

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

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

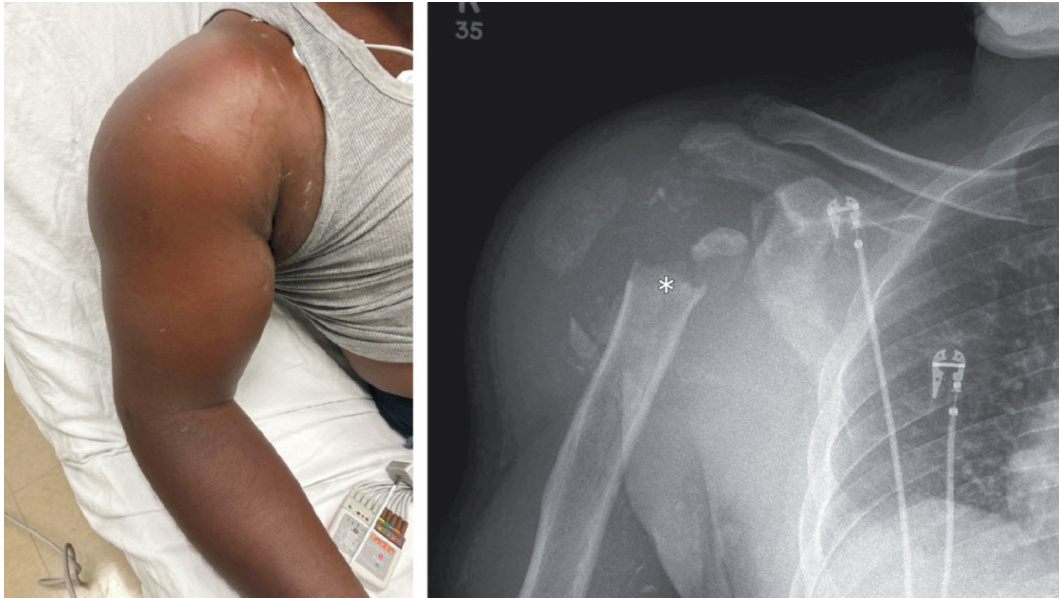
Usually every Wednesday 17:00 - 18:00



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!](#)



Milwaukee shoulder syndrome is a destructive arthropathy 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.

A 45-year-old man presented 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. An MRI showed destructive arthropathy of the glenohumeral joint associated with a large effusion, free-floating calcific fragments, and full-thickness tears of the rotator cuff tendons. Analysis of the synovial fluid revealed hemorrhagic, noninflammatory fluid with negative cultures and no visible crystals. What is the most likely diagnosis?

Avascular necrosis of the humeral head

Calcium pyrophosphate deposition disease

Joint sarcoma

☒ Milwaukee shoulder syndrome

Rotator cuff tear arthropathy

Das Milwaukee-Schultersyndrom (MSS) ist eine seltene, stark destruktive Gelenkerkrankung, die durch die Ablagerung von Kalziumhydroxylapatit-Kristallen im Schultergelenk verursacht wird. Es betrifft überwiegend ältere Frauen und ist durch Gelenkverschleiß, Knorpelschäden, Gelenkergüsse und den schnellen Verfall der Rotatorenmanschette gekennzeichnet.

Ursachen und Pathomechanismus

Die Erkrankung gehört zur Gruppe der Kalziumphosphatkristall-Arthropathien. Die genauen Auslöser sind noch nicht vollständig geklärt, aber der primäre Mechanismus umfasst Folgendes:

Freisetzung von Kalziumhydroxylapatit-Kristallen in die Gelenkflüssigkeit (Synovia).

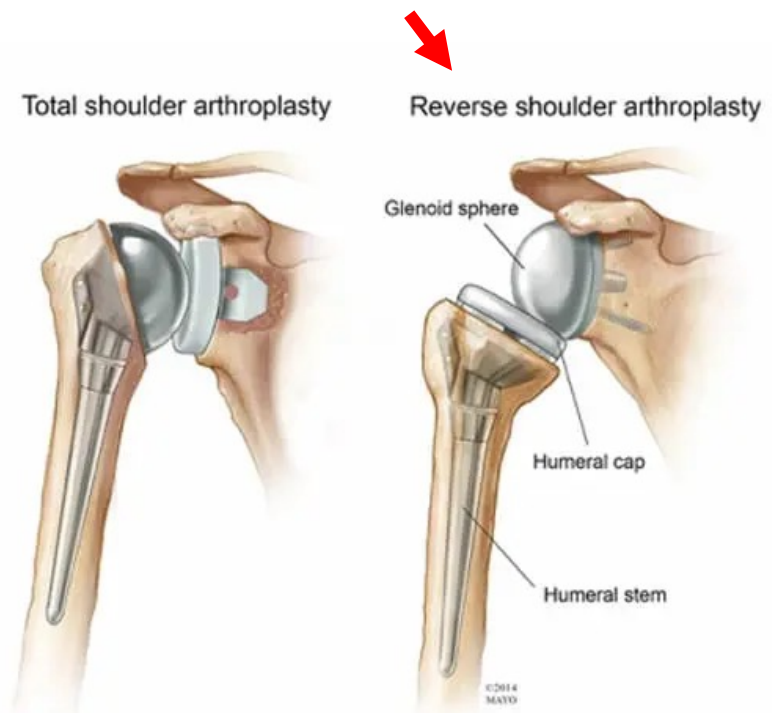
Diese Kristalle lösen eine Reaktion aus, bei der Fresszellen (Phagozyten) sogenannte Proteasen und Kollagenasen freisetzen.

Diese Enzyme führen zu einer raschen und oft unumkehrbaren Zerstörung von Gewebe, Gelenkknorpel und Sehnen.



Eine **Gelenkersatzoperation (Arthroplastik)** ist die wichtigste chirurgische Option bei einem fortgeschrittenen Milwaukee-Schulter-Syndrom, wenn konservative Therapien versagt haben. Das Milwaukee-Schulter-Syndrom ist eine seltene, rapide fortschreitende Zerstörung des Schultergelenks, die durch die Ablagerung von Calciumphosphat-Kristallen ausgelöst wird und fast immer mit einem **kompletten Riss der Rotatorenmanschette** einhergeht.

Inverser Schultergelenkersatz (Inverse Totalendoprothese / RSA): Dies ist das **Verfahren der Wahl**. Bei einer inversen Prothese werden die anatomischen Formen von Gelenkkopf und Gelenkpfanne vertauscht. Das Design verlagert den Drehpunkt des Gelenks nach innen und unten. Dadurch kann der **Deltamuskel** (die äußere Schultermuskulatur) die Funktion der zerstörten Rotatorenmanschette übernehmen. Das ermöglicht es den Betroffenen, den Arm wieder anzuheben.

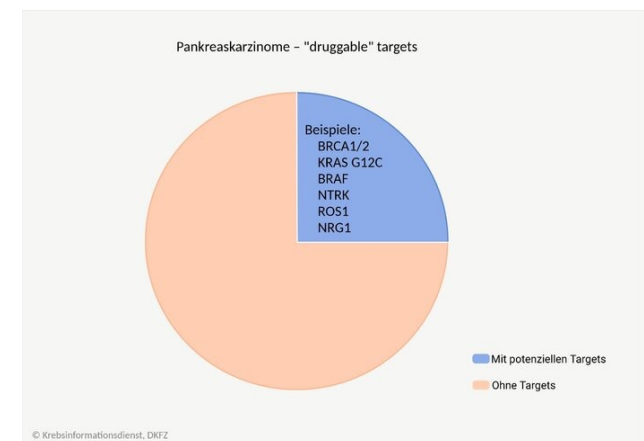
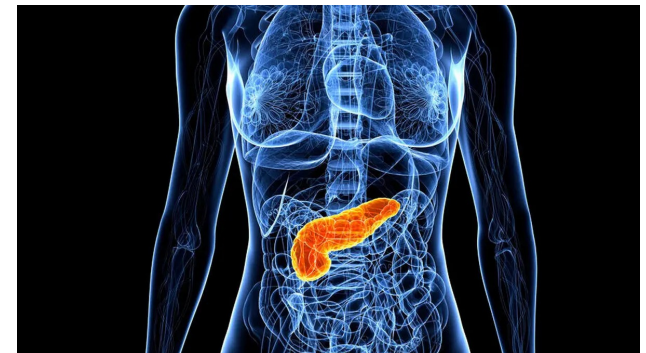


Bei über 90 % der Pankreaskarzinome (Bauchspeicheldrüsenkrebs) liegt eine Mutation im **KRAS-Gen** vor, was es zur zentralen Treibermutation macht. Sie treibt das unkontrollierte Tumorwachstum an. Lange Zeit galt KRAS als "undruggable" (nicht medikamentös angreifbar), doch neue Behandlungsansätze befinden sich in der klinischen Erprobung.

Ein vielversprechender Durchbruch bei fortgeschrittenen, KRAS-mutierten Tumoren ist der Wirkstoff **Daraxonrasib** (ein oraler RAS(ON)-Inhibitor). In aktuellen klinischen Studien konnte das Medikament bei den häufigen Mutationen wie G12D und G12V die Überlebenszeit signifikant verlängern. Für die seltenere Mutation G12C stehen zudem bereits zugelassene Inhibitoren wie Sotorasib oder Adagrasib zur Verfügung.

Ergänzend laufen neue Ansätze, wie die Erforschung von zielgerichteten Impfstoffen bei Hochrisikopatienten oder der Einsatz von Substanzen, die gezielt den Zelltod (Nekroptose) in KRAS-mutierten Zellen auslösen.

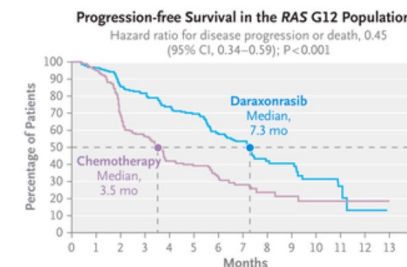
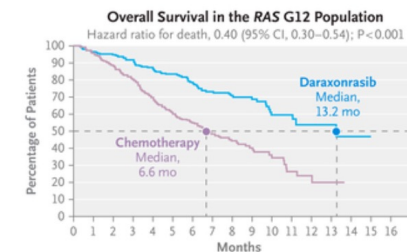
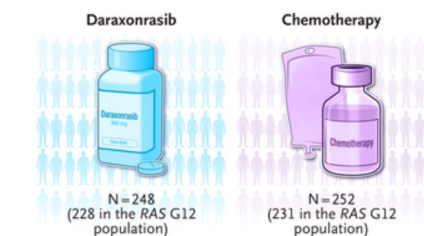
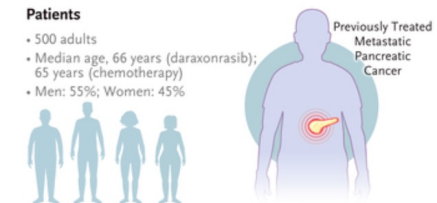
Patienten ohne KRAS-Mutation (sogenannter KRAS-Wildtyp, ca. 10 %) weisen oft andere therapierbare genetische Veränderungen auf, wie zum Beispiel *NTRK*- oder *NRG1*-Fusionen



Daraxonrasib or Chemotherapy in Previously Treated Metastatic Pancreatic Cancer

Current therapies offer limited benefit for patients with previously treated metastatic pancreatic ductal adenocarcinoma (mPDAC). **Aberrant activation of the RAS pathway is the key driver of PDAC, with oncogenic RAS mutations present in more than 90% of cases.** Daraxonrasib is an oral RAS(ON) multiselective, tri-complex inhibitor of the active guanosine triphosphate-bound state of mutant and wild-type RAS.

In this phase 3, international, open-label, randomized trial, we randomly assigned patients with previously treated mPDAC to receive daraxonrasib or chemotherapy of the investigator's choice. The dual primary end points were overall survival and progression-free survival in the subpopulation of patients with RAS G12 mutations (the RAS G12 population). Key secondary end points included **overall survival and progression-free survival** in the overall population (which included patients with RAS G12, G13, or Q61 mutations or with no RAS mutation identified) and objective response and patient-reported quality of life in the RAS G12 and overall populations. Safety was also assessed.



Oncogenic mutations of the gene family that encodes rat sarcoma virus (*RAS*) are primary drivers of PDAC that are present in more than 90% of tumors, and most of these mutations (>80%) involve substitutions at *KRAS* codon 12. These alterations result in constitutive activation of *RAS* with accumulation of the guanosine triphosphate (GTP)–bound state of *RAS*, known as *RAS*(ON), which drives aberrant signaling. Tumors lacking *RAS* mutations and other clinically actionable mutations can also be dependent on *RAS* signaling through genomic amplification or alterations in upstream or downstream components of the *RAS*–mitogen-activated protein kinase (MAPK) pathway.

Daraxonrasib is an oral, potent *RAS*(ON) multiselective, tri-complex inhibitor that binds to cyclophilin A intracellularly to form a binary complex that engages *RAS*(ON) and suppresses downstream signaling. Daraxonrasib is selective for the active state of both mutant and wild-type *RAS* across *KRAS*, *NRAS*, and *HRAS*, including variants with mutations at glycine 12 (G12), glycine 13 (G13), and glutamine 61 (Q61). In a phase 1–2 trial, daraxonrasib showed clinical activity with mainly low-grade adverse events, including rash and gastrointestinal side effects, in patients with advanced PDAC. These findings led to the phase 3 *RASolute* 302 trial, in which daraxonrasib is being compared with the investigator's choice of standard chemotherapy in patients with previously treated mPDAC. Here, we report the primary results of the *RASolute* 302 trial.

Patients

Eligible patients were at least 18 years of age, had histologically or cytologically confirmed mPDAC, and had previous disease progression after the receipt of one previous line of a fluoropyrimidine- or gemcitabine-based therapy for metastatic disease or after the receipt of neoadjuvant or adjuvant therapy if metastatic disease was diagnosed less than 6 months after the last dose of such therapy. Patients were required to have measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1; an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 (on a scale of 0 to 5, with higher scores indicating greater disability); and adequate organ function. Additional eligibility criteria included a tumor with a documented *RAS* mutational status, defined as either a nonsynonymous mutation in *KRAS*, *NRAS*, or *HRAS* at codon 12, 13, or 61 (G12, G13, or Q61), or no tumor with a *RAS* mutation identified. Patients who did not have a tumor harboring an identified *RAS* mutation but who had another actionable driver alteration were required to have received approved targeted therapy. Key exclusion criteria were known central nervous system metastases and previous *RAS*-targeted therapy. Full eligibility criteria are provided in the protocol.

Randomization and Treatment

Patients were randomly assigned in a 1:1 ratio to receive **daraxonrasib at a dose of 300 mg orally once daily** or the investigator's choice of chemotherapy (gemcitabine plus nab-paclitaxel, modified FOLFIRINOX [fluorouracil, irinotecan, leucovorin, and oxaliplatin], FOLFOX [fluorouracil, leucovorin, and oxaliplatin], or liposomal irinotecan plus fluorouracil and leucovorin). Chemotherapy was administered according to the local prescribing practice.

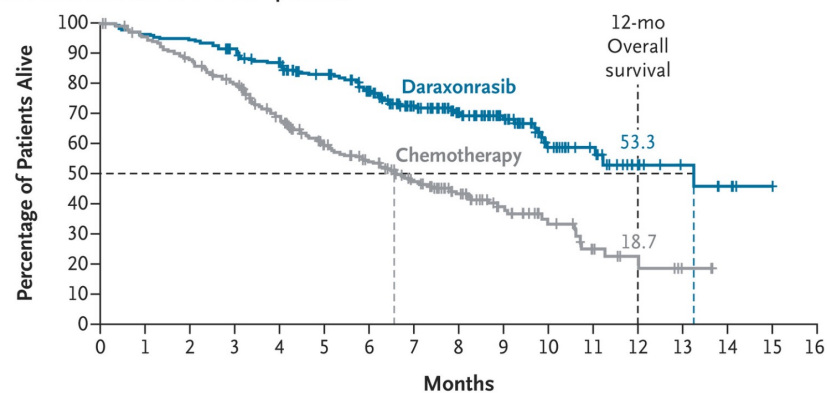
End Points

The dual primary end points were **overall survival** and **progression-free survival** as assessed by blinded independent central review according to RECIST, version 1.1, in the subpopulation of patients with *RAS* G12 mutations (the *RAS* G12 population).

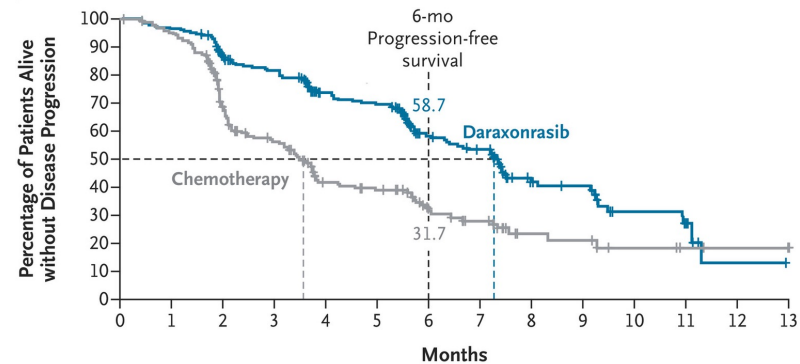
Characteristic	RAS G12 Population		Overall Population	
	Daraxonrasib (N=228)	Chemotherapy (N=231)	Daraxonrasib (N=248)	Chemotherapy (N=252)
Median age (range) — yr	66 (30–88)	65 (36–86)	66 (30–88)	65 (36–86)
Age ≥65 yr — no. (%)	123 (53.9)	121 (52.4)	134 (54.0)	131 (52.0)
Sex — no. (%)				
Female	111 (48.7)	100 (43.3)	117 (47.2)	108 (42.9)
Male	117 (51.3)	131 (56.7)	131 (52.8)	144 (57.1)
Race or ethnic group — no. (%)†				
American Indian or Alaska Native	0	1 (0.4)	0	1 (0.4)
Asian	29 (12.7)	25 (10.8)	29 (11.7)	28 (11.1)
Black	6 (2.6)	14 (6.1)	7 (2.8)	15 (6.0)
White	155 (68.0)	152 (65.8)‡	172 (69.4)	167 (66.3)‡
Other	5 (2.2)	5 (2.2)	5 (2.0)	6 (2.4)
Race or ethnic group not obtained	30 (13.2)	27 (11.7)	32 (12.9)	28 (11.1)
Unknown	3 (1.3)	7 (3.0)	3 (1.2)	7 (2.8)
Geographic region — no. (%)				
North America	132 (57.9)	143 (61.9)	145 (58.5)	158 (62.7)
Europe	80 (35.1)	70 (30.3)	87 (35.1)	74 (29.4)
Asia Pacific	16 (7.0)	18 (7.8)	16 (6.5)	20 (7.9)
ECOG performance-status score — no. (%)§				
0	120 (52.6)	109 (47.2)	129 (52.0)	118 (46.8)
1¶	108 (47.4)	122 (52.8)	119 (48.0)	134 (53.2)
Metastatic disease at initial diagnosis — no. (%)	139 (61.0)	140 (60.6)	154 (62.1)	154 (61.1)
No. of previous systemic therapies for metastatic disease — no. (%)				
0	41 (18.0)	33 (14.3)	42 (16.9)	34 (13.5)
1	187 (82.0)	198 (85.7)	206 (83.1)	218 (86.5)
Select previous chemotherapy regimens for metastatic disease — no. (%)				
Modified FOLFIRINOX or FOLFIRINOX	91 (39.9)	98 (42.4)	98 (39.5)	105 (41.7)
Gemcitabine plus nab-paclitaxel	85 (37.3)	82 (35.5)	94 (37.9)	94 (37.3)
NALIRIFOX	4 (1.8)	7 (3.0)	4 (1.6)	8 (3.2)
Liposomal irinotecan plus fluorouracil and leucovorin	1 (0.4)	3 (1.3)	2 (0.8)	3 (1.2)
FOLFOX	2 (0.9)	3 (1.3)	2 (0.8)	3 (1.2)
Previous pancreatectomy — no. (%)	80 (35.1)	86 (37.2)	83 (33.5)	92 (36.5)
Previous Whipple procedure	54 (23.7)	52 (22.5)	57 (23.0)	56 (22.2)
Sites of metastases — no. (%)				
Liver	161 (70.6)	162 (70.1)	174 (70.2)	176 (69.8)
Lung	89 (39.0)	82 (35.5)	96 (38.7)	88 (34.9)
Peritoneum	72 (31.6)	77 (33.3)	76 (30.6)	83 (32.9)
Blood level of CA 19-9 ≥40 U/ml — no. (%)	194 (85.1)	179 (77.5)	211 (85.1)	195 (77.4)
RAS mutational status — no. (%)				
RAS G12D or G12V mutation	197 (86.4)	197 (85.3)	197 (79.4)	197 (78.2)
Other RAS G12 mutation	31 (13.6)	34 (14.7)	31 (12.5)	34 (13.5)
RAS G13 or Q61 mutation, or no RAS mutation identified	0	0	20 (8.1)**	21 (8.3)**

Event	Daraxonrasib (N=241)	Chemotherapy (N=214)
	no. of patients (%)	
Any adverse event	241 (100)	209 (97.7)
Grade ≥3 event	149 (61.8)	149 (69.6)
Treatment-related adverse event	236 (97.9)	200 (93.5)
Grade ≥3 treatment-related adverse event	105 (43.6)†	123 (57.5)
Serious treatment-related adverse event	26 (10.8)	40 (18.7)
Grade 5 treatment-related adverse event	1 (0.4)	0
Treatment-related adverse event leading to dose modification	137 (56.8)	153 (71.5)
Dose interruption	135 (56.0)	118 (55.1)
Dose reduction	87 (36.1)	123 (57.5)
Treatment-related adverse event leading to treatment discontinuation	3 (1.2)‡	24 (11.2)
Treatment-related adverse event of any grade reported in ≥10% of patients; corresponding grade ≥3 treatment-related adverse event		
Rash§	206 (85.5); 33 (13.7)	12 (5.6); 0
Diarrhea	140 (58.1); 13 (5.4)	81 (37.9); 15 (7.0)
Stomatitis¶	128 (53.1); 29 (12.0)	37 (17.3); 6 (2.8)
Nausea	112 (46.5); 5 (2.1)	84 (39.3); 4 (1.9)
Vomiting	89 (36.9); 1 (0.4)	47 (22.0); 1 (0.5)
Fatigue	56 (23.2); 9 (3.7)	95 (44.4); 12 (5.6)
Anemia	44 (18.3); 10 (4.1)	85 (39.7); 35 (16.4)
Decreased appetite	41 (17.0); 3 (1.2)	48 (22.4); 1 (0.5)
Paronychia	40 (16.6); 0	0; 0
Dry skin	32 (13.3); 0	4 (1.9); 0
Aspartate aminotransferase increased	30 (12.4); 6 (2.5)	22 (10.3); 2 (0.9)
Asthenia	26 (10.8); 1 (0.4)	31 (14.5); 4 (1.9)
Neutropenia	18 (7.5); 4 (1.7)	82 (38.3); 59 (27.6)
Alanine aminotransferase increased	23 (9.5); 4 (1.7)	22 (10.3); 1 (0.5)
Edema peripheral	21 (8.7); 0	27 (12.6); 0
Thrombocytopenia**	24 (10.0); 5 (2.1)	71 (33.2); 21 (9.8)
Alopecia	8 (3.3); 0	32 (15.0); 0
Pyrexia	7 (2.9); 0	23 (10.7); 2 (0.9)
Peripheral neuropathy††	4 (1.7); 0	54 (25.2); 7 (3.3)

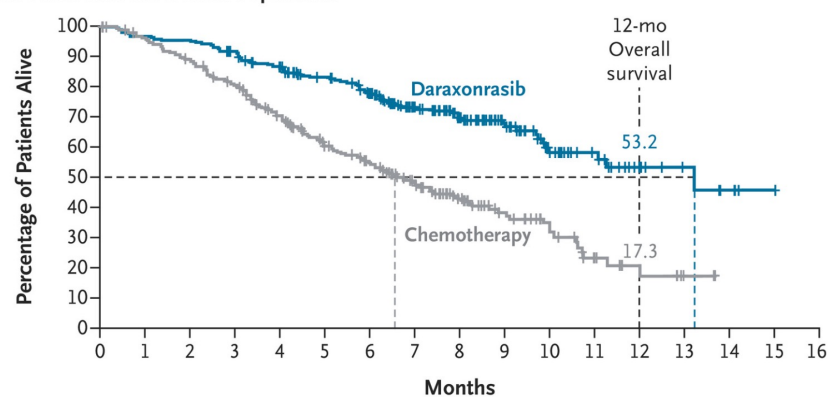
A Overall Survival in the RAS G12 Population



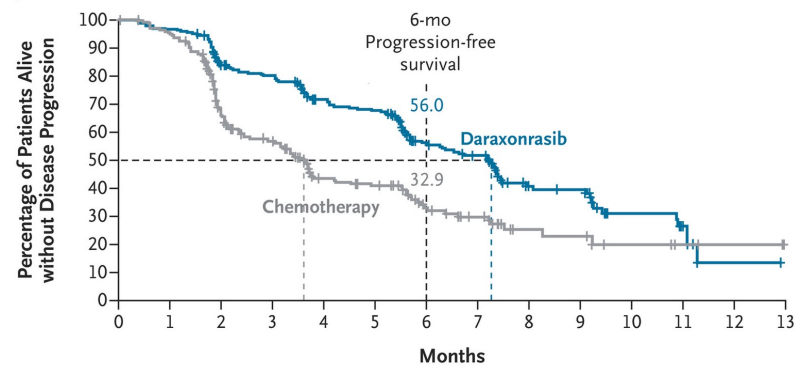
A Progression-free Survival in the RAS G12 population

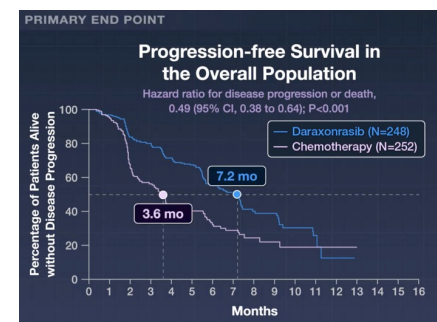
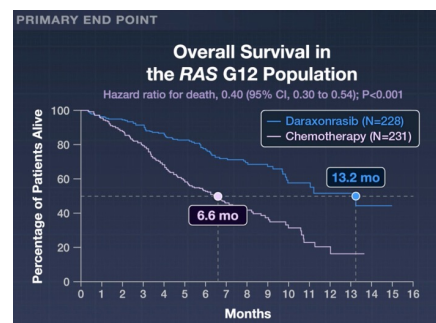
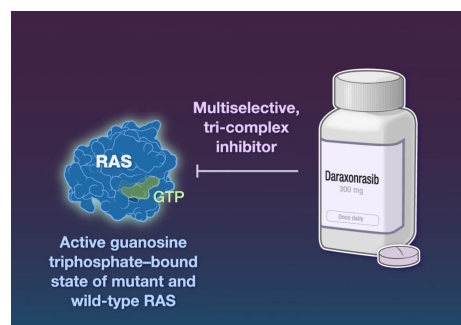
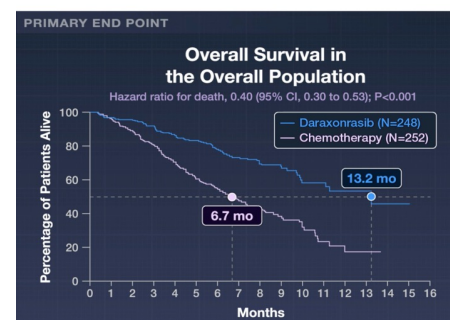
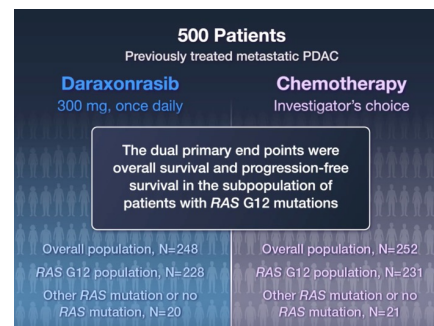
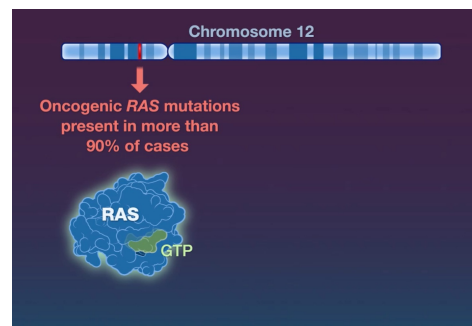
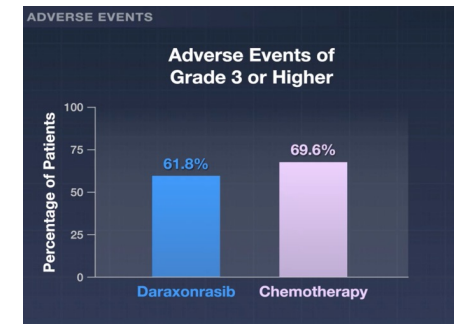
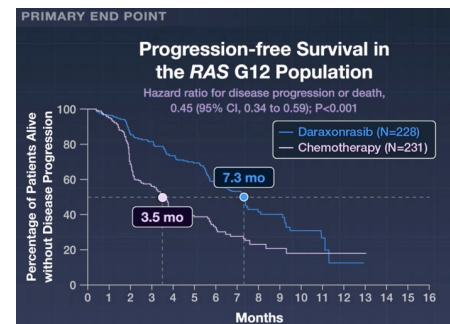
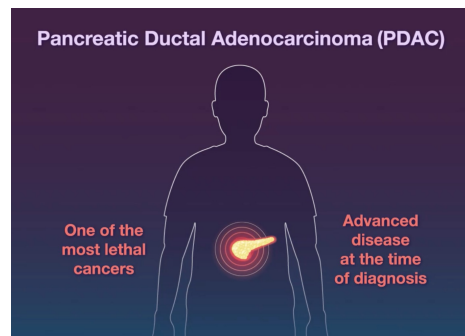


B Overall Survival in the Overall Population



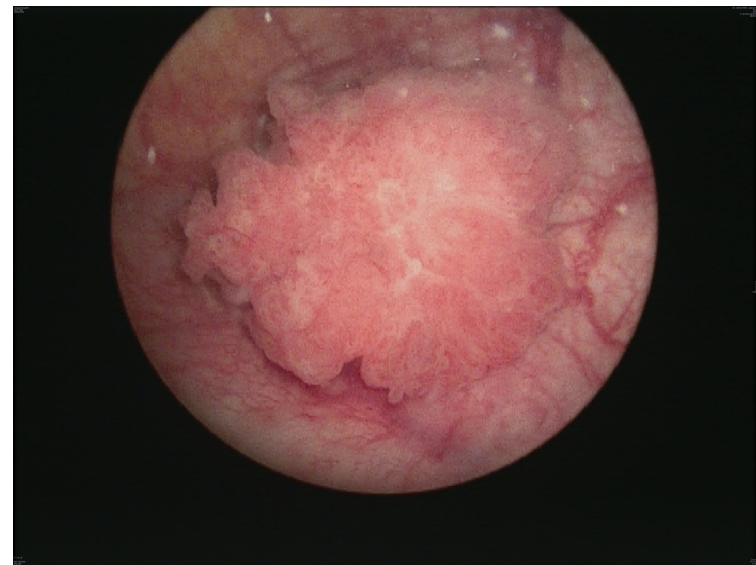
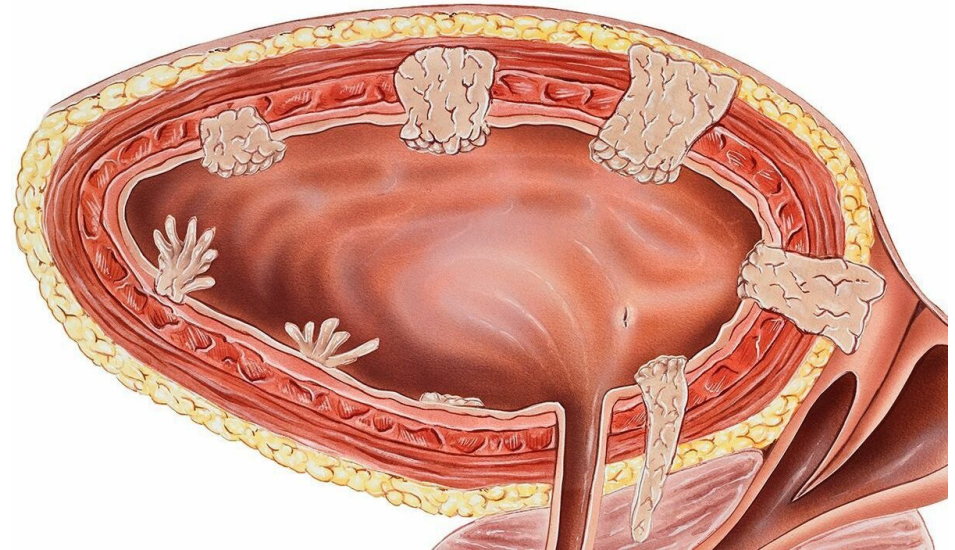
B Progression-free Survival in the Overall Population





Blasenkrebs (Harnblasenkarzinom) ist ein bösartiger Tumor der Harnblase, der meistens von den Zellen der inneren Blasenschleimhaut (Urothel) ausgeht. Das wichtigste und häufigste Warnzeichen ist **schmerzloses Blut im Urin**, welches die Flüssigkeit rosa, rot oder braun färben kann. Jährlich erkranken in Deutschland rund 31.000 Menschen neu daran, wobei Männer deutlich häufiger betroffen sind als Frauen.

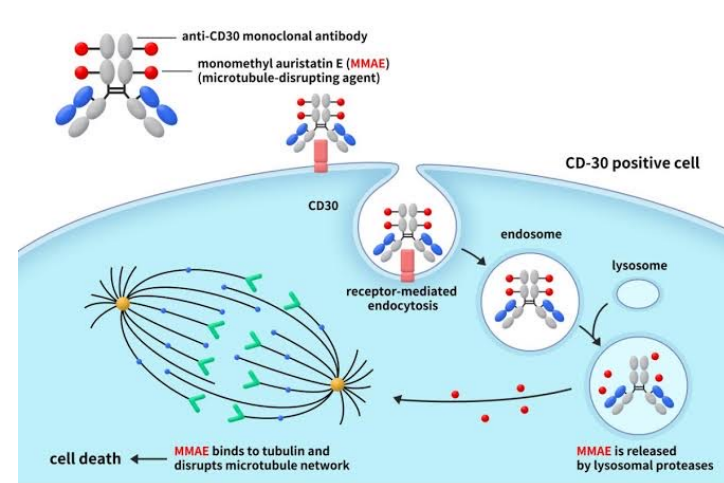
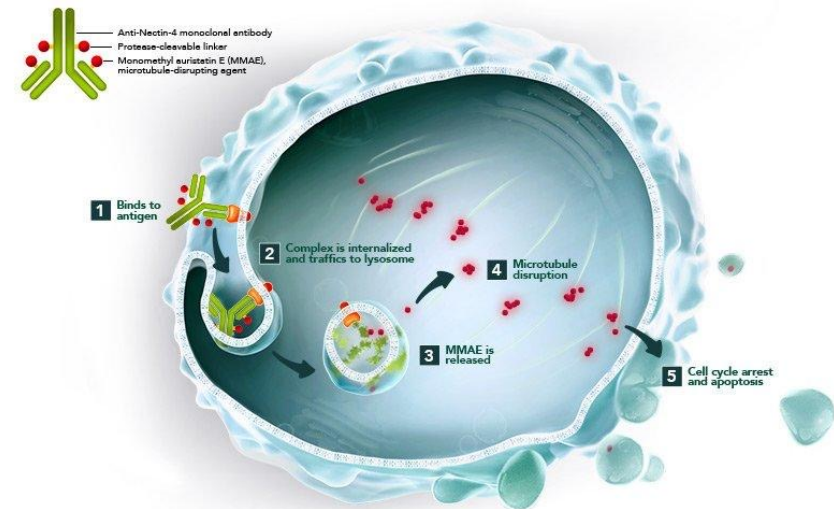
Muskelinvasiver Blasenkrebs (tief wachsend): Der Krebs hat die Blasenmuskulatur erreicht, wodurch das Risiko für Metastasen steigt. Hier ist meist die vollständige operative Entfernung der Harnblase ([radikale Zystektomie](#)) notwendig. Als Ersatz wird eine künstliche Harnableitung (z. B. eine aus Darmgewebe geformte Neoblase oder ein künstlicher Ausgang/Stoma) angelegt. Begleitend kommt häufig eine Chemotherapie zum Einsatz.



Enfortumab-Vedotin ist ein modernes, zielgerichtetes Krebsmedikament zur Behandlung von **fortgeschrittenem, metastasiertem oder muskelinvasivem Urothel- und Blasenkarzinom**. Es gehört zur Klasse der Antikörper-Wirkstoff-Konjugate (Antibody-Drug Conjugates, ADCs).

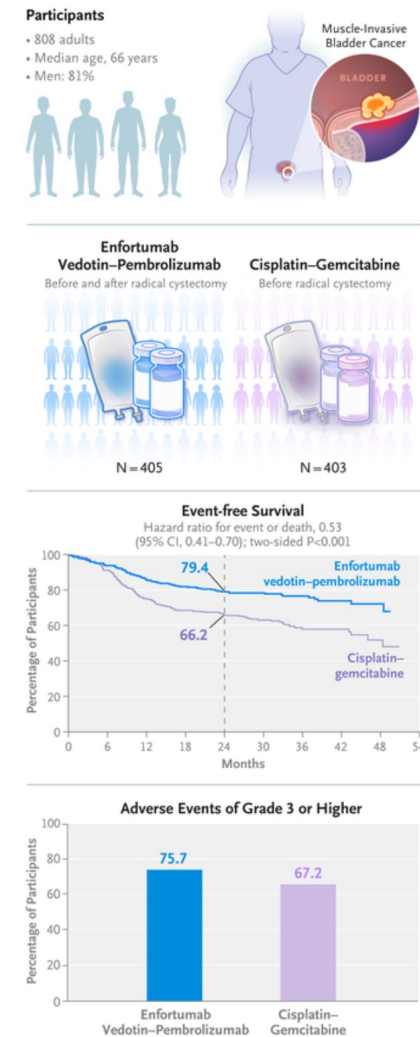
Das Medikament funktioniert wie ein "Trojanisches Pferd" im Körper:

- Zielsteuerung:** Ein monoklonaler Antikörper bindet gezielt an das Protein **Nectin-4**, welches auf der Oberfläche von Blasenkrebszellen in großen Mengen vorkommt.
- Zelluläre Aufnahme:** Nach dem Andocken wird der gesamte Komplex in das Innere der Krebszelle transportiert.
- Zerstörung:** Im Zellinneren wird ein hochwirksames Zellgift (MMAE) freigesetzt, das die Zellteilung blockiert und die Tumorzelle zerstört.



Enfortumab Vedotin and Pembrolizumab in Cisplatin-Eligible Bladder Cancer

Neoadjuvant cisplatin-based chemotherapy is a standard therapy for muscle-invasive bladder cancer. The efficacy and safety of neoadjuvant and adjuvant (perioperative) enfortumab vedotin–pembrolizumab as compared with neoadjuvant cisplatin-based chemotherapy in persons with this cancer are unclear. We conducted a phase 3, open-label, randomized trial involving adults with muscle-invasive bladder cancer eligible for cisplatin-based chemotherapy and radical cystectomy with pelvic lymph-node dissection (cystectomy). Participants were assigned to receive neoadjuvant enfortumab vedotin–pembrolizumab (4 cycles; enfortumab vedotin [1.25 mg per kilogram of body weight on days 1 and 8] and pembrolizumab [200 mg on day 1] every 3 weeks), cystectomy, and 5 cycles of enfortumab vedotin and 13 cycles of pembrolizumab as adjuvant therapy or to receive neoadjuvant cisplatin–gemcitabine (4 cycles; cisplatin [70 mg per square meter of body-surface area on day 1] plus gemcitabine [1000 mg per square meter on days 1 and 8] every 3 weeks) and cystectomy. The primary end point was event-free survival; key secondary end points were overall survival and pathological complete response. Safety was assessed.



Enfortumab vedotin is a nectin-4-directed **antibody–drug conjugate** with a **monomethyl auristatin E payload**, which had superior efficacy to chemotherapy in patients with previously treated advanced urothelial carcinoma in the phase 3 EV-301 trial. Enfortumab vedotin plus the anti-programmed death 1 **(PD-1) antibody pembrolizumab** represented a major advancement in the treatment of metastatic urothelial carcinoma, becoming a first-line standard of care in place of traditional chemotherapy. Both have shown promising single-agent activity in conjunction with cystectomy in patients with muscle-invasive bladder cancer.

These findings culminated in the phase 3 KEYNOTE-905/EV-303 trial, which showed that neoadjuvant and adjuvant (perioperative) enfortumab vedotin–pembrolizumab with cystectomy resulted in significantly better efficacy outcomes than cystectomy alone in patients with muscle-invasive bladder cancer who were ineligible for cisplatin-based neoadjuvant chemotherapy. The Food and Drug Administration approved this regimen in this context in November 2025. We conducted the phase 3 KEYNOTE-B15 trial to evaluate the efficacy and safety of perioperative enfortumab vedotin–pembrolizumab as compared with **neoadjuvant cisplatin–gemcitabine** in participants with **muscle-invasive bladder cancer** who were eligible for cisplatin-based therapy and cystectomy.

Participants

Eligible participants were 18 years of age or older and had histologically confirmed **muscle-invasive bladder cancer** (clinical stage T2 to T4a with N0M0 or T1 to T4a with N1M0, confirmed by central pathological review and central imaging assessment) with predominant ($\geq 50\%$) urothelial histologic features. Participants had to have an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (on a 5-point scale in which higher numbers indicate greater disability), be eligible for curative radical cystectomy and pelvic lymph-node dissection, and meet none of the criteria for cisplatin ineligibility.

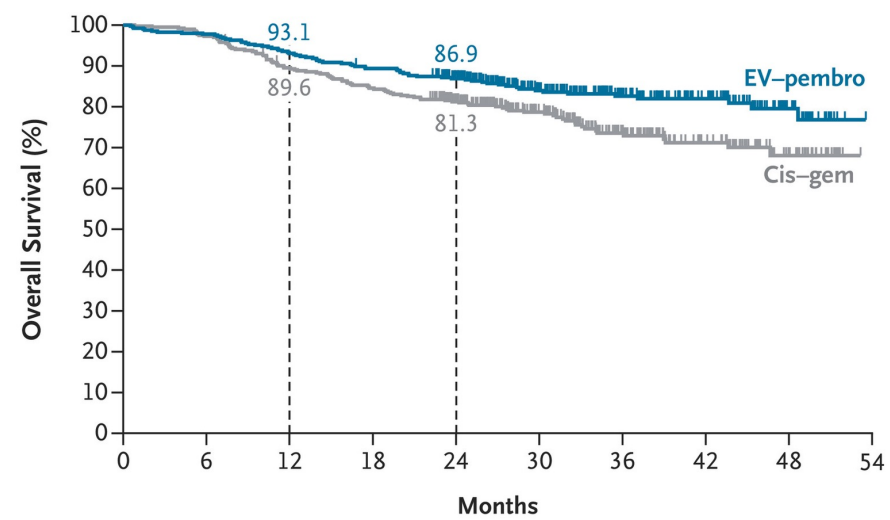
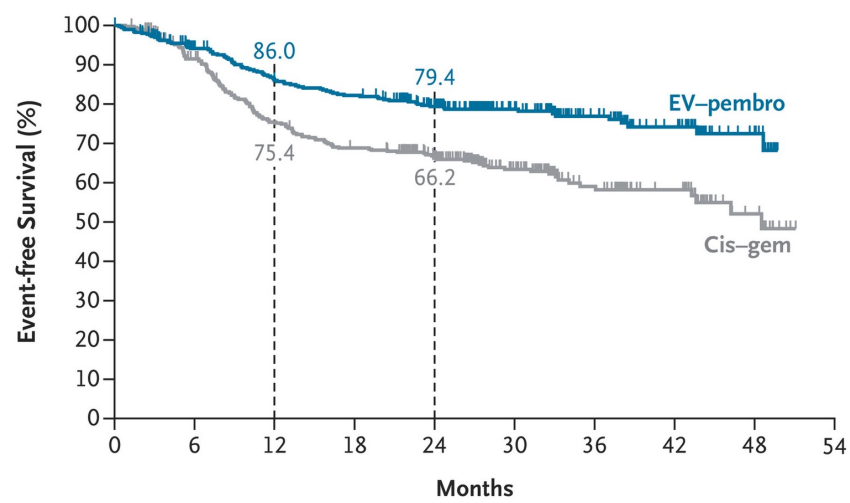
End Points and Assessments

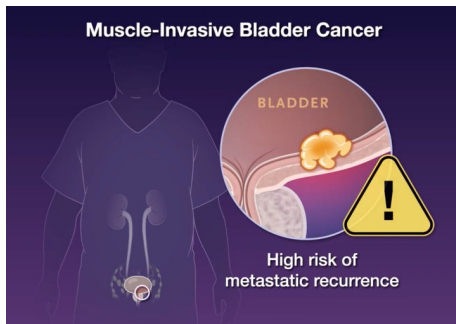
The **primary end point was event-free survival**, defined as the time from randomization to any of the following: radiographic disease progression precluding curative-intent cystectomy as assessed by blinded independent central review (central review).

Characteristic	Enfortumab Vedotin– Pembrolizumab (N = 405)	Cisplatin– Gemcitabine (N = 403)
Age		
Median (range) — yr	66.0 (35–83)	66.0 (37–85)
≥65 Yr — no. (%)	247 (61.0)	247 (61.3)
Male sex — no. (%)	327 (80.7)	327 (81.1)
ECOG performance-status score — no. (%)†		
0	317 (78.3)	310 (76.9)
1	88 (21.7)	93 (23.1)
Geographic region — no. (%)		
United States	59 (14.6)	59 (14.6)
European Union	206 (50.9)	205 (50.9)
Rest of the world	140 (34.6)	139 (34.5)
Race or ethnic group — no. (%)‡		
American Indian or Alaska Native	3 (0.7)	2 (0.5)
Asian	63 (15.6)	74 (18.4)
Black	5 (1.2)	5 (1.2)
Multiple	5 (1.2)	6 (1.5)
White	329 (81.2)	314 (77.9)
Missing	0	2 (0.5)
PD-L1 status — no. (%)§		
CPS ≥10	233 (57.5)	230 (57.1)
CPS <10	171 (42.2)	173 (42.9)
Missing	1 (0.2)	0
Tumor stage — no. (%)¶		
T2N0	79 (19.5)	77 (19.1)
T3N0 or T4aN0	293 (72.3)	293 (72.7)
T1 to T4a with N1	33 (8.1)	33 (8.2)
Creatinine clearance — no. (%)		
≥90 ml/min	149 (36.8)	156 (38.7)
60 to <90 ml/min	252 (62.2)	245 (60.8)
30 to <60 ml/min	4 (1.0)	2 (0.5)
Histologic features — no. (%)		
Pure urothelial carcinoma	370 (91.4)	353 (87.6)
Urothelial carcinoma with glandular differentiation	9 (2.2)	12 (3.0)
Urothelial carcinoma with squamous differentiation	17 (4.2)	22 (5.5)
Urothelial carcinoma with other variant histologic features	9 (2.2)	16 (4.0)
Smoking status — no. (%)		
Never smoked	92 (22.7)	98 (24.3)
Former smoker	191 (47.2)	201 (49.9)
Current smoker	122 (30.1)	104 (25.8)

Adverse Events

Event	Enfortumab Vedotin– Pembrolizumab (N = 403)		Cisplatin– Gemcitabine (N = 396)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of participants (percent)			
Pruritus	186 (46.2)	13 (3.2)	18 (4.5)	0
Diarrhea	137 (34.0)	9 (2.2)	65 (16.4)	4 (1.0)
Alopecia	127 (31.5)	2 (0.5)	44 (11.1)	0
Anemia	126 (31.3)	26 (6.5)	223 (56.3)	61 (15.4)
Decreased appetite	115 (28.5)	4 (1.0)	72 (18.2)	2 (0.5)
Nausea	114 (28.3)	4 (1.0)	185 (46.7)	2 (0.5)
Fatigue	111 (27.5)	6 (1.5)	111 (28.0)	3 (0.8)
Constipation	107 (26.6)	3 (0.7)	147 (37.1)	2 (0.5)
Rash	101 (25.1)	15 (3.7)	11 (2.8)	1 (0.3)
Urinary tract infection	101 (25.1)	40 (9.9)	84 (21.2)	38 (9.6)
Dysgeusia	100 (24.8)	0	37 (9.3)	0
Aspartate aminotransferase increased	98 (24.3)	12 (3.0)	20 (5.1)	0
Alanine aminotransferase increased	97 (24.1)	18 (4.5)	39 (9.8)	0
Asthenia	92 (22.8)	5 (1.2)	94 (23.7)	6 (1.5)
Weight decreased	87 (21.6)	10 (2.5)	25 (6.3)	1 (0.3)
Rash maculopapular	83 (20.6)	19 (4.7)	14 (3.5)	0
Neuropathy peripheral	69 (17.1)	6 (1.5)	12 (3.0)	1 (0.3)
Neutropenia	59 (14.6)	30 (7.4)	218 (55.1)	131 (33.1)
Blood creatinine increased	50 (12.4)	2 (0.5)	73 (18.4)	2 (0.5)
Leukopenia	13 (3.2)	1 (0.2)	75 (18.9)	17 (4.3)
Thrombocytopenia	9 (2.2)	1 (0.2)	113 (28.5)	36 (9.1)



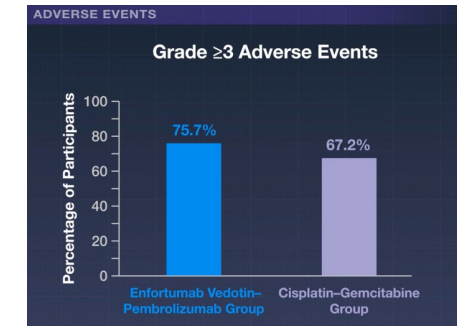
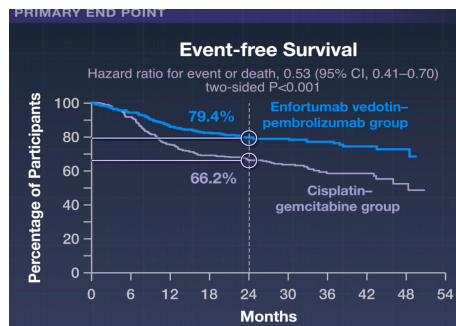
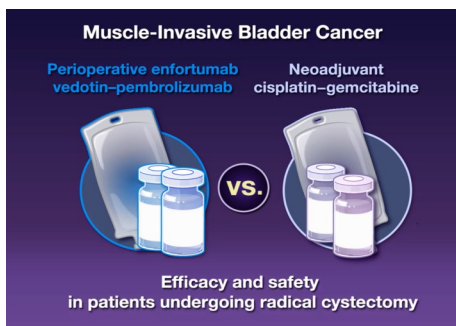
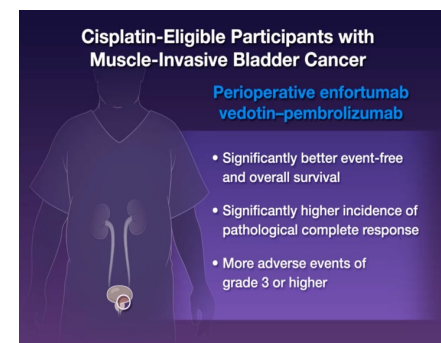
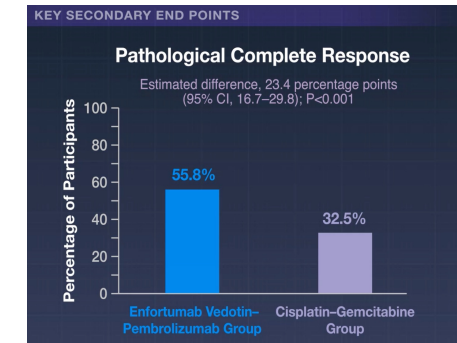
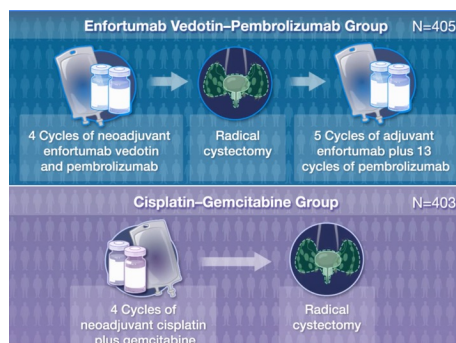
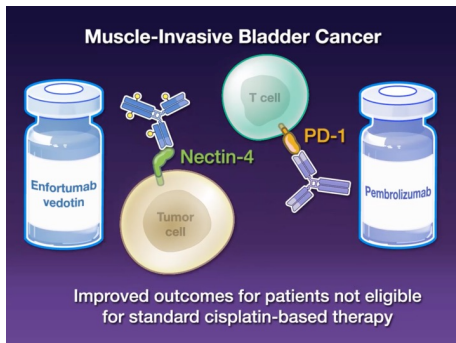
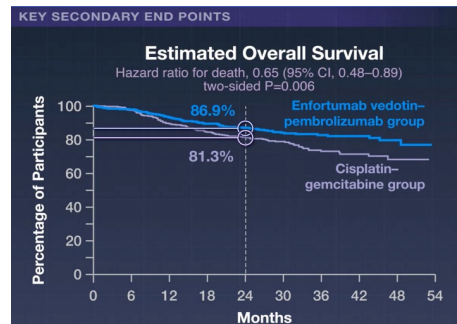


KEYNOTE-B15/ EV-304 TRIAL

- Phase 3
- Multicenter
- Open-label
- Randomized

808 Participants

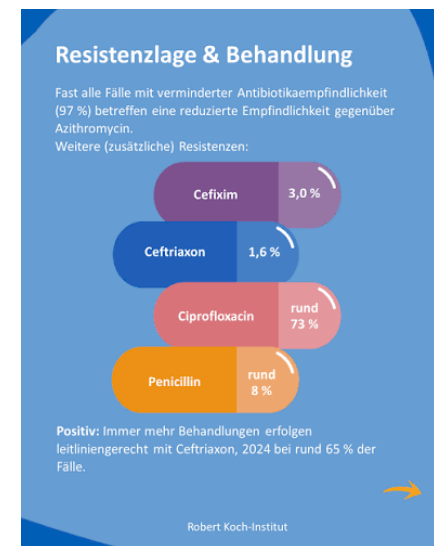
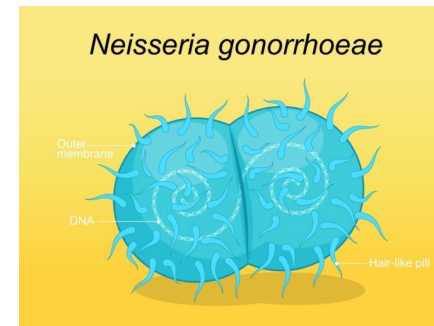
- With muscle-invasive bladder cancer
- Eligible for cisplatin-based therapy
- Eligible for curative radical cystectomy and pelvic lymph-node dissection



Aktuell gibt es **keinen spezifisch zugelassenen Impfstoff gegen Gonorrhoe** (Tripper). Die Erforschung eines wirksamen Schutzes ist jedoch aufgrund weltweit steigender Fallzahlen und zunehmender Antibiotikaresistenzen der Gonokokken-Bakterien im Fokus der Wissenschaft.

Der Meningokokken-B-Impfstoff (4CMenB): Da die Erreger von Meningitis B und Gonorrhoe genetisch sehr eng verwandt sind, hoffte die Forschung lange auf einen sogenannten Kreuzschutz. Ältere Beobachtungsstudien deuteten darauf hin, dass diese Impfung das Risiko für eine Tripper-Infektion senken könnte.

Neue ernüchternde Studiendaten (2026): Die im Juli 2026 im *New England Journal of Medicine (NEJM)* veröffentlichte klinische Studie „GoGoVax“ zeigte leider, dass der Vier-Komponenten-Impfstoff 4CMenB bei Personen mit hohem Expositionsrisiko **keinen kreuzprotektiven Schutz gegen Gonorrhoe** bietet.



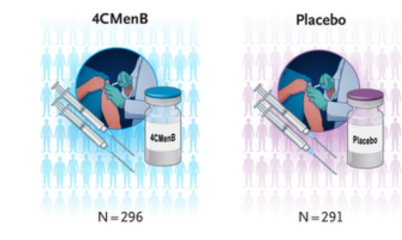
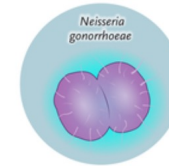
Meningococcal B Vaccine to Prevent *Neisseria gonorrhoeae* Infection

No vaccines are currently licensed for the prevention of *Neisseria gonorrhoeae* infection. Observational studies suggest that the four-component meningococcal serogroup B vaccine (4CMenB) may reduce the risk of gonorrhea.

In this multicenter, double-blind, randomized, placebo-controlled trial, we assigned, in a 1:1 ratio, men who have sex with men (MSM) to receive two doses of 4CMenB or placebo. All the participants had recently received a diagnosis of *N. gonorrhoeae* infection or infectious syphilis and either tested negative for human immunodeficiency virus (HIV) and were receiving HIV preexposure prophylaxis or were living with HIV. Screening for sexually transmitted infections, including *N. gonorrhoeae* nucleic acid amplification testing of samples obtained from urogenital, anorectal, and oropharyngeal sites, was performed quarterly for 2 years. The primary outcome was a first *N. gonorrhoeae* infection after the receipt of vaccine or placebo in the per-protocol population (participants who received both 4CMenB or placebo doses, attended at least two scheduled follow-up visits after the second dose, and did not meet any exclusion criterion pertinent to the assessment of efficacy).

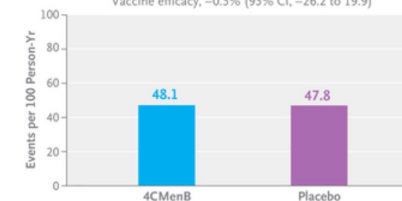
Participants

- 587 adults
- Mean age, 34 years
- 98% identified as men



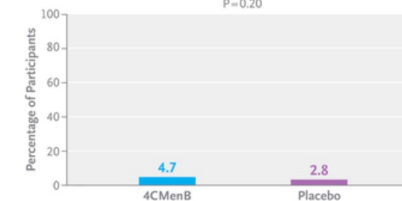
First Episode of *N. gonorrhoeae* Infection ≥ 4 Weeks after Second Dose

Incidence rate ratio, 1.01 (95% CI, 0.80 to 1.26); $P=0.97$
Vaccine efficacy, -0.5% (95% CI, -26.2 to 19.9)



Serious Adverse Events

$P=0.20$



N. gonorrhoeae is closely related to *Neisseria meningitidis*. The four-component meningococcal serogroup B outer membrane vesicle (OMV) vaccine, 4CMenB, has been associated with a reduced incidence of gonorrhea in several observational studies, with a recent meta-analysis showing an estimated risk reduction of 38% (95% confidence interval [CI], 28 to 48). Given the presence of shared antigens between *N. gonorrhoeae* and *N. meningitidis*, cross-protection is biologically plausible and has been supported by laboratory data. Programs for 4CMenB immunization have been implemented on the basis of observational data to prevent gonorrhea in adults 18 to 65 years of age in **Galicia, Spain, and in MSM** at high risk for **gonorrhea in the United Kingdom**. Recently, an open-label, randomized trial involving MSM in France, ANRS 174 DOXYVAC, did not show significant protection against the first episode of gonorrhea after vaccination, with wide confidence intervals (adjusted hazard ratio, 0.78; 95% CI, 0.60 to 1.01; $P=0.06$). Here we report the efficacy and safety of 4CMenB for the prevention of *N. gonorrhoeae* infection in MSM.

Trial Procedures

Participants were randomly assigned in a 1:1 ratio to receive two intramuscular injections, administered 3 months apart, of 4CMenB or saline placebo. Randomization was performed by means of a Web-based system and a permuted-block scheme stratified according to trial site. The treatment assignment was concealed from the participants, investigators, site clinicians and coordinators, and trial personnel who were responsible for outcome assessment. The pharmacists and drug managers at the trial sites who prepared the trial interventions, along with the vaccinators who administered them, were aware of the trial-group assignments but had no role in outcome evaluation.

Follow-up visits were scheduled to occur every 3 months over a 24-month period. At each visit, participants underwent testing for sexually transmitted infections (STIs), including nucleic acid amplification testing (NAAT) for *N. gonorrhoeae*. Data on demographic characteristics, sexual behavior, and antibiotic use were collected. Unscheduled visits were permitted for participants seeking treatment of symptomatic or asymptomatic *N. gonorrhoeae* infection or for those attending a test-of-cure visit if such tests were routinely conducted at the clinic.

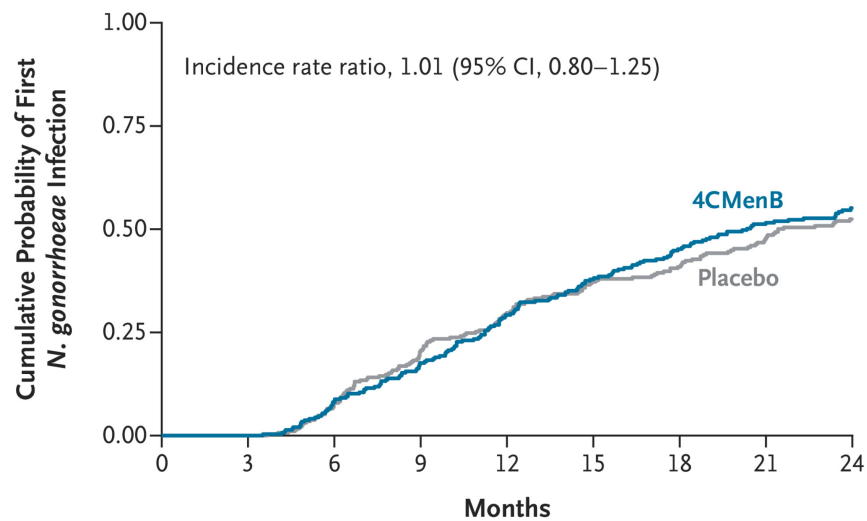
Outcomes

The primary efficacy outcome was a first *N. gonorrhoeae* infection at least 4 weeks after the second dose of vaccine or placebo. *N. gonorrhoeae* infection was defined by a urethral, anorectal, oropharyngeal, or vaginal swab specimen that was positive on NAAT.

Characteristic	Per-Protocol Population		Modified Intention-to-Treat Population	
	4CMenB (N = 296)	Placebo (N = 291)	4CMenB (N = 313)	Placebo (N = 307)
Age — yr	34.0±6.3	34.5±6.7	33.9±6.2	34.3±6.7
HIV status — no. (%)				
Negative	266 (89.9)	265 (91.1)	279 (89.1)	280 (91.2)
Positive	30 (10.1)	26 (8.9)	34 (10.9)	27 (8.8)
Sex at birth — no. (%)				
Male	295 (99.7)	288 (99.0)	312 (99.7)	304 (99.0)
Female	1 (0.3)	3 (1.0)	1 (0.3)	3 (1.0)
Gender identity — no. (%)				
Male	288 (97.3)	289 (99.3)	305 (97.4)	305 (99.3)
Female	3 (1.0)	1 (0.3)	3 (1.0)	1 (0.3)
Nonbinary	4 (1.4)	1 (0.3)	4 (1.3)	1 (0.3)
Other	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)
Sexual orientation — no. (%)				
Gay or homosexual	271 (91.6)	262 (90.0)	288 (92.0)	275 (89.6)
Other	25 (8.4)	29 (10.0)	25 (8.0)	32 (10.4)
Country of birth — no. (%)				
Australia	150 (50.7)	156 (53.6)	157 (50.2)	164 (53.4)
Other	146 (49.3)	135 (46.4)	156 (49.8)	143 (46.6)
<i>N. gonorrhoeae</i> infection in previous 18 mo — no. (%)				
No	25 (8.4)	34 (11.7)	26 (8.3)	37 (12.1)
Yes	270 (91.2)	256 (88.0)	286 (91.4)	269 (87.6)
Missing data	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Infectious syphilis in previous 18 mo — no. (%)†				
No	239 (80.7)	234 (80.4)	254 (81.2)	247 (80.5)
Yes	56 (18.9)	56 (19.2)	58 (18.5)	59 (19.2)
Missing data	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
No. of sex partners in previous 6 mo — no. (%)				
0–1	1 (0.3)	4 (1.4)	2 (0.6)	4 (1.3)
2–5	53 (17.9)	41 (14.1)	55 (17.6)	42 (13.7)
6–10	51 (17.2)	68 (23.4)	55 (17.6)	73 (23.8)
11–50	151 (51.0)	146 (50.2)	158 (50.5)	156 (50.8)
>50	29 (9.8)	21 (7.2)	32 (10.2)	21 (6.8)
Missing data	11 (3.7)	11 (3.8)	11 (3.5)	11 (3.6)
Condom use with casual sex partners in previous 6 mo — no. (%)				
Never	102 (34.5)	103 (35.4)	108 (34.5)	112 (36.5)
Occasional or often	172 (58.1)	172 (59.1)	183 (58.5)	178 (58.0)
Always	5 (1.7)	2 (0.7)	5 (1.6)	2 (0.7)
No sex with casual sex partners	6 (2.0)	2 (0.7)	6 (1.9)	3 (1.0)
Missing data	11 (3.7)	12 (4.1)	11 (3.5)	12 (3.9)
Group sex in previous 6 mo — no. (%)‡				
Never	63 (21.3)	85 (29.2)	69 (22.0)	91 (29.6)
Once a month or less	208 (70.3)	178 (61.2)	217 (69.3)	187 (60.9)
More than once a month	14 (4.7)	16 (5.5)	16 (5.1)	17 (5.5)
Missing data	11 (3.7)	12 (4.1)	11 (3.5)	12 (3.9)

Primary and Secondary Analyses.

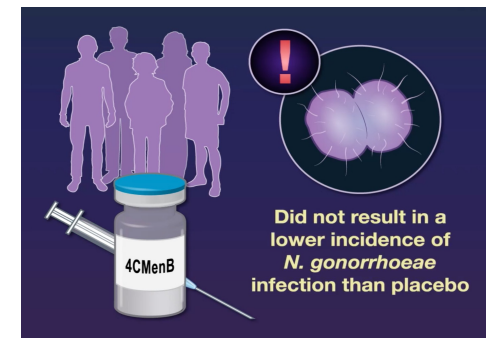
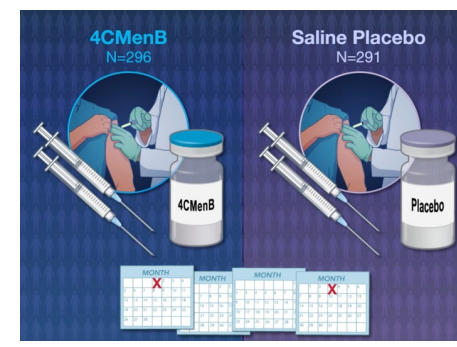
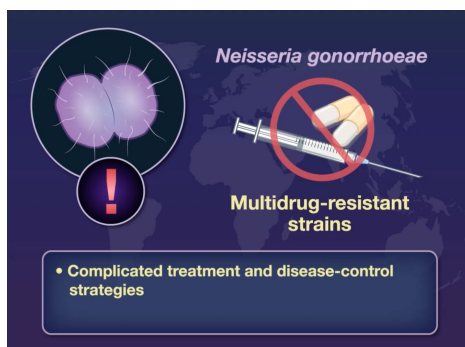
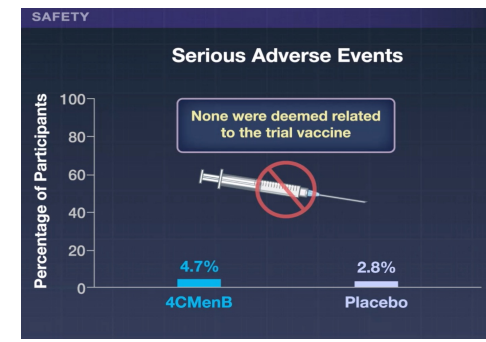
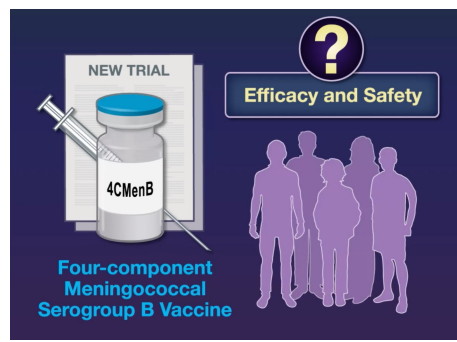
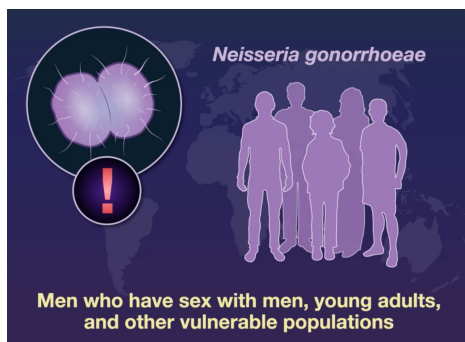
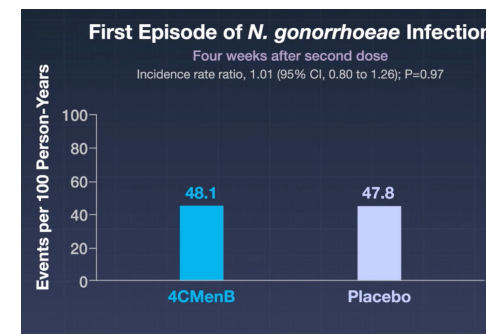
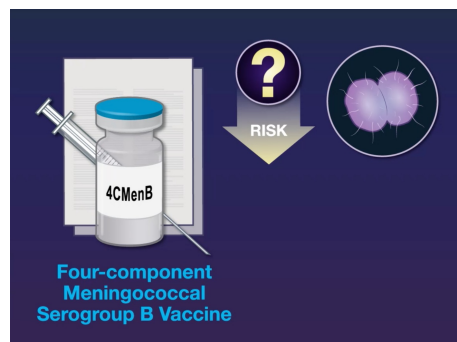
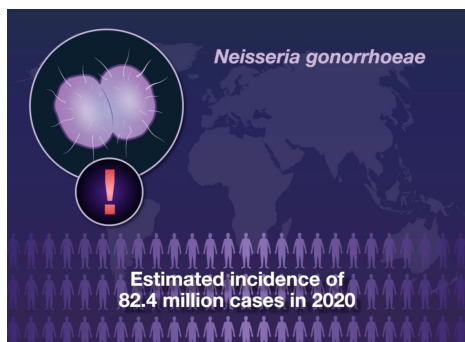
Analysis and Population	4CMenB			Placebo			Incidence Rate Ratio (95% CI)	Vaccine Efficacy (95% CI)
	No. of Events	No. of Person-Yr	Incidence	No. of Events	No. of Person-Yr	Incidence		
			events per 100 person-yr			events per 100 person-yr		
Primary analysis								
Per-protocol population†								
Primary outcome: first infection	160	330.0	48.1	155	324.2	47.8	1.01 (0.80 to 1.26)	-0.5 (-26.2 to 19.9)‡
All new infections§	291	486.5	59.8	285	468.7	60.8	0.98 (0.81 to 1.20)	1.6 (-16.3 to 16.7)
Modified intention-to-treat population¶								
First infection	184	388.5	47.4	173	400.7	43.2	1.10 (0.89 to 1.36)	-9.7 (-35.8 to 11.3)
Secondary analysis								
Per-protocol population†								
First symptomatic infection	34	379.8	9.0	35	369.5	9.5	0.95 (0.59 to 1.52)	5.5 (-56.0 to 42.8)
First asymptomatic infection	82	379.8	21.6	75	369.5	20.3	1.06 (0.78 to 1.46)	-6.4 (-47.5 to 23.2)
First urogenital infection	46	448.2	10.3	37	432.6	8.6	1.20 (0.78 to 1.86)	-20.0 (-90.2 to 23.9)
First anorectal infection	112	377.9	29.6	109	372.1	29.3	1.01 (0.77 to 1.32)	-1.2 (-33.0 to 23.0)
First oropharyngeal infection	113	392.1	28.8	112	378.6	29.6	0.97 (0.75 to 1.26)	2.6 (-27.7 to 25.7)



Subgroup	4CMenB no. of events/total person-yr (per 100 person-yr)	Placebo no. of events/total person-yr (per 100 person-yr)	Incidence Rate Ratio (95% CI)
Overall	160/330.0 (48.1)	155/324.2 (47.8)	1.01 (0.80–1.25)
HIV status			
Negative	142/298.0 (47.6)	135/301.3 (44.8)	1.06 (0.85–1.32)
Positive	18/34.9 (51.5)	20/22.9 (87.3)	0.59 (0.28–1.25)
Sexual orientation			
Gay or homosexual	147/307.1 (47.9)	143/286.3 (49.9)	0.96 (0.78–1.18)
Other	13/25.9 (50.2)	12/37.9 (31.7)	1.58 (0.68–3.68)
Age			
18–24 yr	5/9.3 (53.7)	6/7.3 (82.5)	0.64 (0.24–1.71)
25–34 yr	81/134.4 (60.3)	63/129.1 (48.8)	1.24 (1.01–1.52)
35–39 yr	46/105.1 (43.8)	45/106.2 (42.4)	1.03 (0.81–1.31)
≥40 yr	28/84.2 (33.3)	41/81.5 (50.3)	0.66 (0.44–1.00)
History of <i>N. gonorrhoeae</i> infection in previous 18 mo			
No	8/36.5 (21.9)	15/44.3 (33.9)	0.67 (0.31–1.44)
Yes	152/296.5 (51.3)	140/279.9 (50.0)	1.02 (0.81–1.28)
History of infectious syphilis in previous 18 mo			
No	132/262.0 (50.4)	125/261.7 (47.8)	1.05 (0.84–1.31)
Yes	28/70.9 (39.5)	30/62.4 (48.0)	0.81 (0.54–1.21)
No. of sex partners in previous 6 mo			
2–5	12/61.4 (19.5)	20/63.3 (31.6)	0.61 (0.31–1.21)
6–10	19/60.3 (31.5)	27/57.7 (46.8)	0.67 (0.43–1.04)
11–50	87/136.7 (63.6)	77/124.1 (62.0)	1.02 (0.81–1.29)
>50	23/27.3 (84.1)	12/16.3 (73.8)	1.16 (0.61–2.21)
Condom use with casual sex partners in previous 6 mo			
Never	59/141.4 (41.7)	69/135.6 (50.9)	0.81 (0.61–1.08)
Occasional or often	81/140.4 (57.7)	67/137.7 (48.7)	1.18 (0.95–1.47)
Group sex in previous 6 mo			
Never	24/101.8 (23.6)	22/120.2 (18.3)	1.28 (0.78–2.09)
Once a month or less	109/188.8 (57.7)	107/163.3 (65.5)	0.88 (0.71–1.09)
More than once a month	9/12.7 (70.7)	7/9.5 (73.6)	0.95 (0.41–2.14)
Follow-up period			
First year	117/231.2 (50.6)	112/221.9 (50.5)	1.01 (0.81–1.26)
Second year	43/101.7 (42.3)	43/102.3 (42.1)	1.01 (0.78–1.31)

0.1 1.0 10

4CMenB Better Placebo Better

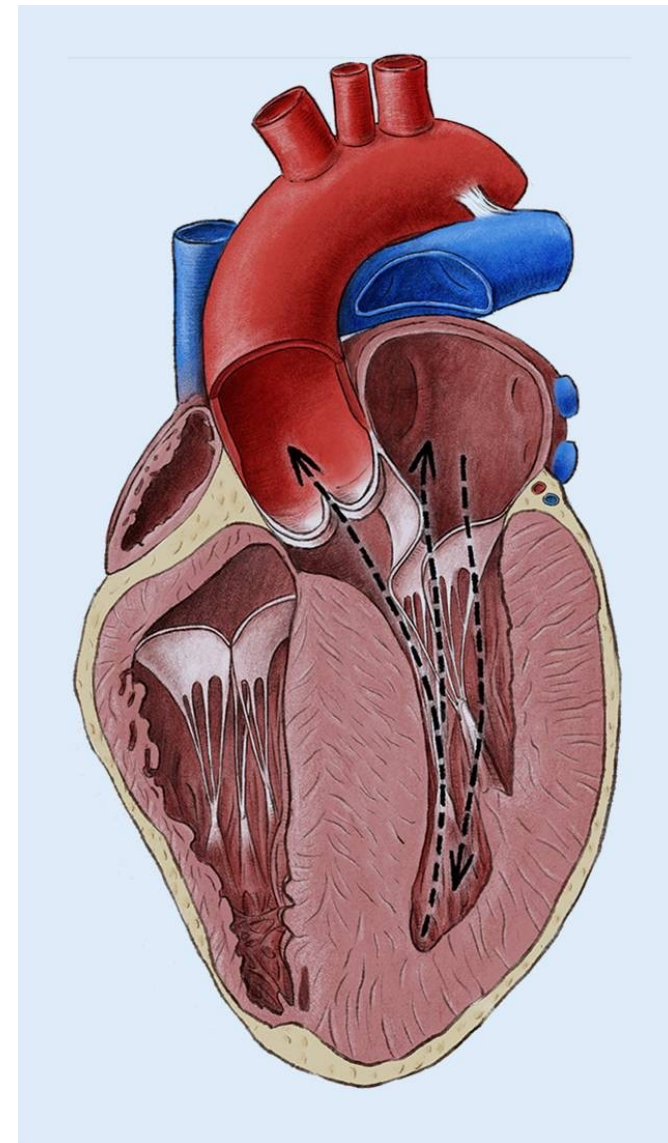


Die **hypertrophe obstruktive Kardiomyopathie (HOCM)** ist eine meist genetisch bedingte, chronische Erkrankung des Herzmuskels, bei der eine **krankhafte Verdickung (Hypertrophie) der Herzwand** den Blutfluss aus der linken Herzkammer in die Hauptschlagader (Aorta) behindert. Sie ist die häufigste primäre Herzmuskelerkrankung und betrifft etwa 1 von 500 Personen.

Die Ursache: Fehler im Erbgut (Genmutationen) führen dazu, dass sich die Herzmuskelzellen unkontrolliert verdicken.

Das Problem: Meist verdickt sich die Trennwand (Septum) zwischen den Herzkammern. Dadurch wird die Ausflussbahn des Blutes eingeengt (Obstruktion).

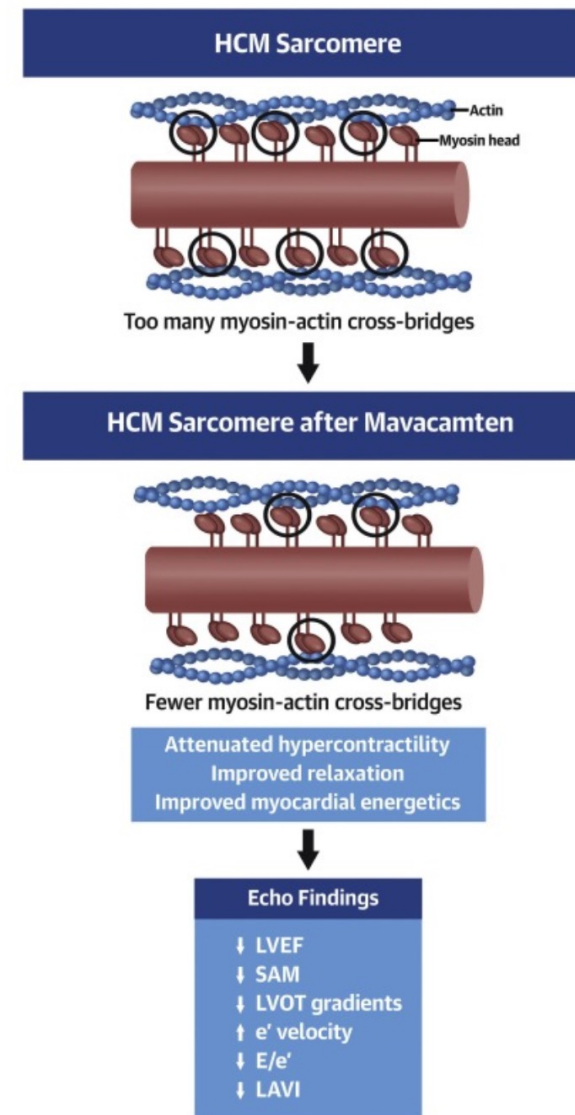
Die Folge: Das Herz muss permanent gegen einen massiven Widerstand anpumpen. Zudem verliert der Muskel seine Elastizität und kann sich in der Entspannungsphase schlechter mit Blut füllen.



Mavacamten ist ein neuartiger, hochspezifischer Herzmedikament-Wirkstoff, der zur Behandlung der **hypertroph-obstruktiven Kardiomyopathie (HOCM)** bei Erwachsenen eingesetzt wird. Er stellt den ersten Vertreter einer neuen Medikamentenklasse dar, den sogenannten **kardialen Myosininhibitoren**.

Bei der HOCM ist der Herzmuskel genetisch bedingt krankhaft verdickt. Das führt dazu, dass sich das Herz zu stark zusammenzieht (Hyperkontraktilität) und den Blutausfluss aus der linken Herzkammer blockiert.

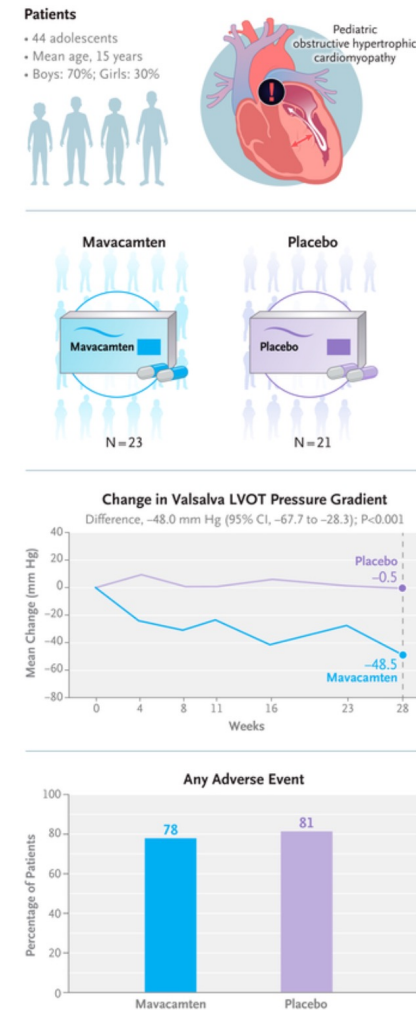
- Mavacamten bindet gezielt an das Protein **Myosin**.
- Es reduziert die übermäßige Brückenbildung zwischen Myosin und Aktin.
- Dadurch **entspannt sich der Herzmuskel** in der Dehnungsphase (Diastole) besser.
- Die Blockade des Blutflusses wird nachweislich verringert und das Herz entlastet.



Mavacamten in Adolescents with Obstructive Hypertrophic Cardiomyopathy

Approved pharmacologic therapies for pediatric **hypertrophic cardiomyopathy** are lacking, and surgical intervention may be indicated in patients with left ventricular outflow tract obstruction. The efficacy and safety of mavacamten, a cardiac myosin inhibitor that is available for adults, warrant evaluation in adolescents.

We conducted a phase 3, double-blind, randomized, placebo-controlled trial involving symptomatic adolescents (12 to <18 years of age) with New York Heart Association class II or III obstructive hypertrophic cardiomyopathy. The patients were randomly assigned in a 1:1 ratio to receive **mavacamten** or **placebo**. The primary end point was the change from baseline to week 28 in left ventricular outflow tract pressure gradient provoked by the Valsalva maneuver.



Administration or the European Medicines Agency for **pediatric hypertrophic cardiomyopathy**, and current pharmacologic recommendations are extrapolated from evidence obtained in studies involving adults. Such recommendations include the use of beta-blockers, nondihydropyridine calcium-channel blockers, and disopyramide. However, these treatments provide symptomatic relief only. Approximately 7 to 23% of pediatric patients undergo surgical myectomy to relieve left ventricular outflow tract obstruction. Thus, there remains a need for targeted pharmacologic therapy that can effectively reduce left ventricular outflow tract obstruction and mitigate symptoms in pediatric patients with obstructive hypertrophic cardiomyopathy.

Mavacamten is a selective, cardiac-specific myosin inhibitor approved for the treatment of adults with symptomatic New York Heart Association (NYHA) class II or III obstructive hypertrophic cardiomyopathy. The efficacy and favorable safety profile of mavacamten in adults were shown in five phase 3 clinical trials, sustained in subsequent long-term extension studies, and confirmed in observational studies. Although mavacamten was shown to be efficacious in genotypically diverse induced pluripotent stem-cell–derived cardiomyocytes from pediatric patients, it was not clinically assessed in a pediatric cohort. Here, we report the results for the primary and secondary efficacy and safety end points in a phase 3 trial conducted to evaluate the efficacy and safety of mavacamten, as compared with placebo, in symptomatic adolescent patients (12 to <18 years of age) with obstructive hypertrophic cardiomyopathy.

Trial Population

Adolescent patients (12 to <18 years of age) were eligible for inclusion if they had received a diagnosis of hypertrophic cardiomyopathy, had a left ventricular outflow tract pressure gradient during the Valsalva maneuver (a provocation maneuver involving forceful expiration against a closed glottis) of 30 mm Hg or greater, had a maximal left ventricular outflow tract gradient (at rest, during a Valsalva maneuver, or after exercise) of 50 mm Hg or greater, had a left ventricular ejection fraction (LVEF) of 60% or greater, and had NYHA functional class II or III symptoms. Patients with hypertrophic cardiomyopathy phenocopies (e.g., Noonan syndrome and Fabry disease) were excluded.

Procedures

Randomization was performed with the use of interactive response technology (YPrime) and was stratified according to age (12 to <15 years or 15 to <18 years) and beta-blocker use (yes or no). Mavacamten therapy was initiated at a once-daily dose of 5 mg in patients with a body weight of 45 kg or greater at baseline or at a once-daily dose of 2.5 mg in patients with a body weight of 35 kg to less than 45 kg. The dose of mavacamten could be adjusted down (at weeks 5 and 9) or up (at weeks 12 and 24) by one dose level on the basis of echocardiographic assessment of the Valsalva left ventricular outflow tract gradient and LVEF.

End Points and Safety

The primary end point was the change in left ventricular outflow tract pressure gradient provoked by the Valsalva maneuver from baseline to week 28.

Variable	Mavacamten (N = 23)	Placebo (N = 21)
Demographic characteristics		
Age — yr	14.7±1.7	14.6±1.7
Female sex at birth — no. (%)	8 (35)	5 (24)
Race or ethnic group — no. (%)†		
White	15 (65)	15 (71)
Black or African American	3 (13)	0
Asian	0	2 (10)
Unknown	1 (4)	1 (5)
Not reported	4 (17)	3 (14)
Geographic region — no. (%)		
United States	15 (65)	14 (67)
Australia, Canada, or Europe	8 (35)	7 (33)
Clinical characteristics		
Body weight — kg	71.1±19.1	67.4±18.6
Hypertrophic cardiomyopathy genotype — no. (%)		
Pathogenic or likely pathogenic mutation	12 (52)	12 (57)
Variant of uncertain significance	5 (22)	6 (29)
Negative	5 (22)	2 (10)
Missing	1 (4)	1 (5)
Background therapy for hypertrophic cardiomyopathy — no. (%)‡		
Beta-blocker	19 (83)	18 (86)
Calcium-channel blocker	3 (13)	2 (10)
Disopyramide	4 (17)	5 (24)
NYHA functional class — no. (%)		
II	19 (83)	18 (86)
III	4 (17)	3 (14)
Median NT-proBNP (IQR) — pg/ml§	1776 (1226–2816)	1294 (670–2702)
Median high-sensitivity cardiac troponin I (IQR) — pg/ml¶	36.1 (13.2–168.0)	22.7 (14.5–59.6)
Echocardiographic measures		
LVOT gradient — mm Hg		
Resting	64.8±30.9	65.2±38.1
During a Valsalva maneuver	78.4±34.1	80.8±47.4
After exercise	89.5±42.8	104.7±51.7
LVEF — %	69.0±3.9	67.4±4.1
Maximal left ventricular wall thickness — mm	28.3±6.0	24.7 ±7.1
E/e' ratio		
Lateral	14.3±8.6	12.5±6.9
Septal**	18.8±7.1	14.9±4.6
Average**	16.7±7.1	13.6±5.3
Presence of mitral regurgitation — no. (%)		
None	1 (4)	1 (5)
Mild	13 (57)	13 (62)
Moderate	8 (35)	5 (24)
Moderate to severe	1 (4)	2 (10)
Peak oxygen uptake — ml/kg/min††	26.1±7.1	26.1±7.6

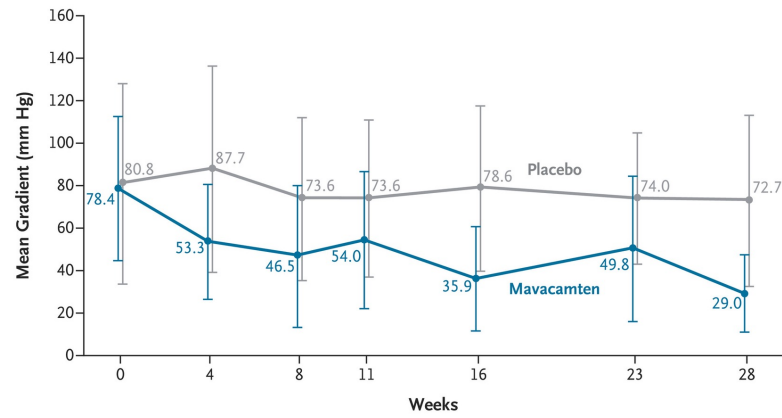
Outcomes

End Point	Mavacamten (N = 23)		Placebo (N = 21)		Difference vs. Placebo (95% CI)
	No. of Patients Evaluated	Least-Squares Mean Change (95% CI)	No. of Patients Evaluated	Least-Squares Mean Change (95% CI)	
Primary end point					
Change from baseline to week 28 in Valsalva LVOT gradient — mm Hg	23	–48.5 (–63.0 to –34.0)	20	–0.5 (–18.7 to 17.6)	–48.0 (–67.7 to –28.3)†
Secondary efficacy end points					
Change from baseline to week 28 in resting LVOT gradient — mm Hg	23	–39.0 (–50.9 to –27.0)	20	8.1 (–5.0 to 21.2)	–47.0 (–62.7 to –31.4)
Change from baseline to week 28 in postexercise LVOT gradient — mm Hg	16	–31.2 (–46.3 to –16.1)	16	10.5 (–5.5 to 26.6)	–41.7 (–59.7 to –23.7)
Change from baseline to week 28 in maximal LV wall thickness — mm	23	–2.5 (–3.7 to –1.3)	20	–0.7 (–2.1 to 0.7)	–1.8 (–3.4 to –0.2)
Change from baseline to week 28 in E/e' ratio					
Lateral	23	–3.8 (–5.4 to –2.3)	19	–0.6 (–2.3 to 1.1)	–3.2 (–5.2 to –1.3)
Septal	22	–3.5 (–5.1 to –1.8)	20	–0.7 (–2.6 to 1.2)	–2.8 (–5.0 to –0.5)
Average	22	–3.7 (–5.0 to –2.4)	19	–0.4 (–1.8 to 1.1)	–3.4 (–5.1 to –1.6)
Change from baseline to week 28 in HCM5Q SoB domain score — points‡	19	–1.1 (–2.4 to 0.2)	16	–0.8 (–2.3 to 0.6)	–0.3 (–2.0 to 1.5)

Safety

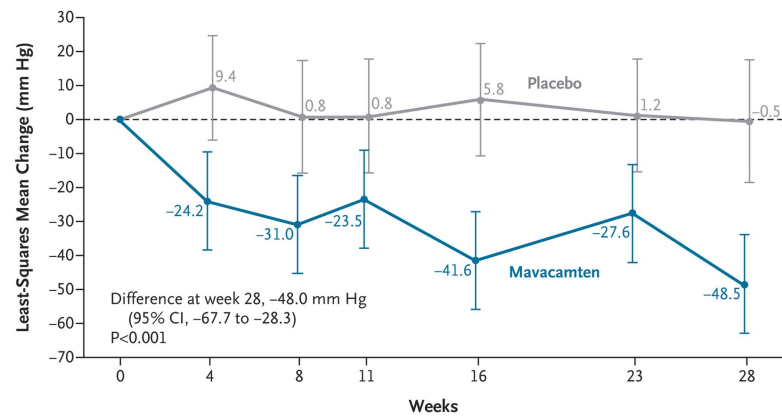
Adverse Event	Mavacamten (N = 23)	Placebo (N = 21)
	<i>no. of patients (%)</i>	
Any adverse event	18 (78)	17 (81)
Any treatment-related adverse event	2 (9)	3 (14)
Any serious adverse event	2 (9)	2 (10)
Any treatment-related serious adverse event	1 (4)	0
Any adverse event leading to an interruption in the trial regimen	1 (4)†	1 (5)
Any adverse event leading to discontinuation of the trial regimen	0	0
Any adverse event that resulted in death	0	0
Decrease in LVEF to <50%	0	0
Decrease in LVEF to ≤30%	0	0

A Valsalva LVOT Gradient over Time

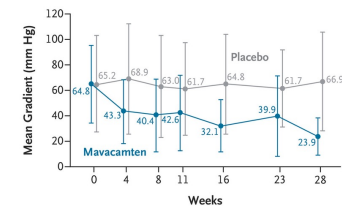


No. of Patients at Visit							
Placebo	21	21	20	20	20	20	20
Mavacamten	23	23	23	23	23	23	23

B Change in Valsalva LVOT Gradient

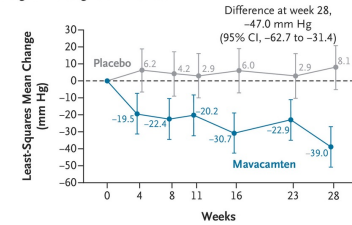


A Resting LVOT Gradient over Time



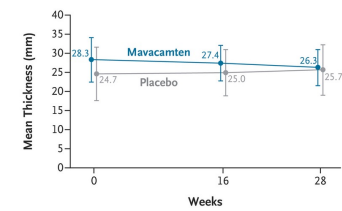
No. of Patients at Visit							
Placebo	21	21	20	20	20	20	20
Mavacamten	23	23	23	23	23	23	23

B Change in Resting LVOT Gradient



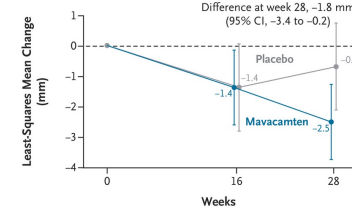
No. of Patients with Available Data							
Placebo	21	20	20	20	20	20	20
Mavacamten	23	23	23	23	23	23	23

C Maximal LV Wall Thickness over Time



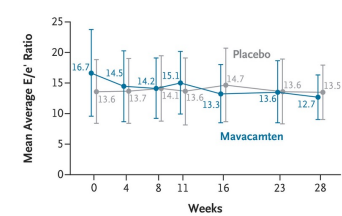
No. of Patients at Visit							
Placebo	21	20	20	20	20	20	20
Mavacamten	23	23	23	23	23	23	23

D Change in Maximal LV Wall Thickness

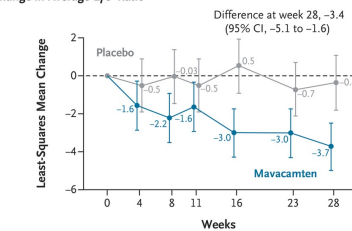


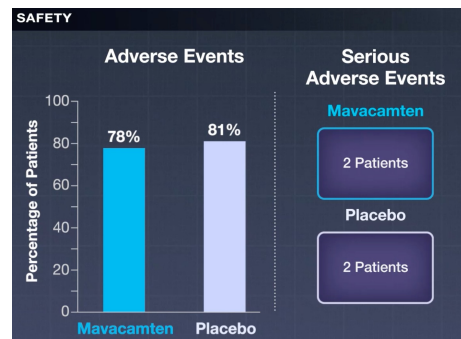
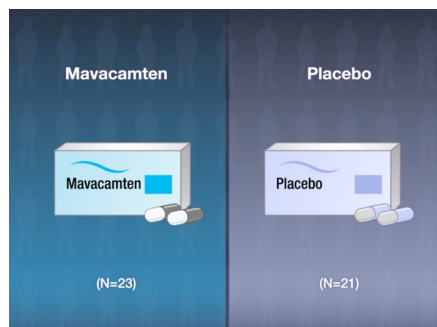
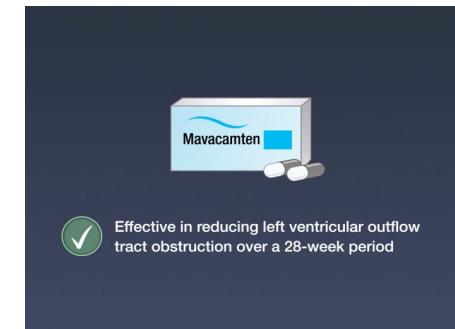
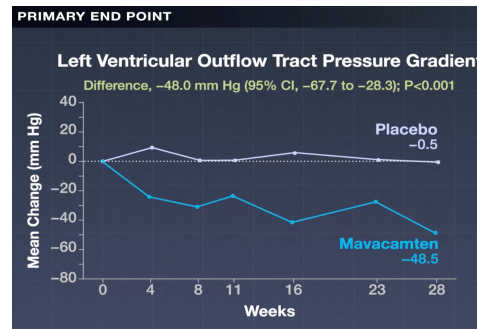
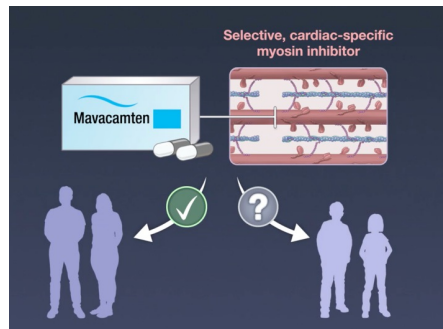
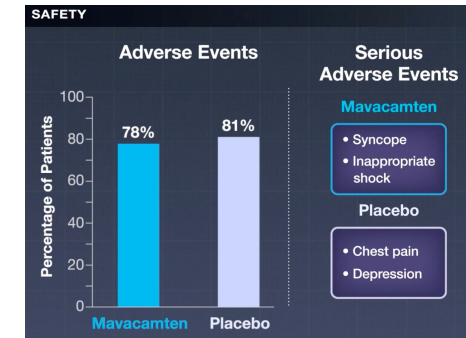
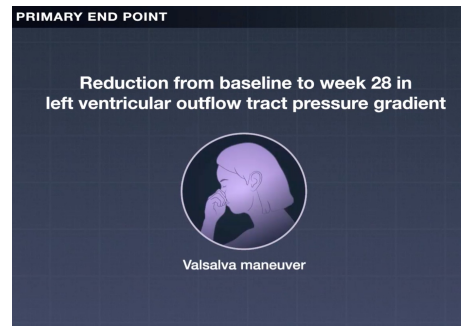
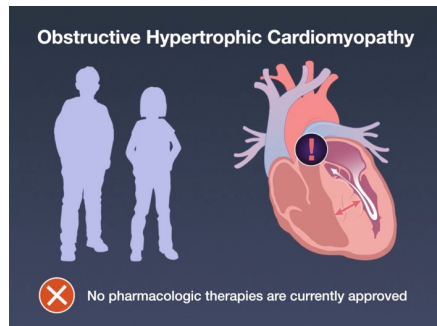
No. of Patients with Available Data							
Placebo	20	20	20	20	20	20	20
Mavacamten	23	23	23	23	23	23	23

E Average E/e' Ratio over Time



F Change in Average E/e' Ratio





Mavacamten (Handelsname *Camzyos*) ist ein negativ inotroper Wirkstoff. Es senkt die Kontraktilität des Herzmuskels, indem es als allosterischer Modulator direkt an das kardiale Myosin bindet und die übermäßige Anzahl von Aktin-Myosin-Querbrückenbindungen reduziert.

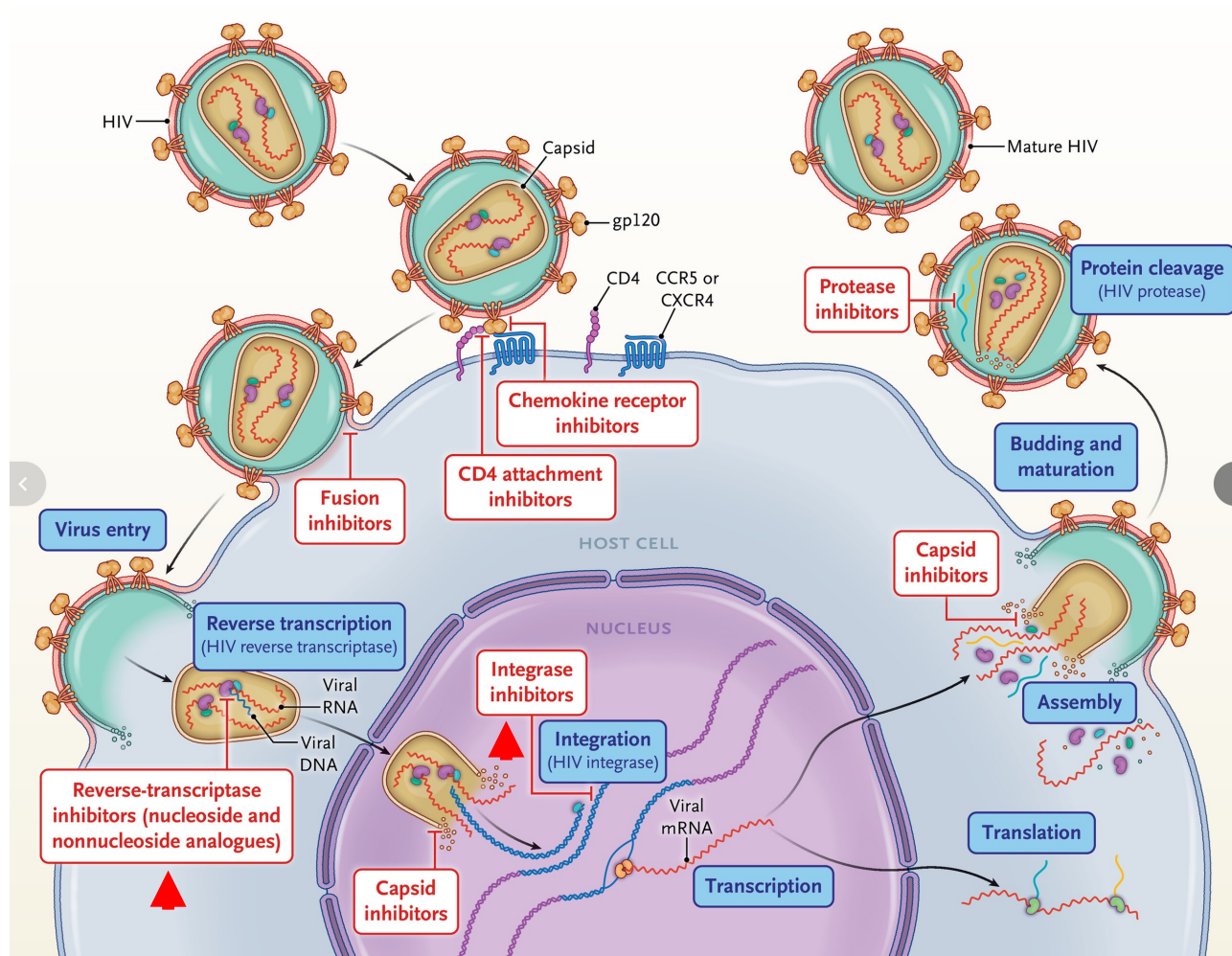
Antiretroviral Therapy

Summary

The development of effective treatment strategies for human immunodeficiency virus (HIV) infection is a major achievement. Antiretroviral drugs inhibit key steps in the viral replication cycle and consist of six mechanistic classes: HIV entry inhibitors, reverse-transcriptase inhibitors (both nucleosides and nonnucleosides), capsid inhibitors, integrase inhibitors, and protease inhibitors. Antiretroviral therapy (ART) suppresses viral replication, thereby enhancing immune function, decreasing morbidity and mortality, and preventing viral transmission. Consequently, ART is recommended for all persons with HIV infection. On the basis of randomized clinical trials, the Food and Drug Administration has approved 36 antiretroviral drugs for the treatment of HIV infection since 1987; of these, 28 are currently available in the United States, and combination ART regimens are used. Initial preferred ART regimens are potent, convenient, and unlikely to cause side effects and consist of an HIV integrase inhibitor with a high barrier to resistance combined with one or two nucleoside reverse-transcriptase inhibitors. In the majority of patients using current ART regimens, viral replication is durably suppressed below detectable levels. Patients receiving ART are monitored for virologic response over time, and if virologic failure occurs, the next regimen is selected on the basis of treatment history and the results of drug-resistance testing; often, antiretroviral drugs from new classes are administered. Today, the life expectancy of someone with HIV infection who consistently takes ART approaches that of the general population.

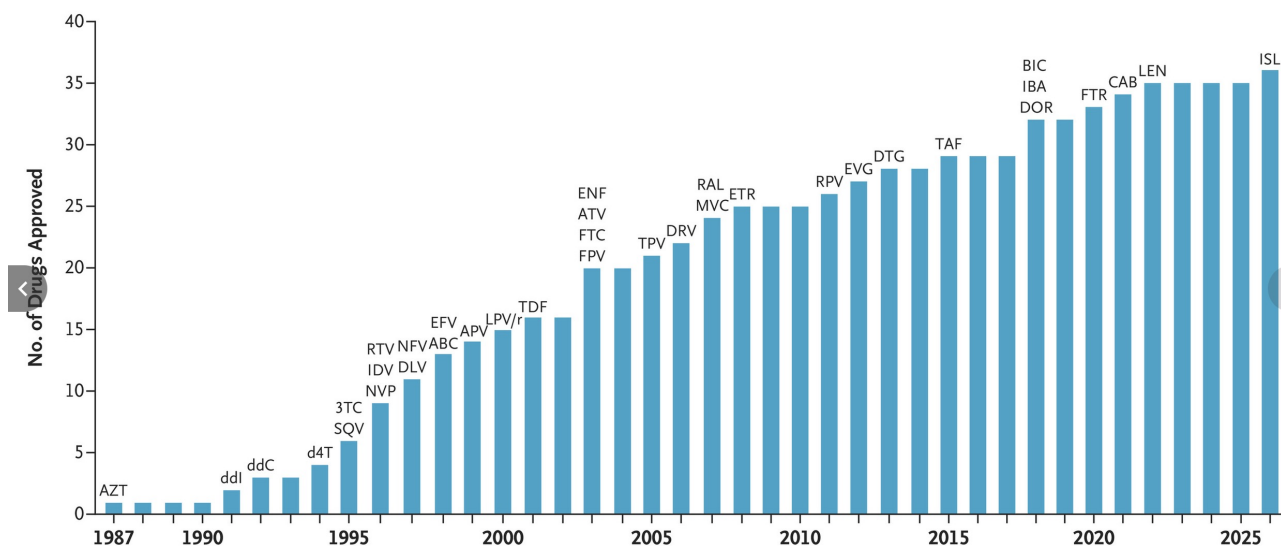
Antiretroviral Therapy

- Antiretroviral therapy (ART) is recommended for all persons with human immunodeficiency virus (HIV) infection, both for their own health and to prevent HIV transmission to others.
- Current first-line ART regimens are potent, convenient, and unlikely to be associated with unacceptable side effects and consist of one or two nucleoside reverse-transcriptase inhibitors together with an integrase inhibitor administered as one- or two-pill, once-daily therapy.
- In persons with suppressed HIV RNA levels, changing ART regimens (e.g., for regimen simplification or because of toxic effects) is usually successful if there is no drug resistance.
- In persons with virologic failure, changing ART regimens warrants a review of the ART history and results of drug-resistance testing to design a new regimen, optimally with two or three fully active drugs.
- Today, the life expectancy of a person with HIV infection appropriately managed with ART is approaching that of the general population.
- Future ART innovations include once-weekly oral regimens, longer-acting fully injectable therapy, and novel delivery systems such as implants and patches.



Cycle of HIV Replication and Antiretroviral Mechanisms of Action.

Human immunodeficiency virus (HIV) replicates in the host CD4+ T lymphocyte through a series of steps (blue boxes): HIV attachment to the cell with fusion of membranes and entry into the cell, reverse transcription of viral RNA into viral DNA, migration to the nucleus, uncoating of the capsid, integration of transcribed viral DNA into the host-cell DNA, transcription of host-cell and viral RNA, translation of viral messenger RNA (mRNA) into viral proteins, assembly into new viral particles that bud off the cell, and then postbudding cleavage of viral precursor proteins for full maturation and infectiousness. Antiretroviral drugs (red boxes) work by inhibiting the specific steps and enzymes of the HIV replication cycle. The abbreviation gp120 denotes glycoprotein 120.



Food and Drug Administration Approval of Antiretroviral Drugs from 1987 through 2026.

On the basis of the results of clinical trials, the Food and Drug Administration (FDA) approved 36 antiretroviral drugs between 1987 and 2026 for the treatment of HIV infection. FDA-approved antiretroviral drugs that are no longer marketed are amprenavir (APV), delavirdine (DLV), didanosine (ddl), enfuvirtide (ENF), indinavir (IDV), saquinavir (SQV), stavudine (d4T), and zalcitabine (ddC). 3TC denotes lamivudine, ABC abacavir, ATV atazanavir, AZT zidovudine, BIC bictegravir, CAB cabotegravir, DOR doravirine, DRV darunavir, DTG dolutegravir, EFV efavirenz, ETR etravirine, EVG elvitegravir, FPV fosamprenavir, FTC emtricitabine, FTR fostemsavir, IBA ibalizumab, ISL islatravir, LEN lenacapavir, LPV/r lopinavir with ritonavir, MVC maraviroc, NFV nelfinavir, NVP nevirapine, RAL raltegravir, RPV rilpivirine, RTV ritonavir, TAF tenofovir alafenamide, TDF tenofovir disoproxil fumarate, and TPV tipranavir.

Generic Drug Name	Common Trade Names	Common Coformulations	Date of Approval
HIV capsid inhibitors			
Lenacapavir (LEN)	Sunlenca		2022
HIV entry inhibitors			
Fostemsavir (FTR)	Rukobia		2020
Ibalizumab (IBA)	Trogarzo		2018
Maraviroc (MVC)	Selzentry		2007
HIV integrase inhibitors			
Bictegravir (BIC)	Biktarvy	Bictegravir, tenofovir alafenamide, and emtricitabine	2018
Cabotegravir (CAB)	Vocabria, Cabenuva	Cabotegravir and rilpivirine (Cabenuva)	2021
Dolutegravir (DTG)	Tivicay, Triumeq, Dovato	Dolutegravir, abacavir, and lamivudine (Triumeq); dolutegravir and lamivudine (Dovato)	2013
Elvitegravir (EVG)	Vitekta, Stribild, Genvoya	Elvitegravir, cobicistat, tenofovir disoproxil fumarate, and emtricitabine (Stribild); elvitegravir, cobicistat, tenofovir alafenamide, and emtricitabine (Genvoya)	2012
Raltegravir (RAL)	Isentress		2007
HIV NNRTIs			
Doravirine (DOR)	Pifeltro, Delstrigo	Doravirine, tenofovir disoproxil fumarate, and lamivudine (Delstrigo)	2018
Efavirenz (EFV)	Sustiva		1998
Etravirine (ETR)	Intelence		2008
Nevirapine (NVP)	Viramune		1996
Rilpivirine (RPV)	Edurant, Complera, Odefsey	Rilpivirine, tenofovir disoproxil fumarate, and emtricitabine (Complera); rilpivirine, tenofovir alafenamide, and emtricitabine (Odefsey)	2011
HIV NRTIs			
Abacavir (ABC)	Ziagen, Kivexa	Abacavir and lamivudine (Kivexa)	1998
Emtricitabine (FTC)	Emtriva		2003
Islatravir (ISL)	Idvynso	Islatravir and doravirine	2026
Lamivudine (3TC)	Epivir		1995
Tenofovir alafenamide (TAF)	Vemlidy, Descovy	Tenofovir alafenamide and emtricitabine (Descovy)	2015
Tenofovir disoproxil fumarate (TDF)	Viread, Truvada, Cimduo	Tenofovir disoproxil fumarate and emtricitabine (Truvada); tenofovir disoproxil fumarate and lamivudine (Cimduo)	2001
Zidovudine (ZDV and AZT)	Retrovir		1987
HIV protease inhibitors			
Atazanavir (ATV)	Reyataz, Evotaz	Atazanavir and cobicistat (Evotaz)	2003
Darunavir (DRV)	Prezista, Prezcobix, Symtuza	Darunavir and cobicistat (Prezcobix); darunavir, cobicistat, tenofovir alafenamide, and emtricitabine (Symtuza)	2006
Lopinavir (LPV)	Kaletra	Lopinavir and ritonavir	2000
Nelfinavir (NFV)	Viracept		1997
Ritonavir (RTV)	Norvir		1996
Tipranavir (TPV)	Aptivus		2005

Guidelines of the Department of Health and Human Services for Initial Antiretroviral Regimens in Adults and Adolescents.

Mechanistic Class	No. of Pills per Day	Selected Considerations
Recommended for most people		
INSTI plus 2 NRTIs		
Bictegravir, tenofovir alafenamide, and emtricitabine†	1	
Dolutegravir plus tenofovir (either alafenamide or disoproxil fumarate) plus either emtricitabine or lamivudine‡	2 or 3	
INSTI plus 1 NRTI		
Dolutegravir and lamivudine§	1	Not currently recommended for patients with HIV RNA level >500,000 copies/mL¶ with concomitant hepatitis B infection, or without an HIV genotype result available
Recommended for people previously treated with cabotegravir as preexposure prophylaxis		
Pharmacologically boosted PI plus 2 NRTIs		
Cobicistat-boosted darunavir plus tenofovir alafenamide and emtricitabine	1	Drug–drug interactions with cobicistat
Cobicistat-boosted darunavir** or ritonavir-boosted darunavir plus tenofovir (either alafenamide or disoproxil fumarate) plus either emtricitabine or lamivudine‡	2 to 4	Drug–drug interactions with cobicistat or ritonavir
Alternative for certain clinical scenarios		
INSTI plus 2 NRTIs		
Dolutegravir, abacavir, and lamivudine††	1	Do not use if HLA-B*5701 is present
NNRTI plus 2 NRTIs		
Doravirine, tenofovir disoproxil fumarate, and lamivudine‡‡	1	
Doravirine plus tenofovir alafenamide and emtricitabine‡	2	
Rilpivirine, tenofovir alafenamide, and emtricitabine§§	1	Do not use if HIV RNA level is >100,000 copies/mL or CD4 count is <200 cells/μL
Pharmacologically boosted PI plus 2 NRTIs		
Cobicistat-boosted darunavir plus tenofovir alafenamide and emtricitabine	1	Drug–drug interactions with cobicistat
Cobicistat-boosted darunavir** or ritonavir-boosted darunavir plus tenofovir (either alafenamide or disoproxil fumarate) plus either emtricitabine or lamivudine‡ or abacavir and lamivudine¶¶	2 to 4	Drug–drug interactions with cobicistat or ritonavir

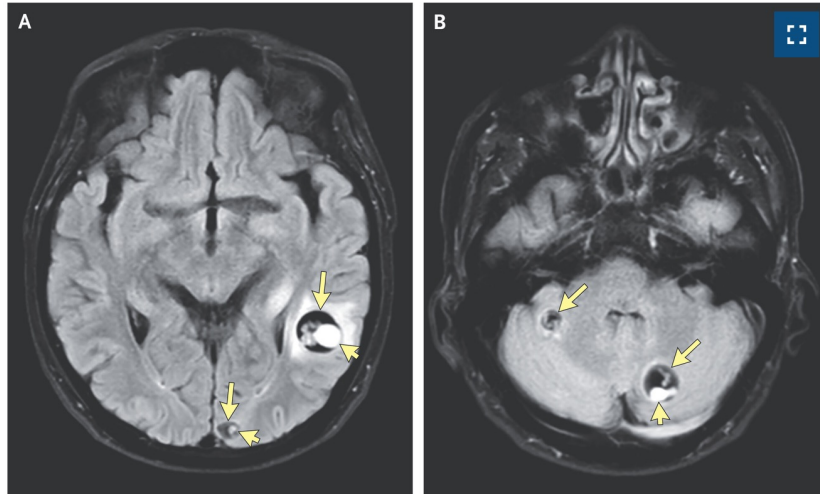
International Guidelines for Initial Antiretroviral Regimens Recommended for Most Adults and Adolescents.

Guideline	Three-Drug Regimens	Two-Drug Regimens
U.S. Department of Health and Human Services, 2026 ²⁵	Bictegravir, tenofovir alafenamide, and emtricitabine* Dolutegravir plus either tenofovir alafenamide or tenofovir disoproxil fumarate and either emtricitabine or lamivudine†	Dolutegravir and lamivudine‡
International Antiviral Society—USA Panel, 2024 ²⁶	Bictegravir, tenofovir alafenamide, and emtricitabine* Dolutegravir plus either tenofovir alafenamide or tenofovir disoproxil fumarate and either emtricitabine or lamivudine†	Dolutegravir and lamivudine‡
British HIV Association, 2025 ²⁷	Bictegravir, tenofovir alafenamide, and emtricitabine* Dolutegravir plus either tenofovir alafenamide or tenofovir disoproxil fumarate and either emtricitabine or lamivudine†	Dolutegravir and lamivudine‡
European AIDS Clinical Society, 2025 ²⁸	Bictegravir, tenofovir alafenamide, and emtricitabine* Dolutegravir plus tenofovir (either alafenamide or disoproxil fumarate) plus either emtricitabine or lamivudine† Doravirine plus tenofovir alafenamide and emtricitabine; or doravirine plus tenofovir disoproxil fumarate and either emtricitabine or lamivudine†§	Dolutegravir and lamivudine‡ or dolutegravir and emtricitabine
World Health Organization, 2025 ²⁹	Dolutegravir, tenofovir alafenamide or tenofovir disoproxil fumarate, and emtricitabine or lamivudine†¶	None

Conclusions

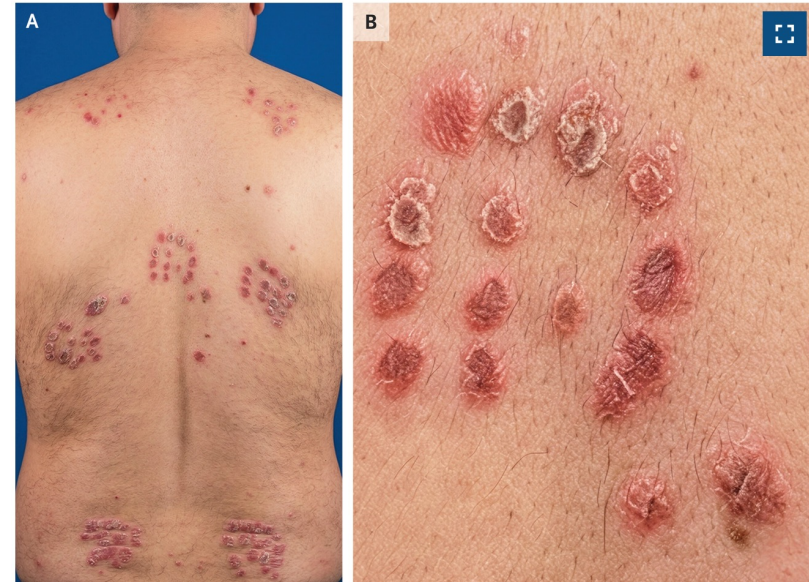
ART is recommended for all persons with HIV infection to control viremia, enhance immune function, decrease morbidity and mortality, and prevent transmission. The optimal choice of an ART regimen depends on consideration of virologic potency, convenience, side-effect profile, drug–drug interactions, patient factors, coinfections and coexisting conditions, and access. Currently recommended initial ART consists of two- or three-drug, coformulated, once-daily, oral regimens that are potent, convenient, and unlikely to be associated with unacceptable side effects. Newer innovations include weekly oral regimens, fully injectable regimens, and newer strategies of administration including infusions, implants, and patches. Persons with HIV infection who start ART promptly and take it consistently and whose treatment is managed appropriately have a life expectancy approaching that of the general population and do not transmit HIV to others.

Neurocysticercosis



A previously healthy 52-year-old woman presented to the emergency department with a 4-month history of headaches and visual hallucinations and a 1-month history of incoherent speech. On physical examination, the patient was awake and alert but unable to follow simple commands. Her speech was fluent but nonsensical, with paraphasic errors and impairment in naming and repetition. Computed tomography of the head revealed several hypodense lesions with internal hyperdensities scattered throughout the brain. Electroencephalography showed posterior temporal interictal epileptiform discharges from the left side. Results of an analysis of cerebrospinal fluid were normal. Magnetic resonance imaging of the brain revealed cystic lesions (arrows) in the temporal and occipital lobes on the left side (Panel A, fluid-attenuated inversion recovery [FLAIR] image), in the cerebellar hemispheres (Panel B, FLAIR image) and frontal lobes on both sides, and in the parietal lobe on the right side. The cysts contained bright, eccentric nodules (arrowheads) representing the scolices (anterior end) of tapeworms, a finding known as the “dot-in-hole” sign that is pathognomonic for neurocysticercosis. A diagnosis of parenchymal neurocysticercosis was made. Treatment with praziquantel, albendazole, and adjunctive glucocorticoids was given, along with levetiracetam for suspected seizures. At follow-up 1 month after starting treatment, her symptoms had abated, and repeat imaging showed smaller cysts without scolices.

Koebner Phenomenon from Wet Cupping



A 35-year-old man with a history of moderate-to-severe plaque psoriasis presented to the dermatology clinic with new skin lesions. His psoriasis had been in remission for the previous 18 months while he was receiving treatment with risankizumab. Two weeks before presentation, the patient had undergone wet cupping for the first time to treat low back pain. During the treatment, clusters of small incisions had been made at different sites across his back, after which glass cups had been applied with negative pressure to draw out small amounts of blood. On physical examination, well-demarcated, erythematous, scaly papules and plaques were present at the sites of the incisions on his shoulders and middle and lower back (Panel A; Panel B, middle of the back). A diagnosis of Koebner phenomenon from wet cupping was made. The Koebner phenomenon — also known as the isomorphic response — is the appearance of new skin lesions associated with a preexisting dermatosis (e.g., psoriasis, vitiligo, or lichen planus) at sites of previously uninvolved skin and result from cutaneous trauma. The phenomenon may occur even in patients with good control of their skin condition. The patient ceased wet cupping and continued to receive the same dose of risankizumab. At a 3-month follow-up visit, the skin lesions had abated.

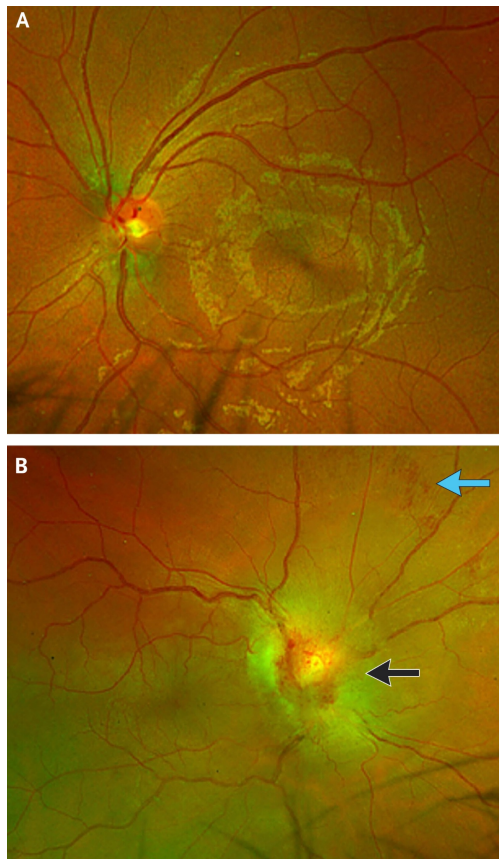
Case 21-2026: A 28-Year-Old Man with Headache and Vision Loss in the Right Eye

A 28-year-old man was admitted to this hospital for a **headache and vision loss in the right eye**.

The patient had been in his usual state of health until 2 weeks before the current admission, when a sore throat developed, along with facial swelling on the right side involving the right nasolabial fold, cheek, and lower eyelid; **test results were reportedly consistent with streptococcal infection**, and treatment with amoxicillin was started. Both the sore throat and the facial swelling resolved.

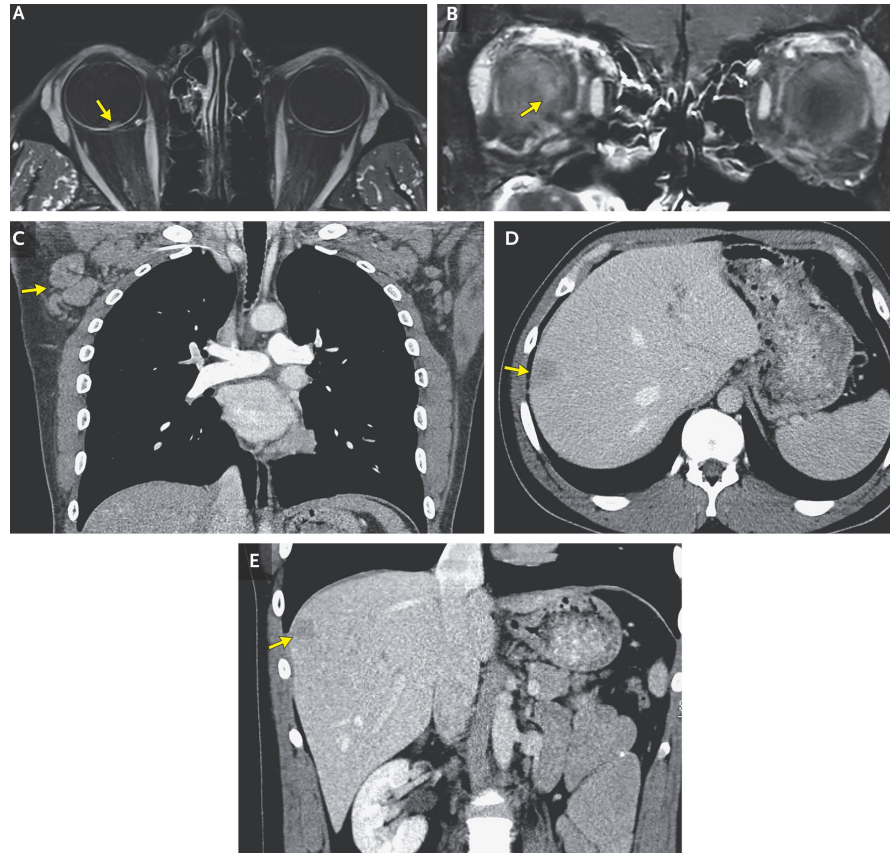
Seven days before the current admission, after the patient had abruptly lifted a very heavy object at work, he noticed floaters and flashes in his right eye. He also had neck pain, a right frontal headache, and right retro-orbital pain that worsened with eye movement. **During the next week, the patient noticed progressive vision loss in the right eye**. The night before the current admission, he was evaluated in the emergency department of an affiliated hospital that specializes in ophthalmology.

The temporal temperature was 36.3°C, the heart rate 73 beats per minute, the blood pressure 126/80 mm Hg, and the oxygen saturation 100% while the patient was breathing ambient air. The visual acuity was 20/20 in the left eye and **20/250 in the right eye**. On the Ishihara color test, **0 of 8 color plates** were identified correctly with the right eye, and 8 of 8 color plates were identified correctly with the left eye. The pupils were equal, round, and reactive to light, with a relative afferent pupillary defect in the right eye. On confrontation testing, a partial deficiency in the inferior nasal visual field of the right eye was detected. Automated perimetry revealed **severe generalized visual field loss in the right eye**, with normal findings in the left eye. The intraocular pressure was 9 mm Hg (reference range, 10 to 21) in both eyes.



Initial Fundusoscopic Photographs.

On presentation to the emergency department of the other hospital, a fundus photograph of the left eye (Panel A) shows no abnormalities, and a fundus photograph of the right eye (Panel B) shows optic disk swelling with hemorrhages (black arrow) and peripheral hemorrhages (blue arrow).



MRI and CT Studies.

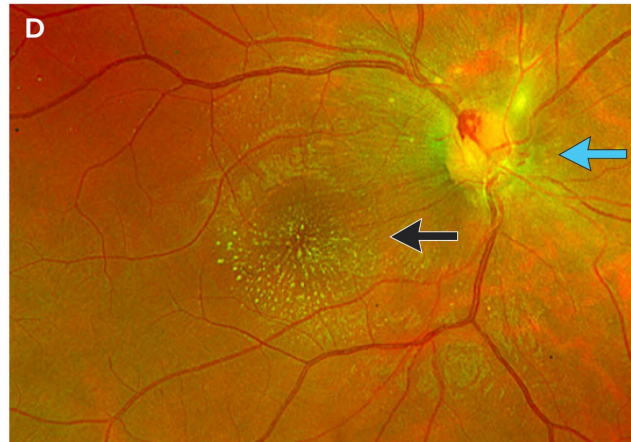
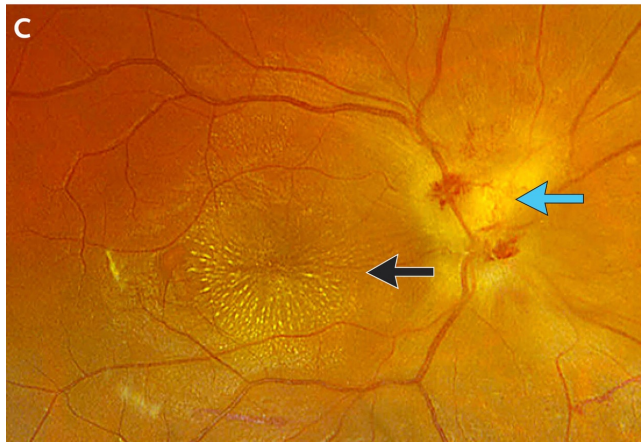
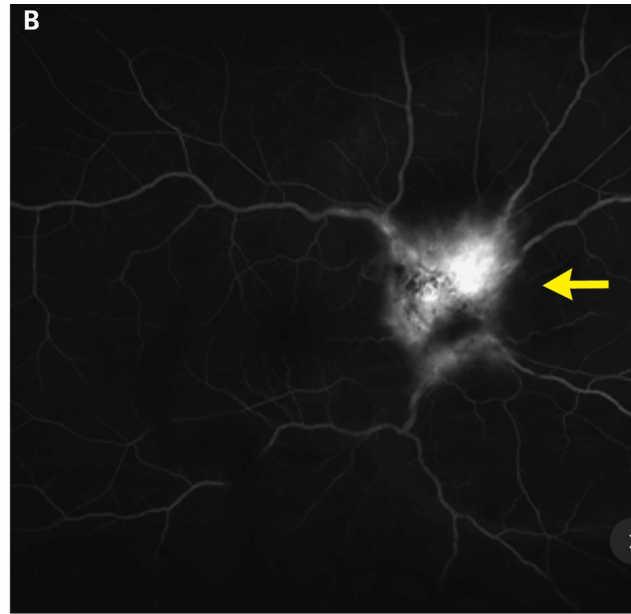
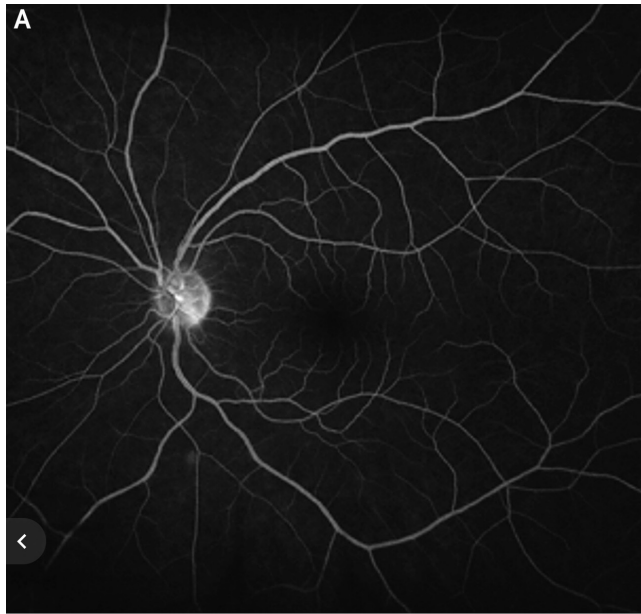
MRI of the brain and orbits was performed on presentation to the emergency department of the other hospital. An axial T1-weighted, fat-suppressed image (Panel A), obtained after the administration of contrast material, shows focal enhancement of the right optic nerve head without extension along the remainder of the optic nerve (arrow). A coronal T1-weighted postcontrast image (Panel B) confirms that the enhancement is localized to the junction of the optic nerve and the globe (arrow). CT of the chest, abdomen, and pelvis was performed on the fifth hospital day. A coronal CT scan of the chest (Panel C), obtained after the administration of intravenous contrast material, shows axillary lymphadenopathy that was present predominantly on the right side (arrow). Axial and coronal contrast-enhanced CT scans of the abdomen (Panels D and E, respectively) show an ill-defined hypodense lesion at the periphery of liver segment 8 (arrows).

C, rechts im Vergleich mit links.

The patient also had a **history of heavy alcohol use**, with consumption of up to one bottle of liquor daily; during the past month, the patient had consumed approximately one bottle of wine per day. He had no history of alcohol withdrawal. He **smoked marijuana daily** but used no other substances. He worked in construction and lived in a suburb of Boston **with his partner, two adult cats, and a dog**. He was **sexually active with men**; he reported having two partners in the preceding 6 months, with incomplete use of barrier protection. He took no medications, and he had no known adverse reactions to medications. There was no family history of vision problems.

The blood levels of electrolytes, alanine aminotransferase, aspartate aminotransferase, bilirubin, total protein, and albumin were normal, as were the complete blood count and differential count and the results of tests of kidney function and coagulation. The **erythrocyte sedimentation rate was 33** mm per hour (reference range, 0 to 14), and the blood level of **C-reactive protein was 7.1** mg per liter (reference value, <8.0). Blood specimens were obtained for culture. Tests for Lyme disease and syphilis were negative. A rapid test for human immunodeficiency virus **(HIV) types 1 and 2 was positive**. Treatment with intravenous ceftriaxone, vancomycin, ampicillin, and acyclovir was started.

Headache and vision changes persisted. On the fifth hospital day, a lumbar puncture was performed. Analysis of the CSF revealed 17 red cells per microliter (reference range, 0 to 5) and **235 nucleated cells per microliter** (reference range, 0 to 5), with 87% lymphocytes, 7% monocytes, 4% neutrophils, and 1% eosinophils; the CSF **glucose level was 40 mg per deciliter** (reference range, 50 to 75), and the total **protein level was 98 mg per deciliter** (reference range, 5 to 55).



Fluorescein Angiographic Images and Follow-up Fundus Photographs.

Fluorescein angiography was performed on the sixth hospital day. An angiographic image of the left eye (Panel A) shows normal findings. An angiographic image of the right eye (Panel B) shows abnormal leakage at the optic disk (arrow). Fundus photographs of the right eye obtained on the tenth hospital day (Panel C) and 30 days later (Panel D) show optic disk swelling with hemorrhages (blue arrows) and a macular star (black arrows).

Optic neuritis is inflammation of the optic nerve. It is highly associated with autoimmune diseases like Multiple Sclerosis (MS) and typically features painful vision loss but a normal-looking retina. **Neuroretinitis is a specific subtype of optic neuritis that also involves the retina.** It is usually caused by infections (like cat-scratch disease), rarely causes pain, and is distinguished by fluid leakage forming a "macular star" pattern in the eye

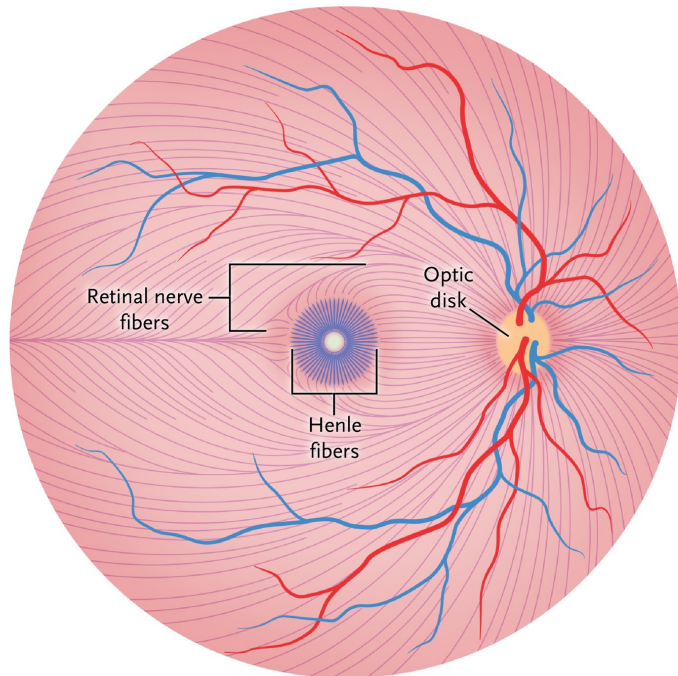
Optic Neuritis

Optic neuritis (inflammation of the optic nerve) is frequently idiopathic but most commonly occurs in the context of **autoimmune demyelinating disease**. It can also be associated with other autoimmune diseases, or it can be caused by **infection**. Isolated inflammation of the optic disk can occur in patients with optic neuritis, particularly in those with myelin oligodendrocyte glycoprotein antibody–associated disease (MOGAD), but it is less common than retrobulbar involvement. **Pain with eye movement is a hallmark of optic neuritis** ([Table 1](#)). The pain is hypothesized to result from traction on the optic nerve sheath at the origins of the medial and superior rectus muscles, which is why it most commonly occurs with intraorbital optic nerve involvement. This patient’s pain with eye movement, despite the presence of inflammation that was limited to the intraocular optic nerve, was somewhat unexpected. Regardless, he had no history of other neurologic symptoms, no radiologic features of demyelinating disease, and no evidence of a systemic autoimmune disorder. Optic neuritis remains a consideration, however.

Feature	Optic Neuritis	Neuroretinitis
Pain with eye movement	Common	Less prominent
Optic disk edema	None, mild, or moderate	Often marked
Macular star	Absent	Present (onset delayed 1 to 2 weeks after development of optic disk edema)
Optic nerve enhancement	Typical	Often absent

The macular star is composed of lipids deposited from exudative leakage that tracks along obliquely oriented, radially arranged Henle fibers in the outer plexiform layer. Neuroretinitis can be idiopathic, or it can be caused by immune-mediated or inflammatory diseases, but infection is the most common cause. **Approximately two thirds of cases of neuroretinitis are caused by bartonella infection,**

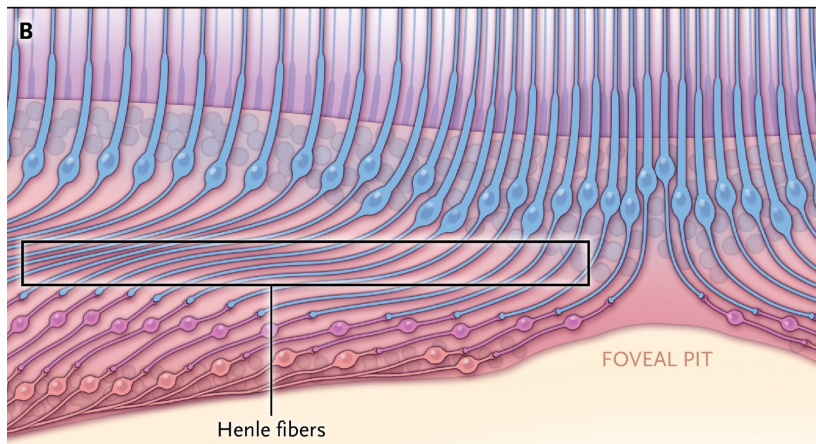
A



Formation of a Macular Star.

To minimize light scatter and maximize visual acuity, the inner retinal layers are laterally displaced at the fovea, forming the foveal pit. This arrangement requires oblique projection of photoreceptor axonal processes to reach synaptic terminals in the outer plexiform layer. These obliquely oriented fibers, known as the Henle fiber layer, have a radial arrangement that creates a starburst pattern along which deposits from exudative leakage can accumulate, forming a macular star. Panel A shows the radial orientation of Henle fibers. Panel B shows the oblique profile of Henle fibers as viewed on cross section.

B



Synthesis

This patient with cat exposure, a prodrome of **pharyngitis and facial swelling**, and newly diagnosed HIV infection presented with **unilateral optic disk edema**, without retrobulbar pathologic changes, that progressed to fulminant neuroretinitis with a **macular star and optic disk neovascularization** in the context of ipsilateral regional lymphadenopathy and hepatic lesions. This is a compelling narrative for **bartonella infection**, possibly with disseminated disease affecting the liver in the context of **HIV-1 infection**. I suspect that the diagnostic test in this patient's case was positive for antibodies against bartonella.

Diagnostic Testing

Early testing in this patient confirmed the diagnosis of HIV-1 infection of unknown duration and moderate immunocompromise. Key subsequent diagnostic tests that showed negative results included three sputum smears that were negative for acid-fast bacilli, an interferon- γ release assay that was nonreactive for *Mycobacterium tuberculosis*, negative Venereal Disease Research Laboratory testing, and negative testing for CSF levels of *Toxoplasma gondii* IgG and IgM.

On **hospital day 10**, results of tests of the patient's blood sample that had been obtained on hospital day 5 became available; **testing for *Bartonella henselae* IgG was positive**, with a titer of 1:4096. The *B. henselae* IgM titer was less than 1:20. These findings, along with optic nerve and retinal findings, strongly supported the diagnosis of bartonella neuroretinitis. Bacterial, fungal, and mycobacterial CSF cultures remained without growth.

Discussion of Management

Cat scratch disease is the most common manifestation of *B. henselae* infection. Features include fever, malaise, anorexia, and tender regional lymphadenopathy, which typically occur 1 to 2 weeks after infection with *B. henselae*. Visceral involvement is less common and can include hepatosplenomegaly, meningoencephalitis, bacteremia, and bacillary angiomatosis. Ocular symptoms, which are uncommon, include Parinaud oculoglandular syndrome involving the anterior segment of the eye. Ocular manifestations involving the posterior segment are varied and can include optic neuritis, neuroretinitis, and macular exudates, as in this patient.

Posterior-segment ocular disease (defined as any pathologic condition affecting posterior eye structures, specifically the vitreous, retina, choroid, and optic nerve) associated with *B. henselae* occurs in approximately 4% of all cases of cat scratch disease. Among patients with *B. henselae* infection who have HIV infection, ocular disease is most common in those with late-stage HIV disease, typically with a CD4+ T-cell count below 50 per microliter. Neuroretinitis is characterized by optic disk edema with serous retinal detachment. The classic macular star formation seen in patients with bartonella neuroretinitis develops 2 to 4 weeks after the occurrence of optic disk edema due to inflammation of the disk vasculature with exudation through the outer plexiform layer. Exudates in the formation of a macular star were not initially present in this patient, perhaps owing to the short time interval between his presentation with optic disk edema and the initial retinal examination. Once present, the macular star can take 12 months to resolve

The entity that is now known as neuroretinitis was described in 1916 as “stellate maculopathy.”

However, this definition was challenged in 1977, when it was reported that optic disk edema generally precedes macular findings by 1 to 2 weeks. At an early stage, fluorescein angiography can be used to confirm pathologic disk edema. A high index of suspicion for neuroretinitis must be maintained even when only disk edema is detected, and follow-up funduscopy examinations performed at short intervals to evaluate for the development of a macular star can be critical in unexplained cases of optic neuropathy.

The inflammation associated with neuroretinitis causes optic nerve and macular edema, which has both lipid and aqueous components. The macular star associated with neuroretinitis develops because the lipid-rich exudate penetrates into, and becomes deposited in, the outer plexiform layer of the retina. The aqueous phase, however, penetrates beneath the sensory retina, where it can be identified as subretinal fluid. During the resolution of neuroretinitis, the subretinal fluid resolves much more quickly than the macular star, as was seen in this patient’s follow-up images obtained 4 weeks after the initiation of antibiotic treatment.

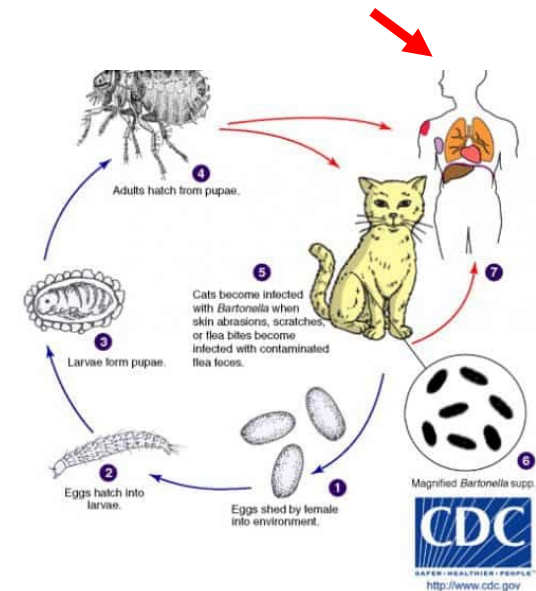
Different approaches to treating bartonella neuroretinitis have been proposed, with no consensus, and data are lacking from randomized trials. Although some small series have shown similar outcomes in treated and untreated patients, a larger series has suggested better outcomes with antibiotic therapy. Most clinicians treat with systemic antibiotics when vision-threatening ocular involvement is present. In immunosuppressed persons, adjunctive glucocorticoids are used in selected cases after other infectious causes have been ruled out.

Bartonella henselae ist ein **gramnegatives, stäbchenförmiges Bakterium**, das weltweit verbreitet ist und als Haupterreger der **Katzenkratzkrankheit (KKK)** gilt.

Übertragungsweg und Vorkommen

- **Hauptreservoir:** Haus- und Streunerkatzen dienen als Hauptwirt. Die Tiere sind selbst meist **völlig symptomlos**, tragen das Bakterium aber im Blut.
- **Vektoren:** Unter Katzen wird der Erreger primär durch den **Katzenfloh (*Ctenocephalides felis*)** bzw. dessen Kot übertragen. Auch Zecken kommen als Vektoren infrage.
- **Infektion des Menschen:** Erfolgt meist durch **Kratz- oder Bisswunden** einer infizierten Katze. Der **infektiöse Flohkot** gelangt dabei über die **Krallen des Tieres in die Wunde**. eine Übertragung von Mensch zu Mensch existiert nicht.

Und nun Auge



Adipöse und nicht-adipöse Menschen erhalten im Gesundheitssystem oft nicht dieselbe Versorgungsqualität, da Übergewichtige strukturelle Benachteiligungen, Stigmatisierung in Arztpraxen und Lücken bei der Kostenübernahme von Spezialtherapien durch die gesetzlichen Kassen erleben.

Gesetzlicher Anspruch vs. Realität

Gleicher Grundanspruch: Offiziell garantiert das deutsche Recht jedem Versicherten unabhängig vom Gewicht die Behandlung akuter Krankheiten.

Versorgungslücken: Spezifische Therapien gegen starkes Übergewicht (Adipositas) werden von den gesetzlichen Krankenkassen oft nur eingeschränkt oder gar nicht übernommen, weil Adipositas im Sozialgesetzbuch V noch nicht flächendeckend als eigenständige chronische Krankheit anerkannt ist.

Medikamenten-Ausschluss: Moderne Abnehmspritzen gelten rechtlich häufig als sogenannte Lifestyle-Arzneimittel und müssen von Betroffenen oft selbst bezahlt werden



Metabolic traits in obesity and normal BMI in industrialised countries: a multi-country analysis of national population-based studies

Summary

Background Effective treatments are available for obesity and for hypertension and hypercholesterolaemia, which mediate the cardiovascular and renal effects of obesity. Our aim was to compare blood pressure, cholesterol, and the use of antihypertensive and lipid-lowering medicines in people with obesity and normal weight and assess whether the BMI-associated excess risk has diminished.

Methods Our primary outcomes were mean systolic blood pressure (SBP), non-HDL cholesterol and HDL cholesterol, and the proportion of the participants who used antihypertensive and lipid-lowering medicines. We used data from 110 health surveys conducted from 1990 to 2024 with 978 425 participants aged 20–79 years sampled from national populations of seven countries: Japan, South Korea, Taiwan, Thailand, Finland, England, and the USA. We used graphical presentation and trend analysis to evaluate changes over time in these outcomes in participants in the normal BMI range (20.0 to <25.0 kg/m²), and changes in the difference between participants with obesity (separately for class I obesity [30.0 to <35.0 kg/m²] and class II and III obesity [BMI ≥35.0 kg/m²]) or overweight (25.0 to <30.0 kg/m²) and those in the normal BMI range.

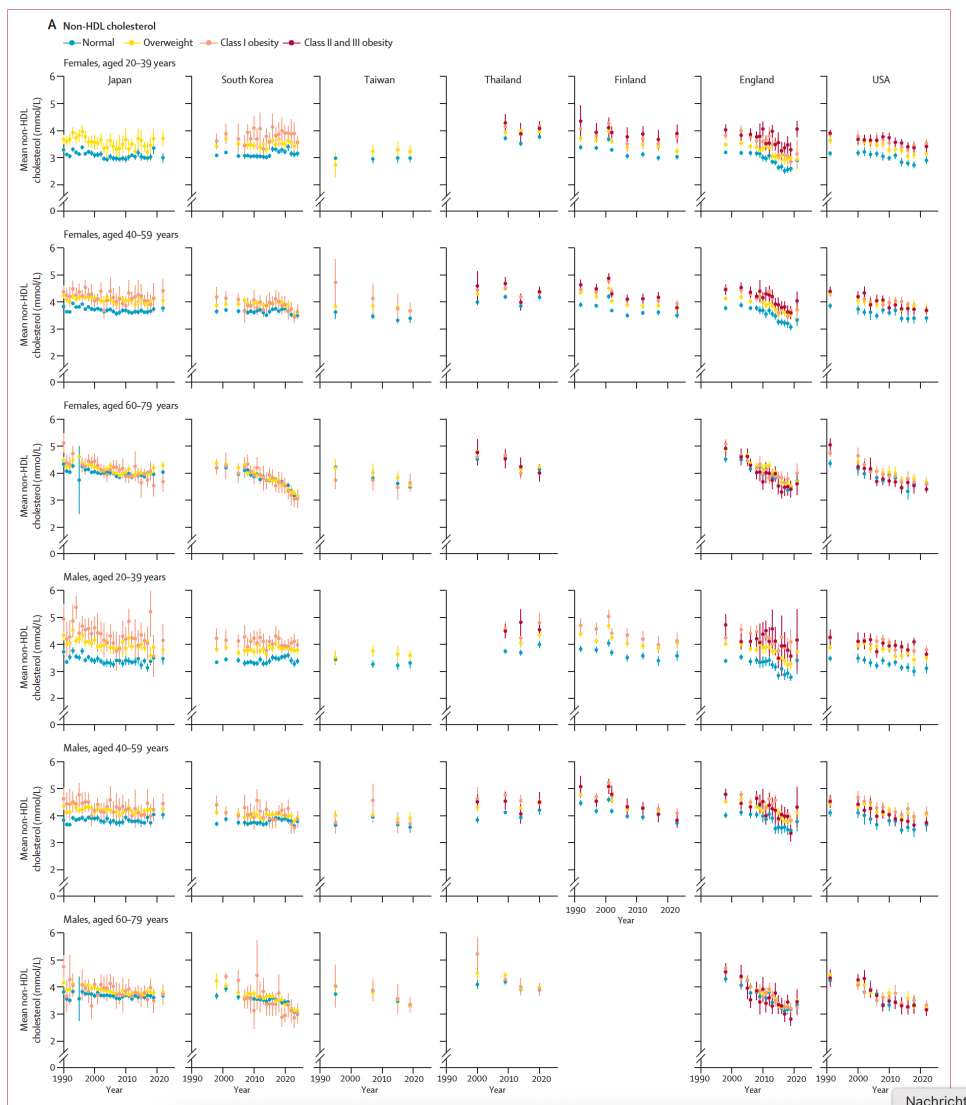
The obese have higher blood pressures and lipids than the non-obese.

Are blood pressure and cholesterol in the obese being lowered over time?

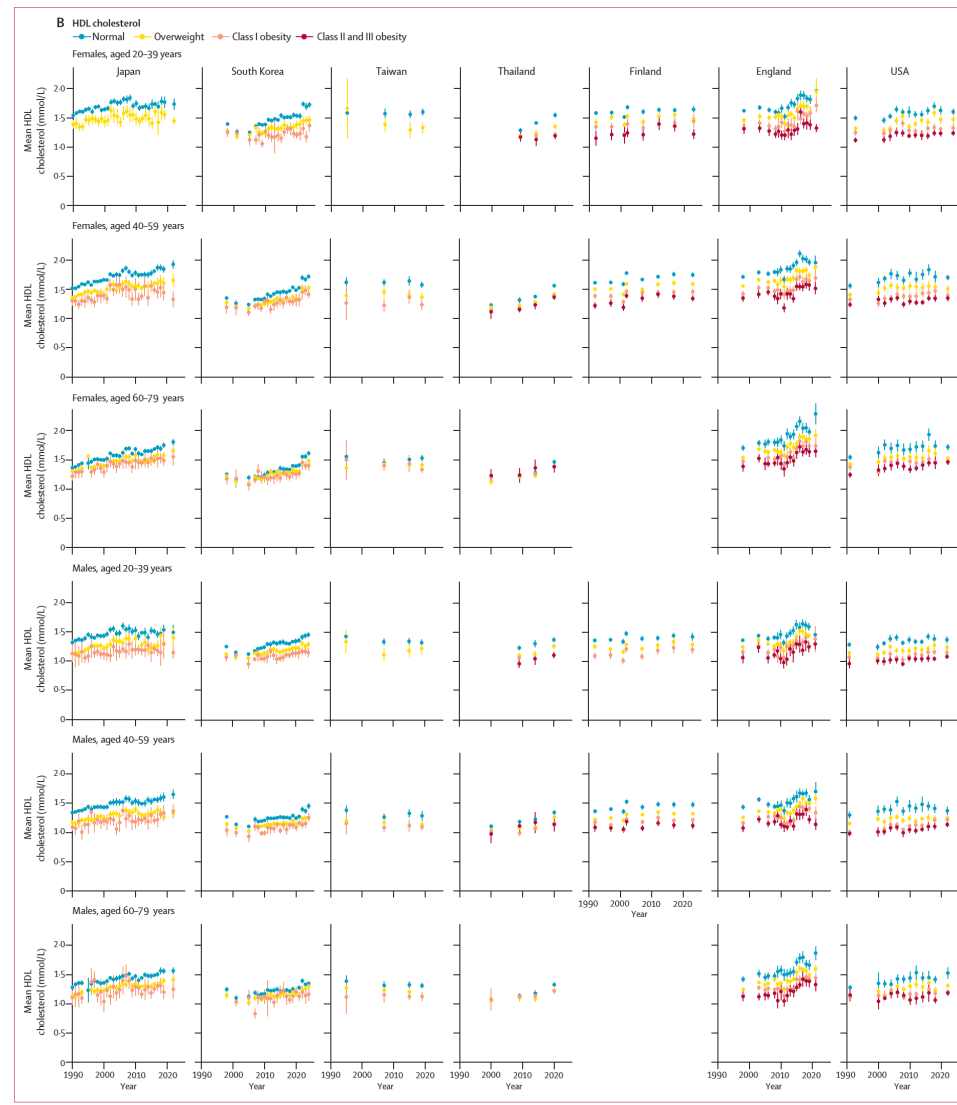
Is the effect similar to the „less“ obese?

Findings Mean non-HDL cholesterol and SBP declined over time, especially among those older than 40 years, with the notable exception of some sex-age groups in Thailand. When pooled across all countries, age groups, and obesity and overweight BMI ranges, the difference in mean non-HDL cholesterol with normal BMI became smaller by -0.05 mmol/L per decade (95% CI -0.07 to -0.03) for females and -0.07 mmol/L per decade (-0.09 to -0.05) for males. For SBP, the pooled estimate of change in the difference with normal BMI across all countries, age groups, and obesity and overweight BMI ranges was -0.7 mmHg per decade (95% CI -1.0 to -0.4) for females and -0.6 mmHg per decade (-0.9 to -0.4) for males. The declines were larger in individuals with obesity, especially class II and III obesity, than in normal BMI, leading to a convergence of these risk factors between obesity and normal BMI in people older than 40 years. As a result of these trends, in England, the USA, Thailand, South Korea, and Japan, older people with obesity often became indistinguishable from, or better off than, those with normal BMI in terms of non-HDL cholesterol and SBP. These trends accompanied a larger increase in the use of lipid-lowering and antihypertensive medicines in middle-aged and older people with obesity than in those with normal BMI. The pooled estimate for the increase in difference in lipid-lowering medicines compared with normal BMI across all countries, age groups, and obesity and overweight BMI ranges was 1.5 percentage points per decade (1.0–2.1) for females and 1.6 percentage points per decade (1.0–2.2) for males. For antihypertensive medicines, the pooled estimate was 0.7 percentage points per decade (0.3–1.0) for females and 2.0 percentage points per decade (1.3–2.8) for males. Mean HDL cholesterol increased more in people with normal BMI than those with obesity, leading to a divergence. For people younger than 40 years, there has been little change in the gap between those with obesity or overweight and those with normal BMI; young adults were rarely treated for high cholesterol or blood pressure regardless of their BMI.

Interpretation In industrialised countries, blood pressure and non-HDL cholesterol in older adults with obesity are increasingly similar to those with normal BMI, with higher use of antihypertensive and lipid-lowering medicines a possible driver of this convergence. There is nonetheless heterogeneity across countries in the extent of convergence. Young adults with obesity remain metabolically at higher risk than their counterparts with normal weight.



(Figure 1 continues on next page)



(Figure 1 continues on next page)

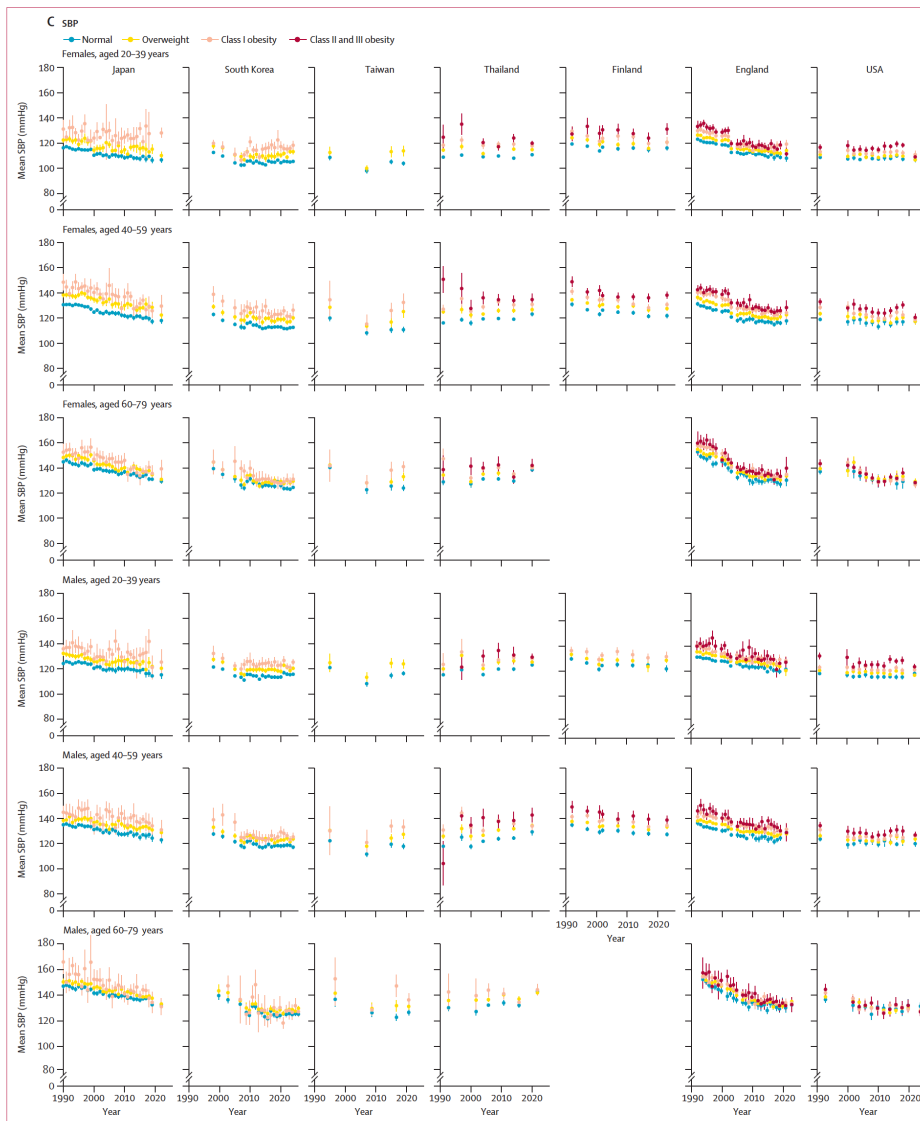


Figure 1: Trends in age-standardised mean non-HDL cholesterol, HDL cholesterol, and SBP, by BMI range

Each point represents one sex-age-BMI range group from one study; error bars show 95% CIs. See the appendix for the difference between obesity or overweight and normal BMI (pp 29–32), the datapoints together with fitted trends for normal BMI (pp 50–57), and the figure without exclusions based on number of participants (pp 82–85). Age range for data from Finland is 30–59 years, grouped into 30–39 years and 40–59 years. SBP=systolic blood pressure.

Treatment values for obese and non-obese are increasingly similar over time.

Research in context

Evidence before this study

We searched PubMed for articles published from database inception to Nov 10, 2025, with no language restrictions, using the following search terms: ("Body Mass Index"[mh] OR Obesity[mh:noexp] OR Overweight[mh:noexp] OR overnutrition[mh:noexp]) AND ("Blood Pressure"[mh] OR "Lipoproteins, LDL"[mh] OR "Lipoproteins, HDL"[mh] OR "Hypertension"[mh] OR "Dyslipidemias"[mh:noexp] OR "Hyperlipidemias"[mh] OR (cardiovascular[tiab] AND risk factor*[tiab])) AND ("body mass index group*[tiab] OR "BMI group*[tiab] OR "body mass index categor*[tiab] OR "BMI categor*[tiab] OR "body mass index range*[tiab] OR "BMI range*[tiab]) AND trend*[tiab] AND "Adult"[mh] AND "Humans"[mh] NOT (Clinical Trial[ptyp] OR Randomized Controlled Trial[ptyp] OR Comment[ptyp] OR Case Reports[ptyp])).

Many studies explored the association between BMI and blood pressure, lipids, or cardiovascular disease in specific cohorts, but these studies did not report time trends of these conditions and risk factors at different BMI ranges. These studies generally found that higher BMI is associated with higher blood pressure and LDL or non-HDL cholesterol, or with higher prevalence of hypertension and dyslipidaemia. Eight studies reported time trends in hypertension, mean blood pressure, dyslipidaemia, or cholesterol stratified by BMI. These studies were all conducted in single countries (the USA, England, Peru, Brazil, and Sweden), some using data from national populations and others from specific communities or subgroups of the population. Five studies found that hypertension prevalence or mean blood pressure decreased more in individuals in higher BMI ranges than those with a normal BMI. Four studies found

that there was a greater decrease of dyslipidaemia prevalence or serum cholesterol in people in higher BMI ranges than those with a normal BMI.

Added value of this study

To our knowledge, this is the first study that uses repeated population-based data from national populations of multiple countries to characterise blood pressure, cholesterol, and their respective treatments in people with obesity or overweight compared with those with a normal BMI. We used data from seven industrialised countries in Asia, Europe, and North America. We also evaluated changes in the difference in blood pressure and cholesterol between obesity or overweight and normal BMI and whether the differences have shrunk over decades when prevention and treatment of hypertension and hypercholesterolaemia have been increasingly incorporated into public health programmes and clinical guidelines.

Implications of all the available evidence

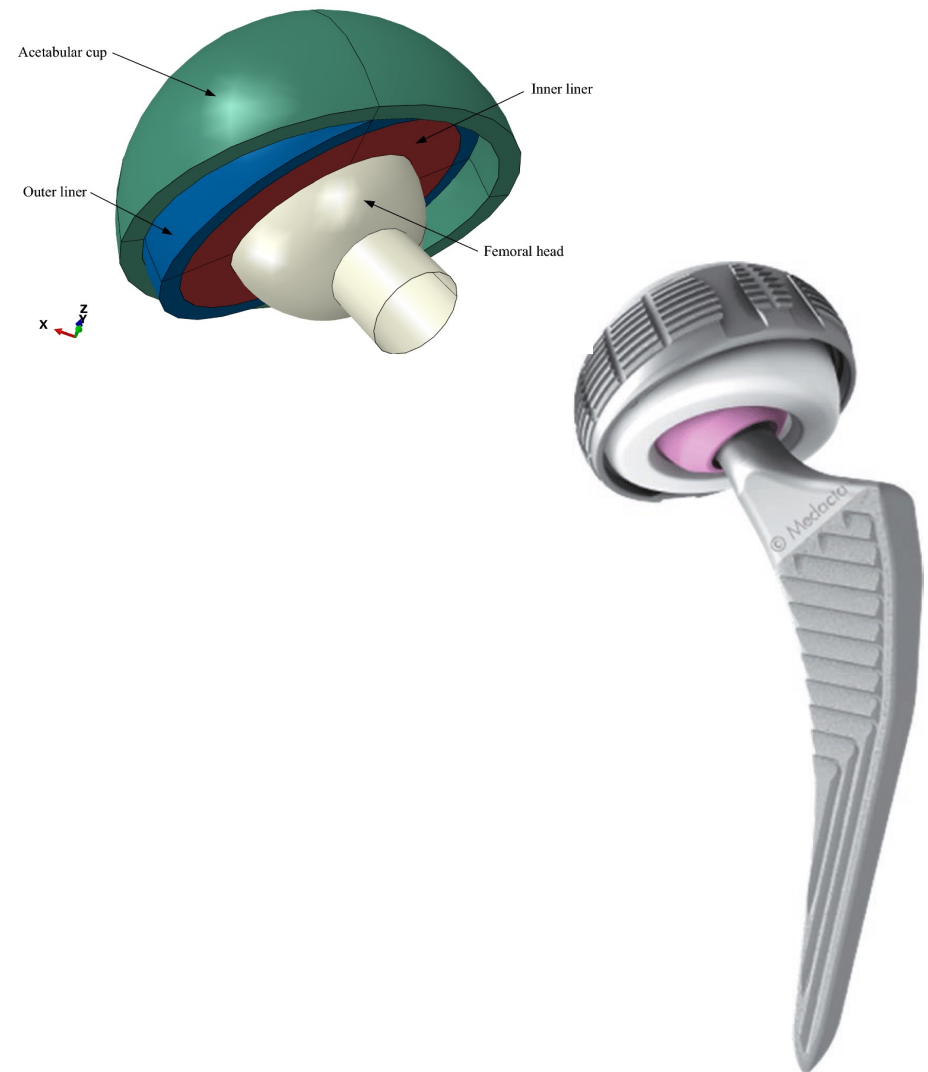
In industrialised countries, there have been major shifts in the adverse cardiometabolic traits associated with obesity and the age groups affected by them since the last decade of the 20th century. As a result, systolic blood pressure and non-HDL cholesterol of older people with obesity are similar to, and in some cases even lower than, those of people with a normal BMI. This finding might be partly because older people with obesity use more antihypertensive and lipid-lowering medicines than those with a normal BMI. Young adults with obesity remain metabolically at higher risk than their counterparts with a normal BMI and should be a focus of prevention and, when relevant, treatment.

Eine **Dual-Mobility-Hüfttotalendoprothese (Dual-Mobility-HTEP)** ist ein fortschrittliches Implantatsystem für den Hüftersatz, das speziell entwickelt wurde, um das Risiko einer **Luxation (Ausrenken des Gelenks)** drastisch zu senken.

Im Gegensatz zu einer klassischen Hüftprothese verfügt dieses System über **zwei bewegliche Artikulationsflächen (Gelenkebenen)** statt nur einer.

Die innere Gelenkebene: Ein kleinerer Kopf (meist aus Keramik oder Metall) bewegt sich in einem dicken Kunststoff-Inlay (Polyethylen).

Die äußere Gelenkebene: Dieses mobile Kunststoff-Inlay bewegt sich wiederum frei innerhalb der metallischen Hüftpfanne, die im Becken verankert ist.



Dual mobility versus
standard to reduce
dislocations

(introduced about
2010)

**Dual mobility versus standard cups in total hip replacement
for displaced femoral neck fractures (Duality):
an international, multicentre, randomised, controlled,
superiority trial**

Summary

Background Dislocation is the most common early surgical complication in patients with hip fractures treated with total hip replacement (THR). Dual mobility total hip replacement (DM-THR) was developed to increase joint stability, but no randomised trial has investigated its efficacy and safety. We aimed to compare the risk of dislocation in patients receiving DM-THR versus conventional THR.

Methods We included people aged 65 years or older with a displaced femoral neck fracture attending 20 Swedish and 24 UK hospitals in this pragmatic, registry-based, randomised superiority trial. Participants eligible for THR were randomly allocated in a 1:1 ratio to either DM-THR or standard THR with the use of remote, web-based, country-specific sequences. Neither participants nor members of the direct clinical care teams were masked, but research investigators and statisticians were masked until the trial analysis was completed. The primary outcome was dislocation of the index joint, treated with closed reduction or open surgery within 1 year, analysed in the modified intention-to-treat population including all consenting participants receiving any type of hip replacement and excluding those with major protocol deviations. This trial is registered with ClinicalTrials.gov (NCT03909815) and ISRCTN11895196.

Findings Between Jan 9, 2020, and April 2, 2024, 2934 eligible patients were screened, of whom 1334 were not enrolled, mainly due to surgeon's preference (n=560), because they had already been treated at the time of screening (n=257), or because informed consent was not obtained (n=213). 1600 participants (64% female, 36% male) were thus randomly assigned to either DM-THR (n=798) or THR (n=802). After exclusion of 34 participants due to prespecified protocol deviations, 1566 participants (97·9%) contributed to the modified intention-to-treat analysis. A dislocation, the primary outcome, occurred in ten (1·3%) of 779 participants in the DM-THR group and in 33 (4·2%) of 787 in the THR group (adjusted hazard ratio 0·27, 95% CI 0·13–0·56; p<0·0001).

Interpretation The use of DM-THR substantially reduced the risk of dislocation and of any surgical complication among people treated with THR after a displaced femoral neck fracture. DM-THR can thus be recommended for this group of patients.

	DM-THR (n=779)	THR (n=787)
Age, years	76.1 (6.0)	76.1 (6.1)
Sex		
Female	492 (63.2%)	518 (65.8%)
Male	287 (36.8%)	269 (34.2%)
Country		
Sweden	669 (85.9%)	676 (85.9%)
UK	110 (14.1%)	111 (14.1%)
Fracture type		
Femoral neck fracture	752 (96.5%)	738 (93.8%)
Basocervical fracture	27 (3.5%)	49 (6.2%)
BMI	24.8 (4.2)	24.7 (4.1)
ASA score		
1	63 (8.1%)	73 (9.3%)
2	440 (56.5%)	444 (56.4%)
3	257 (33.0%)	251 (31.9%)
4*	9 (1.2%)	11 (1.4%)
Missing	10 (1.3%)	8 (1.0%)
Surgical approach		
Direct lateral	369 (47.4%)	402 (51.1%)
Posterior	409 (52.5%)	383 (48.7%)
Missing	1 (0.1%)	2 (0.3%)
Type of replacement, n (%)		
Cemented THR	609 (78.2%)	657 (83.5%)
Hybrid THR	144 (18.5%)	94 (11.9%)
Reverse hybrid THR	2 (0.3%)	2 (0.3%)
Cementless THR	2 (0.3%)	8 (1.0%)
Cemented hemiarthroplasty	22 (2.8%)	26 (3.3%)
Cup diameter (mm)	50 (38–66)	50 (42–64)
Femoral head diameter† (mm)	28 (22–54)	32 (22–52)
Femoral neck length		
Standard	590 (75.7%)	597 (75.9%)
Extended	155 (19.9%)	137 (17.4%)
Extra extended	6 (0.8%)	15 (1.9%)
Missing	28 (3.6%)	38 (4.8%)
EQ-5D-5L utility score‡	0.82 (0.20)	0.81 (0.23)
EQ-5D-5L VAS score§	77.3 (19.4)	76.6 (20.4)

Data are mean (SD), number (%), or median (range). Percentages might not total 100 because of rounding. The modified intention-to-treat population included all randomly assigned participants, except 34 who were randomly assigned without properly documented consent or were unable to consent, had other fracture types than those specified in the inclusion criteria, or were treated with internal fixation, preventing them from experiencing the primary outcome of reduction of a hip replacement. ASA=American Society of Anesthesiologists. DM-THR=dual mobility total hip replacement. THR=total hip replacement. VAS=visual analogue scale.

*One participant with ASA score 5 was grouped together with ASA score 4. †Head diameters larger than 36 mm are due to inclusion of participants treated with hemiarthroplasty in the modified intention-to-treat analysis. ‡Utility scores on the EQ-5D-5L questionnaire range from -0.594 to 1, with higher scores indicating better quality of life. Scores were calculated according to the UK index valuation. Data were available for 372 participants in the DM-THR group and 352 participants in the THR group. §Scores on the VAS of the EQ-5D-5L questionnaire range from 0 to 100, with higher scores indicating better quality of life. Baseline data were available for 373 participants in the DM-THR group and 357 participants in the THR group.

Table 1: Participant demographical characteristics by randomised treatment (modified intention-to-treat population)

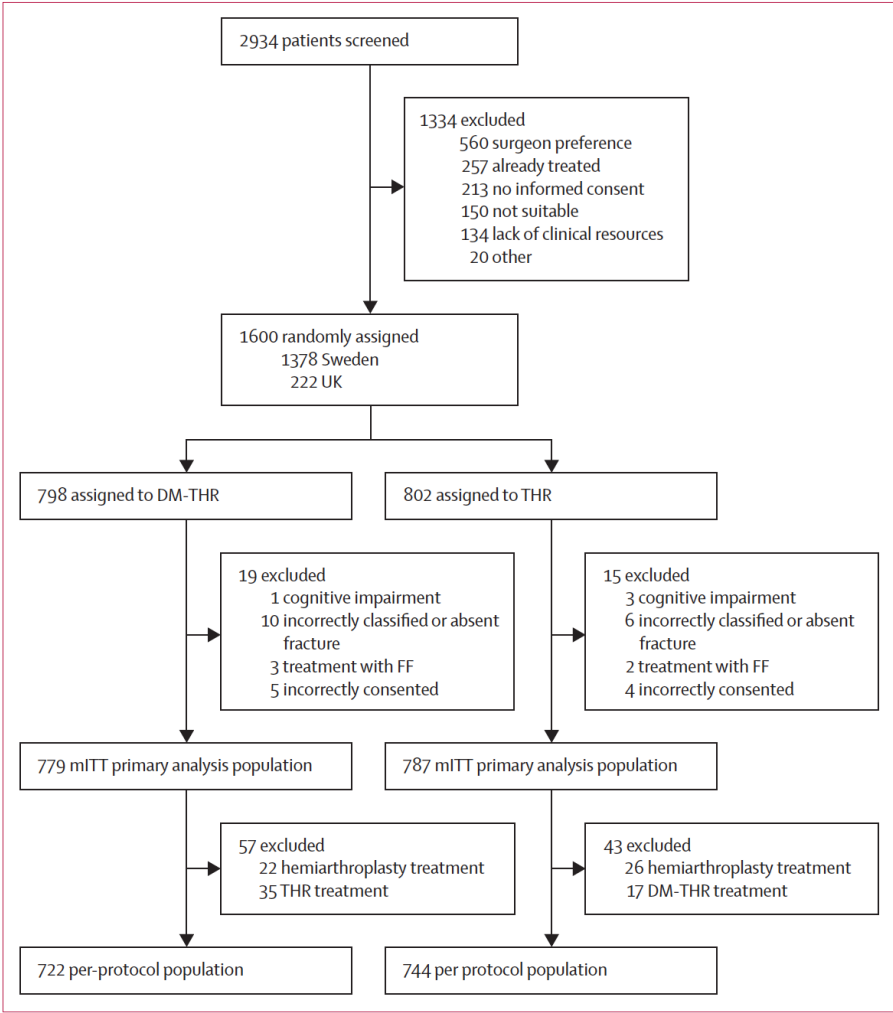


Figure 1: Trial profile

DM-THR=dual mobility total hip replacement. FF=fracture fixation. mITT=modified intention-to-treat. THR=total hip replacement.

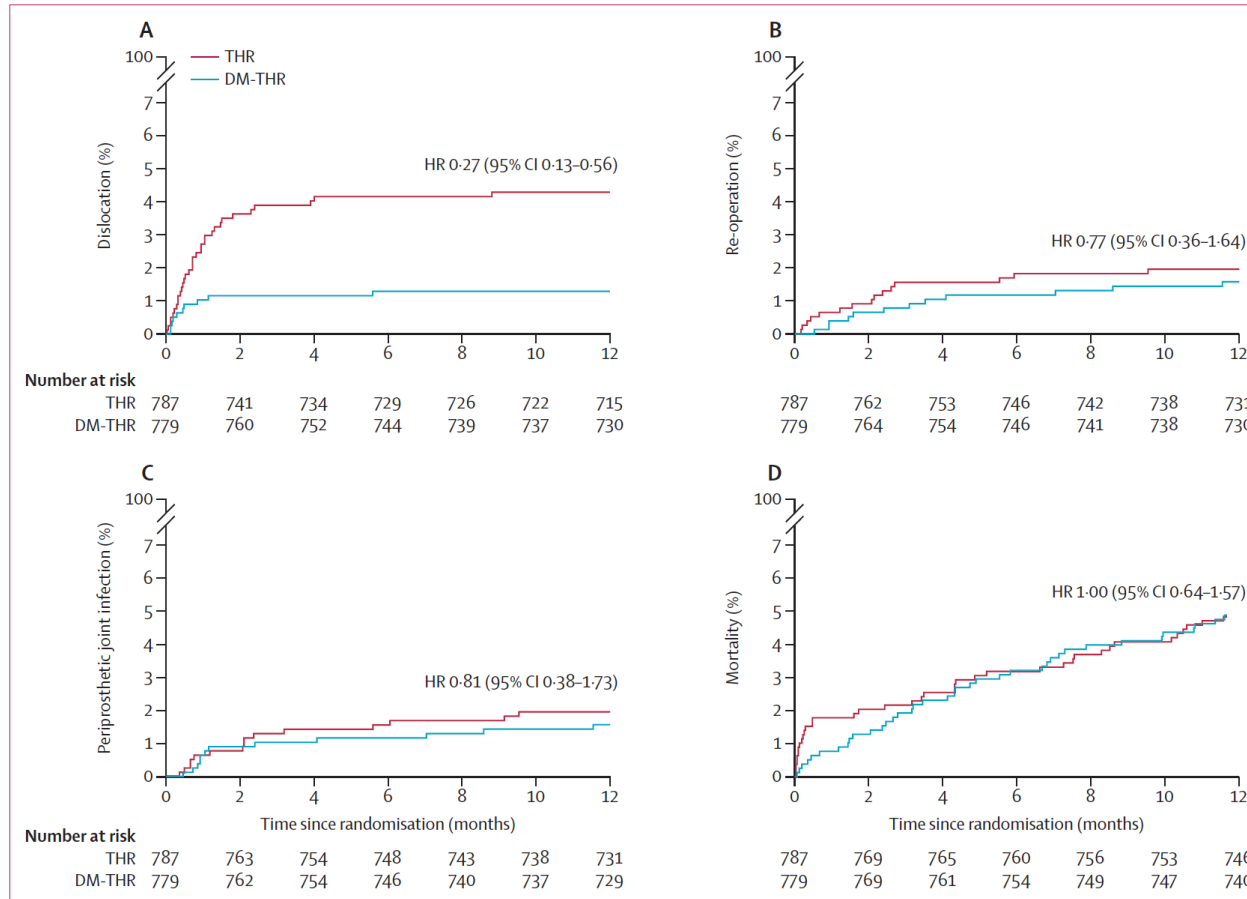


Figure 2: Cumulative incidence of dislocation and secondary outcomes within 1 year after randomisation

Kaplan-Meier estimates for the cumulative incidence of dislocation (A), any re-operation (B), prosthetic joint infection (C), and mortality (D), in the modified intention-to-treat population according to randomised treatment within 1 year after randomisation. Numbers at risk are given below each panel, and HRs derived from adjusted Cox regression models are given with 95% CIs. DM-THR=dual mobility total hip replacement. HR=hazard ratio. THR=total hip replacement.

	DM-THR (n=779)	THR (n=787)	Adjusted HR* (95% CI)	p value
Primary outcome				
Dislocation within 1 year	10 (1.3%)	33 (4.2%)	0.27 (0.13 to 0.56)	<0.0001
Dislocation treated with closed reduction	9 (1.2%)	25 (3.2%)	NA	NA
Dislocation treated with open reduction	1 (0.1%)	8 (1.0%)	NA	NA
Secondary outcomes				
Prosthetic joint infection within 1 year	12 (1.5%)	15 (1.9%)	0.81 (0.38 to 1.73)	0.59
Re-operation within 1 year	12 (1.5%)	15 (1.9%)	0.77 (0.36 to 1.64)	0.49
Any surgical complication within 1 year†	23 (3.0%)	48 (6.1%)	0.45 (0.27 to 0.74)	0.001
Mortality within 90 days	15 (1.9%)	17 (2.2%)	0.86 (0.43 to 1.74)	0.68
Mortality within 1 year	38 (4.9%)	38 (4.8%)	1.00 (0.64 to 1.57)	1.0
Dislocation or mortality within 1 year	48 (6.2%)	69 (8.8%)	0.66 (0.46 to 0.95)	0.026
EQ-5D-5L utility score,‡ mean (SD)	0.77 (0.20)	0.77 (0.20)	0.00 (−0.03 to 0.03)§	0.79
EQ-5D-5L VAS score,¶ mean (SD)	75.6 (17.8)	74.7 (17.9)	0.87 (0.66 to 1.14)	0.31

DM-THR=dual mobility total hip replacement. HR=hazard ratio. NA=not available. OR=odds ratio. THR=total hip replacement. VAS=visual analogue scale. *The adjusted HR is for DM-THR as compared with THR with 95% CI; adjusted Cox proportional hazard models include age, sex, surgical approach, and country. †Any surgical complication indicates that at least one of dislocation, prosthetic joint infection, or re-operation was recorded for a participant within 1 year. Not all dislocations and prosthetic joint infections resulted in re-operations, and some patients had more than one of these complications. ‡Mean (SD) utility scores on the EQ-5D-5L questionnaire range from −0.594 to 1, with higher scores indicating better quality of life. Scores calculated according to the UK index valuation. §Data presented as mean difference (95% CI). ¶Mean (SD) scores on the VAS of the EQ-5D-5L questionnaire range from 0 to 100, with higher scores indicating better quality of life. ||Results from proportional odds logistic regression model; odds ratios for having lower values in VAS (ie, worse outcome) in DM-THR compared with THR. Model includes baseline VAS score and randomised treatment. Baseline score was entered as numeric variable modelled as restricted cubic spline with four knots placed at 5, 35, 65, and 95 percentiles.

Table 2: Trial outcomes (modified intention-to-treat population)

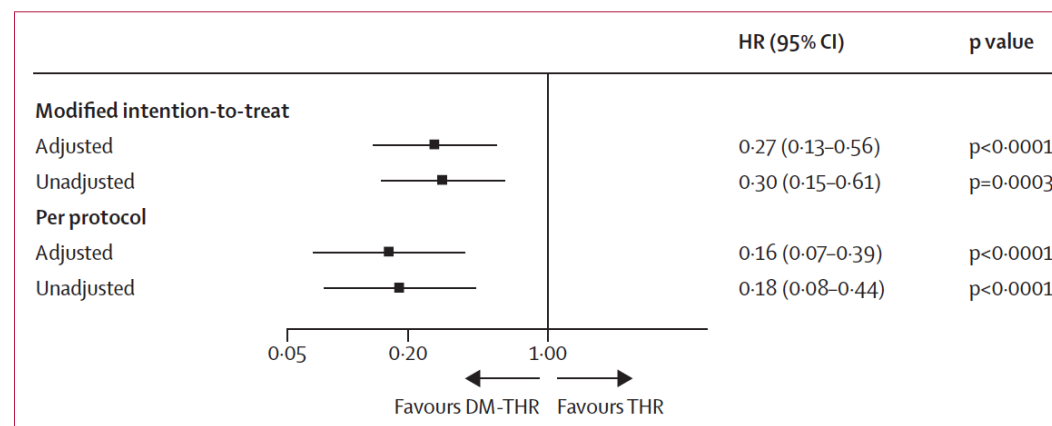


Figure 3: Adjusted and unadjusted HRs for the risk of dislocation within 1 year after randomisation, in the modified intention-to-treat and per-protocol populations

Effects are HRs derived from Cox proportional hazard models for DM-THR as compared with THR with 95% CI. Models are adjusted for age, sex, surgical approach, and country. DM-THR=dual mobility total hip replacement. HR=hazard ratio. THR=total hip replacement.

Research in context

Evidence before this study

Total hip replacement (THR), in which both the ball and the socket of the hip are replaced, is recommended for older, active individuals with a displaced fracture of the femoral neck. The most common surgical complication after THR for hip fracture is dislocation, occurring in 6–10% of patients. Dual mobility (DM)-THR, in which the small ball of the THR is encased in a much larger plastic ball, creating two articulations, was developed to reduce dislocation risk. We performed a search between Dec 17, 2018 and July 10, 2020, and then repeated the search iteratively throughout the trial, of MEDLINE, Embase, Web of Science, the Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects, Health Technology Assessment database, Epistemonikos, Proquest Dissertations and Theses, and National Technical Information Service, for evidence comparing the risk of dislocation in DM-THR with conventional THR. We used combinations of the terms “(femoral) fracture”, “hip (s)”, “(trans-) cervical”, “intracapsular”, “arthroplasty”, “replacement”, “hip prosthesis”, “joint prosthesis”, and “randomised controlled trial”, with Boolean operators and truncation as appropriate. Multiple non-randomised studies and two small randomised trials suggest that DM-THR might be associated with a reduced dislocation risk—but increased risk of prosthetic joint infection. A Cochrane review published in 2022

identified few, small randomised trials and encouraged researchers to investigate the efficacy of DM-THR. To date, no pivotal trial has provided definitive evidence of the efficacy and safety of DM-THR compared with standard THR.

Added value of this study

The Duality trial randomly allocated 1600 participants aged 65 years or older treated with THR for a displaced femoral neck fracture at 20 hospitals in Sweden and 24 in the UK to either DM-THR or standard THR. 98% of participants provided data for the primary intention-to-treat analysis. The study found a statistically significant and clinically important reduced risk of dislocation for DM-THR after 1 year. The risk of any surgical complication was also reduced in the DM-THR group; there were no differences between groups regarding other secondary outcomes.

Implications of all the available evidence

The Duality trial provides evidence that DM-THR reduces the risk of the most common surgical complication for patients with a displaced femoral neck fracture treated with a THR. This information is important for clinicians and policy makers alike, and implementation into clinical practice is both feasible and desirable to improve care of older adults with this common and hazardous injury.

Der Hauptunterschied zwischen **unfraktioniertem** und **fraktioniertem (niedermolekularem) Heparin** liegt in der **Molekülgröße**, der **Wirkungsweise auf Gerinnungsfaktoren** sowie der **Notwendigkeit von Blutwertkontrollen**.

Unfraktioniertes Heparin (UFH / Standardheparin)

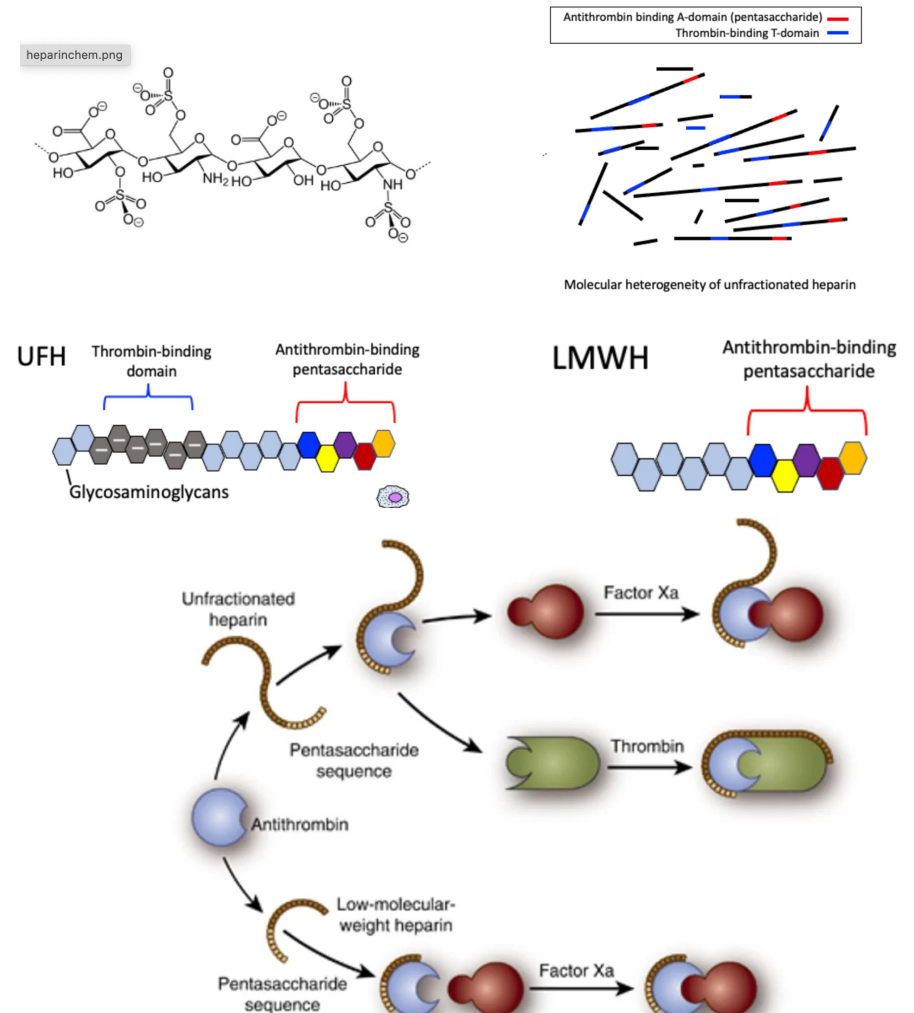
Molekülgröße: Große, ungespaltene Polysaccharidketten.

Wirkung: Hemmt sowohl **Faktor IIa (Thrombin)** als auch **Faktor Xa** über Antithrombin in gleichem Maße.

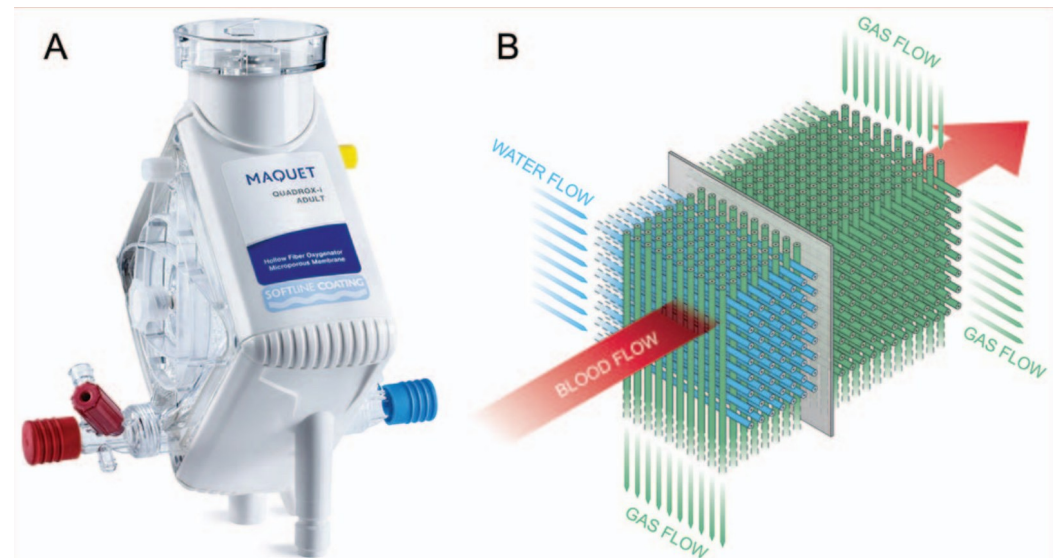
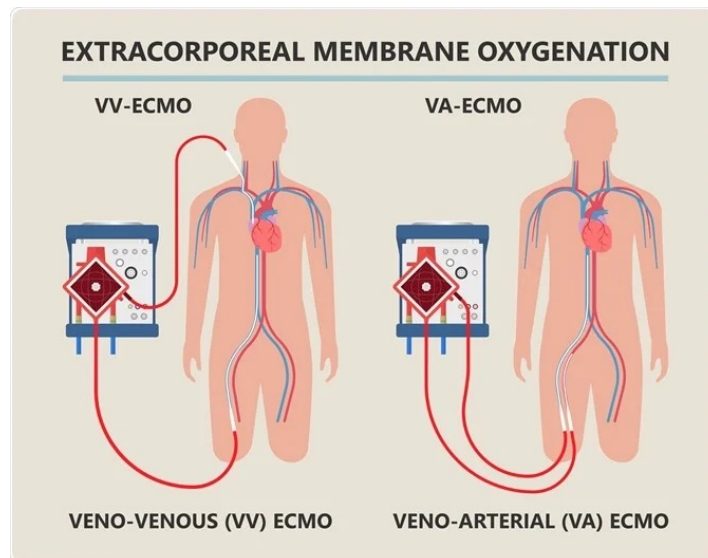
Überwachung: Erfordert eine regelmäßige Kontrolle der Blutgerinnung über die **aPTT** (partielle Thromboplastinzeit).

Gegenmittel: Durch **Protamin** zu 100 % neutralisierbar.

Anwendung: Häufig bei akutem Bedarf, während Operationen (z. B. Herz-Kreislauf-Chirurgie) oder bei schwerer **Niereninsuffizienz**.



Ein **ECMO-Membranaustausch** (Circuit- oder Oxygenatortausch) beschreibt das medizinische Verfahren, bei dem das künstliche Lungenelement (der Oxygenator) oder das gesamte Schlauchsystem einer ECMO-Maschine während einer laufenden Lebenserhaltungstherapie gewechselt werden muss. Da Patienten auf ECMO oft vollständig von diesem System abhängig sind, handelt es sich hierbei um ein hochkritisches Manöver, das von einem spezialisierten Team (Perfusionisten und Intensivmedizinern) unter extremem Zeitdruck durchgeführt wird



Standard-dose unfractionated heparin versus low-dose unfractionated heparin and low-molecular-weight heparin in extracorporeal life support (RATE): an open-label, randomised, non-inferiority trial

Summary

Background In patients receiving extracorporeal membrane oxygenation (ECMO), standard practice is full-dose intravenous unfractionated heparin (UFH) targeting an activated partial thromboplastin time of 2·0–2·5 times baseline to reduce thrombotic risk. This approach can increase bleeding without further reducing thrombosis compared with low-dose UFH. Robust evidence to guide anticoagulation targets is absent because anticoagulation targets in ECMO have never been assessed in a sufficiently powered randomised trial. We aimed to determine whether low-dose UFH or therapeutic low-molecular-weight heparin (LMWH) is non-inferior to standard-dose UFH in patients receiving ECMO.

Methods In this open-label, three-arm, randomised, non-inferiority trial at seven Dutch intensive care units (ICUs), adults aged 18 years or older supported with veno-venous or veno-arterial ECMO at the ICU without vital indication for full-dose anticoagulation (eg, mechanical mitral valve) were randomly assigned to intravenous standard-dose UFH (activated partial thromboplastin time 2·0–2·5 times baseline), intravenous low-dose UFH (1·5–2·0 times baseline), or therapeutic subcutaneous LMWH. The primary outcome was a composite of severe bleeding during ECMO support, severe thromboembolic complications during ECMO support, or all-cause mortality at 6 months, and was assessed in all randomly assigned patients with deferred informed consent and 6-month follow-up data according to the intention-to-treat principle. Non-inferiority was met if the upper 95% CI limit for the absolute risk difference was less than 7·5 percentage points. This trial is registered at ClinicalTrials.gov (NCT04536272) and the Dutch trial register (NL7976).

Findings Between Oct 22, 2020, and Sept 12, 2024, 330 patients were enrolled: 110 were randomly assigned to standard-dose UFH, 110 to low-dose UFH, and 110 to LMWH. Of 330 enrolled patients, 320 (225 [70%] males, 95 [30%] females; median age 56 years [IQR 45–65]; 255 [80%] White ethnicity) were analysed at 6 months. The composite primary outcome occurred in 87 (81%) of 107 patients with standard-dose UFH, 78 (72%) of 108 with low-dose UFH (absolute risk difference –9·1 percentage points [95% CI –20·3 to 2·1]), and 79 (75%) of 105 with LMWH (–6·1 percentage points [–17·2 to 5·0]), meeting non-inferiority for both interventions. The frequency of severe bleeding was lower with low-dose UFH and LMWH than with standard-dose UFH (63 [58%] patients and 62 [59%] vs 70 [65%]), without excess severe thromboembolic complications (11 [10%] and nine [9%] vs 12 [11%]), although these differences did not reach statistical significance. At 6 months, 54 (50%) patients in the standard-dose UFH group, 45 (42%) in the low-dose UFH group, and 46 (44%) in the LMWH group had died.

Interpretation Low-dose UFH and therapeutic LMWH were non-inferior to standard-dose UFH. This finding supports reconsideration of anticoagulation targets in ECMO. Given the global expansion of ECMO, these findings suggest that reduced anticoagulation targets could substantially reduce bleeding-related harm.

Is LMWH
„as good
as“ UFH?

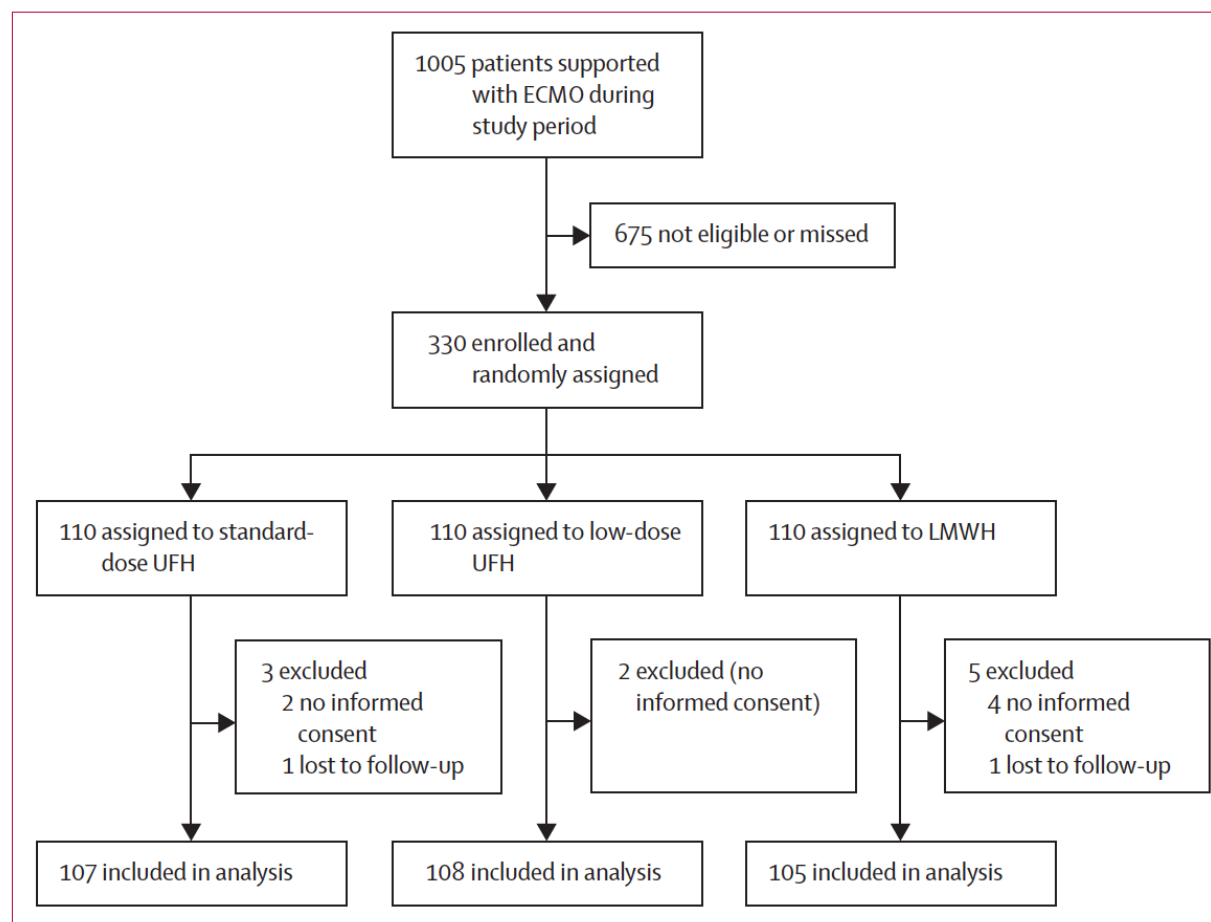


Figure 1: Trial profile

ECMO=extracorporeal membrane oxygenation. LMWH=low-molecular-weight heparin. UFH=unfractionated heparin.

	Standard-dose UFH group (n=107)	Low-dose UFH group (n=108)	LMWH group (n=105)
Sex			
Male	70 (65%)	79 (73%)	76 (72%)
Female	37 (35%)	29 (27%)	29 (28%)
Age, years	55 (43-64)	56 (45-64)	58 (47-68)
Ethnicity			
White	85 (79%)	89 (82%)	81 (77%)
Asian	4 (4%)	3 (3%)	1 (1%)
Black	4 (4%)	5 (5%)	3 (3%)
Other	4 (4%)	3 (3%)	7 (7%)
Unknown	10 (9%)	8 (7%)	13 (12%)
BMI, kg/m ²	27.8 (23.0-31.4)	27.9 (24.7-31.5)	28.1 (24.7-32.7)
APACHE IV score*	61 (48-89)	70 (52-90)	73 (55-96)
SOFA score†	11 (8-13)	11 (9-14)	12 (8-13)
ECMO blood flow, L/min	3.38 (0.68)	3.45 (0.75)	3.38 (0.73)
ECMO mode			
Veno-venous	46 (43%)	40 (37%)	42 (40%)
Veno-arterial	61 (57%)	68 (63%)	63 (60%)
ECMO indication			
Pulmonary	47 (44%)	43 (40%)	45 (43%)
Cardiac	50 (47%)	55 (51%)	49 (47%)
Extracorporeal cardiopulmonary resuscitation	10 (9%)	10 (9%)	11 (11%)
COVID-19	15 (14%)	17 (16%)	14 (13%)
Cannulation method			
Central	15 (14%)	14 (13%)	12 (11%)
Peripheral	92 (86%)	94 (87%)	93 (89%)
Cannula			
Heparin coated	85 (79%)	90 (83%)	86 (82%)
Non-heparin coated	22 (21%)	18 (17%)	19 (18%)
ECMO equipment			
Cardiohelp	89 (83%)	91 (84%)	89 (84%)
Xenios	11 (10%)	13 (12%)	11 (11%)
Other	7 (7%)	4 (4%)	5 (5%)
Antiplatelets			
Aspirin	8 (8%)	14 (13%)	6 (6%)
Cangrelor	0	3 (3%)	4 (4%)
Clopidogrel	5 (5%)	4 (4%)	10 (10%)
Ticagrelor	5 (5%)	6 (6%)	7 (7%)

Data are n (%), median (IQR), or mean (SD). APACHE=Acute Physiology and Chronic Health Evaluation. ECMO=extracorporeal membrane oxygenation. LMWH=low-molecular-weight heparin. SOFA=Sequential Organ Failure Assessment. UFH=unfractionated heparin. *APACHE IV score on the day of admission to the intensive care unit, with higher values indicating higher mortality risk. †SOFA score on the day of ECMO cannulation (higher scores indicate more severe organ dysfunction and a correspondingly higher risk of mortality in the intensive care unit).

Table 1: Baseline characteristics

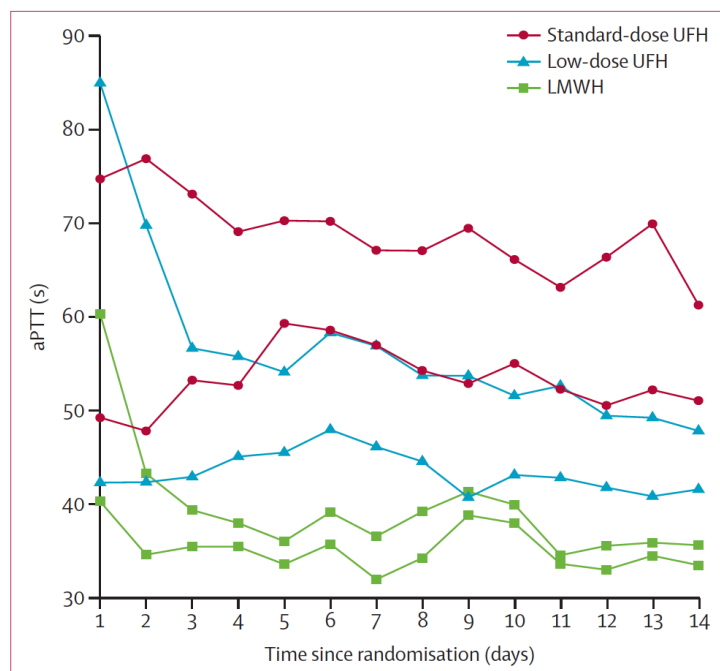


Figure 2: Lowest and highest aPTT values per day
aPPT=activated partial thromboplastin time. LMWH=low-molecular-weight heparin. UFH=unfractionated heparin.

A negatively charged contact activator is added in the [Medscape Reference on aPTT](#) test, with the common options being kaolin, silica, celite, or ellagic acid. These substances trigger the coagulation cascade by activating factor XII

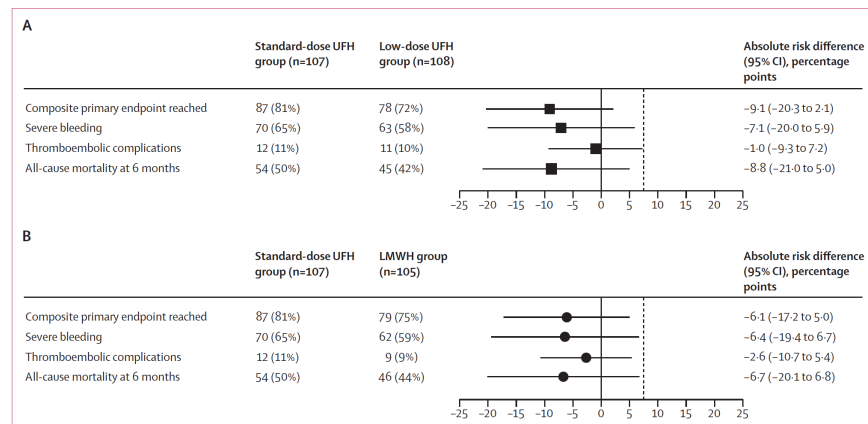


Figure 3: Absolute risk difference of primary composite endpoint
LMWH=low-molecular-weight heparin. UFH=unfractionated heparin.

Low molecular weight heparin is actually used for dialysis in many parts of the world like Europe, but it is **not approved or commonly used** in the United States mainly due to drug clearance issues, accumulation risks, higher costs, and lack of routine monitoring tools.

	Standard-dose UFH group (n=107)	Low-dose UFH group (n=108)	p value	LMWH group (n=105)	p value
Reason for ECMO discontinuation	..	..	0.41	..	0.023
Expected recovery	60 (56%)	72 (66%)	..	73 (70%)	..
Died on extracorporeal life support	29 (27%)	22 (20%)	..	20 (19%)	..
Diagnosis incompatible with life	6 (6%)	6 (6%)	..	10 (10%)	..
Left ventricular assist device, heart transplant, or lung transplant	9 (8%)	4 (4%)	..	2 (2%)	..
ECMO complication	3 (3%)	4 (4%)	..	0	..
Tracheostoma	8 (8%)	16 (15%)	0.083	21 (20%)	0.0070
Alive at discharge	58 (54%)	66 (61%)	0.31	60 (57%)	0.67
Discharge location	..	..	0.90	..	0.41
Home	20/58 (34%)	20/62 (32%)	..	23/60 (38%)	..
Referral hospital	12/58 (21%)	15/62 (24%)	..	7/60 (12%)	..
Other	26/58 (45%)	27/62 (44%)	..	30/60 (50%)	..
Mechanical ventilation duration, days	13 (6–29)	10 (5–20)	0.27	13 (7–23)	0.98
ICU length of stay, days	16 (7–33)	13 (8–25)	0.38	18 (8–34)	0.45
Hospital length of stay, days	41 (19–64)	35 (20–52)	0.35	36 (23–60)	0.56
ECMO duration, days	7 (3–12)	8 (4–13)	0.61	6 (4–12)	0.69
EQ-5D-5L, index	0.80 (0.59–0.89)	0.83 (0.65–0.89)	0.50	0.79 (0.66–0.89)	0.70
EQ-5D-5L, VAS	70 (60–80)	72 (60–80)	0.44	70 (60–85)	0.36
Alive at day 60, days					
Without ECMO	0 (0–53)	39 (0–55)	0.45	44 (0–54)	0.24
Without mechanical ventilation	0 (0–48)	15 (0–50)	0.53	9 (0–48)	0.69
ICU free	0 (0–41)	8 (0–42)	0.25	0 (0–40)	0.61
Data are n (%) or median (IQR). Percentages might not sum to 100 because of rounding. ECMO=extracorporeal membrane oxygenation. ICU=intensive care unit. LMWH=low-molecular-weight heparin. UFH=unfractionated heparin. VAS=visual analogue scale.					
Table 2: Secondary outcomes					

Research in context

Evidence before this study

We searched PubMed from inception to June 29, 2025, for studies on anticoagulation strategies in adult extracorporeal membrane oxygenation (ECMO) using terms including “ECMO”, “anticoagulation”, “heparin”, and “low-molecular-weight heparin”. Evidence consisted mainly of observational studies, registry analyses, and one small pilot randomised trial. These studies suggested that lower-intensity anticoagulation might reduce bleeding without increasing thrombosis, but were limited by small sample sizes, heterogeneity, and risk of bias. No adequately powered randomised controlled trials comparing anticoagulation intensity strategies in ECMO have been completed.

Added value of this study

This multicentre, randomised, non-inferiority trial provides the first adequately powered comparison of standard-dose

unfractionated heparin with low-dose unfractionated heparin and therapeutic low-molecular-weight heparin in ECMO. Both strategies were non-inferior to the standard dose for the composite endpoint consisting of severe bleeding, severe thromboembolic complications, and 6-month mortality, with consistent signals towards reduced bleeding and improved cost-effectiveness.

Implications of all the available evidence

The evidence supports reducing anticoagulation intensity in ECMO because lower-intensity strategies seem to be safe and might reduce bleeding complications and costs. These findings support reconsideration of current anticoagulation targets and might inform future guideline development and clinical decision making.

Inherited retinal degenerations: clinical phenotypes and emerging therapies

Inherited retinal degenerations are a diverse group of genetic disorders that result in progressive vision loss. Advances in genetic testing have revealed pathogenic variants in hundreds of genes, reflecting the remarkable heterogeneity of these conditions and pointing to the complexity of the developmental and homoeostatic processes needed for a lifetime of good vision. This Review summarises the clinical presentation of inherited retinal degenerations, outlines broad disease categories based on the primary type of retinal cell affected, and highlights novel treatment approaches including gene, cell, optogenetic, and implantable chip therapies. Prompt referral of patients to eye care professionals is essential for early and accurate diagnoses, coordinated care, and optimal visual outcomes.

Autosomal recessive inheritance is the single most common pattern for **inherited retinal degenerations (IRDs)**, though these conditions can also be inherited in **autosomal dominant** or **X-linked** ways.

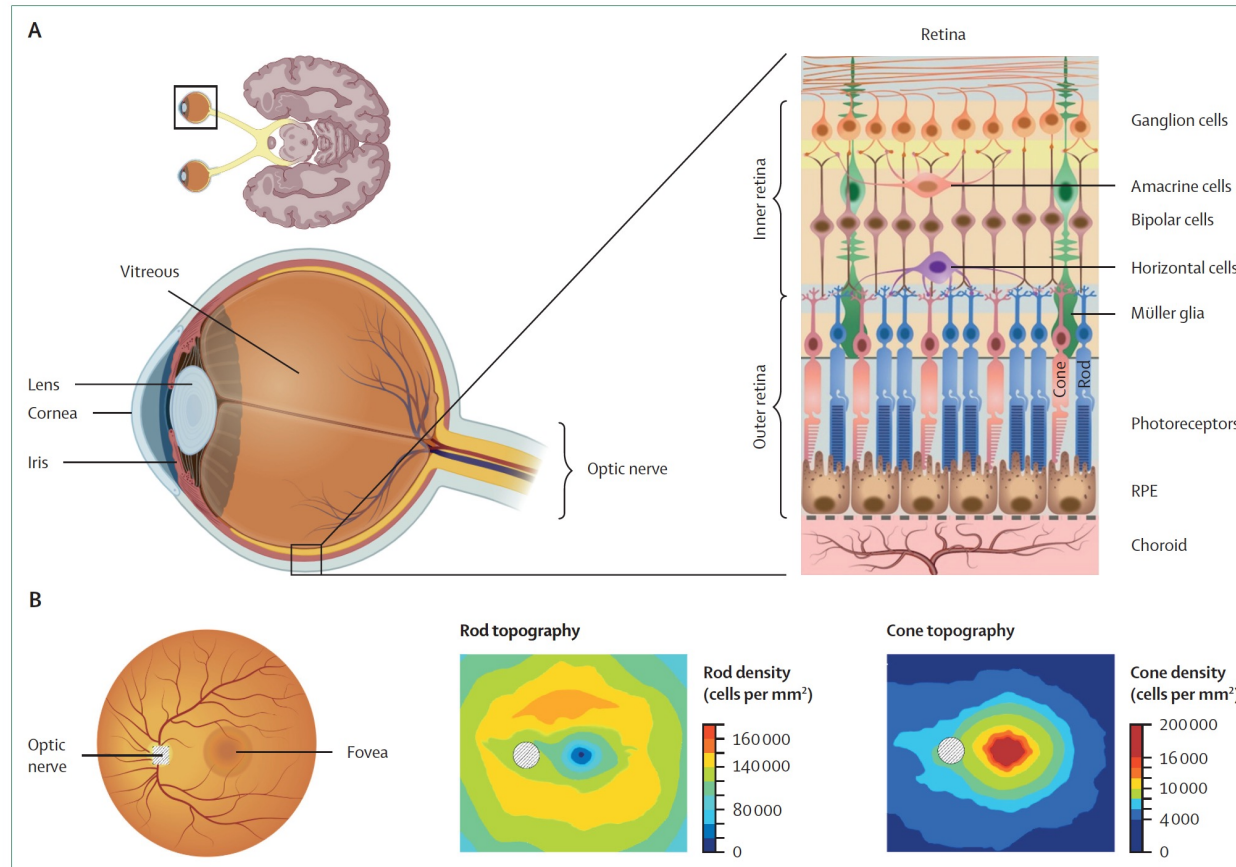


Figure 1: Anatomy of the eye and retina

(A) Schematic of the eye connected to the CNS and ocular structures. Magnified inset illustrates the retinal cell types organised naturally into distinct layers (modified from Ferrara and colleagues³⁰). (B) En face view of the retina and matching topographic distribution of photoreceptor cell densities (lower row, modified from Jacobson and colleagues³¹). Notably, the highest density of rod photoreceptors forms a ring in the midperipheral retina and the highest density of cone photoreceptors form a small spot at the fovea (with additional cones distributed between rods). Figure created with BioRender.com. RPE=retinal pigment epithelium.

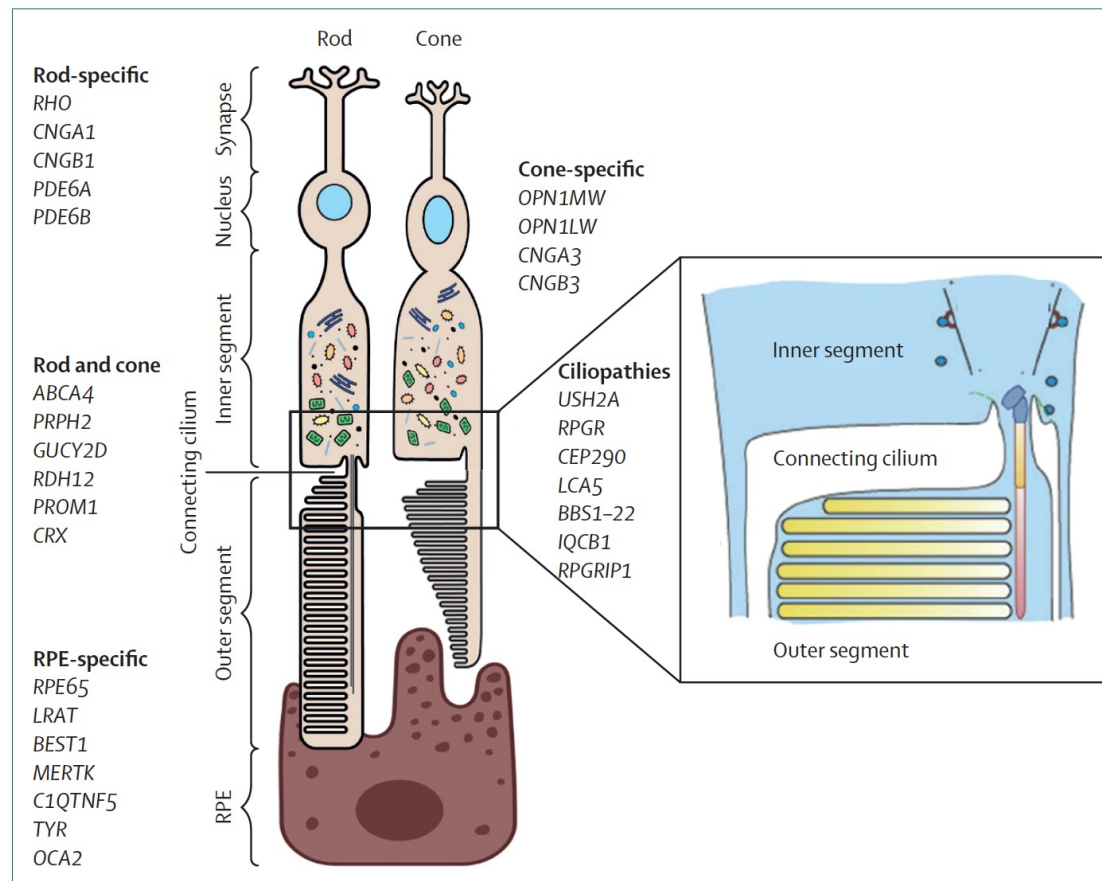


Figure 2: Photoreceptor structure and molecular mechanisms of disease

Rod (left) and cone (right) photoreceptor cell structure. Genes listed are commonly associated with rod-specific, cone-specific, photoreceptor-specific, and RPE-specific inherited retinal degenerations, respectively. Magnified inset shows the connecting cilium involved in bi-directional protein trafficking of proteins between the inner segment and the outer segment (modified from Megaw and colleagues³²); genes listed are associated with ciliopathies. RPE=retinal pigment epithelium.

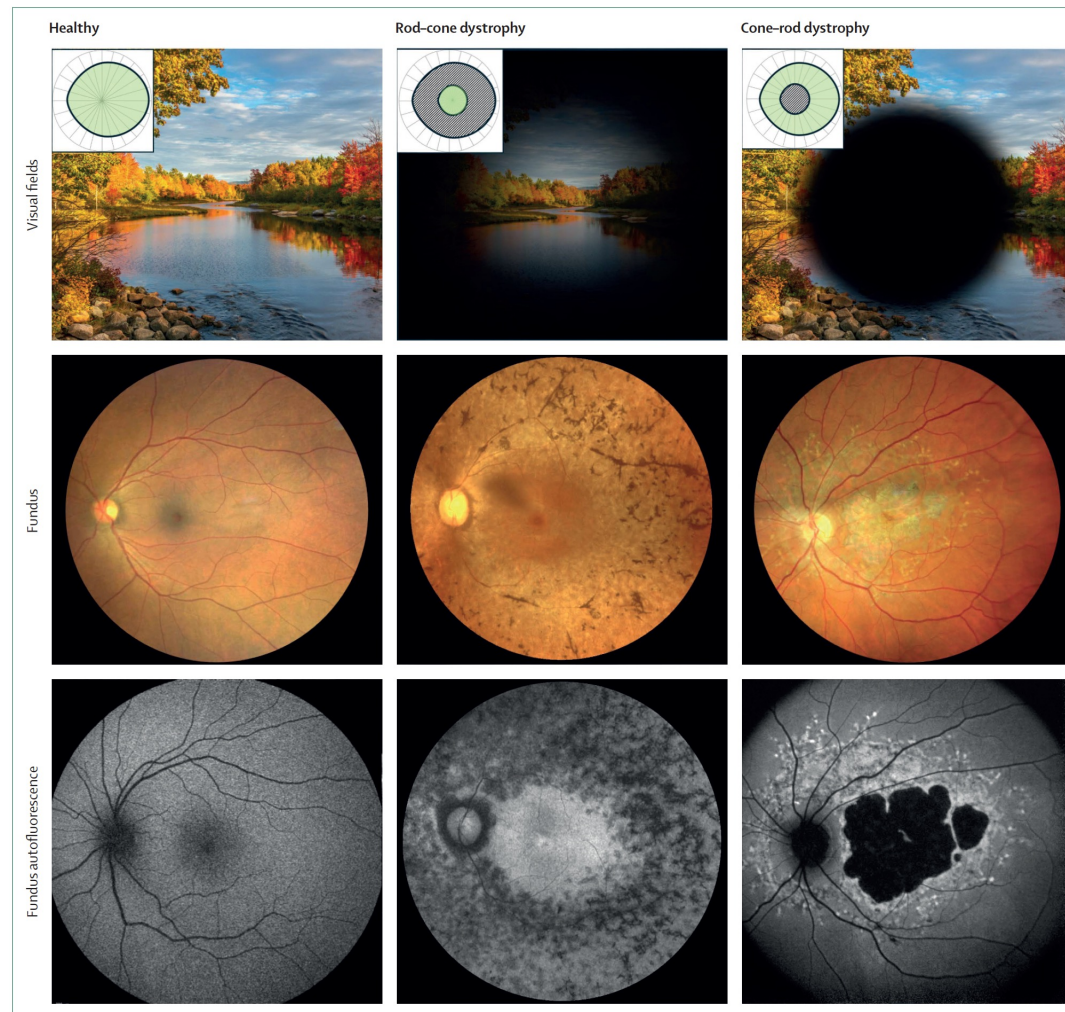


Figure 3: Clinical presentation of inherited retinal degenerations

Representative visual fields (inset: green indicates intact vision; shaded regions indicate blind spots) of a simulated scene as it appears to patients, ocular fundus photos, and short-wavelength fundus autofluorescence images, of a healthy patient (left panel) compared with a patient with a rod-cone dystrophy (middle panel) and cone-rod dystrophy (right panel) indicating disease distributions that mirror the topography of the affected cell type.

Gene therapy

	Route	Agent	Phase	Trial ID
ABCA4				
RNA trans-splicing	Subretinal	AAV*†	1/2	NCT06467344
Gene augmentation	Subretinal	AAV*†‡	1/2	NCT07161544
Gene augmentation	Subretinal	AAV*‡	1/2	NCT06942572
Gene augmentation	Subretinal	EIAV*	1/2	NCT01367444
AIPL1				
Gene augmentation	Subretinal	AAV*‡	1/2	MRHA Specials Licence MS45522
BEST1				
Gene augmentation	Subretinal	AAV	1/2	NCT07185256
CEP290				
Pseudoxon skipping	Intravitreal	ASO*†‡	3	NCT06891443 (see also NCT04855045, NCT03913143, and NCT03140969)
Gene editing	Subretinal	AAV*‡	1/2	NCT03872479
CNGA3				
Gene augmentation	Subretinal	AAV*†‡	1/2	NCT03758404
Gene augmentation	Subretinal	AAV*	1/2	NCT02935517
CNGB3				
Gene augmentation	Subretinal	AAV*	1/2	NCT02599922
Gene augmentation	Subretinal	AAV	1/2	NCT03001310
FLVCR1				
Pseudoxon skipping	Intravitreal	ASO	1	NCT06565572
GUCY2D				
Gene augmentation	Subretinal	AAV*‡	1/2	NCT03920007
LCA5				
Gene augmentation	Subretinal	AAV*‡	1/2	NCT05616793
MERTK				
Gene augmentation	Subretinal	AAV	1	NCT01482195
MYO7A				
Gene augmentation	Subretinal	AAV‡	1/2	NCT06591793
Gene augmentation	Subretinal	EIAV*	1/2	NCT01505062
PDE6A				
Gene augmentation	Subretinal	AAV	1/2	NCT04611503
PDE6B				
Gene augmentation	Subretinal	AAV *	1/2	NCT03328130
(Table continues on next page)				

	Route	Agent	Phase	Trial ID
(Continued from previous page)				
PRPF31				
Upregulation	Intravitreal	ASO	2/3	NCT06455826 (see also NCT05902962 and NCT06852963)
CHM				
Gene augmentation	Subretinal	AAV†‡	3	NCT03496012 (see also NCT03507686, NCT03584165, NCT02077361, NCT02553135, NCT01461213, NCT02671539, and NCT02407678)
Gene augmentation	Subretinal	AAV‡	1/2	NCT02341807
Gene augmentation	Intravitreal	AAV	1	NCT04483440
RHO				
Knockdown	Intravitreal	ASO†‡	1/2	NCT04123626
RLBP1				
Gene augmentation	Subretinal	AAV	1/2	NCT03374657
RPE65				
Gene augmentation	Subretinal	AAV*‡	4	NCT03597399 (see also NCT00999609, NCT00481546, NCT01208389, NCT00516477, NCT03602820, and NCT00643747)
Gene augmentation	Subretinal	AAV*	1/2	NCT00749957
Gene augmentation	Subretinal	AAV*	1/2	NCT01496040
Gene augmentation	Subretinal	AAV	1/2	NCT02781480
RPGR				
Gene augmentation	Subretinal	AAV*†‡	3	NCT04671433 (see also NCT03252847, NCT04312672, NCT04794101, NCT5926583, and NCT06646289)
Gene augmentation	Subretinal	AAV*‡	3	NCT03116113 (see also NCT03584165)
Gene augmentation	Subretinal	AAV*†‡	2	NCT04850118 (see also NCT07174726, NCT06275620, NCT03316560, and NCT06333249)
Gene augmentation	Intravitreal	AAV*†‡	1/2	NCT04517149
RS1				
Gene augmentation	Intravitreal	AAV *	1/2	NCT02416622
Gene augmentation	Intravitreal	AAV	1/2	NCT02317887
Gene augmentation	Subretinal	AAV*†‡	1/2	NCT05878860
USH2A				
Exon skipping	Intravitreal	ASO*†‡	2	NCT06627179 (see also NCT03780257, NCT05176717, NCT05158296, and NCT05085964)
AAV=adeno-associated virus. ASO=antisense oligonucleotide. EIAV=equine infectious anaemia virus. FDA=US Food and Drug Administration. MRHA=Medicines and Healthcare products Regulatory Agency. *Paediatric cohort. †Fast Track (FDA). ‡Orphan designation (FDA).				
Table: Gene-based therapeutics for inherited retinal disease by target and approach				

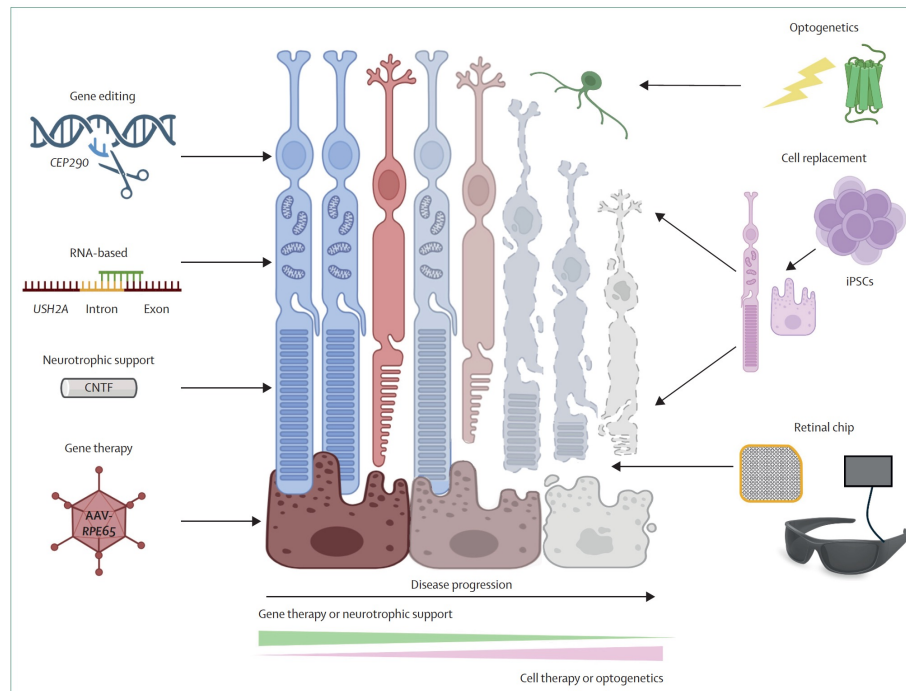


Figure 4: Emerging treatments for inherited retinal degenerations

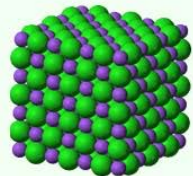
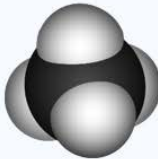
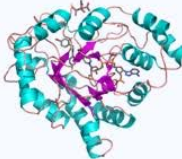
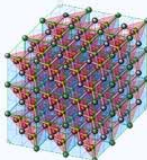
Gene therapy, gene editing, and RNA-based approaches aim to correct the underlying molecular defect of inherited retinal degenerations; neurotrophic support is a gene-independent approach to promote the survival of existing cells. Specific gene examples noted where relevant. As retinal disease progresses, photoreceptor and RPE loss leads to cellular death (grey cells) and retinal remodelling. Cell replacement (purple cells), optogenetics, and implantable chips hold promise for restoring vision in late-stage disease. Figure created with BioRender.com. AAV=adeno-associated virus. RPE=retinal pigment epithelium. iPSC=induced pluripotent cell.

Conclusions and the future

Collectively, recent therapeutic advances have provided hope to patients with inherited retinal degenerations. With currently approved therapies and many more in development with promising early efficacy signals, altering the disease course of genetic blindness and restoring visual function is now a reality. Early detection, genetic diagnostics, and multidisciplinary management are key as inherited retinal degenerations are becoming increasingly treatable conditions. Primary care physicians should thus have a low threshold for referring patients for an eye examination, particularly if there are concerning symptoms such as new or worsening vision loss (at any age), night blindness, decreased peripheral vision (bumping into objects or falls), impaired central vision (difficulty reading or seeing faces), syndromic features, or a family history of inherited retinal degenerations. Eye care professionals should, in turn, have a low threshold for promptly referring patients with a concerning history or examination findings to an inherited retinal degeneration specialist, who can perform specialised assessments of retinal function, organise genetic testing and interpretation, coordinate multidisciplinary care, provide accurate prognostic information, and assess eligibility for clinical trials.

Die drei Hauptarten der chemischen Bindung sind die **Kovalente Bindung** (Elektronenpaarbindung), die **Ionenbindung** (Salzbindung) und die **Metallische Bindung**. Es gibt auch schwächere Wechselwirkungen (**Intermolekulare Kräfte**).

Wasserstoffbrückenbindung: Eine spezielle, relativ starke, anziehende Wechselwirkung zwischen einem Wasserstoffatom und stark electronegativen Atomen wie Sauerstoff, Stickstoff oder Fluor. **Van-der-Waals-Kräfte:** Sehr schwache, temporäre Anziehungskräfte zwischen unpolaren Molekülen oder Atomen aufgrund von kurzen Ladungsverschiebungen.

Bindungsart	ionische Bindung	metallische Bindung	kovalente Bindung		
Art der Elemente	Metalle und Nichtmetalle	Metalle unter sich	Nichtmetalle unter sich		
Anziehung zwischen	Anionen und Kationen	Atomrümpfen + Elektronengas	Atomrümpfen + Elektronen		
Art der Teilchen oder Verbände	Riesiger Ionenverband	riesiger Atomverband	kleine Moleküle	riesige Moleküle	riesiger Atomverband
Stoffklasse	salzartige Stoffe	metallische Stoffe	flüchtige Stoffe	hochmolekulare Stoffe	diamantartige Stoffe
Abbildungen					

Wasser nutzt **zwei Arten** von chemischen Bindungen: **Atombindungen** innerhalb des Moleküls und **Wasserstoffbrückenbindungen** zwischen den Molekülen

Der englische Begriff **covalent bond** bedeutet auf Deutsch **kovalente Bindung**. In der deutschen Chemie-Fachsprache und im Schulunterricht wird sie auch sehr häufig als **Atombindung** oder **Elektronenpaarbindung** bezeichnet.

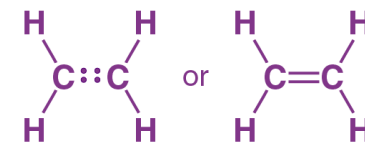
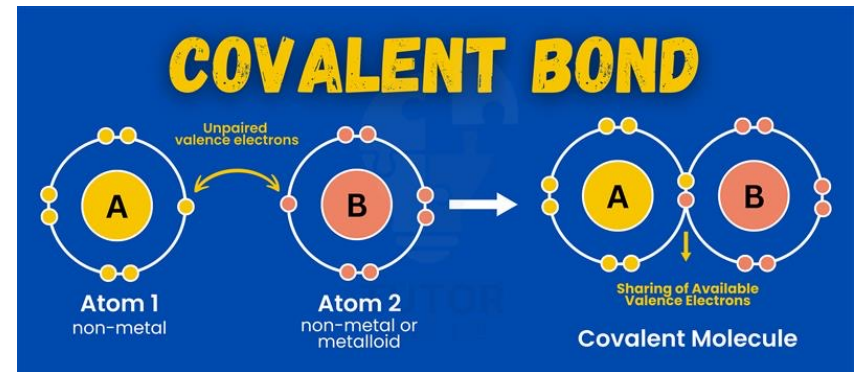
Wichtigste Merkmale im Überblick

• **Das Prinzip:** Mindestens zwei Atome (meistens Nichtmetalle) teilen sich ein oder mehrere Elektronenpaare (Valenzelektronen).

• **Das Ziel:** Die Atome erreichen dadurch die stabile **Edelgaskonfiguration** (meistens 8 Außenelektronen, auch bekannt als Oktettregel).

• **Die Bindungsarten:** Es gibt Einfachbindungen (1 geteiltes Paar), Doppelbindungen (2 geteilte Paare) oder Dreifachbindungen (3 geteilte Paare).

Holz wird durch eine Kombination aus **kovalenten Bindungen** (innerhalb der Polymere), **Wasserstoffbrückenbindungen** (zwischen den Polymerketten) und **Ester- bzw. Etherbindungen** (die Lignin und Kohlenhydrate verknüpfen) zusammengehalten.



•Die Polarität:

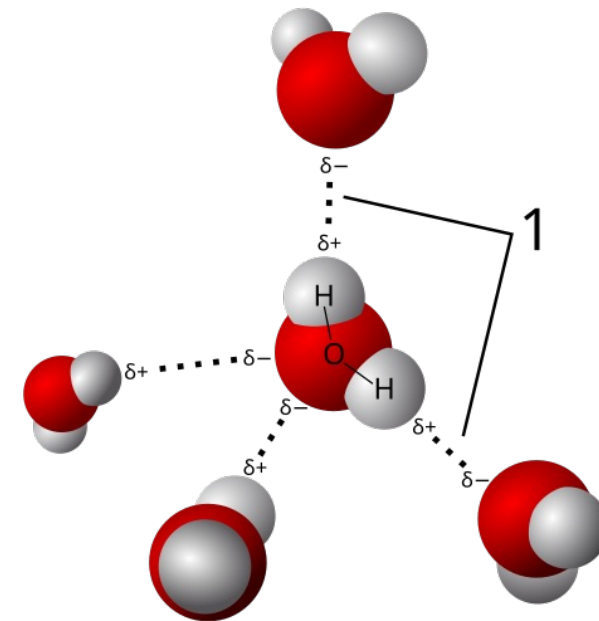
- **Unpolare kovalente Bindung:** Die Elektronen werden gleichmäßig aufgeteilt (z.B. im Wasserstoffmolekül H_2 oder Sauerstoffmolekül O_2).
- **Polare kovalente Bindung:** Ein Atom zieht die Elektronen stärker an als das andere (hohe Elektronegativität), wodurch Teilladungen entstehen (z.B. im Wassermolekül H_2O).

In einer **Wasserstoffbrückenbindung** (hydrogen bond) werden keine Elektronen im klassischen Sinn „geteilt“ oder als Elektronenpaar zwischen den Bindungspartnern ausgetauscht. Stattdessen handelt es sich primär um eine **elektrostatische Anziehungskraft** zwischen einem positiv polarisierten Wasserstoffatom und einem freien Elektronenpaar (Lone Pair) eines elektronegativen Atoms (wie Sauerstoff oder Stickstoff).

Grundlagen der Bindung

Elektrostatik: Das Wasserstoffatom sitzt an einem starken Magneten (z. B. O-H). Es verliert dort elektronische Dichte, wird positiv $\delta+$ und zieht das freie Elektronenpaar des Nachbaratoms an $\delta-$.

Kein Teilen: Es wird kein neues Elektronenpaar gebildet wie bei einer kovalenten Bindung (Elektronenpaarbindung).



Van-der-Waals-Kräfte sind **schwache Anziehungskräfte** zwischen Atomen und Molekülen, die durch **kurzzeitige Ladungsverschiebungen** (temporäre Dipole) entstehen. Sie gehören zu den zwischenmolekularen Kräften und nehmen mit steigender Molekülmasse und Oberfläche zu.

Medikamente nutzen vor allem **nicht-kovalente (schwächer anziehende) Wechselwirkungen** wie **Wasserstoffbrücken, elektrostatische Kräfte, hydrophobe Effekte und Van-der-Waals-Kräfte**, um reversibel an Zielmoleküle (wie Proteine oder Rezeptoren) zu binden.

Medikamente binden an ihre Zielstrukturen (Targets) überwiegend über **schwache, reversible Wechselwirkungen**, seltener über **starke, irreversible Bindungen**. Zu den wichtigsten Bindungsarten gehören elektrostatische Anziehungen, Wasserstoffbrücken, hydrophobe Effekte und kovalente Bindungen.

Die meisten Arzneistoffe müssen sich wieder von ihrem Target lösen können, damit die Wirkung steuerbar bleibt.

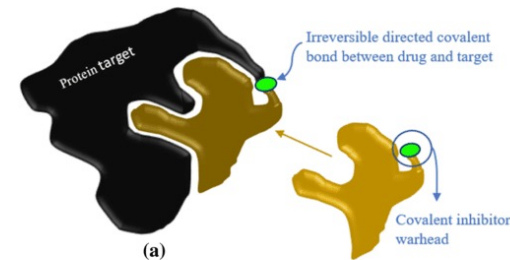
Ionenbindungen (elektrostatische Wechselwirkungen):

Entstehen zwischen positiv und negativ geladenen Gruppen des Moleküls und des Proteins.

Wasserstoffbrückenbindungen: Bilden sich zwischen elektronegativen Atomen (wie Sauerstoff oder Stickstoff) und Wasserstoffatomen; sie sorgen für die genaue Ausrichtung im Wirkort.

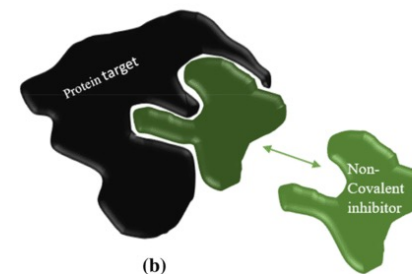
Hydrophobe Wechselwirkungen: Treten auf, wenn wassermeidende (lipophile) Bereiche des Medikaments in einer wasserfreien Tasche des Proteins zusammenrücken.

Van-der-Waals-Kräfte: Schwache Anziehungskräfte zwischen sehr nahe beieinander liegenden Atomen.



Irreversible Covalent drug bond

Covalent irreversible inhibitors bind specifically to a drug target and model a precisely directed permanent bond with their target.



Reversible Non-covalent drug

Common reversible inhibitors interact with their target constantly through binding, rebinding, and unbinding.

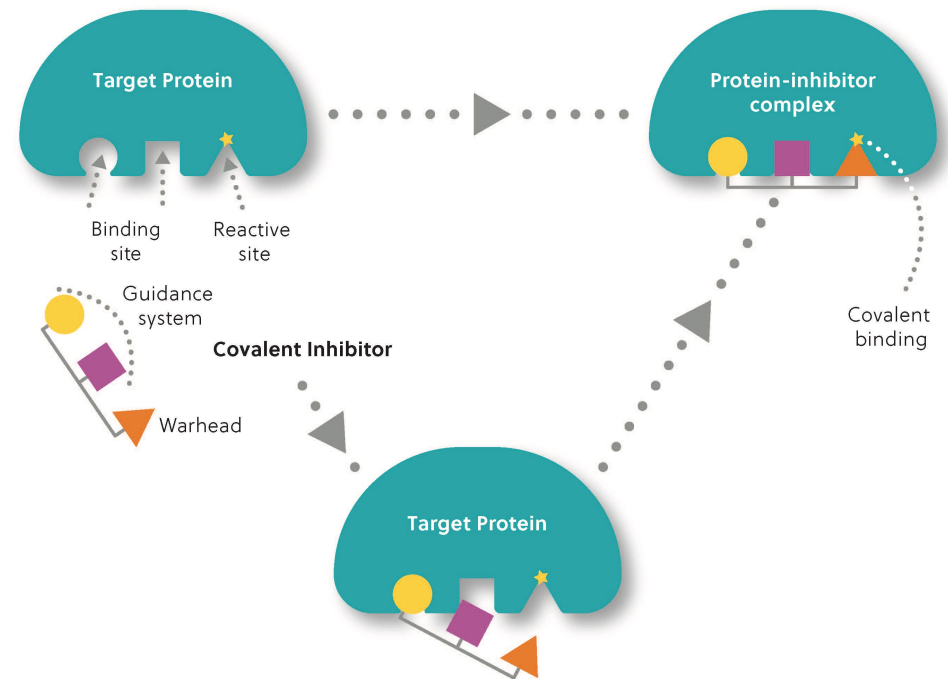
Kovalente Medikamente (Covalent Drugs) sind pharmazeutische Wirkstoffe, die eine stabile, dauerhafte **chemische (kovalente) Bindung** mit ihrem Zielprotein (Target) im Körper eingehen. Im Gegensatz zu klassischen, nicht-kovalenten Medikamenten, die nur lose und temporär an ein Protein andocken, „verkleben“ kovalente Inhibitoren das Target dauerhaft und schalten dessen Funktion oft irreversibel aus

Das Funktionsprinzip: Der „Zwei-Schritt-Mechanismus“

Moderne kovalente Medikamente nutzen eine präzise Strategie, um Nebenwirkungen zu minimieren:

1. Spezifische Erkennung (Schlüssel-Schloss-Prinzip): Das Medikament bindet zunächst rein physikalisch und hochselektiv an die Bindungstasche des Zielproteins.

2. Die chemische Reaktion: Erst wenn das Medikament perfekt sitzt, reagiert eine hochspezifische chemische Gruppe am Medikament – die sogenannte „**Warhead**“ (**Sprengkopf**) – mit einer passenden Aminosäure des Proteins (meist *Cystein*, seltener *Lysin* oder *Serin*). Es entsteht die unzertrennliche kovalente Bindung.



Numerous modern and classic drugs rely on covalent bonding, including **aspirin**, **penicillin**, and **ibrutinib**. These medications use a reactive chemical group (a "warhead") to form a permanent or long-lasting bond with their specific protein targets.

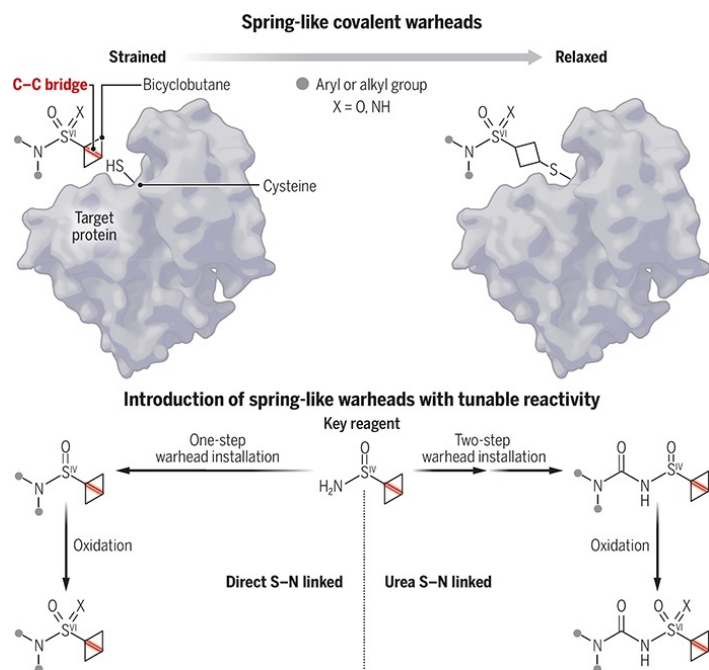
No strain, no gain



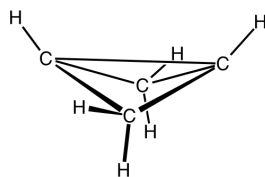
Drug candidates that form covalent bonds with their targets were historically avoided because of toxicity concerns. However, covalent drugs with controlled reactivity are now recognized as promising agents that combine manageable safety with substantial advantages, including enhanced potency, prolonged target residence times, and access to challenging targets. This shift is reflected in recent covalent drug approvals, particularly those targeting protein-phosphorylating enzymes (kinases) and cancer drivers such as the oncogenic protein KRAS. A central feature of these drugs is a “warhead” reacting with an amino acid residue in the target protein to form a covalent bond. Yet the repertoire of drug-like, chemically accessible reactive moieties remains limited. Shultz *et al.* report streamlined access to an underexplored warhead type with well-tempered reactivity that can be appended to complex scaffolds late in synthesis, enabling practical use in drug discovery.

Warheads must have preferential reactivity toward a specific functional group (chemoselectivity) and productive engagement with an individual amino acid residue in a target protein (site selectivity). The initial noncovalent interaction between a drug and the protein positions a warhead close to a specific amino acid. This positioning makes the reaction at the exact target residue fast, with similar amino acids elsewhere much less likely to react, resulting in a specific covalent modification. Among the most widely used warheads are acrylamides, which preferentially target cysteine, a reactive sulfur-containing amino acid that is commonly addressed in contemporary covalent drug discovery.

Acrylamides have quickly become an industry standard because they exhibit moderate, tunable reactivity that can help limit nonspecific protein modification, have favorable properties in living organisms, and are easily attached to drug-like molecules at a late stage of synthesis. These advantages may have contributed to the slower adoption of alternative covalent warheads, thereby limiting the chemical diversity of clinically used covalent reactive groups. A new class of covalent warheads for drug discovery are sulfur(VI) bicyclobutanes, in which a highly electron-deficient form of sulfur (oxidation state: +VI) is attached at the bridgehead carbon of two three-membered hydrocarbon rings that share a common bond. Bicyclobutane is a structure that exhibits spring-like behavior. The strained bridging C-C bond, which is polarized by the sulfur(VI) group, breaks upon attack by an electron-rich chemical species (nucleophile) through a nucleophile-induced ring-opening reaction irreversibly.



Bicyclobutanes are highly strained bicyclic organic molecules, valued building blocks in synthesis, and unique structural motifs featuring a central C–C bond. They are defined by a butterfly conformation, intense ring strain, and facile bond cleavage.



Gespannte Ring-Struktur

The study of Shultz *et al.* highlights the importance of the **three-dimensional arrangement of substituents around the sulfur(VI) center of sulfonimidamide bicyclobutanes**. This emphasizes the need to develop synthetic methods that produce defined geometries around the sulfur(VI) atom. **Broadening the strategy to other spring-loaded warhead topologies, such as housanes (bicyclopentanes), could further expand its utility in covalent drug discovery.** It will also be important to test whether observed chemoselectivity is preserved across the full proteome of a target cell or tissue. For example, residue-resolved chemical proteomics can comprehensively identify which residues on a given protein are modified. Although the **therapeutic value of bicyclobutane-type covalent warheads** remains to be proven, Shultz *et al.* provide a **key advance** that may help translate the promising chemical properties of these motifs into clinical reality.

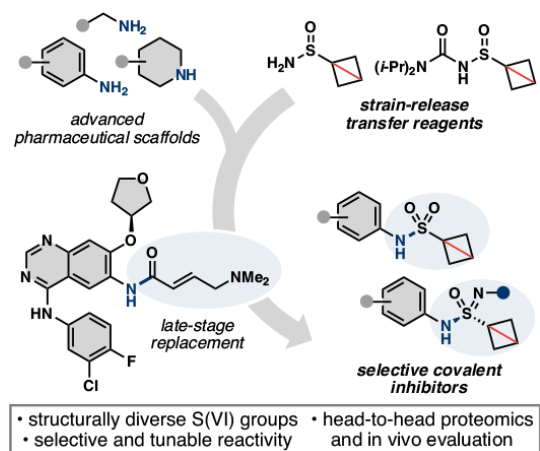
Late-stage functionalization with strain-release warheads enables tunable covalent inhibition

INTRODUCTION: Covalent drugs are transforming targeted therapy by forming durable bonds with disease-driving proteins, yet most rely on a narrow set of reactive groups, particularly acrylamides. These conventional approaches, although effective, can lead to off-target interactions and restrict broader application by their limited structural design. Expanding covalent drug design beyond these established chemotypes is essential to improve both selectivity and therapeutic performance.

RATIONALE: We sought to establish a general platform for replacing acrylamide-based covalent reactive groups in complex drug molecules with alternative chemotypes that offer improved control over reactivity. Our approach centers on bicyclobutanes that are integrated with sulfur-based functional groups commonly used in medicinal chemistry. To enable broad application, we developed a reagent-based strategy that allows these strain-release elements to be installed at the final stage of a synthesis from widely accessible amine precursors. This modular S(IV)-based platform provides a unified entry to multiple sulfur oxidation states and connectivity patterns, enabling systematic tuning of covalent reactivity and target engagement while preserving the parent-drug architecture. By design, this approach allows direct, head-to-head comparison with established covalent inhibitors.

RESULTS: We developed stable, scalable reagents that enable efficient late-stage **installation of strain-release bicyclobutane groups** across a wide range of clinically relevant scaffolds, including **multiple approved kinase inhibitors**. This strategy enables direct bioisosteric replacement of acrylamide warheads without modifying the underlying pharmacophore. These S(VI) strain-release groups are highly chemoselective for thiols, and their intrinsic reactivity can be tuned over a broad range through structural modification.

Notably, compounds with similar intrinsic reactivity displayed markedly different levels of target inhibition, demonstrating that productive covalent engagement depends not only on electrophile reactivity but also on molecular orientation within the protein binding site. In cellular systems, the modified inhibitors retained potent activity and effectively suppressed target signaling. Structural analysis confirmed covalent bond formation at the intended site. Across kinase panels and proteome-wide profiling experiments, these **strain-release analogs** displayed **improved selectivity** and **reduced off-target interactions** relative to their acrylamide counterparts. Importantly, these advances translated beyond in vitro systems, with strain-release analogs demonstrating favorable pharmacokinetic properties and efficacy in preclinical in vivo mice models.



Selective strain-release covalent inhibition. Development of S(IV) strain-release reagents enables late-stage functionalization of complex pharmaceuticals for preclinical evaluation as next-generation covalent inhibitors. i-Pr, isopropyl; Me, methyl.

CONCLUSION: This work establishes a reagent-enabled, late-stage functionalization platform for the bioisosteric replacement of acrylamides using **strain-release bicyclobutanes**, bridging chemical innovation to preclinical validation. More broadly, it further supports that effective covalent inhibition is governed not only by intrinsic electrophile reactivity but also by its integration with molecular recognition, providing a framework for designing **more selective and clinically effective covalent therapies**.

Supreme Court to decide if man will lose his plane over illicit beer

A pilot who was about to transport beer to a “dry” village argues Alaska’s effort to confiscate his plane violates a constitutional protection against “excessive fines.”



Pilot Ken Jouppi was about to take off in his 1969 Cessna airplane to shuttle a passenger to a remote village in Alaska when state troopers stopped the plane and searched it.

They found a six-pack of Budweiser and more beer among the passenger’s groceries, a total of nine gallons. That was a problem because Jouppi and his passenger were bound for Beaver, a “dry” village that bans alcohol.

The state has since sought to confiscate Jouppi’s plane over the 2012 incident. But Jouppi has challenged that penalty for more than a decade.

On Monday, the U.S. Supreme Court agreed to weigh Jouppi’s argument that taking away his plane amounts to a violation of the Constitution’s guarantee to be free of “excessive fines.”

The court will review Jouppi’s appeal of an Alaska Supreme Court opinion that found the state could confiscate the plane, valued at \$95,000, because “the illegal importation of even a six-pack of beer causes grave societal harm.”

The state argues that the harm is real: Many small communities in Alaska ban or restrict alcohol because they lack the law enforcement and public health resources to combat alcohol abuse and alcohol-fueled violence.

“Given that many communities are accessible primarily by air, the legislature provided that any airplane used to illegally import alcohol into a dry community was subject to forfeiture,” the state wrote in its brief to the court.

At trial in 2013, Jouppi was found guilty of knowingly trying to transport beer to the village — a misdemeanor. (A trooper testified that Jouppi would have had to be “blind” not to notice the six-pack in a grocery bag on the plane.) He was fined \$1,500 and sentenced to three days in jail. The passenger, who said she was bringing the beer as a gift to her husband, pleaded guilty to the same crime.

Alaska courts have tussled over whether the state could confiscate the airplane, which presently sits on a tarmac in Alaska. Jouppi and his attorneys argue that would be disproportional to the gravity of his offense.

“I’m in my 80s now, and I’ve been fighting this for over a decade because I see it as my duty to ensure that the Bill of Rights actually means something in protecting against government overreach,” Jouppi said in a news release Monday.

He is being represented by the Institute for Justice, a libertarian legal nonprofit. The high court is likely to hear oral arguments in Jouppi’s case after it begins its new term in October.

