
Any stent thrombosis	1 (<1%)	0.2 (0.0–1.3)	1 (<1%)	0.2 (0.0–1.3)	0.0 (–0.5 to 0.5)	0.99 (0.06–15.78)
Definite stent thrombosis	1 (<1%)	0.2 (0.0–1.3)	1 (<1%)	0.2 (0.0–1.3)	0.0 (–0.5 to 0.5)	0.99 (0.06–15.78)
Probable stent thrombosis	0	0.0 (0.0–0.7)	0	0.0 (0.0–0.7)	0.0 (–0.7 to 0.7)	Not estimable
Silent occlusion	0	0.0 (0.0–0.7)	0	0.0 (0.0–0.7)	0.0 (–0.7 to 0.7)	Not estimable
Stroke	4 (1%)	0.7 (0.3–2.0)	4* (1%)	0.8 (0.3–2.0)	0.0 (–1.0 to 1.0)	0.99 (0.25–3.96)
Ischaemic (cerebral thrombosis or embolism)	3 (1%)	0.6 (0.2–1.7)	4 (1%)	0.8 (0.3–2.0)	–0.2 (–1.2 to 0.8)	0.74 (0.17–3.32)
Haemorrhagic stroke (intracerebral haemorrhage)	1 (<1%)	0.2 (0.0–1.3)	1 (<1%)	0.2 (0.0–1.3)	0.0 (–0.5 to 0.5)	0.99 (0.06–15.79)
Systemic embolism	0	0.0 (0.0–0.7)	0	0.0 (0.0–0.7)	0.0 (–0.7 to 0.7)	Not estimable
Bleeding events†						
Major bleeding	18 (3%)	3.4 (2.1–5.3)	23 (4%)	4.3 (2.9–6.4)	–1.0 (–3.3 to 1.3)	0.77 (0.42–1.43)
Clinically relevant non-major bleeding	7 (1%)	1.3 (0.6–2.7)	26 (5%)	4.9 (3.4–7.1)	–3.6 (–5.7 to –1.5)	0.26 (0.11–0.61)

Data are n (%) or estimates (95% CI). Kaplan–Meier estimates are percentages and absolute risk differences are percentage points. Events are reported through day 360, and Kaplan–Meier estimates are at day 360. Hazard ratios were estimated using Cox proportional-hazards models with follow-up censored at day 360. Hazard ratios were not estimable when one or both treatment groups had no events. Confidence intervals for secondary outcomes have not been adjusted for multiplicity; results should be interpreted with caution. Bleeding events were assessed primarily according to the International Society on Thrombosis and Haemostasis definition. Bleeding was also classified according to the Bleeding Academic Research Consortium criteria and the Thrombolysis in Myocardial Infarction definition (appendix 2 pp 33–38). ARC=Academic Research Consortium. ARC-2=Academic Research Consortium-2. *One patient had both ischaemic and haemorrhagic stroke. †Component rows count patients with each specific event type and are not mutually exclusive because some patients had more than one type of bleeding event; therefore, the sum of the components exceeds the total composite bleeding count.

Table 2: Primary and key secondary endpoints at 12 months after percutaneous coronary intervention in the full analysis set

Table 2: Primary and key secondary endpoints at 12 months after percutaneous coronary intervention in the full analysis set

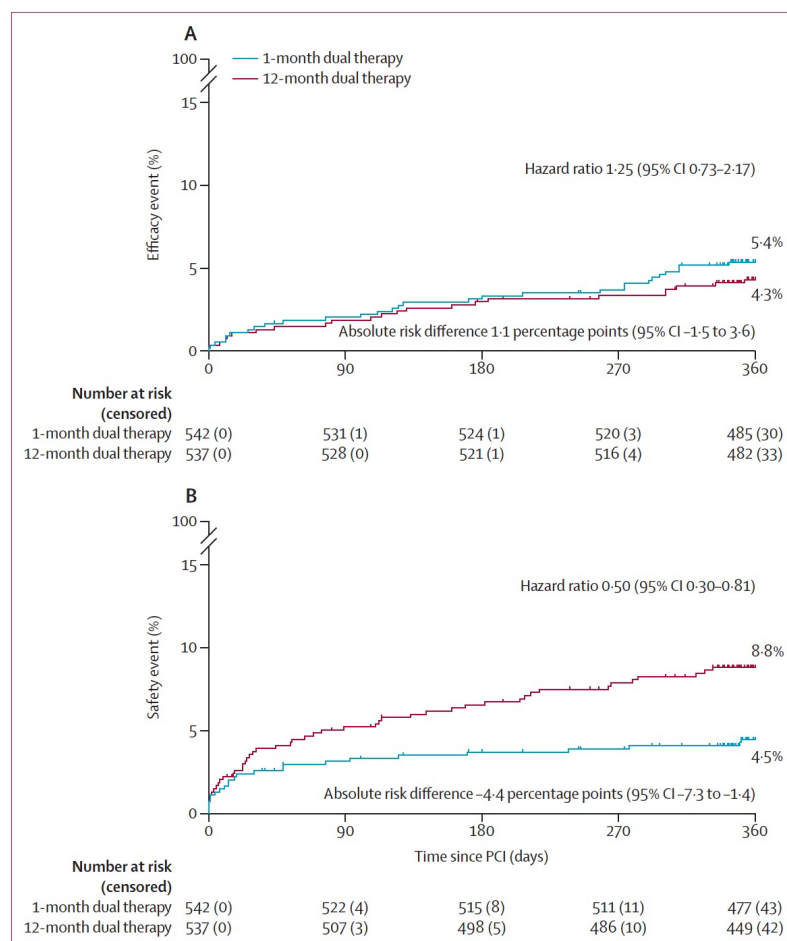


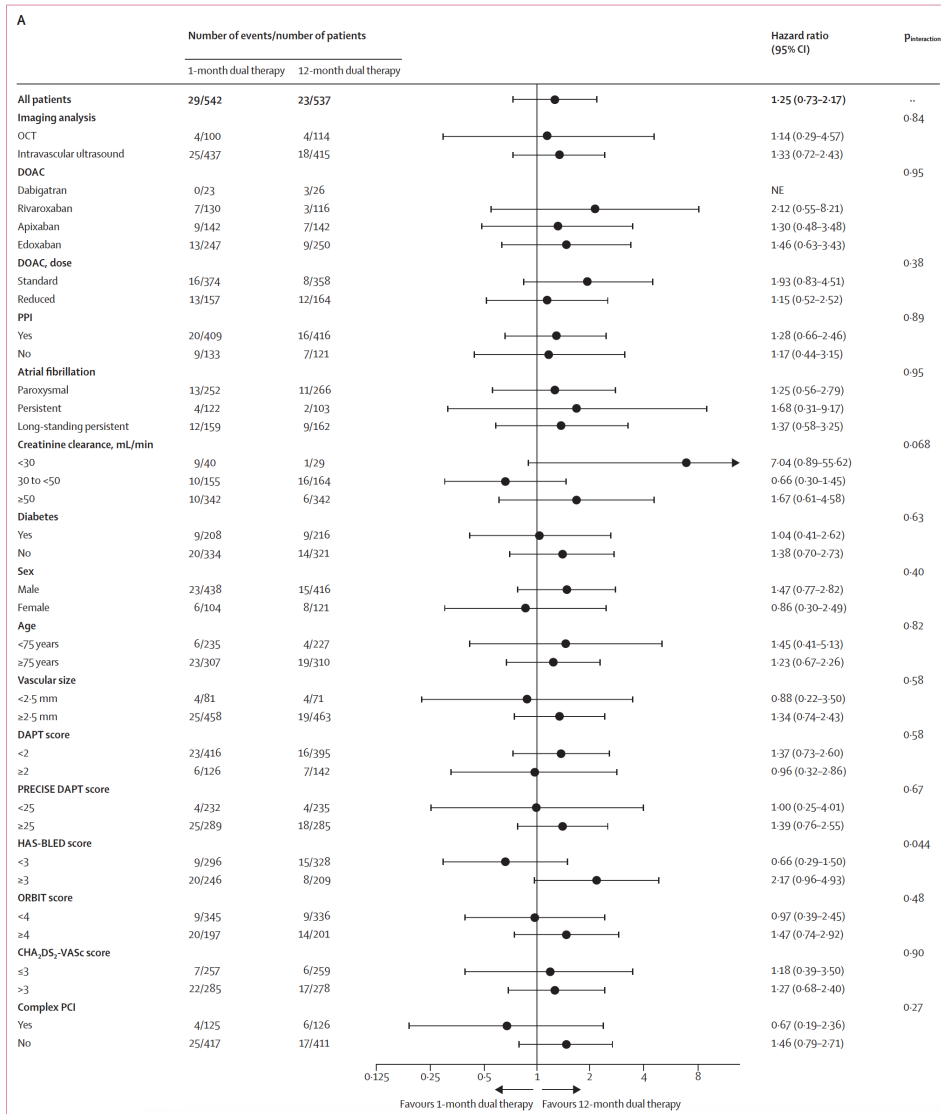
Figure 2: Kaplan-Meier analysis of the primary efficacy and safety endpoints (full analysis set)

(A) The incidence of the primary efficacy endpoint, defined as a composite of all-cause death or thromboembolic events (myocardial infarction, definite stent thrombosis, stroke, or systemic embolism). (B) The primary safety endpoint, defined as bleeding (International Society on Thrombosis and Haemostasis major or clinically relevant non-major bleeding). Percentages are Kaplan-Meier estimates at 12 months (day 360). Hazard ratios compare the 1-month dual therapy group with the 12-month dual therapy group and were estimated using Cox proportional-hazards models with follow-up censored at day 360. PCI=percutaneous coronary intervention.

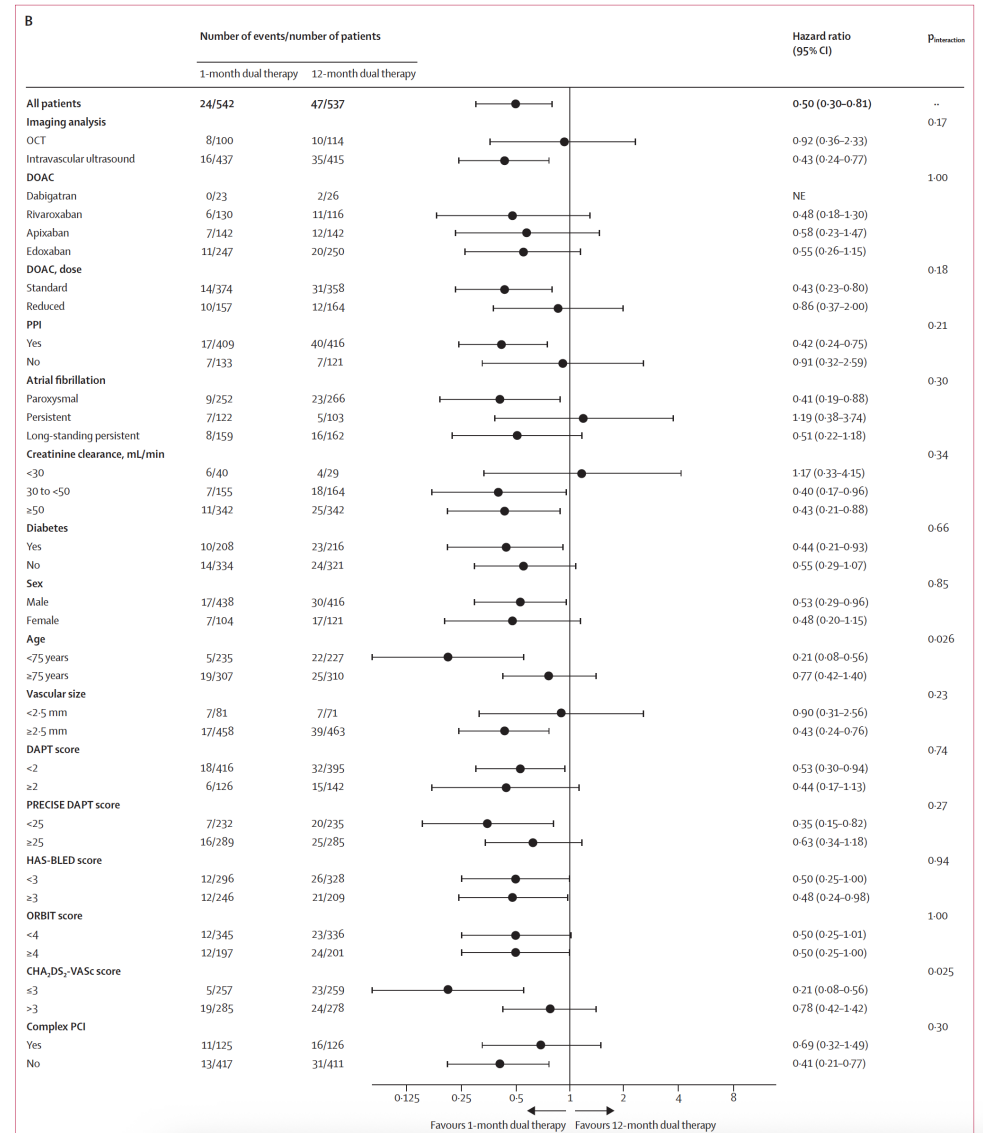
	1-month dual therapy (n=542)	12-month dual therapy (n=538)
ISTH bleeding classification		
Major bleeding	18/542 (3%)	24/538 (4%)
Clinically relevant non-major bleeding	7/542 (1%)	26/538 (5%)
BARC bleeding classification		
BARC type 2-5	23/542 (4%)	48/538 (9%)
BARC type 3-5	14/542 (3%)	22/538 (4%)

Data are n/N (%) with events to day 360 in the safety analysis set. Detailed endpoint definitions are provided in appendix 2 (pp 34-38). BARC=Bleeding Academic Research Consortium. ISTH=International Society on Thrombosis and Haemostasis.

Table 3: Harms in the safety analysis set



(Figure 3 continues on next page)



Research in context

Evidence before this study

We searched PubMed and MEDLINE from database inception to Aug 31, 2025, without language restrictions, using terms related to “atrial fibrillation”, “percutaneous coronary intervention”, “antithrombotic therapy”, “oral anticoagulant”, “direct oral anticoagulant”, “P2Y12 inhibitor”, and “randomised controlled trial”. We included randomised trials in adults with atrial fibrillation or another indication for oral anticoagulation undergoing percutaneous coronary intervention (PCI) that compared dual antithrombotic therapy with triple antithrombotic therapy and reported bleeding and thromboembolic or ischaemic outcomes within 12 months after PCI. We excluded non-randomised studies, trials terminated prematurely with insufficient statistical power, studies in patients without atrial fibrillation or another indication for oral anticoagulation, and studies not focused on post-PCI antithrombotic treatment. We identified five major randomised trials—WOEST, PIONEER AF-PCI, RE-DUAL PCI, AUGUSTUS, and ENTRUST-AF PCI—that informed current practice. The randomised trials generally used blinded outcome assessment, although most used an open-label design. Collectively, they showed a consistent reduction in bleeding with dual antithrombotic therapy compared with triple antithrombotic therapy, whereas effects on thromboembolic or ischaemic outcomes remained less certain. Relevant meta-analyses of randomised trials broadly supported the same direction of effect. However, we found no randomised trial that directly evaluated whether dual antithrombotic therapy could be shortened to 1 month after PCI in patients with atrial fibrillation.

Added value of this study

This randomised trial provides direct evidence on the duration of dual antithrombotic therapy after PCI in patients with atrial

fibrillation treated with contemporary drug-eluting stents and direct oral anticoagulants. By testing a 1-month dual therapy strategy against a 12-month strategy, OPTIMA-AF helps to address whether dual therapy can be shortened before transition to direct oral anticoagulant monotherapy. The trial met non-inferiority for the primary efficacy endpoint of all-cause death or thromboembolic events and showed superiority for major or clinically relevant non-major bleeding, although efficacy findings require cautious interpretation because event rates were lower than anticipated.

Implications of all the available evidence

Trials including AFIRE and EPIC-CAD have supported oral anticoagulant monotherapy as long-term antithrombotic therapy in patients with atrial fibrillation and stable coronary artery disease, and AQUATIC provided related evidence in patients with chronic coronary syndrome receiving oral anticoagulation. OPTIMA-AF complements this evidence by addressing the early post-PCI period—predominantly in patients with chronic coronary syndrome—and providing evidence relevant to the timing of de-escalation from combination antithrombotic therapy to DOAC monotherapy. Taken together, the available evidence supports cautious consideration of earlier de-escalation of combination antithrombotic therapy after PCI in patients with atrial fibrillation, with careful attention to bleeding and thromboembolic risks. However, because the observed event rates were lower than anticipated under a fixed non-inferiority margin, efficacy estimates warrant cautious interpretation. Further adequately powered trials are needed to clarify applicability in acute coronary syndrome populations and in clinically important subgroups.

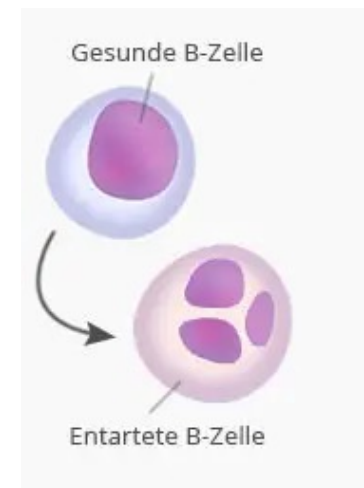
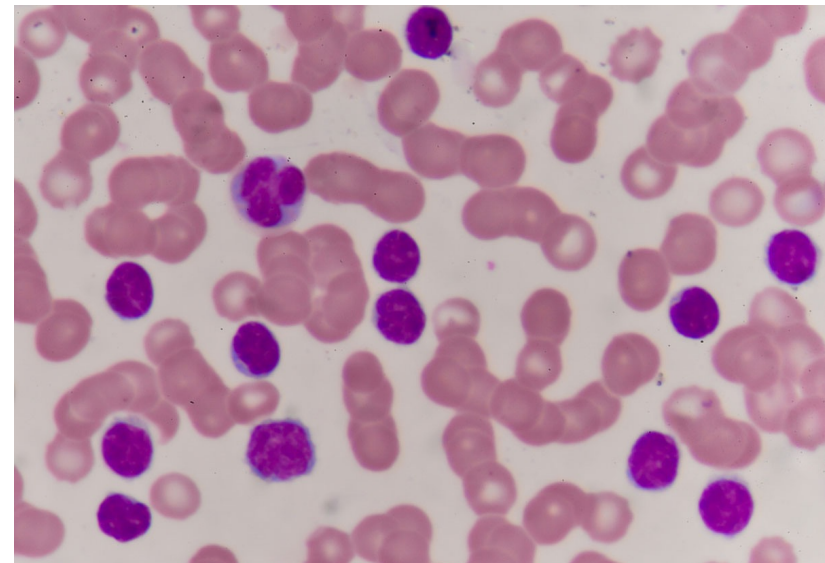
Die **chronische lymphatische Leukämie (CLL)** ist eine langsame Blutkrebserkrankung, die vor allem ältere Menschen betrifft und durch die unkontrollierte Vermehrung weißer Blutzellen im Knochenmark und Blut gekennzeichnet ist. Oft ist zu Beginn keine sofortige Behandlung nötig, sondern nur eine engmaschige Überwachung.

Verlauf und Behandlung

Warten und Beobachten: Im frühen Stadium wird meist abgewartet, da die Krankheit oft über Jahre hinweg langsam verläuft und keine Beschwerden verursacht.

Therapiebeginn: Erst bei starker Vergrößerung von Organen, Abfall der Blutwerte oder Beschwerden wird gezielt behandelt.

Moderne Therapien: Zielgerichtete Medikamente und schonende Wirkstoffe können die Krankheit sehr gut kontrollieren und eine hohe Lebensqualität sichern



Venetoclax ist ein **oral wirksamer, zielgerichteter Krebswirkstoff** zur Behandlung von bestimmten Formen von Blutkrebs. Er blockiert gezielt das BCL-2-Protein, welches Krebszellen am Absterben hindert

Anwendungsgebiete (Indikationen)

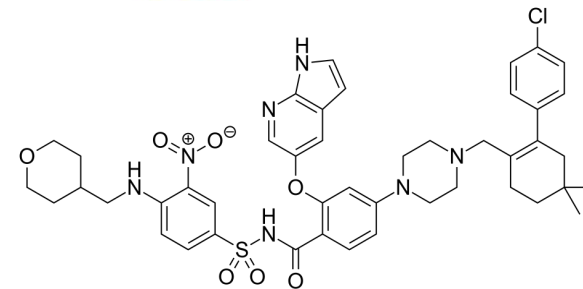
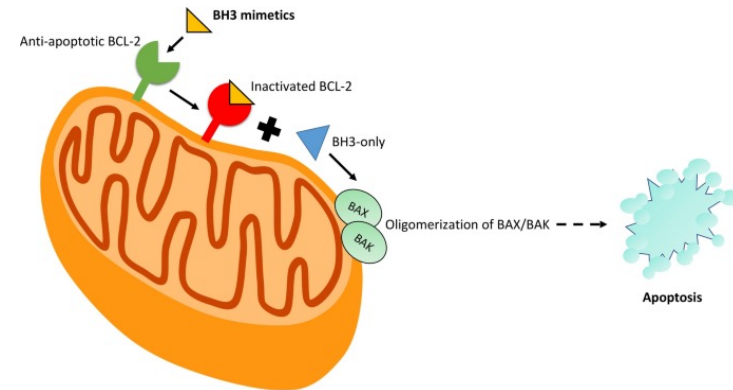
Der Arzneistoff wird bei Erwachsenen in folgenden Bereichen eingesetzt:

Chronisch lymphatische Leukämie (CLL): Entweder als Monotherapie bei bestimmten genetischen Mutationen (wie 17p-Deletion oder TP53-Mutation) oder in **Kombination** mit Antikörpern wie Obinutuzumab oder Rituximab.

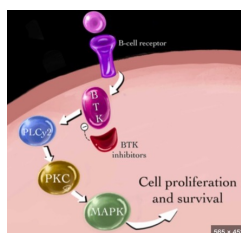
Akute myeloische Leukämie (AML): In Kombination mit einer demethylierenden Substanz (Azacitidin oder Decitabin) oder niedrig dosiertem Cytarabin für Patienten, die nicht für eine intensive Chemotherapie geeignet sind.

Wirkungsweise

Krebszellen nutzen das Protein **BCL-2**, um den programmierten Zelltod (Apoptose) zu blockieren und dadurch unsterblich zu werden. Venetoclax bindet hochspezifisch an BCL-2, hebt diesen Block auf und zwingt die Leukämiezellen dazu, abzusterben



BH-3 medicine typically refers to **BH3 mimetics**, a class of targeted cancer drugs. They work by binding to and blocking anti-apoptotic (cell-survival) proteins like BCL-2, BCL-xL, and MCL-1. By neutralizing these proteins, BH3 mimetics force cancer cells to undergo programmed cell death (apoptosis)

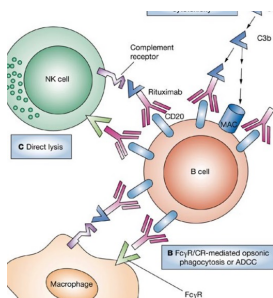
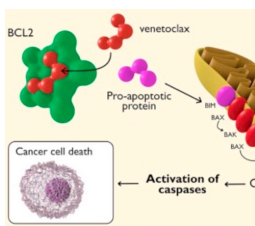


Fixed-duration pirtobrutinib plus venetoclax–rituximab versus venetoclax–rituximab for patients with previously treated chronic lymphocytic leukaemia or small lymphocytic lymphoma (BRUIN CLL-322): an open-label, multicentre, randomised, controlled, phase 3 trial

Summary

Background Venetoclax–rituximab (VR) following covalent Bruton tyrosine kinase (BTK) inhibitor therapy is the fixed-duration standard of care for patients with chronic lymphocytic leukaemia (including small lymphocytic lymphoma). Pirtobrutinib, a non-covalent BTK inhibitor, is approved for use after treatment with a covalent BTK inhibitor as a continuous therapy option. We aimed to evaluate the addition of pirtobrutinib to VR as a fixed-duration regimen in patients with relapsed or refractory chronic lymphocytic leukaemia.

Methods This open-label, multicentre, randomised, controlled, phase 3 trial was conducted at 152 sites (comprising community hospitals and academic centres) across 22 countries. Eligible patients were aged 18 years or older, had a confirmed diagnosis of chronic lymphocytic leukaemia (including small lymphocytic lymphoma), and had previously been treated with at least one line of therapy that could include a covalent BTK inhibitor. Patients who had previously received a non-covalent BTK inhibitor, venetoclax, or another BCL2 inhibitor were not eligible. Enrolled patients were randomly assigned (1:1) using an interactive web-based randomisation system, stratified by del(17p) status and previous exposure to covalent BTK inhibitors, and assigned to receive either pirtobrutinib plus VR (PVR) or VR. Both groups received oral venetoclax (25 cycles) and intravenous rituximab (six cycles); the PVR group also received oral pirtobrutinib for 28 cycles, with a three-cycle pirtobrutinib–rituximab lead-in before venetoclax initiation. For this prespecified interim analysis, the primary endpoint was progression-free survival in the intention-to-treat population, assessed by a masked independent review committee (IRC) as per 2018 International Workshop on Chronic Lymphocytic Leukemia guidelines. Safety analyses were conducted in the safety population, defined as all randomly assigned patients who took at least one dose of any study treatment. All analyses were based on a data cutoff date of Feb 2, 2026. The trial is registered at ClinicalTrials.gov, NCT04965493, and is ongoing but no longer recruiting.



Br + V + R
vs.
V + R alone

Findings Between Oct 13, 2021, and Oct 28, 2024, 784 patients were screened, of whom 639 were randomly assigned: 321 to the PVR group and 318 to the VR group. The median age of patients was 68·0 years (IQR 60·0–74·0), of whom 439 (69%) were male and 200 (31%) were female. The median number of previous therapies was 2 (IQR 1–3); 510 (80%) of 639 patients had previous exposure to covalent BTK inhibitors, of whom 362 (71%) discontinued their most recent drug of this class owing to progressive disease. At a median follow-up of 27·3 months (IQR 19·5–38·7), PVR showed a significant improvement in IRC-assessed progression-free survival compared with VR (hazard ratio 0·547 [95% CI 0·400–0·748]; $p=0·0001$). The median 24-month progression-free survival rate was 87% (95% CI 82·3–90·4) in the PVR group versus 72% (65·7–77·0) in the VR group, and the median progression-free survival was not reached (IQR 31·7–not estimable) in the PVR group versus 39·7 months (21·5–50·0) in the VR group. This benefit was consistent across prespecified subgroups, including patients with previous exposure to covalent BTK inhibitors. The most frequent treatment-emergent adverse event of any grade in both groups was diarrhoea, reported in 106 (34%) of 316 patients in the PVR group and 110 (35%) of 311 patients in the VR group. The frequency of treatment-emergent adverse events of grade 3 or higher was similar in both groups (249 [79%] of 316 patients in the PVR group vs 227 [73%] of 311 patients in the VR group); the rate of tumour lysis syndrome of grade 3 or higher was lower in the PVR group (1%; three of 316) than in the VR group (4%; 12 of 311). Rates of atrial fibrillation or flutter of any grade were low (11 [3%] of 316 patients in the PVR group vs eight [3%] of 311 patients in the VR group). Rates of treatment discontinuation owing to treatment-emergent adverse events deemed as related to any of the study drugs were similar: 5% (17 of 316 patients) in the PVR group versus 5% (16 of 311 patients) in the VR group. There were five treatment-related deaths: one in the PVR group and four in the VR group.

Interpretation In patients with previously treated chronic lymphocytic leukaemia, PVR showed significant improvement in progression-free survival compared with VR, with consistent results in patients who had previously received covalent BTK inhibitors and no new safety signals. To our knowledge, these results represent the first randomised phase 3 evidence comparing a novel fixed-duration regimen to the current standard of VR in relapsed or refractory chronic lymphocytic leukaemia, supporting PVR as a potential new standard of care.

	PVR group (n=321)	VR group (n=318)
Median age, years	68.0 (61.0-73.0)	67.0 (58.0-74.0)
Age category, years		
<65	123 (38%)	137 (43%)
≥65	198 (62%)	181 (57%)
<75	253 (79%)	243 (76%)
≥75	68 (21%)	75 (24%)
<85	320 (100%)	316 (99%)
≥85	1 (<1%)	2 (1%)
Race		
White	246 (77%)	248 (78%)
Asian	58 (18%)	52 (16%)
Other*	17 (5%)	18 (6%)
Sex		
Male	216 (67%)	223 (70%)
Female	105 (33%)	95 (30%)
Region		
North America	104 (32%)	110 (35%)
Europe	149 (46%)	141 (44%)
Asia	55 (17%)	50 (16%)
Australia and New Zealand	8 (2%)	9 (3%)
Middle East	5 (2%)	8 (3%)
Ethnicity		
Hispanic or Latino	8 (2%)	9 (3%)
Not Hispanic or Latino	303 (94%)	301 (95%)
Not reported or unknown	10 (3%)	8 (3%)
Baseline ECOG performance status		
0	150 (47%)	145(46%)
1	150 (47%)	156 (49%)
2	20 (6%)	16 (5%)
Missing data	1 (<1%)	1 (<1%)
Median duration of disease, years†	8.61 (4.91-12.44)	8.42 (5.34-13.08)
Rai stage‡		
0-II	188/293 (64%)	180/293 (61%)
III or IV	105/293 (36%)	113/293 (39%)
Bulky disease§		
Yes; target lesion ≥5 cm	116 (36%)	107 (34%)
No; target lesion <5 cm	174 (54%)	192 (60%)
No; no measurable lesion	30 (9%)	19 (6%)
Missing data	1 (<1%)	0
β2 microglobulin		
≤3.5 mg/L	123 (38%)	137 (43%)
>3.5 mg/L	195 (61%)	173 (54%)
Missing data	3 (1%)	8 (3%)
Risk of tumour lysis syndrome		
High	68 (21%)	70 (22%)
Medium	138 (43%)	139 (44%)
Low	113 (35%)	108 (34%)
Missing data	2 (1%)	1 (<1%)

(Table 1 continues in next column)

	PVR group (n=321)	VR group (n=318)
(Continued from previous column)		
del(11q)¶		
Present	69 (21%)	65 (20%)
Absent	183 (57%)	185 (58%)
Missing data	69 (21%)	68 (21%)
del(17p)¶		
Present	66 (21%)	71 (22%)
Absent	235 (73%)	217 (68%)
Missing data	20 (6%)	30 (9%)
TP53 mutation status¶		
Present	106 (33%)	112 (35%)
Absent	150 (47%)	151 (47%)
Missing data	65 (20%)	55 (17%)
TP53 mutation and/or del(17p)¶		
Present	126 (39%)	132 (42%)
Absent	130 (40%)	134 (42%)
Missing data	65 (20%)	52 (16%)
IGHV mutation status¶		
Unmutated	203 (63%)	225 (71%)
Mutated	50 (16%)	36 (11%)
Missing data	68 (21%)	57 (18%)
Complex karyotype¶**		
Yes	84 (26%)	117 (37%)
No	121 (38%)	103 (32%)
Missing data	116 (36%)	98 (31%)
Median previous lines of systemic therapy	2 (1-3)	2 (1-3)
Number of previous lines of systemic therapy		
1	135 (42%)	143 (45%)
2	90 (28%)	88 (28%)
≥3	96 (30%)	87 (27%)
Previous experience with covalent BTK inhibitors††		
Discontinued due to progressive disease	181 (56%)	181 (57%)
Discontinued due to intolerance	44 (14%)	35 (11%)
Discontinued for other reasons	31 (10%)	38 (12%)
No previous covalent BTK inhibitors	65 (20%)	64 (20%)

(Table 1 continues in next column)

	PVR group (n=321)	VR group (n=318)
(Continued from previous column)		
Type of previous chronic lymphocytic leukaemia therapy		
Covalent BTK inhibitors	256 (80%)	254 (80%)
Ibrutinib	168/256 (66%)	175/254 (69%)
Acalabrutinib	64/256 (25%)	57/254 (22%)
Zanubrutinib	38/256 (15%)	39/254 (15%)
Other‡‡	23/256 (9%)	20/254 (8%)
Anti-CD20	219 (68%)	210 (66%)
Chemotherapy	213 (66%)	208 (65%)
Other§§	75 (23%)	76 (24%)

Data are median (IQR) or n (%). BTK=Bruton tyrosine kinase. CAR=chimeric antigen receptor. ECOG=Eastern Cooperative Oncology Group. PVR=pirtobrutinib plus venetoclax-rituximab. VR=venetoclax-rituximab. *Other includes American Indian or Alaska Native (n=0 in PVR group; n=0 in VR group), Black or African American (n=5 in PVR group; n=7 in VR group), Native Hawaiian or Other Pacific Islander (n=0 in PVR group; n=0 in VR group), other race (n=3 in PVR group; n=3 in VR group), and not reported or unknown (n=9 in PVR group; n=8 in VR group). †Defined as the time between initial diagnosis of chronic lymphocytic leukaemia (including small lymphocytic lymphoma) and study entry. ‡Summarised for patients with chronic lymphocytic leukaemia (not including small lymphocytic lymphoma; n=293 in both groups). §Determined by measurement of nodal target lesion (ie, lymph node). ¶Tested by a central laboratory. Reasons for missing data include lack of sample collection, samples received outside of stability limits, inadequate samples, and samples failing the testing process or yielding indeterminate results, among other reasons. Additionally, for patients in China, only data on del(17p) status were available. ||Associated with high risk. **Defined as three or more chromosomal abnormalities. ††Based on Electronic Data Capture software. ‡‡Including investigational drugs and orelabrutinib. §§Including other systemic therapy (n=67 in PVR group; n=72 in VR group; includes PI3K inhibitors, steroids, immunomodulatory drugs, other immunotherapies excluding anti-CD20 agents, other molecular pathway or small-molecule inhibitors, and investigational therapies as part of a clinical trial); stem-cell transplantation (n=3 autologous and n=4 allogeneic in PVR group; n=1 autologous and n=2 allogeneic in VR group); other transplantation (n=1 in PVR group; n=0 in VR group); and CAR T-cell therapy (n=0 in PVR group; n=1 in VR group).

Table 1: Baseline characteristics of the intention-to-treat population

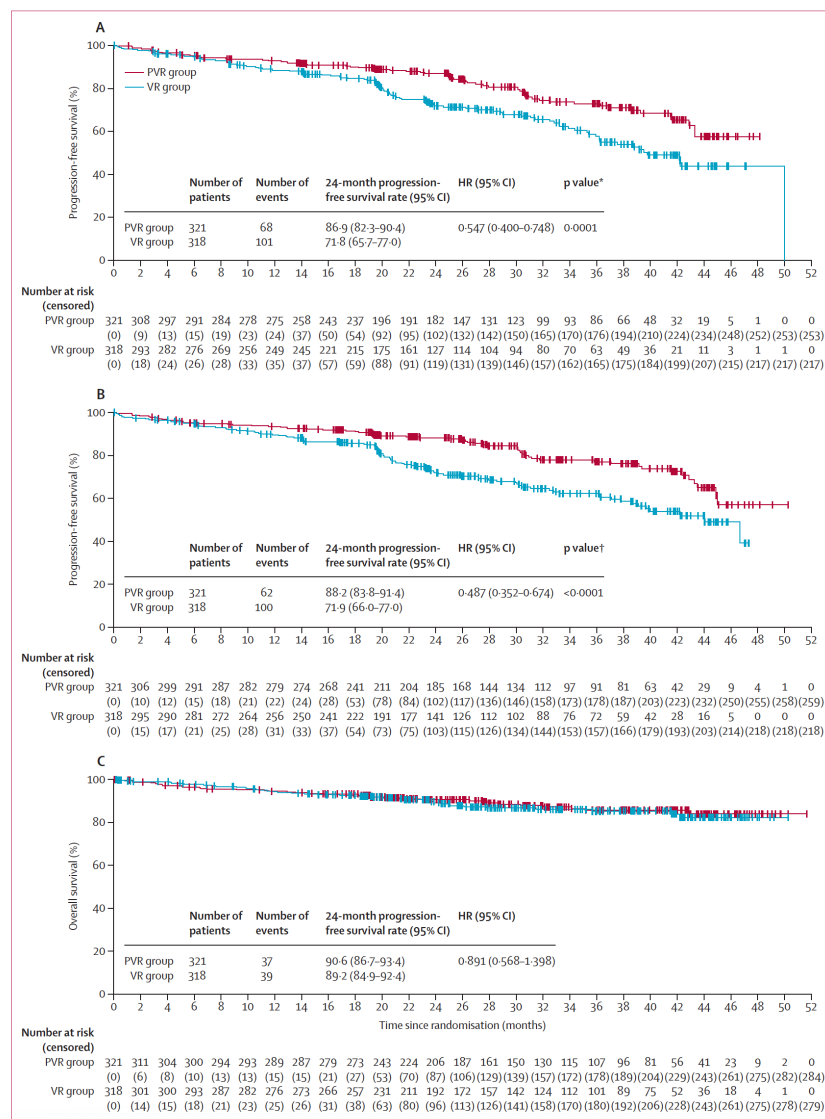
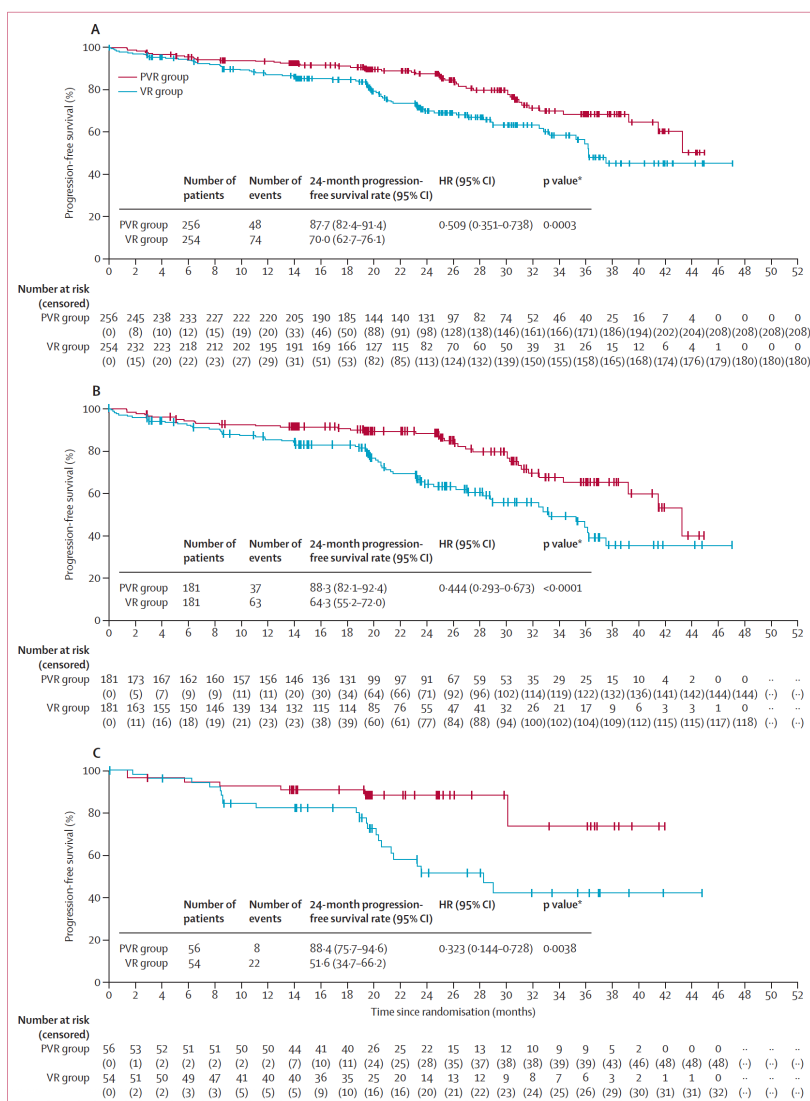


Figure 2: Progression-free survival and overall survival in the intention-to-treat population

Kaplan-Meier estimates, in the intention-to-treat population, of IRC-assessed progression-free survival (A), investigator-assessed progression-free survival (B), and overall survival (C). Two-sided p values are based on the stratified log-rank test, stratified by previous exposure to BTK inhibitors and del(17p) status. BTK=Bruton tyrosine kinase. HR=hazard ratio. IRC=independent review committee. ITT=intention-to-treat. PVR=pirtobrutinib plus venetoclax-rituximab. VR=venetoclax-rituximab. *The prespecified p value boundary for this analysis was 0.03104. †This p value is nominal.



(Figure 3 continues on next page)

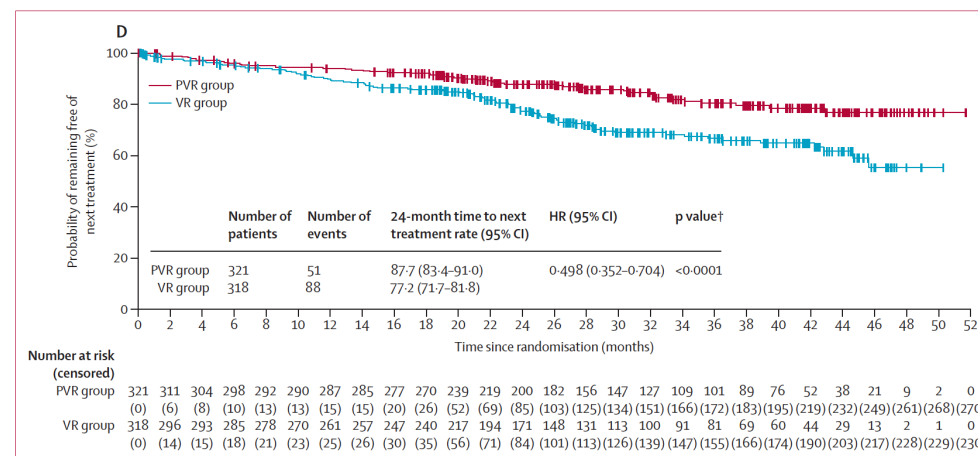


Figure 3: Progression-free survival in patients with previous exposure to covalent BTK inhibitors and time to next treatment

Kaplan-Meier estimates of IRC-assessed progression-free survival in patients with previous exposure to covalent BTK inhibitors (A), IRC-assessed progression-free survival in patients who discontinued a previous covalent BTK inhibitor owing to progressive disease (B), IRC-assessed progression-free survival in patients who received only one previous line of therapy, which was a covalent BTK inhibitor that was discontinued owing to progressive disease (C), and time to next treatment (D). BTK=Bruton tyrosine kinase. IRC=independent review committee. PVR=pirtobrutinib plus venetoclax-rituximab. VR=venetoclax-rituximab. *Stratified by del(17p) status and reported as a nominal value. †Stratified by previous exposure to covalent BTK inhibitor and del(17p) status, and reported as a nominal value.

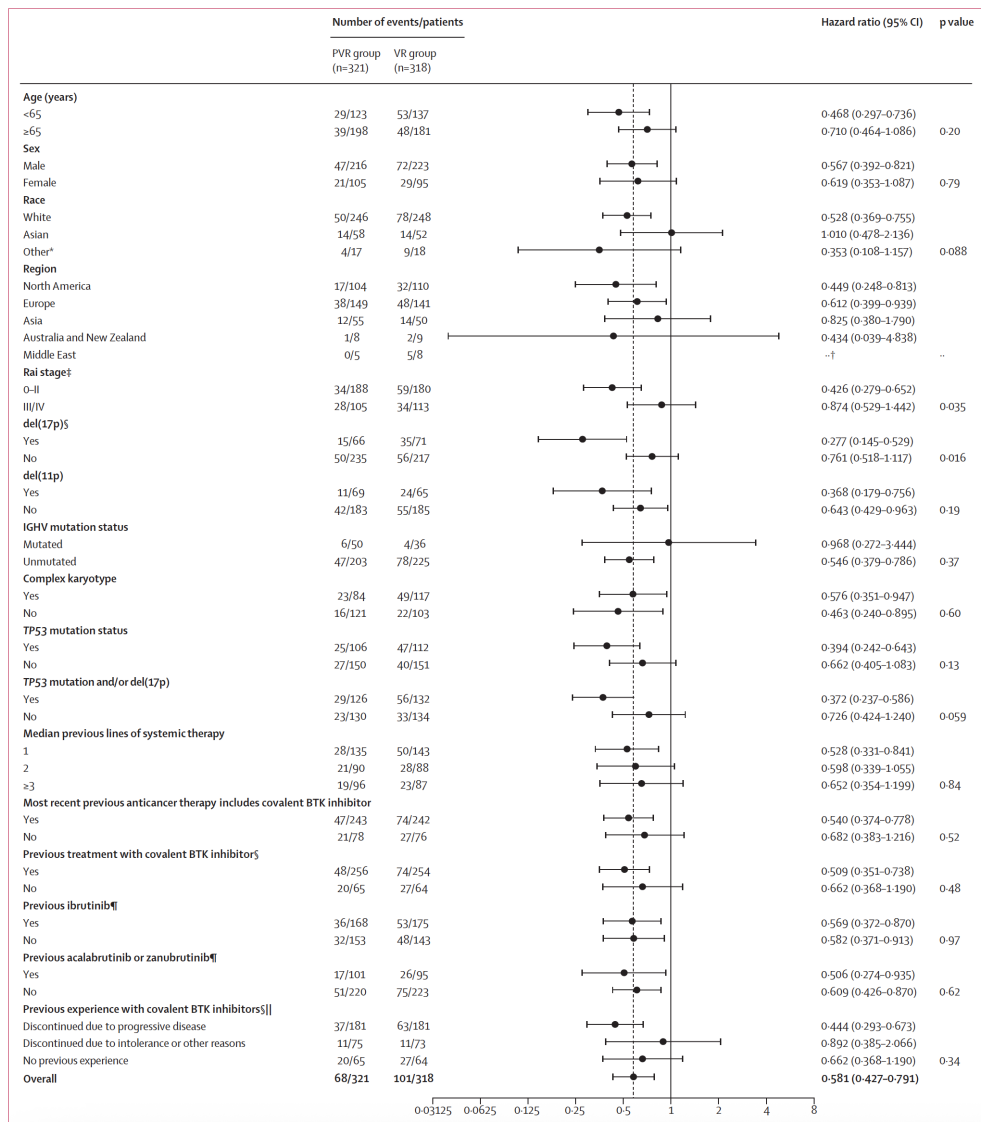


Figure 4: Progression-free survival subgroup analysis

Forest plots showing subgroup analyses of IRC-assessed progression-free survival in the intention-to-treat population. The HR represents the estimated treatment effect within each subgroup, and the interaction p value indicates whether the treatment effect varies across subgroups. The dotted line shows the overall treatment HR and the solid line shows the reference value of HR=1. BTK=Bruton tyrosine kinase. HR=hazard ratio. IRC=independent review committee. IWRS=Interactive Web Response System. PVR=pirtobrutinib plus venetoclax-rituximab. VR=venetoclax-rituximab. *Other includes American Indian or Alaska Native, Black or African American, Native Hawaiian or Other Pacific Islander, other race, and not reported or unknown. †For the Middle East region, HR and 95% CI are not estimable as no events were observed in the PVR group. ‡Summarised for patients with chronic lymphocytic leukaemia (not including small lymphocytic lymphoma). §The stratified Cox proportional hazards model was applied only to the indicated subgroups, in which del(17p) analysis was stratified by previous exposure to covalent BTK inhibitors (as per IWRS) and the analysis by previous experience with BTK inhibitors was stratified by del(17p) status (as per IWRS). ¶Previous exposure to ibrutinib and either zanubrutinib or acalabrutinib are not mutually exclusive; patients who received both ibrutinib and either zanubrutinib or acalabrutinib (n=30 in the PVR group; n=31 in the VR group) are counted in both categories. ||Based on Electronic Capture Data software.

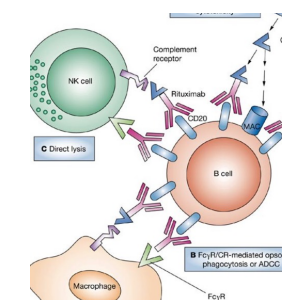
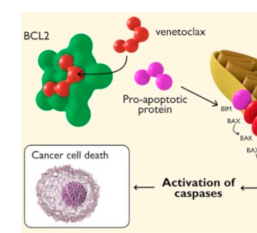
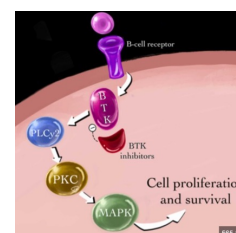
	PVR group (n=316)		VR group (n=311)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Treatment-emergent adverse events present in at least 15% of patients in either group by preferred term				
Any treatment-emergent adverse events	315 (100%)	249 (79%)	305 (98%)	227 (73%)
Diarrhoea	106 (34%)	6 (2%)	110 (35%)	5 (2%)
Neutropenia	100 (32%)	86 (27%)	90 (29%)	79 (25%)
COVID-19	98 (31%)	17 (5%)	80 (26%)	12 (4%)
Neutrophil count decreased	98 (31%)	75 (24%)	82 (26%)	60 (19%)
Anaemia	70 (22%)	20 (6%)	78 (25%)	33 (11%)
Cough	69 (22%)	2 (1%)	67 (22%)	0
Upper respiratory tract infection	69 (22%)	5 (2%)	64 (21%)	6 (2%)
Nausea	67 (21%)	0	78 (25%)	3 (1%)
Pyrexia	60 (19%)	7 (2%)	53 (17%)	4 (1%)
Pneumonia	56 (18%)	35 (11%)	46 (15%)	23 (7%)
Platelet count decreased	53 (17%)	17 (5%)	48 (15%)	15 (5%)
Infusion-related reaction	49 (16%)	2 (1%)	36 (12%)	1 (<1%)
Fatigue	37 (12%)	4 (1%)	50 (16%)	6 (2%)
Adverse events of special interest				
Any adverse events of special interest	299 (95%)	215 (68%)	281 (90%)	184 (59%)
Infection*	249 (79%)	107 (34%)	224 (72%)	72 (23%)
Infection without COVID-19†	224 (71%)	90 (28%)	197 (63%)	63 (20%)
Neutropenia‡	194 (61%)	159 (50%)	168 (54%)	136 (44%)
Thrombocytopenia§	84 (27%)	31 (10%)	84 (27%)	34 (11%)
Bleeding	82 (26%)	9 (3%)	44 (14%)	8 (3%)
Haemorrhage¶	45 (14%)	9 (3%)	33 (11%)	8 (3%)
Bruising	40 (13%)	0	16 (5%)	0
Petechiae and purpura	12 (4%)	0	1 (<1%)	0
Anaemia**	75 (24%)	20 (6%)	80 (26%)	34 (11%)
Atrial fibrillation and atrial flutter	11 (3%)	6 (2%)	8 (3%)	3 (1%)

PVR=pirtobrutinib plus venetoclax-rituximab. VR=venetoclax-rituximab. *Includes all preferred terms indicating infection and including COVID-19 disease. †Includes all preferred terms indicating infection. ‡Includes neutropenia, neutrophil count decreased, febrile neutropenia, neutropenic infection, agranulocytosis, granulocytopenia, and neutropenic sepsis. §Includes thrombocytopenia and platelet count decreased. ¶Includes all preferred terms indicating haemorrhage and haematoma, epistaxis, haematuria, intermenstrual bleeding, haemarthrosis, haemoptysis, haematospermia, blood urine present, haematochezia, and bleeding varicose vein. ||Includes contusion, ecchymosis, and increased tendency to bruise. **Includes anaemia, iron deficiency anaemia, haemoglobin decreased, normocytic anaemia, aplasia pure red cell, and microcytic anaemia.

Table 2: Treatment-emergent adverse events in the safety population

Implications of all the available evidence

These results support pirtobrutinib plus VR (PVR) as an effective, well tolerated, fixed-duration treatment option for patients with previously treated chronic lymphocytic leukaemia, regardless of previous exposure to covalent BTK inhibitors. To our knowledge, these data form the first randomised, phase 3 evidence for a fixed-duration regimen including a BTK inhibitor in this setting, supporting PVR as a potential new standard of care, particularly for patients who have previously been treated with a covalent BTK inhibitor.

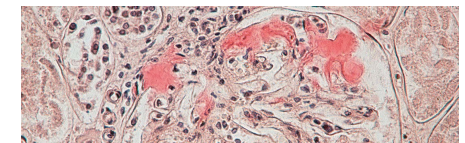
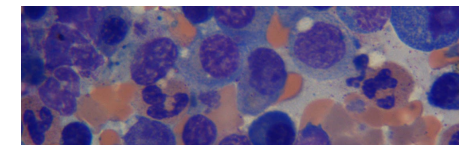
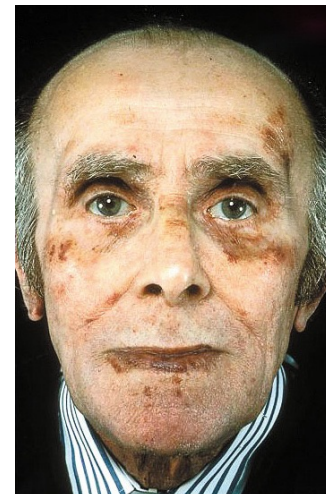
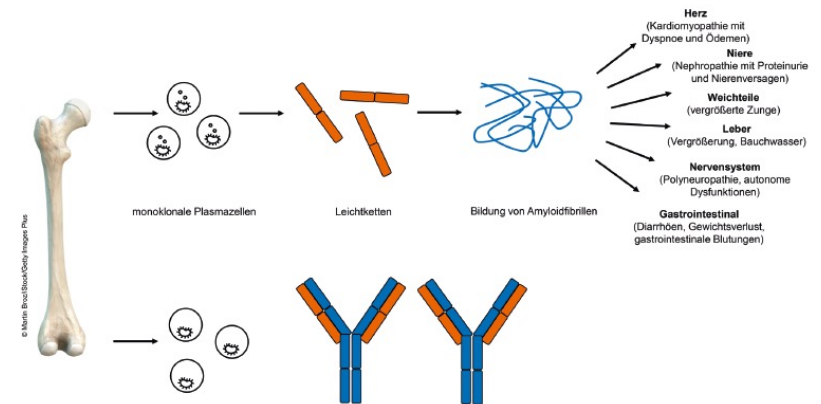


Die **Leichtketten-AL-Amyloidose** (kurz AL-Amyloidose) ist eine seltene, aber potenziell lebensbedrohliche **Proteinfehlfaltungskrankheit**. Sie entsteht durch veränderte Antikörperbestandteile (freie Leichtketten), die sich als unlösliche Ablagerungen (Amyloid) in Organen festsetzen.

Ursache und Entstehung

Auslöser ist eine Fehlfunktion bestimmter Knochenmarkszellen, meist der **Plasmazellen**.

- **Gesunder Zustand:** Plasmazellen produzieren intakte Antikörper (Immunglobuline) zur Infektabwehr.
- **Krankhafter Zustand:** Ein genetisch veränderter Zellklon produziert unkontrolliert strukturell defekte **Leichtketten** (Typ Kappa oder Lambda).
- **Die Folge:** Diese freien Leichtketten zirkulieren im Blut, verknäueln sich zu unlöslichen Fäden (Fibrillen) und lagern sich im Gewebe ab. Der Körper kann diese Ablagerungen kaum selbst abbauen



TTR is made in liver. Life without TTR is no problem

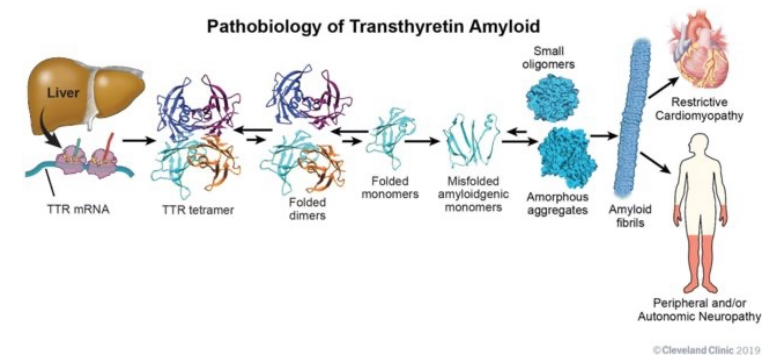
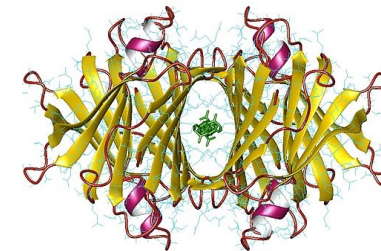
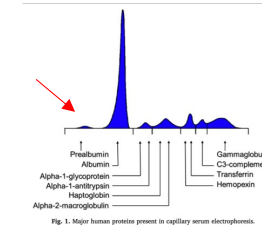
Transthyretin (TTR) ist ein wichtiges Transportprotein im Körper, das vor allem Schilddrüsenhormone und Vitamin A transportiert. Wenn dieses Eiweiß instabil wird und zerfällt, kann es verklumpen und sich in Organen ablagern. Dies führt zu schweren Krankheiten, die als Transthyretin-Amyloidosen (ATTR) bezeichnet werden.

Funktionen und Eigenschaften

Bildung: Wird hauptsächlich in der Leber und im Gehirn (Plexus choroideus) hergestellt.

Aufbau: Besteht aus vier gleichen Teilen (einem Tetramer).

Früherer Name: Ist auch unter dem Begriff Präalbumin (Thyroxin-bindendes Präalbumin) bekannt.



Dara-CyBorD ist eine medizinische **Kombinationstherapie**, die vor allem zur Behandlung der systemischen **Leichtketten-Amyloidose (AL-Amyloidose)** und teilweise bei multiplem Myelom eingesetzt wird. Sie verbindet den Antikörper Daratumumab mit drei klassischen Chemotherapie- und Medikamentenwirkstoffen.

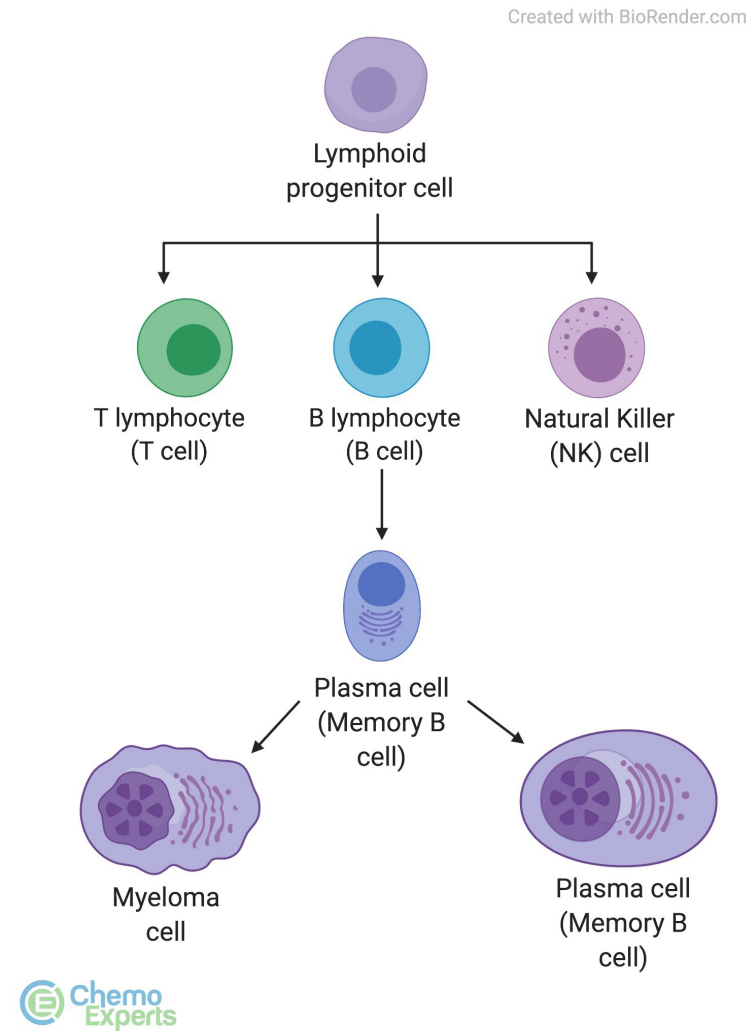
Bestandteile der Kombination

Dara: Daratumumab (ein zielgerichteter Antikörper, der die Krankheitszellen markiert ie CD38)

Cy: Cyclophosphamid (ein Chemotherapeutikum)

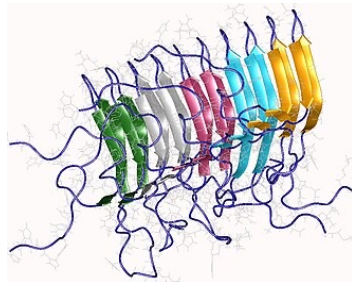
Bor: Bortezomib (ein Proteasom-Inhibitor)

D: Dexamethason (ein Kortisonpräparat zur Entzündungshemmung und Wachstumshemmung)

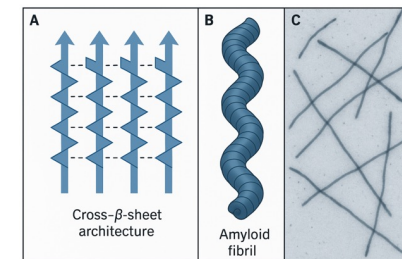


Systemic light chain and transthyretin amyloidosis— treatment advancements and future directions

Once rapidly fatal, neglected, and orphan diseases without approved therapeutic options, systemic amyloidoses are now highly treatable. Basic scientific discoveries regarding the molecular mechanisms of transthyretin misfolding and aggregation have driven the development of drugs for the treatment of transthyretin (ATTR) amyloidosis, with six novel therapies approved since 2018. The combination of daratumumab, cyclophosphamide, bortezomib, and dexamethasone was approved for the treatment of light chain (AL) amyloidosis in 2021. Since then, highly effective immunotherapies, such as bispecific T-cell engagers, have been tested in clinical trials in patients with relapsed AL amyloidosis, with unprecedented efficacy. Thus, suspicion of systemic amyloidosis should be raised early in individuals with a suggestive clinical presentation, followed by rapid tissue diagnosis, with appropriate protein typing and prompt commencement of active therapy. These rapid and exciting therapeutic advancements set the stage for this Review on the epidemiology, pathophysiology, and diagnosis of systemic amyloidosis. Through the lens of the molecular mechanisms underlying amyloidosis pathogenesis, we will focus on approved and investigational therapies. We also discuss future directions and challenges concerning a cure for patients with AL or ATTR amyloidosis.



Amyloid-Fibrillen bestehen im Wesentlichen aus β -Faltblättern (beta pleated sheets). Das Hauptmerkmal und die bestimmende Struktur aller Amyloid-Fasern ist die sogenannte **Cross- β -Struktur (Kreuz- β -Struktur).**



	AL	ATTRwt	ATTRv	Tests
Cardiovascular				
Congestive HF (dyspnoea, pleural effusions, leg oedema, ascites, etc)	X	X	X	ECG; TTE with strain*; NT-proBNP or BNP; troponin T; lipid panel; cardiac MRI; Holter monitoring; cardiac scintigraphy with DPD or PYP†; right heart catheterisation with RV endomyocardial biopsies
Arrhythmia (AF or atrial flutter, VT)	X	X	X	As above
Fatigue and exertional dyspnoea	X	X	X	As above
OH, syncope‡	X	X	X	As above
Progressive decline in blood pressure, or need to taper off anti-hypertensive medications over time‡	X	X	X	As above
Inability to tolerate standard HF therapies (β blockers, ACE inhibitors, ARBs, ARNIs)	X	X	X	As above
Sudden onset, often severe hyperlipidaemia§	X	..	..	As above
Stroke or cardiovascular ischemic events (TIAs, NSTEMI)	X	X	X	As above
Nervous				
Dysaesthesia, allodynia (small fibre neuropathy)	X	..	X	EMG; autonomic tests
Autonomic dysfunction (ie, OH)	X	..	X	As above
Gastrointestinal				
Unintentional weight loss	X	..	..	Liver function tests, including alkaline phosphatase and bilirubin; gastrointestinal endoscopies and biopsies; liver fibroscan
Taste change or loss of taste	X	..	..	As above
Early satiety‡	X	..	..	As above
Dyspepsia, nausea, emesis	X	..	..	As above
Severe, persistent diarrhoea¶	X	..	X	As above plus exocrine pancreatic enzyme deficiency testing
Hepatomegaly without imaging defects	X	..	..	As above
Muscular-skeleton				
Bilateral carpal tunnel syndrome	X	X	X	EMG; spinal MRI
Spinal stenosis, pseudo-claudication	..	X	X	As above
Bicep tendon rupture	..	X	..	As above
Other tendinopathies	..	X	..	As above
Kidney				
Proteinuria, often in the nephrotic range	X	..	..	Complete metabolic panel; urine protein–creatinine ratio; urine albumin–creatinine ratio; UPEP plus IFE
Peripheral oedema, ascites, anasarca	X	..	..	As above
Progressive renal failure	X	..	X	As above
Skin and soft tissue				
Purpura on the face or neck	X	..	..	CBC, PT, or INR, aPTT, Factor X concentration, monoclonal protein studies (SPEP plus IFE, UPEP plus IFE, and serum FLC)
Macroglossia	X	..	..	As above
Muscle pseudo-hypertrophy (shoulder pad)	X	..	..	As above
Hoarseness	X	..	..	As above

(Table 1 continues on next page)

	AL	ATTRwt	ATTRv	Tests
(Continued from previous page)				
Haematology				
Anaemia	X	..	..	aPTT; PT or INR; factor X concentration; iron studies; monoclonal protein studies (SPEP plus IFE, UPEP plus IFE, and serum FLC); bone marrow aspirate or biopsy for morphological review; flow cytometry analysis; FISH for plasma cell disorder abnormalities; Congo red stain
Other cytopenia	X	..	..	As above
Venous thrombosis	X	..	..	As above
Bleeding or easy bruising	X	..	..	As above
Endocrine				
Hypothyroidism§	X	..	..	TSH and free thyroxine
Genitourinary				
Erectile dysfunction, vaginal dryness	X	X	X	Free and total testosterone

ACE=angiotensin converting enzyme. AF=atrial fibrillation. AL=light chain. aPTT=activated prothrombin time. ARB=angiotensin receptor blocker. ARNI=angiotensin receptor neprilysin inhibitor. ATTR=transthyretin amyloidosis. ATTRv=transthyretin amyloidosis variant. ATTRwt=transthyretin amyloidosis wild-type. CBC=cell blood count. DPD=3,3'-diphosphono-1,2'-propanodicarboxylic acid. ECG=electrocardiography. EMG=electromyography. FISH=fluorescence in situ hybridisation. FLC=free light chains. HF=heart failure. IFE=immunofixation. INR=international normalised ratio. NSTEMI=non-ST-segment elevation myocardial infarction. OH=orthostatic hypotension. PT=prothrombin time. PYP=³³mTc-labelled pyrophosphate. RV=right ventricle. SPEP=serum protein electrophoresis. TIAs=transient ischaemic attacks. TSH=thyroid stimulating hormone. TTE=transthoracic echocardiography. UPEP=urine protein electrophoresis. VT=ventricular tachycardia. * Cardiac MRI is more sensitive and specific than TTE and should be considered before excluding amyloidosis based on TTE. †For patients in whom a plasma cell disorder has been ruled out and ATTR is suspected. ‡Typically secondary to autonomic dysfunction. §Typically secondary to nephrotic syndrome. ¶Diarrhoea can be secondary to autonomic dysfunction or, more rarely, pancreatic insufficiency. Constipation can also occur secondary to autonomic dysfunction. ||A 24-h urine collection is key to accurately ascertain proteinuria and the presence or absence of a monoclonal spike.

Table 1: Common symptoms, signs, and laboratory or imaging findings suggesting AL, ATTRwt, or ATTRv amyloidosis, and testing (clinical red flags)

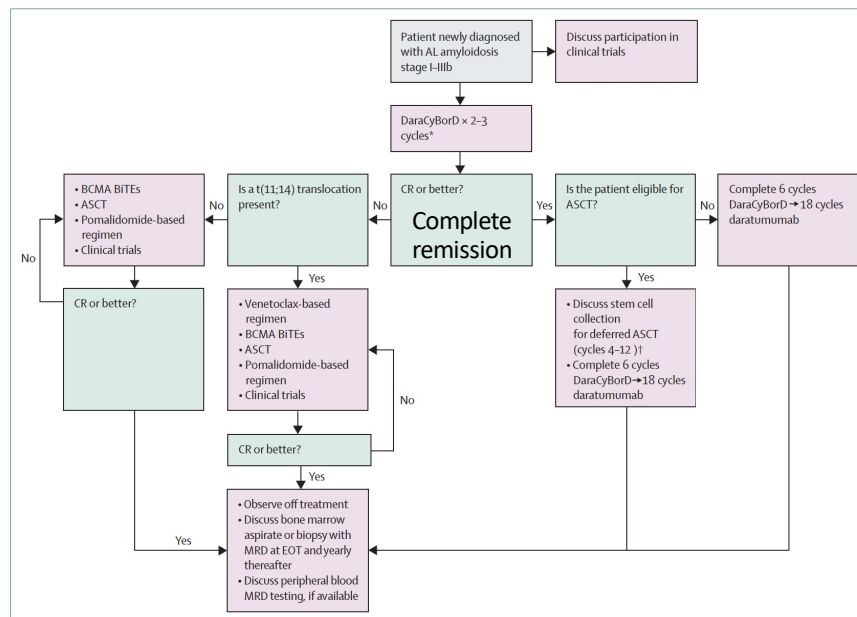


Figure 3: Treatment approach for patients who are newly diagnosed with AL amyloidosis

We encourage discussion of participation in clinical trials with every patient. Our approach is to typically use DaraCyBorD for all patients, regardless of staging and transplantation eligibility, unless there are obvious patient-related contraindications or preferences. The goal of therapy is to reach complete haematological remission by cycle two. If this does not occur, the next treatment approach is determined by the presence of a t(11;14) translocation. If present, a venetoclax-based regimen is preferred, if the drug can be secured. If not present or venetoclax is not available, we recommend considering stem-cell transplantation in patients eligible, or BCMA-targeting agents, or pomalidomide-based treatment. For patients eligible for stem-cell transplantation that have complete haematological remission by cycle two to four with DaraCyBorD, we recommend stem-cell collection between cycles four and 12, followed by completion of DaraCyBorD, as per the Andromeda protocol.³⁹ If possible, testing for MRD in blood or bone marrow should be done regularly. We do not recommend maintenance in patients with AL amyloidosis in a complete response. AL=light chain amyloidosis. ASCT=autologous stem-cell transplantation. BCMA=B-cell maturation antigen. BiTEs=bispecific T-cell engagers. CR=complete haematological remission. DaraCyBorD: daratumumab-cyclophosphamide-bortezomib-dexamethasone. EOT=end of treatment. MRD=minimal residual disease. *We recommend aiming for complete haematological remission by cycle two. If this goal is not reached, we recommend changing therapy by cycle three to maximise the chances of organ function preservation and survival. †Candidacy for ASCT should be reassessed regularly, because it is a dynamic assessment based on patient-related factors that might change over time.

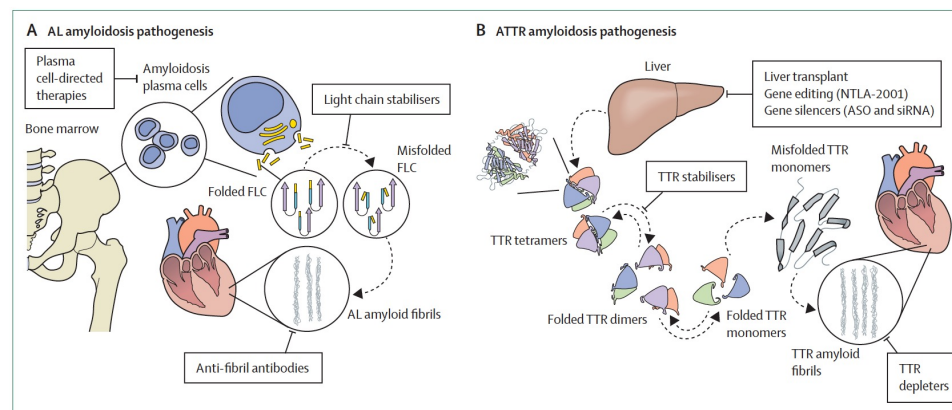


Figure 4: Pathogenesis of AL and ATTR amyloidosis

(A) Pathogenesis of AL amyloidosis from plasma cells expanding in the bone marrow through secretion of folded FLCs, misfolding of circulating FLCs, and finally, formation of AL amyloid fibril deposition in the heart and other organs. (B) Pathogenesis of ATTR amyloidosis from synthesis and secretion of TTR tetramers by the liver, TTR dimer and monomer formation, misfolding of TTR monomers leading to TTR amyloid formation, and finally, deposition in the heart and other organs. The sites of activity of approved and investigational therapies are outlined in rectangles for both disorders. AL=light chain amyloidosis. ASO=antisense oligonucleotides. ATTR=transthyretin amyloidosis. FLC=free light chains. TTR=transthyretin.

	Approval status in ATTR amyloidosis or phase of study	Chemical structure and mechanism of action	Dose and route	Efficacy primary outcomes	Noticeable treatment-related adverse events
TTR stabilisers					
Tafamidis	US FDA approved for ATTRv and ATTRwt CA and PN; EMA approved for ATTRv PN	Benxoxazole derivative of NSAID; binds to thyroxine binding site on TTR, leading to tetramer stabilisation	80 mg orally daily (vyndaqel); 61 mg orally daily (vyndamax)	In ATTR CA, compared with placebo at 30 months: 13% absolute risk reduction in mortality and 32% relative risk reduction in cardiovascular-related admissions to hospital	Minimal; interaction with high-dose rosuvastatin ^{140,148}
Acoramidis	EMA and FDA approved for ATTRv and ATTRwt CA	Thr119Met mimicker; leads to the formation of hydrogen bonds between Ser117 residues in each TTR monomer, causing tetramer stabilisation	800 mg orally twice daily	In ATTR CA, compared with placebo at 30 months: 1.8 win ratio in a 4-step hierarchical analysis of all-cause mortality, cardiovascular admissions to hospital, change in baseline NT-proBNP, and change in baseline 6-min walk test	Minimal ^{149,150}
Diflunisal	Off-label use in ATTRv and ATTRwt CA and PN; ongoing phase 2/3 studies	NSAID; binds to thyroxine binding site on TTR, leading to tetramer stabilisation	250 mg orally twice daily	In ATTR PN, compared with placebo at 2 years: 16.3 point reduction in the rate of progression of neurological impairment (NIS+7 nerve test score) and 6.1 point improvement in QOL (SF-36 physical component)	Cardiovascular thrombotic events; gastrointestinal bleeding; acute kidney injury; fluid retention ¹⁵¹
TTR gene silencers					
Inotersen	FDA and EMA approved for ATTRv PN	2'-O-methoxyethyl-modified phosphorothioate ASO; binds to TTR mRNA in the liver, leading to RNaseH-mediated TTR mRNA degradation	300 mg subcutaneously once weekly; vitamin A 3000 IU daily supplementation	In ATTRv PN, compared with placebo at 15 months: 19.7 point reduction in the progression of neurological impairment (NIS+7 nerve test score) and 11.7 point improvement in QOL (Norfolk QOL-DN score)	Thrombocytopenia (severe and sudden in 3% of patients); glomerulonephritis (3% of patients) ¹⁵²
Eplontersen	FDA and EMA approved for ATTRv PN; phase 3 trial in ATTR CA ongoing	GalNAc-conjugated, inotersen-derived ASO, enhancing liver uptake; similar mechanism of action to inotersen	45 mg subcutaneously every 4 weeks; vitamin A 3000 IU daily supplementation	In ATTRv PN, compared with placebo at 66 weeks: 24.8 point reduction in the progression of neurological impairment (NIS+7 nerve test score) and 19.7 point improvement in QOL (Norfolk QOL-DN score); in ATTR CA: primary endpoint is a composite of cardiovascular mortality and frequency of cardiovascular clinical events at 140 weeks	Minimal ¹⁵³
Patisiran	FDA and EMA approved for ATTRv PN; phase 3 trial completed in ATTR CA—approval declined	Small interfering RNA, targeting the 3' untranslated region of TTR mRNA in the liver; leads to TTR mRNA degradation via cytoplasmic Dicer to form the RNA-RNA-induced silencing complex	0.3 mg/kg intravenous infusion every 3 weeks (max dose 30 mg); vitamin A 3000 IU daily supplementation	In ATTRv PN, compared with placebo at 18 months: 34 point reduction in neurological impairment (NIS+7) and 21.1 point improvement in QOL (Norfolk QOL-DN); in ATTR CA, compared with placebo: 14.7 m improvement in 6-min walk test and 3.7 point improvement in QOL (Kansas City Cardiomyopathy Questionnaire)	Infusion-related reactions (19% of patients) ^{154,155}
Vutrisiran	FDA approved for ATTRv PN and ATTR CA; EMA approved for ATTRv PN	GalNAc-conjugated small interfering RNA targeting TTR mRNA; causes TTR mRNA degradation via RNaseH	25 mg subcutaneously every 12 weeks; vitamin A 3000 IU daily supplementation	In ATTRv PN, compared with placebo at 18 months: 28.6 point reduction in neurological impairment (NIS+7) and 21 point improvement in QOL (Norfolk QOL-DN); in ATTR CA, compared with placebo: 0.72 HR for a composite endpoint of death from any cause and recurrent cardiovascular events	Arthralgias (11% of patients) ^{156,157}
TTR anti-fibril antibody					
ALXN-2200	Phase 3 trial in ATTR CA ongoing (NCT06183931)	Recombinant, IgG1 human monoclonal antibody targeting misfolded, soluble, and insoluble TTRwt and TTRv	Intravenously every 28 days	In ATTRv or ATTRwt CA at 48 months: all-cause mortality and cardiovascular events	Based on a phase 2 study: infusion reactions and arthralgias ¹⁵⁸
Coramitug (PRX004)	Phase 2 trial in ATTR CA completed (NCT05442047)	Human monoclonal antibody targeting misfolded TTR	Intravenously every 28 days	In ATTR CA: change in 6-min walk test and change in NT-proBNP from baseline to week 52	No apparent drug-related serious adverse events ¹⁵⁹
TTR gene editing					
NTLA-2001	Phase 3 trial ongoing in ATTR CA (NCT06128629)	Lipid nanoparticle encapsulated gRNA targeting TTR and Cas9 mRNA; leads to double strand break and non-homologous end joining of the TTR gene, leading to TTR knock out	Single intravenous infusion of NTLA-2001 (55 mg)	In ATTRv or ATTRwt CA at 18–48 months: a composite endpoint of cardiovascular mortality and cardiovascular events	Based on a phase 1 study: vitamin A deficiency ¹⁶⁰

ASO=antisense oligonucleotide. ATTR=transthyretin amyloidosis. ATTRv=transthyretin amyloidosis variant. ATTRwt=transthyretin amyloidosis wild-type. CA=amyloid cardiomyopathy. EMA=European Medicines Agency. FDA=Food and Drug Administration. HR=hazard ratio. IU=international units. NIS+7=Neuropathy Impairment Score+7. NSAID=non-steroidal anti-inflammatory drug. PN=polyneuropathy. QOL=quality of life. QOL-DN=Quality of Life in Diabetic Neuropathy score. SF-36=Short Form-36 Health Survey. TTR=transthyretin.

Table 2: Results for ATTR therapies from completed or ongoing phase 3 clinical studies

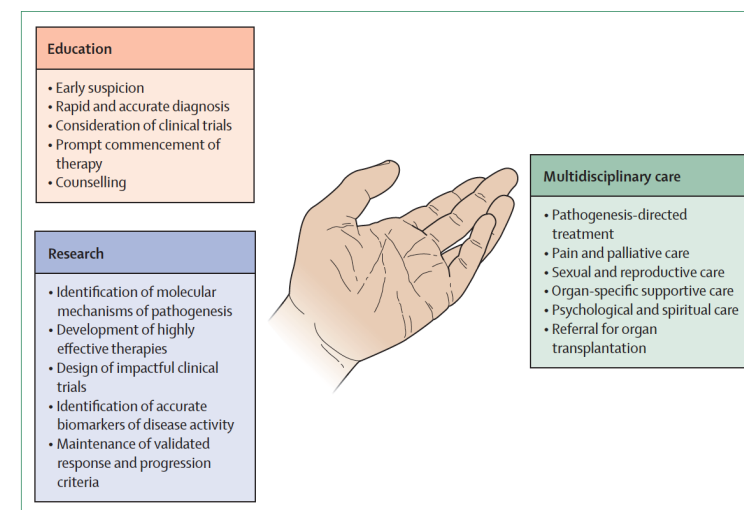


Figure 5: Improving outcomes for patients with amyloidosis

Education, multidisciplinary care, and research are the cornerstones of efforts to improve the lives of patients with amyloidosis.

Conclusions

Over the past decade, remarkable advancements in the treatment of AL and ATTR amyloidosis have been accomplished. We look with optimism at what lies ahead for the future. Commitment to care and investment in research are essential to tackling amyloidosis (figure 5). The overarching goal is to develop screening tests for early detection that can be implemented globally; to discover highly effective, laboratory-based treatments that target the intrinsic vulnerabilities of these diseases with curative intent; and to improve access to multidisciplinary care across racial and socioeconomic differences.



The genomic identity of early smallpox in South America

Smallpox was a major driver of population collapse in the Americas after European contact, yet the genetic identity of the causal strains remains unknown. Here, we report the first ancient smallpox genomes in the Americas, dating to approximately 1492–1631 common era (CE), recovered from two Inca-Colonial individuals in northern Chile. These genomes form a now-extinct lineage that diverged around 1296 CE, after the splitting of early medieval European strains but before the emergence of modern variola lineages, providing direct molecular evidence for smallpox introduction through European colonization. We further identify a constant tempo of gene inactivation until the late 16th century, followed by a phase of constraint and a subsequent rebound in substitution rates, linking variola virus evolution to major shifts in human demography and epidemiology.

For years he'd be found in a stupor, until a fall led to a surprising diagnosis



Heidi Anderson came home to find her husband, Phil, on the front steps in a stupor. His son had just called him and then alerted Heidi to his disturbing demeanor, but Phil Anderson didn't remember the call.

On another night, when Phil returned from walking their dog, he seemed unsteady and in a "trancelike state," Heidi said. He told her he had fallen because his shoes were too big.

Phil's zombielike spells became more frequent, coming on suddenly and usually in the evening. Heidi wondered if Phil, then in his late 50s, was developing dementia. She saw a therapist to learn how to cope.

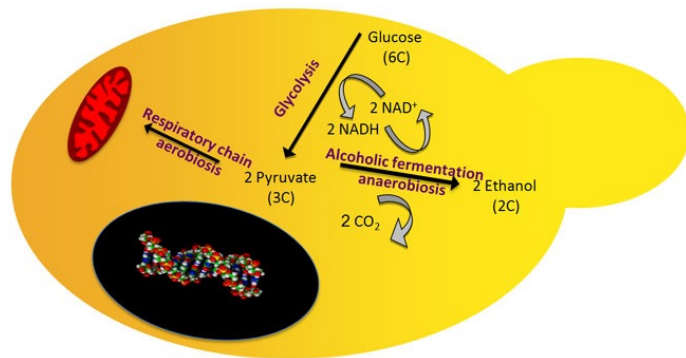
A neurologist ordered a brain MRI, which found that Phil had had some prior small strokes but didn't explain his recent altered consciousness. A second brain scan, a brain electrical activity test, a sleep study and a six-hour psychological evaluation provided no answers.

A test of the electrical activity of Phil's heart and an ultrasound of the main artery to his brain were normal. Images of his heart suggested a hole between the upper chambers, known as a patent foramen ovale. The common condition typically doesn't cause symptoms, but it can increase the risk of strokes.

One night in August 2020, when Heidi came back from walking their dogs, Phil was on the porch in a haze. “He was just staring out into space,” she said. She ushered him inside, where he staggered and hit the coffee table.

At the ER, a blood test yielded a startling result: Phil’s ethanol level was 363 milligrams per deciliter, equivalent to a blood alcohol content of .363%, more than four times the legal limit for driving. But Phil was merely a casual drinker. And he was scheduled to have prostate-reduction surgery in a few days. In preparation, he swore he hadn’t had a drop to drink.

Elizabeth O’Brien, then in just her second month as a full-fledged ER doctor, encouraged Phil to open up about any alcohol abuse and told him about treatment options. When he repeatedly denied drinking, O’Brien wondered if he might be telling the truth. She considered another explanation, she recalled in an interview.



O’Brien told Phil to look into a condition gaining more acceptance in medicine: auto-brewery syndrome. In the condition, intestinal microbes that break down carbohydrates produce unusually high levels of ethanol, leaving people in a drunken state.

Their guts essentially brew their own beer.



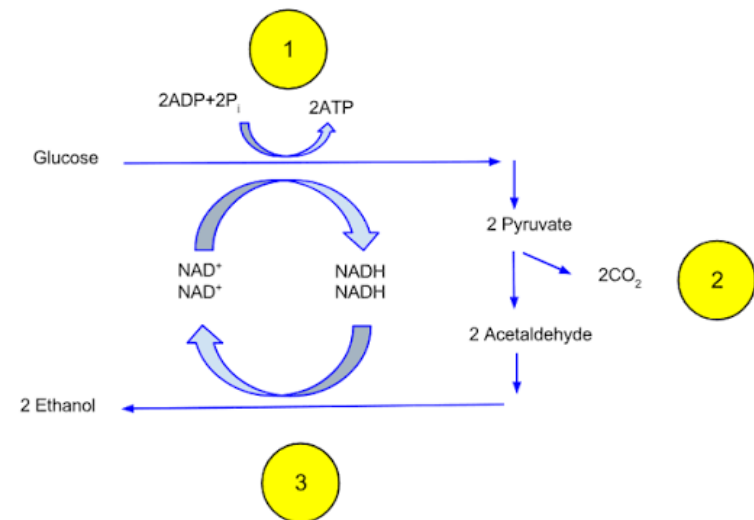
Das Eigenbrauer Syndrom

Hefe wandelt Pyruvat (Brenztraubensäure) in einem zweistufigen Prozess, der als alkoholische Gärung bezeichnet wird, in **Ethanol** und Kohlenstoffdioxid um.

Der Ablauf der Umwandlung

Schritt 1 (Abspaltung): Das Pyruvat verliert eine Carboxylgruppe als Kohlenstoffdioxid (CO_2). Es entsteht Acetaldehyd (Ethanal). Das Enzym dafür heißt **Pyruvat-Decarboxylase**.

Schritt 2 (Reduktion): Das Acetaldehyd wird zu Ethanol reduziert. Dabei wird NADH zu NAD^+ oxidiert, was die Hefe für den Energiestoffwechsel benötigt. Das Enzym dafür ist die Alkohol-Dehydrogenase



Gut microbial ethanol metabolism contributes to auto-brewery syndrome in an observational cohort

Auto-brewery syndrome (ABS) is a rarely diagnosed disorder of alcohol intoxication due to gut microbial ethanol production. Despite case reports and a small cohort study, the microbiological profiles of patients remain poorly understood. Here we conducted an observational study of 22 patients with ABS and 21 unaffected household partners. Faecal samples from individuals with ABS during a flare produced more ethanol *in vitro*, which could be reduced by antibiotic treatment. Gut microbiome analysis using metagenomics revealed an enrichment of Proteobacteria, including *Escherichia coli* and *Klebsiella pneumoniae*. Genes in metabolic pathways associated with ethanol production were enriched, including the mixed-acid fermentation pathway, heterolactic fermentation pathway and ethanolamine utilization pathway. Faecal metabolomics revealed increased acetate levels associated with ABS, which correlated with blood alcohol concentrations. Finally, one patient was treated with faecal microbiota transplantation, with positive correlations between gut microbiota composition and function, and symptoms. These findings can inform future clinical interventions for ABS.

Das **Auto-Brewery-Syndrom (ABS)** wird im Deutschen als **Eigenbrauer-Syndrom** bezeichnet. Es handelt sich um eine extrem seltene Erkrankung, bei der der Magen-Darm-Trakt des Körpers **selbstständig Ethanol (Alkohol) produziert**, indem er Kohlenhydrate aus der Nahrung fermentiert. Betroffene zeigen typische Anzeichen eines Rausches und weisen messbaren Atem- oder Blutalkohol auf, obwohl sie **keinen Alkohol konsumiert** haben

Alcohol Fermentation

