

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

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

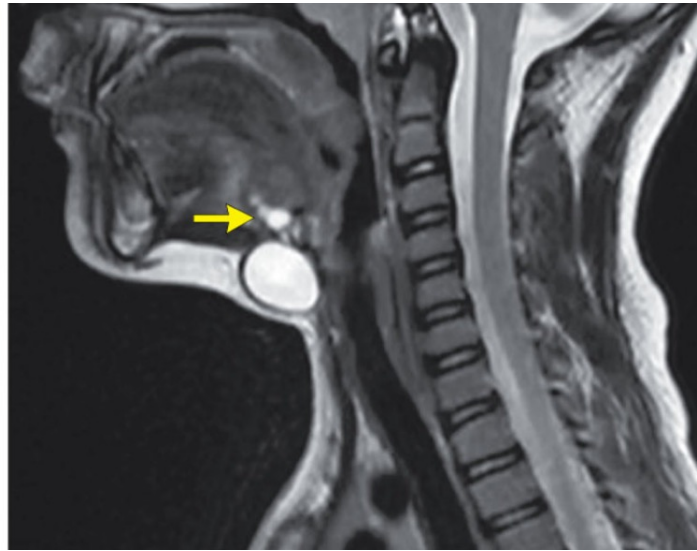
Usually every Wednesday 17:00 - 18:00



Klinische Forschung

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

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



A 6-year-old boy is brought to clinic with a 2-year history of a nontender, mobile midline mass of the anterior neck which moves up with tongue protrusion and swallowing. Physical exam is shown. What is the most likely diagnosis?

Brachial cleft anomaly

Dermoid cyst

Goiter

Lymphadenopathy

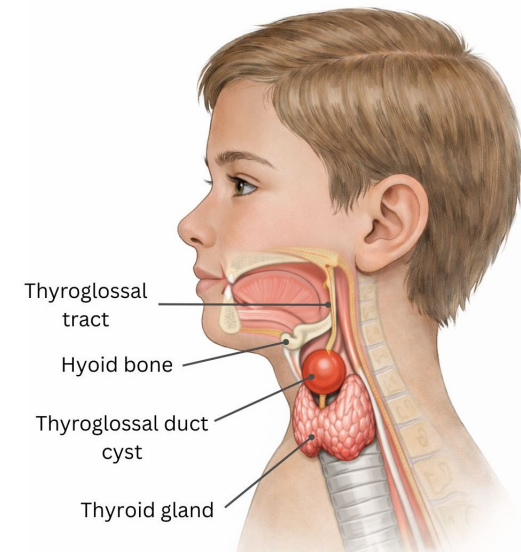
Thyroglossal duct cyst

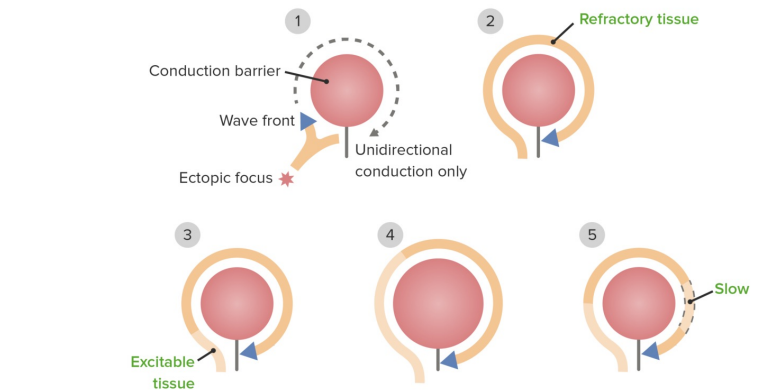
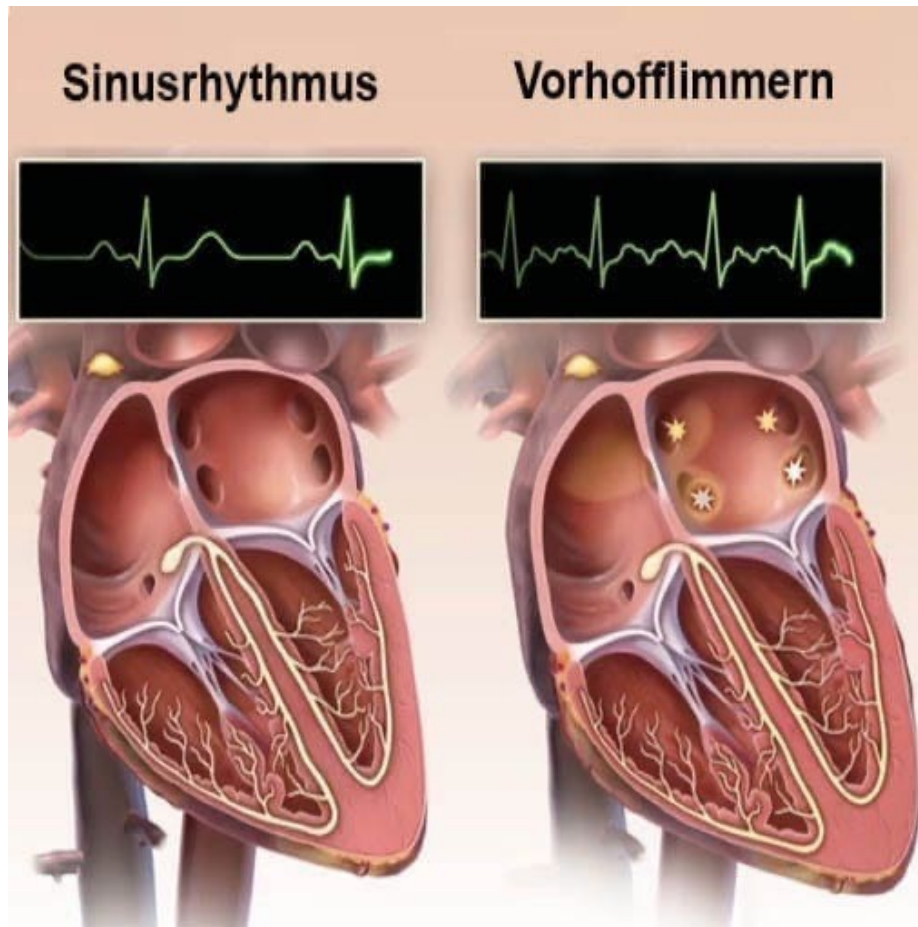
A thyroglossal duct cyst is a common congenital cervical anomaly that results from incomplete or failed obliteration of the embryonic thyroglossal duct, which leaves behind fluid secreting epithelia that generate a cyst. It can be distinguished from dermoid cysts based on mobility with tongue protrusion and swallowing as well as on ultrasound.

Ein "thyroglossal duct cyst" heißt auf Deutsch mediane Halszyste oder Thyreoglossuszyste.

Was ist das?

- Eine angeborene Fehlbildung in der vorderen Halsmitte.
- Sie entsteht aus Resten des *Ductus thyroglossus*, einem Verbindungsgang der Schilddrüse aus der Embryonalzeit.
- Dieser Gang bildet sich normalerweise vor der Geburt zurück; bleibt ein Rest offen, sammelt sich Schleim und es bildet sich eine Zyste.





Der **CHADS2-Score** ist ein medizinisches Bewertungssystem zur Abschätzung des Schlaganfallrisikos bei Patienten mit Vorhofflimmern.

Bedeutung der Buchstaben (Komponenten)

Jeder Faktor gibt bei Vorliegen **1 Punkt**, sofern nicht anders angegeben:

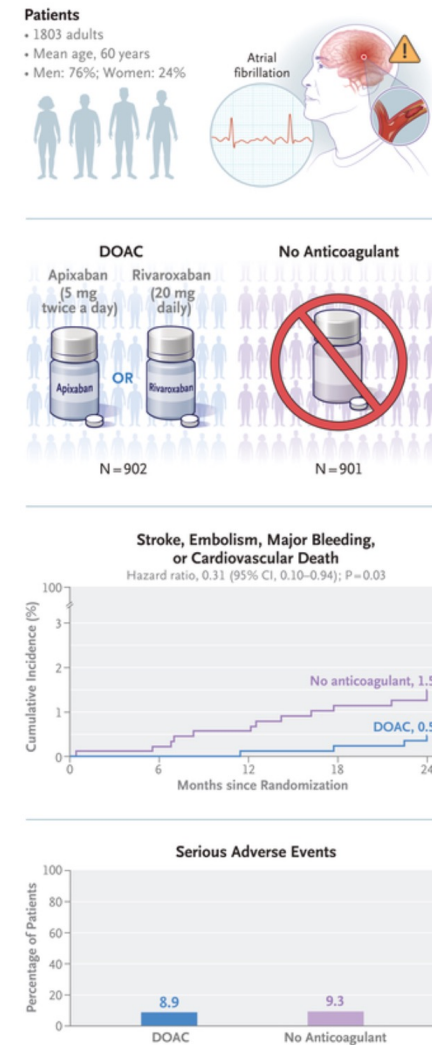
- **C** – *Congestive heart failure*: Herzinsuffizienz (bzw. eingeschränkte linksventrikuläre Pumpfunktion)
- **H** – *Hypertension*: Arterielle Hypertonie (Bluthochdruck)
- **A** – *Age*: Alter von 75 Jahren oder älter (**2 Punkte**)
- **D** – *Diabetes mellitus*: Vorhandener Diabetes
- **S2** – *Stroke / TIA*: Schlaganfall oder transitorisch ischämische Attacke in der Vorgeschichte (**2 Punkte**)

Punktzahl und jährliches Schlaganfallrisiko

- **0 Punkte**: ca. 1,9 % Risiko pro Jahr
- **1 Punkt**: ca. 2,8 % Risiko pro Jahr
- **2 Punkte**: ca. 4,0 % Risiko pro Jahr
- **3 Punkte**: ca. 5,9 % Risiko pro Jahr
- **4 Punkte**: ca. 8,5 % Risiko pro Jahr
- **5 Punkte**: ca. 12,5 % Risiko pro Jahr
- **6 Punkte**: ca. 18,2 % Risiko pro Jahr

Anticoagulation for Atrial Fibrillation with Intermediate Stroke Risk

Current U.S. and European guidelines recommend oral anticoagulation as a class IIa indication in patients with atrial fibrillation at intermediate risk for stroke; however, evidence from randomized trials is needed. We conducted a multicenter, open-label, adjudicator-masked superiority trial in South Korea involving patients with atrial fibrillation and an intermediate risk of stroke (a score of 1 in men and 2 in women on the CHA₂DS₂-VASc scale; range, 0 to 9, with higher scores indicating a greater risk of stroke). Patients were randomly assigned in a 1:1 ratio to receive either direct oral anticoagulant (DOAC) therapy or no anticoagulation. **The primary end point was a composite** of stroke, systemic embolism, major bleeding, or death from cardiovascular causes at 24 months.



Observational studies have provided **conflicting evidence with regard to the net benefit** of oral anticoagulants in patients at intermediate risk. Direct oral anticoagulants (DOACs) offer a better **balance of risks and benefits** than vitamin K antagonists in patients with atrial fibrillation, mainly because DOACs confer a lower risk of intracranial hemorrhage. Although some phase 3 trials of DOACs included patients at low risk for stroke, they did not directly compare anticoagulation with no treatment in intermediate-risk patients. We designed the SINGLE-AF trial to assess whether the risk of adverse clinical events would be lower with oral anticoagulation than with no anticoagulation among patients with atrial fibrillation who are at intermediate risk for stroke.

Methods

Trial Design

We conducted this investigator-initiated, multicenter, open-label, randomized superiority trial with blinded adjudication of outcome events at 18 centers in South Korea.

Patients were eligible to participate in the trial if they were at least 19 years of age, had atrial fibrillation, and were at intermediate risk for stroke (**defined as a CHA₂DS₂-VASc score of 1 in men or 2 in women**). Patients assigned to the DOAC group received either apixaban (5 mg twice daily) or rivaroxaban (20 mg once daily), at the treating physician's discretion, with appropriate dose reductions applied for those who met prespecified criteria

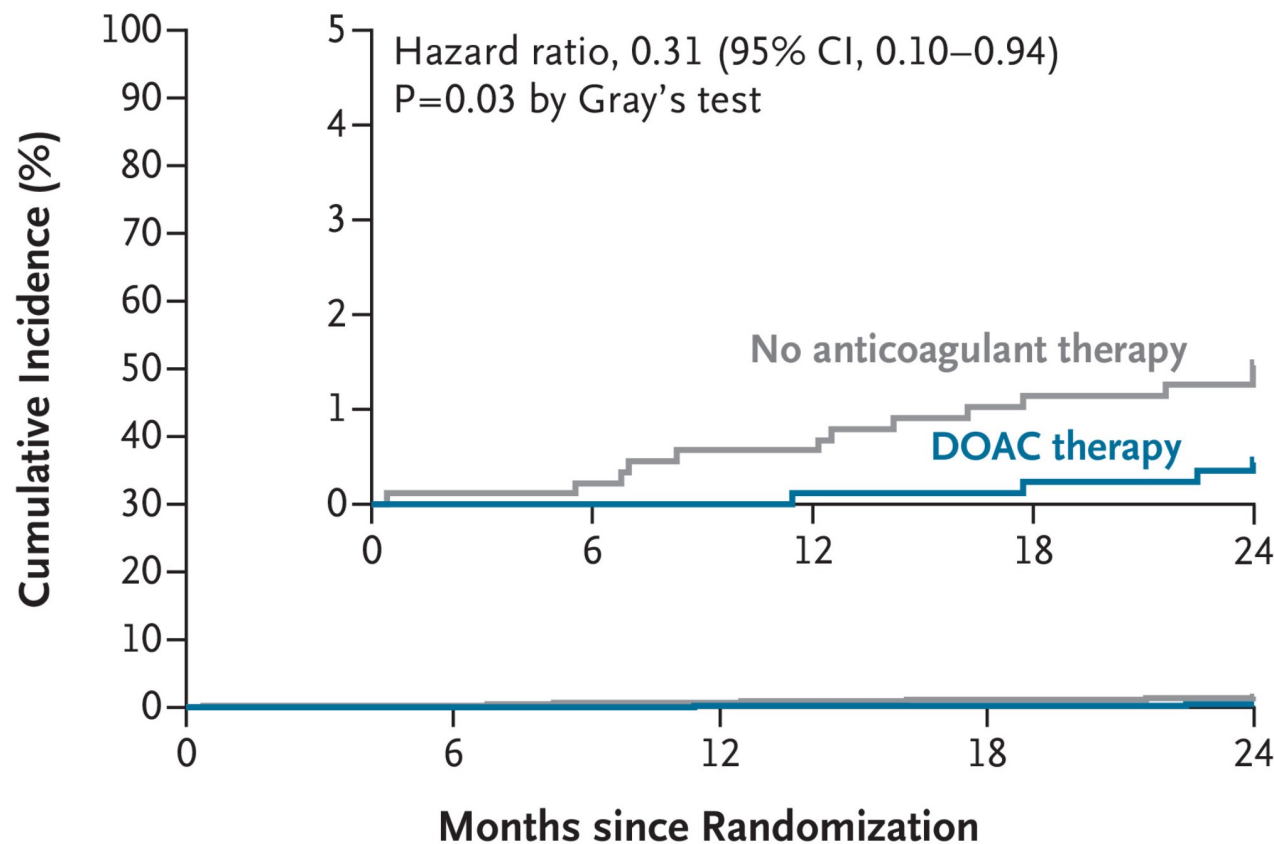
End Points

The primary end point was a **composite of stroke, systemic embolism, major bleeding, or death** from cardiovascular causes at 24 months after randomization.

Characteristic	DOAC Therapy (N = 902)	No Anticoagulant Therapy (N = 901)
Age		
Mean — yr	60.7±7.8	60.0±8.1
≥65 yr — no. (%)	304 (33.7)	282 (31.3)
Male sex — no. (%)	682 (75.6)	694 (77.0)
Type of atrial fibrillation — no. (%)		
Paroxysmal	636 (70.5)	658 (73.0)
Nonparoxysmal	266 (29.5)	243 (27.0)
Median time since atrial fibrillation diagnosis (IQR) — mo	21 (2–60)	21 (2–58)
Medical history — no. (%)		
Hypertension	435 (48.2)	482 (53.5)
Diabetes mellitus	67 (7.4)	70 (7.8)
Heart failure	93 (10.3)	72 (8.0)
Stroke or transient ischemic attack	0 (0)	2 (0.2)
Dyslipidemia	224 (24.8)	193 (21.4)
Myocardial infarction	3 (0.3)	2 (0.2)
Peripheral artery disease	8 (0.9)	4 (0.4)
Previous ablation for atrial fibrillation — no. (%)	266 (29.5)	285 (31.6)
Previous cardioversion — no. (%)	162 (18.0)	137 (15.2)
Current alcohol use — no. (%)	253 (28.0)	265 (29.4)
Current smoker — no. (%)	97 (10.8)	123 (13.7)
CHA ₂ DS ₂ -VASc score†		
Mean	1.3±0.5	1.3±0.5
Median (IQR)	1 (1–1)	1 (1–1)
CHA ₂ DS ₂ -VA score‡		
Mean	1.0±0.1	1.0±0.2
Median (IQR)	1 (1–1)	1 (1–1)
CHADS ₂ score§		
Mean	0.7±0.5	0.7±0.5
Median (IQR)	1 (0–1)	1 (0–1)
HAS-BLED score¶		
Mean	0.5±0.6	0.5±0.7
Median (IQR)	0 (0–1)	0 (0–1)
Blood pressure — mm Hg		
Systolic	125.6±15.4	127.1±14.4
Diastolic	76.6±12.4	77.2±11.8
Body-mass index	25.2±3.2	25.3±3.2
Creatinine clearance — ml/min**	88.7±24.8	90.5±25.8

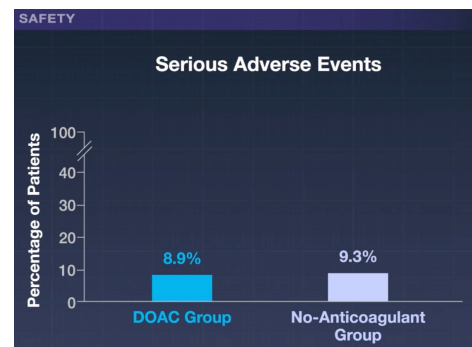
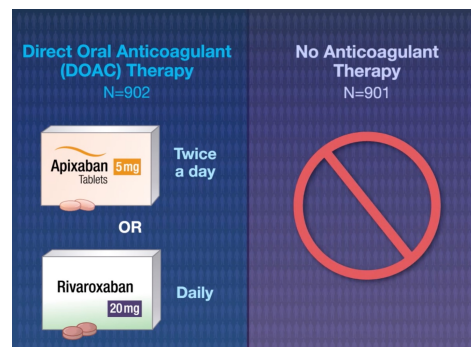
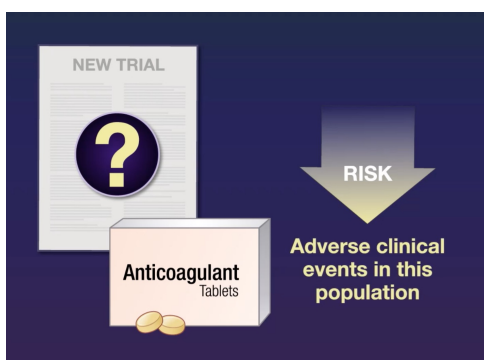
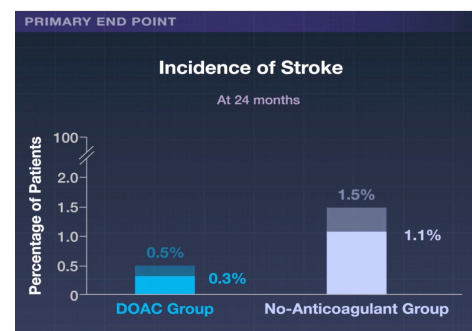
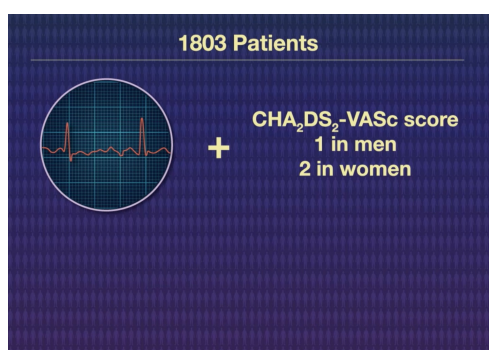
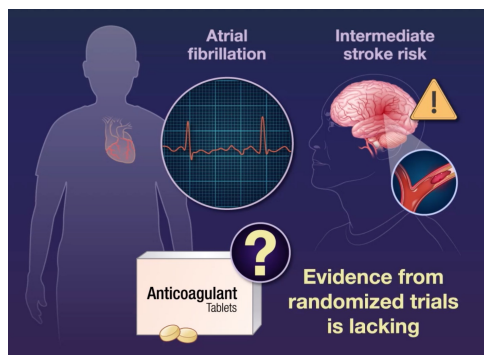
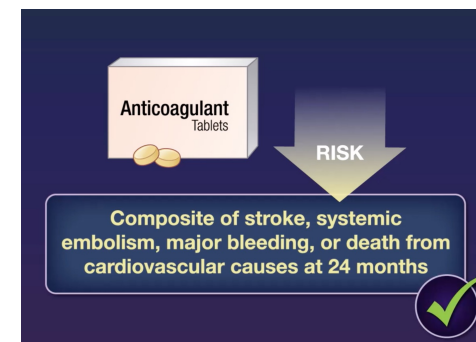
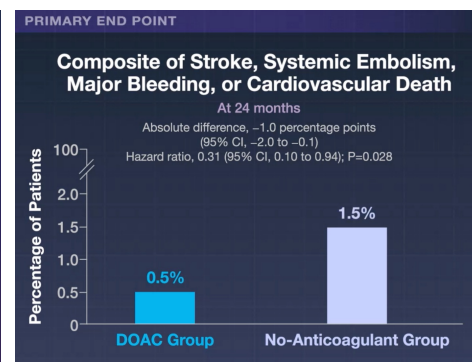
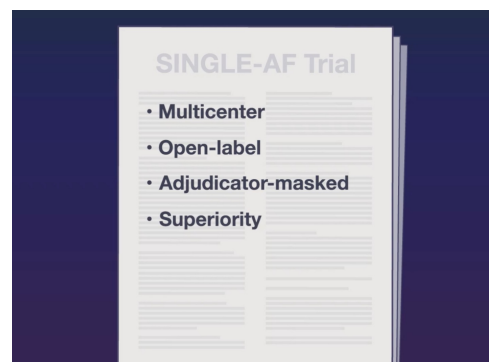
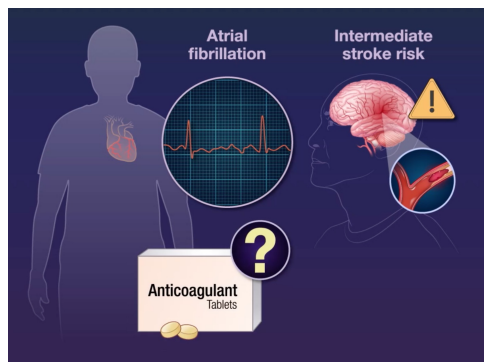
Primary, Secondary, and Exploratory End Points at 24 Months

End Point	DOAC Therapy (N = 902)	No Anticoagulant Therapy (N = 901)	Difference (95% CI)	Hazard Ratio (95% CI)
	no. of patients (estimated %)†		percentage points	
Primary end point				
Composite of stroke, systemic embolism, major bleeding, or death from cardiovascular causes	4 (0.5)	13 (1.5)	−1.0 (−2.0 to −0.1)‡	0.31 (0.10 to 0.94)
Secondary end points§				
Stroke	3 (0.3)	10 (1.1)	−0.8 (−1.6 to 0.0)	0.30 (0.08 to 1.08)
Ischemic event	1 (0.1)	10 (1.1)	−1.0 (−1.8 to −0.3)	0.10 (0.01 to 0.77)
Hemorrhagic event	2 (0.2)	0	0.2 (−0.1 to 0.6)	—
Systemic embolism	0	1 (0.1)	−0.1 (−0.3 to 0.1)	—
Major bleeding¶	3 (0.3)	4 (0.5)	−0.1 (−0.7 to 0.5)	0.75 (0.17 to 3.35)
Intracranial hemorrhage	2 (0.2)	1 (0.1)	0.1 (−0.3 to 0.5)	2.00 (0.18 to 22.05)
Gastrointestinal hemorrhage	1 (0.1)	2 (0.2)	−0.1 (−0.5 to 0.3)	0.50 (0.05 to 5.51)
Fatal bleeding	0	0	—	—
Death from cardiovascular causes	0	0	—	—
Clinically relevant nonmajor bleeding¶	22 (2.5)	14 (1.6)	0.9 (−0.4 to 2.2)	1.58 (0.81 to 3.08)
Death from any cause	3 (0.3)	5 (0.6)	−0.2 (−0.9 to 0.4)	0.60 (0.14 to 2.51)
Transient ischemic attack	0	3 (0.3)	−0.3 (−0.7 to 0.0)	—
Myocardial infarction	0	0	—	—
Hospitalization for any cause	163 (18.6)	154 (17.6)	0.9 (−2.7 to 4.6)	1.07 (0.86 to 1.33)
Exploratory end points§				
Composite of ischemic stroke or systemic embolism**	1 (0.1)	10 (1.1)	−1.0 (−1.8 to −0.3)	0.10 (0.01 to 0.77)
Composite of major bleeding or clinically relevant nonmajor bleeding¶	24 (2.7)	17 (2.0)	0.8 (−0.6 to 2.2)	1.42 (0.76 to 2.63)



Cumulative Incidence of Primary End-Point Events (Intention-to-Treat Population).

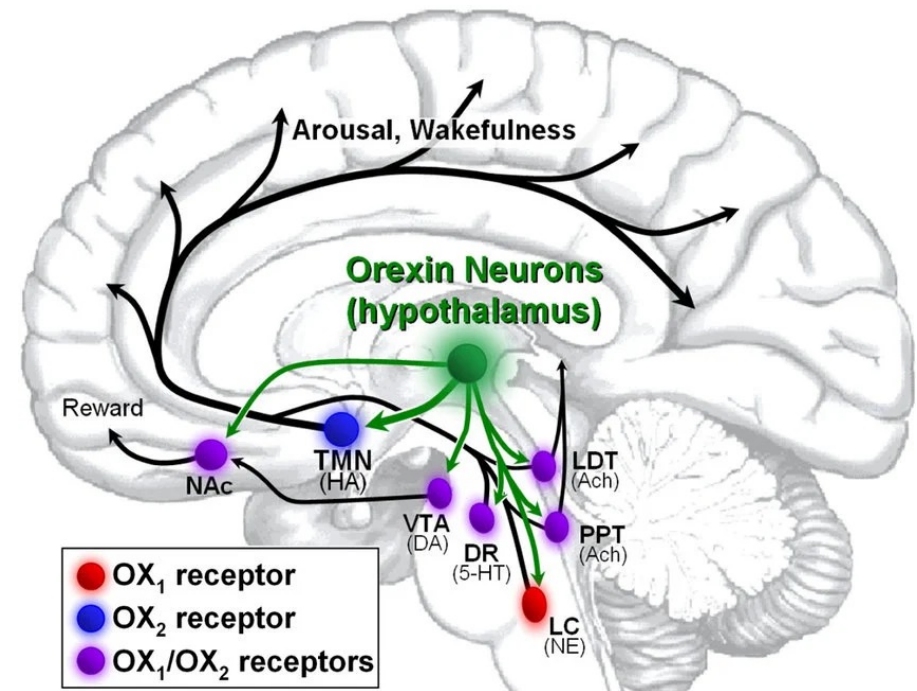
Shown is the cumulative incidence of primary end-point events. The primary end point was a composite of stroke, systemic embolism, major bleeding (as defined by the International Society on Thrombosis and Haemostasis), or death from cardiovascular causes at 24 months. The hazard ratio was calculated as a subhazard ratio with the use of the Fine–Gray method to adjust for death from noncardiovascular causes as a competing risk, and the cumulative incidence was estimated with the cumulative-incidence function. The inset displays the same data on an expanded y axis.

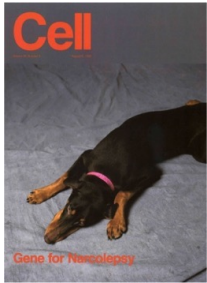


Der Orexin-Signalweg (auch Hypocretin-Signalweg) ist ein zentrales neuronales System im Gehirn, das eine Schlüsselrolle bei der Regulation von Wachheit, Schlaf-Wach-Rhythmus, Appetit und dem Belohnungssystem spielt.

Komponenten des Signalwegs

- **Liganden (Botenstoffe):** Im lateralen Hypothalamus (einem Bereich des Zwischenhirns) bilden spezialisierte Neurone zwei Peptidhormone: **Orexin A** und **Orexin B**.
- **Rezeptoren:** Die Orexine binden an zwei spezifische G-Protein-gekoppelte Rezeptoren:
 - **OX₁-Rezeptor (Orexin-Rezeptor 1):** Bindet bevorzugt Orexin A.
 - **OX₂-Rezeptor (Orexin-Rezeptor 2):** Bindet Orexin A und B mit gleicher Affinität.





Narkolepsie Typ 1 ist eine seltene neurologische Erkrankung der Schlaf-Wach-Regulation, die durch extreme Tagesschläfrigkeit und plötzlichen Muskelkraftverlust (Kataplexie) gekennzeichnet ist.

Ursachen

- **Mangel an Hypokretin (Orexin):** Der Botenstoff, der das Wachsein steuert, fehlt im Gehirn.
- **Autoimmunreaktion:** Das Immunsystem zerstört fehlerhaft die Zellen im Hypothalamus, die Hypokretin bilden.
- **Genetik:** Es gibt eine starke Kopplung an bestimmte Gewebsmerkmale (HLA-Assoziation), aber auch Umweltfaktoren spielen eine Rolle.

Das Gen für Narkolepsie beim Dobermann Pinscher ist das Hypocretin-Rezeptor-2-Gen (HCRTR2).

Hauptsymptome

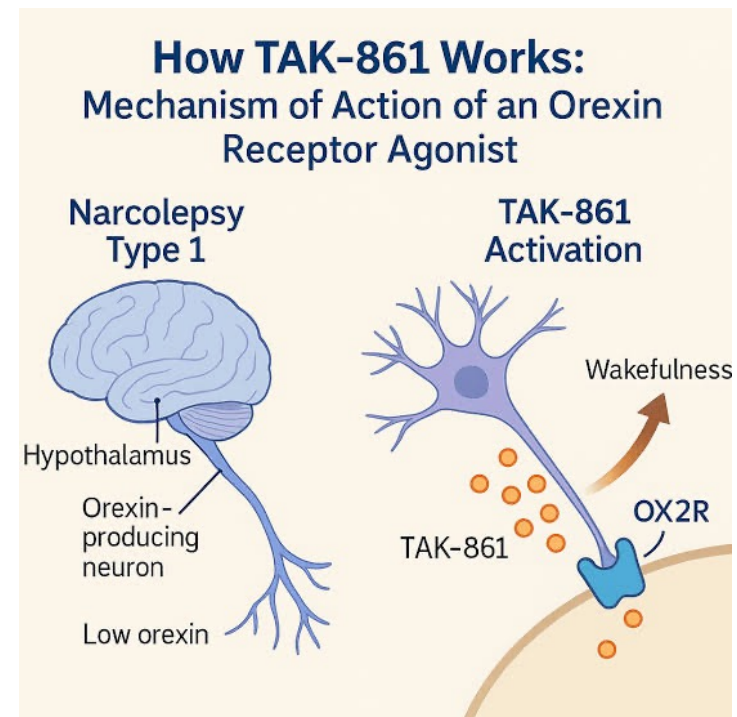
- **Tagesschläfrigkeit:** Betroffene schlafen tagsüber unkontrolliert und plötzlich ein.
- **Kataplexie:** Plötzlicher, kurzer Verlust der Muskelspannung, oft ausgelöst durch Emotionen wie Lachen oder Freude.
- **Gestörter Nachtschlaf:** Häufiges Aufwachen in der Nacht.
- **Schlafparalyse:** Vorübergehende Lähmung beim Aufwachen oder Einschlafen.
- **Halluzinationen:** Sehr lebhaft, trumartige Sinneseindrücke an den Übergängen zum Schlaf

Oveporexton ist ein neuartiger, hochwirksamer Orexin-2-Rezeptor-Agonist zur Behandlung von Narkolepsie vom Typ 1. Der Wirkstoff des japanischen Pharmaunternehmens Takeda setzt direkt an der Ursache der Erkrankung an und gilt in der Neurologie als potenzieller Meilenstein.

Wirkmechanismus

Bei Menschen mit Narkolepsie Typ 1 werden die Orexin-produzierenden Nervenzellen im Hypothalamus (vermutlich durch eine Autoimmunreaktion) zerstört. Dadurch fehlt dem Gehirn der Botenstoff Orexin, der für die Regulierung des Schlaf-Wach-Rhythmus und den Erhalt des Muskeltonus zuständig ist.

Oveporexton überwindet die Blut-Hirn-Schranke und **ersetzt das fehlende Orexin**, indem es gezielt den **Orexin-2-Rezeptor (OX2R) stimuliert**. Es bekämpft somit im Gegensatz zu bisherigen Therapien (wie Stimulanzien) die eigentliche Ursache der Erkrankung.



Oveporexton for Narcolepsy Type 1 — Results from Two Phase 3 Trials

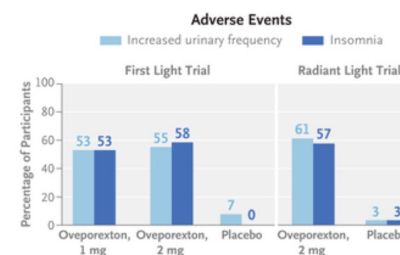
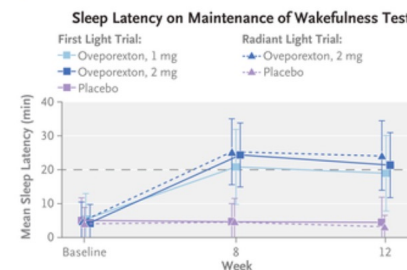
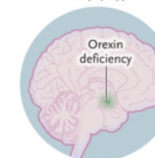
Narcolepsy type 1 is characterized by excessive daytime sleepiness, cataplexy, disrupted sleep, sleep paralysis, and hypnagogic or hypnopompic hallucinations. Oveporexton (TAK-861), an oral orexin receptor 2-selective agonist, reduced symptoms of narcolepsy type 1 in a previous phase 2 trial. We conducted two phase 3, randomized, placebo-controlled trials evaluating the efficacy and safety of oveporexton over a period of 12 weeks. Participants 16 to 70 years of age with narcolepsy type 1 were randomly assigned in a 3:3:2 ratio to receive twice-daily oveporexton (1 mg or 2 mg) or placebo in the First Light trial and in a 2:1 ratio to receive twice-daily oveporexton (2 mg) or placebo in the Radiant Light trial. The primary end point was the change from baseline to week 12 in mean sleep latency (the ability to stay awake under soporific conditions) on the Maintenance of Wakefulness Test (MWT; range, 0 to 40 minutes; normal, ≥ 20). Key secondary end points included the change from baseline to week 12 in the Epworth Sleepiness Scale (ESS) total score (range, 0 to 24; normal, ≤ 10) and the weekly cataplexy rate at week 12.

Participants

- First Light trial: 168 participants
Mean age, 30–34 years
Women: 58%; Men: 42%
- Radiant Light trial: 105 participants
Mean age, 29–34 years
Men: 52%; Women: 48%



Narcolepsy Type 1



Narcolepsy type 1 is a chronic neurologic disorder with core symptoms of excessive daytime sleepiness, cataplexy, disrupted nighttime sleep, hypnagogic or hypnopompic hallucinations, and sleep paralysis; these symptoms can lead to a markedly reduced quality of life. Oveporexton (TAK-861) is a highly potent oral OX2R-selective agonist that addresses orexin deficiency in narcolepsy type 1 by stimulating the dominant receptor involved in sleep–wake regulation, OX2R. In a phase 2, dose-ranging clinical trial, significant and clinically meaningful reductions in symptoms of narcolepsy type 1 were achieved with oveporexton over a period of 8 weeks. We conducted two phase 3 trials (the First Light and Radiant Light trials) in participants with narcolepsy type 1.

Trial Designs

The First Light and Radiant Light trials were phase 3, multicenter, double-blind, randomized, placebo-controlled trials conducted in Asia (both trials), Australia (the Radiant Light trial only), Europe (both trials), and North America (the First Light trial only) to evaluate the efficacy and safety of oveporexton. Participants with narcolepsy type 1 were randomly assigned in permuted blocks, with the use of interactive response technology, to receive twice-daily oveporexton (1 mg or 2 mg per dose) or placebo (3:3:2 ratio) in the First Light trial or to receive twice-daily oveporexton (2 mg per dose) or placebo (2:1 ratio) in the Radiant Light trial; doses were taken at approximately 8 a.m. and 11 a.m. for 12 weeks.

Participants

The trials enrolled participants 16 to 70 years of age with a diagnosis of narcolepsy type 1 (as defined by the International Classification of Sleep Disorders, Third Edition [ICSD-3]).

End Points

The primary end point of both trials was the change from baseline to week 12 in mean sleep latency on the 40-minute Maintenance of Wakefulness Test (MWT).

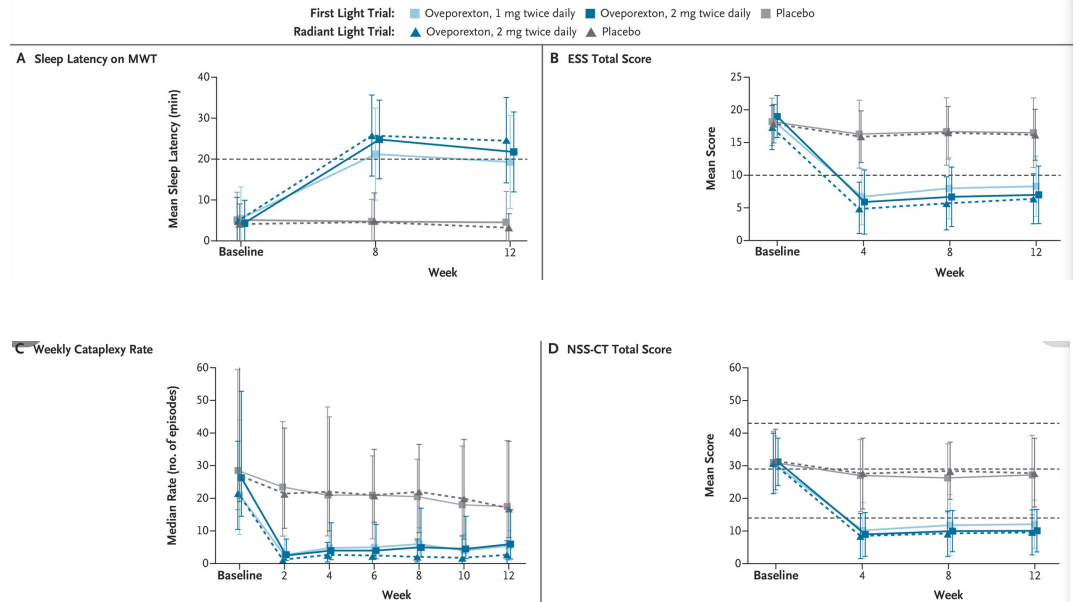
Characteristic	First Light Trial			Radiant Light Trial	
	Placebo (N=41)	Oveporexton, 1 mg Twice Daily (N=61)	Oveporexton, 2 mg Twice Daily (N=66)	Placebo (N=35)	Oveporexton, 2 mg Twice Daily (N=70)
Age — yr					
Mean	30.9±12.7	33.5±11.8	29.7±9.6	34.0±13.1	29.1±9.6
Median (range)	27.0 (16–61)	32.0 (16–65)	26.0 (17–52)	30.0 (18–58)	26.5 (18–62)
Age at symptom onset — yr					
Mean	17.7±9.7	18.6±10.6	17.3±8.3	19.6±11.8	17.8±9.0
Median (range)	15.0 (4–47)	16.0 (6–53)	15.0 (6–44)	17.0 (4–52)	15.0 (6–43)
Age at diagnosis of narcolepsy type 1 — yr					
Mean	23.6±12.3	25.2±11.7	23.5±10.0	24.8±13.2	23.6±9.7
Median (range)	19.4 (5–55)	23.7 (8–56)	20.3 (8–49)	20.5 (7–55)	21.9 (7–47)
Female sex — no. (%)	24 (59)	28 (46)	46 (70)	13 (37)	37 (53)
Race — no. (%)†					
Asian	6 (15)	10 (16)	10 (15)	7 (20)	14 (20)
Black	4 (10)	3 (5)	0	0	0
White	15 (37)	17 (28)	27 (41)	19 (54)	28 (40)
Multiracial	1 (2)	0	0	0	0
Not reported	5 (12)	3 (5)	7 (11)	0	0
Unknown or other	10 (24)	28 (46)	22 (33)	9 (26)	28 (40)
Body-mass index‡					
Mean	26.4±6.0	27.2±5.6	26.2±4.6	27.5±4.5	26.6±4.8
>30 — no. (%)	12 (29)	18 (30)	19 (29)	9 (26)	11 (16)
Receiving medication for narcolepsy type 1 that required washout — no. (%)§	33 (80)	50 (82)	51 (77)	26 (74)	59 (84)
CSF orexin level					
No. of participants evaluated¶	11	21	20	12	28
Mean — pg/ml	16.6±14.1	18.8±20.7	27.8±28.4	12.8±18.7	21.6±19.6
Median (range) — pg/ml	18.0 (0–44)	13.6 (0–86)	16.6 (0–88)	0.5 (0–57)	15.6 (0–73)

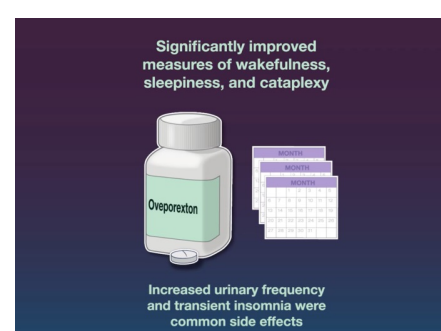
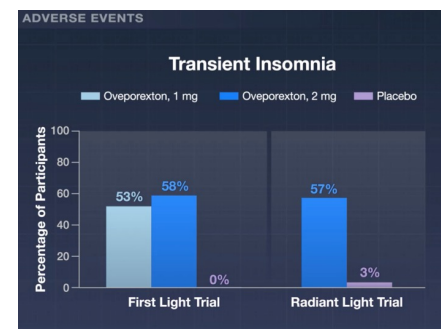
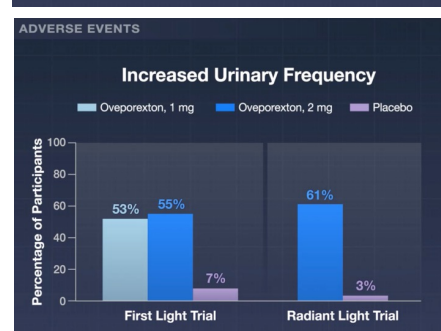
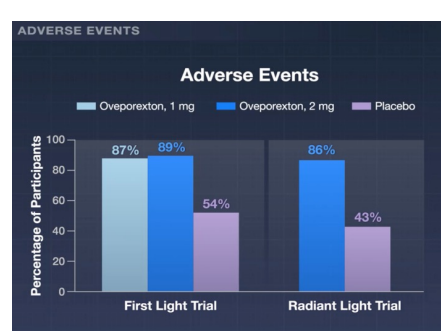
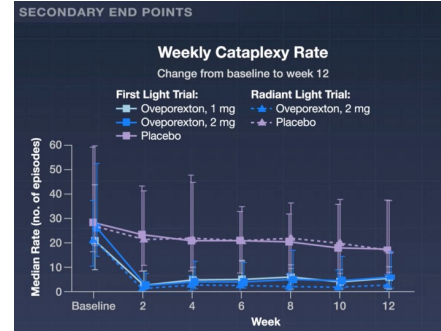
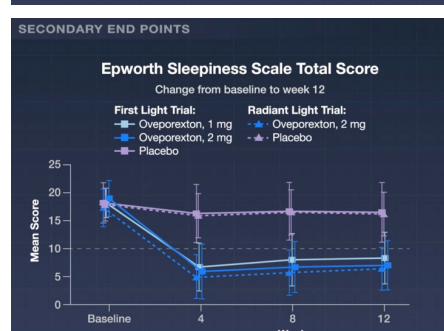
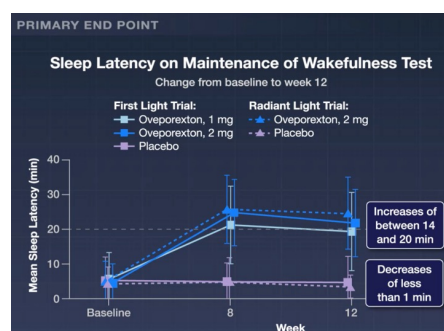
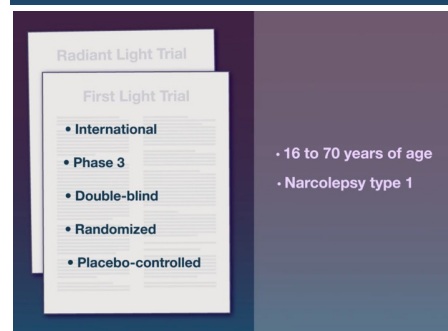
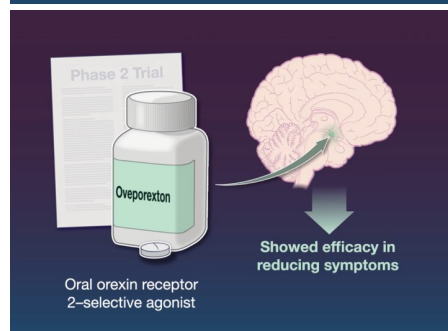
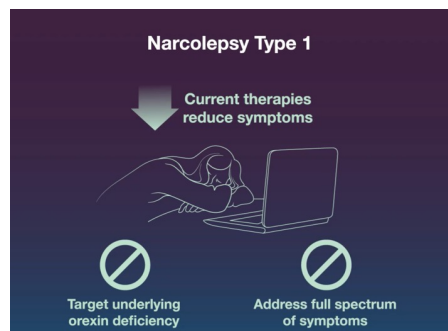
Key Efficacy End Points

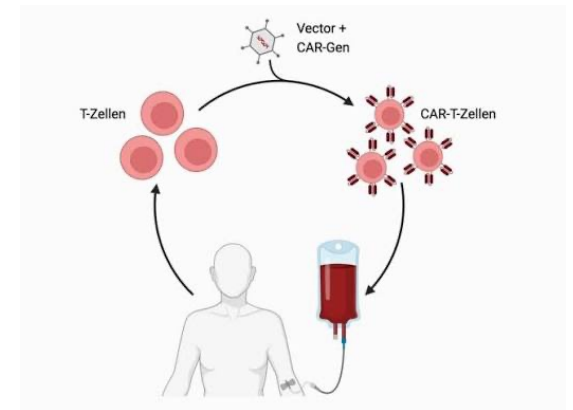
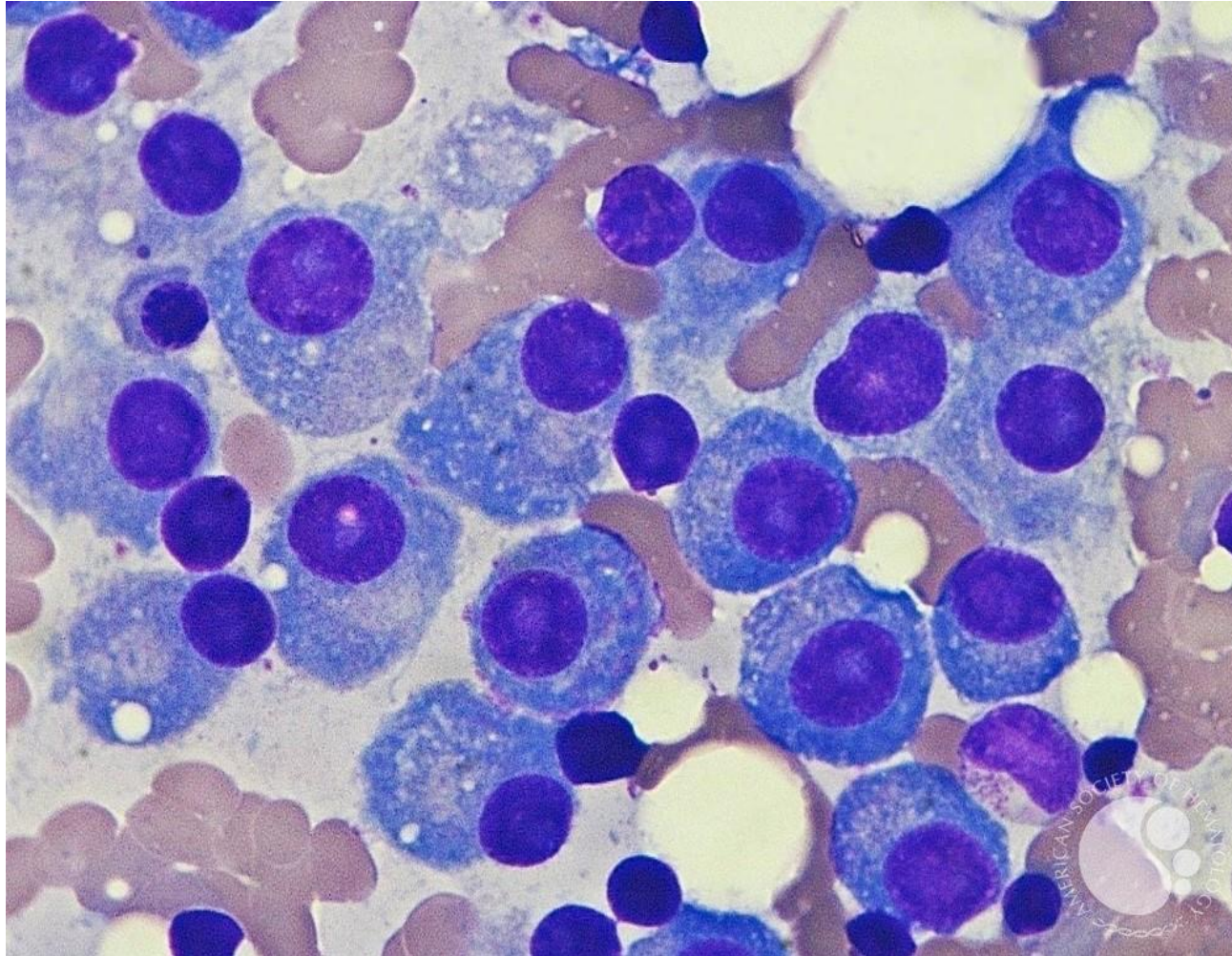
End Point	First Light Trial			Radiant Light Trial	
	Placebo (N=41)	Oveporexton, 1 mg Twice Daily (N=61)	Oveporexton, 2 mg Twice Daily (N=66)	Placebo (N=35)	Oveporexton, 2 mg Twice Daily (N=70)
Mean sleep latency on MWT†					
Mean at baseline — min	5.1±6.8	5.5±7.7	4.4±5.5	4.1±4.9	4.8±4.9
Mean at wk 12 — min	4.5±7.6	19.3±11.4	21.8±9.8	3.3±3.3	24.6±10.5
Mean change from baseline to wk 12 — min	-0.4±4.3	14.3±10.9	17.6±9.3	-0.8±3.6	19.8±9.9
Least-squares mean change from baseline to wk 12 (95% CI) — min	-1.3 (-4.3 to 1.6)	12.5 (10.0 to 15.0)	15.9 (13.5 to 18.2)	-1.0 (-4.0 to 2.0)	19.1 (16.6 to 21.5)
Least-squares mean difference from placebo (95% CI) — min	—	13.8 (10.2 to 17.4)	17.2 (13.7 to 20.7)	—	20.1 (16.6 to 23.6)
Adjusted P value	—	<0.001	<0.001	—	<0.001
ESS total score‡					
Mean at baseline	18.2±3.6	18.2±2.6	19.0±3.2	17.9±3.0	17.3±3.4
Mean at wk 12	16.5±5.3	8.3±4.6	7.0±4.4	16.2±3.9	6.4±3.8
Mean change from baseline to wk 12	-1.5±3.7	-9.7±4.8	-11.8±4.7	-1.7±3.6	-11.0±4.4
Least-squares mean change from baseline to wk 12 (95% CI)	-1.4 (-3.0 to 0.1)	-9.4 (-10.8 to -8.1)	-11.2 (-12.4 to -10.0)	-1.6 (-2.9 to -0.2)	-11.1 (-12.2 to -10.0)
Least-squares mean difference from placebo (95% CI)	—	-8.0 (-9.9 to -6.1)	-9.8 (-11.6 to -7.9)	—	-9.5 (-11.1 to -8.0)
Adjusted P value	—	<0.001	<0.001	—	<0.001
Weekly cataplexy rate					
Median no. of episodes at baseline (IQR)	28.5 (16.5 to 59.5)	21.0 (9.0 to 45.0)	26.3 (14.5 to 52.8)	27.0 (19.0 to 66.5)	21.8 (10.5 to 37.5)
Median no. of episodes at wk 12 (IQR)	17.5 (1.3 to 37.7)	5.5 (1.0 to 10.2)	6.0 (1.4 to 16.5)	17.0 (8.0 to 37.5)	2.7 (0 to 7.0)
Incidence rate ratio vs. placebo (95% CI)	—	0.34 (0.20 to 0.57)	0.38 (0.23 to 0.61)	—	0.25 (0.15 to 0.42)
Adjusted P value	—	<0.001	<0.001	—	<0.001
NSS-CT total score§					
Mean at baseline	31.0±9.6	30.4±8.7	31.2±7.3	31.9±9.3	30.7±9.3
Mean at wk 12	27.2±12.2	12.1±7.4	10.1±6.5	27.9±10.5	9.6±6.9
Least-squares mean change from baseline to wk 12 (95% CI)	-3.0 (-5.8 to -0.2)	-17.4 (-19.8 to -15.0)	-19.9 (-22.0 to -17.7)	-3.0 (-5.7 to -0.4)	-21.2 (-23.3 to -19.0)
Least-squares mean difference from placebo (95% CI)	—	-14.4 (-17.8 to -10.9)	-16.9 (-20.2 to -13.5)	—	-18.1 (-21.3 to -15.0)
Adjusted P value	—	<0.001	<0.001	—	<0.001

Overview of Adverse Events

Event	First Light Trial			Radiant Light Trial	
	Placebo (N=41)	Ovoporexton, 1 mg Twice Daily (N=60)	Ovoporexton, 2 mg Twice Daily (N=66)	Placebo (N=35)	Ovoporexton, 2 mg Twice Daily (N=70)
number of participants (percent)					
Adverse events					
Any	22 (54)	52 (87)	59 (89)	15 (43)	60 (86)
Mild	14 (34)	26 (43)	34 (52)	9 (26)	38 (54)
Moderate	7 (17)	24 (40)	23 (35)	5 (14)	20 (29)
Severe†	1 (2)	2 (3)	2 (3)	1 (3)	2 (3)
Serious adverse event‡	0	1 (2)	1 (2)	0	0
Adverse event considered to be related to trial regimen§	9 (22)	46 (77)	53 (80)	3 (9)	56 (80)
Adverse event leading to discontinuation from trial¶	1 (2)	3 (5)	0	0	2 (3)
Liver-function tests					
ALT increased	1 (2)	2 (3)	0	0	1 (1)
AST increased	1 (2)	1 (2)	0	0	1 (1)
Most frequent adverse events					
Increased urinary frequency	3 (7)	32 (53)	36 (55)	1 (3)	43 (61)
Insomnia	0	32 (53)	38 (58)	1 (3)	40 (57)
Urinary urgency	1 (2)	9 (15)	12 (18)	0	10 (14)
Nasopharyngitis	6 (15)	6 (10)	10 (15)	0	2 (3)
Headache	5 (12)	4 (7)	10 (15)	2 (6)	3 (4)
Salivary hypersecretion	0	5 (8)	4 (6)	0	5 (7)
Weight increased	3 (7)	2 (3)	4 (6)	0	3 (4)
Migraine	3 (7)	0	1 (2)	0	0
Upper respiratory tract infection	2 (5)	2 (3)	2 (3)	2 (6)	3 (4)
Gastroenteritis	1 (2)	0	2 (3)	2 (6)	2 (3)
Rash	0	0	1 (2)	0	4 (6)



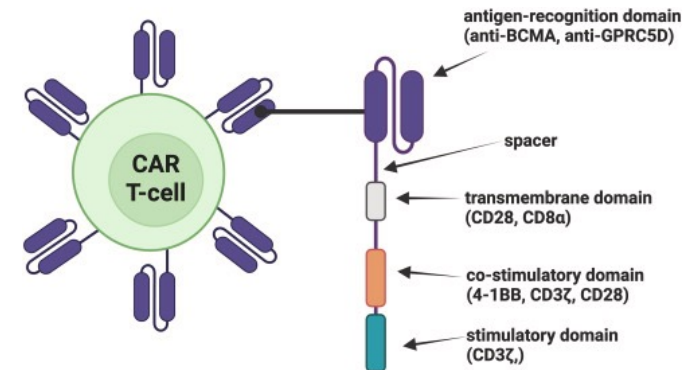




Anito-cel (vollständiger Name: **Anitocabtagene Autoleucel**) ist eine neuartige, experimentelle CAR-T-Zell-Therapie zur Behandlung des rezidierten oder refraktären Multiplen Myeloms (einer Form von Knochenmarkskrebs).

Die wichtigsten Merkmale dieses medizinischen Ansatzes im Überblick:

- **Wirkmechanismus:** Die Therapie richtet sich gezielt gegen das B-Zell-Reifungsantigen (**BCMA**) auf den Myelomzellen. Das Besondere an Anito-cel ist ein synthetisches Bindeglied, die sogenannte „**D-Domain**“. Diese sorgt für eine stabilere Struktur, eine effizientere Herstellung und ermöglicht es den CAR-T-Zellen, nach dem Angriff schneller wieder von der Tumorzelle abzulassen (schnelle „Off-Rate“), was Erschöpfungerscheinungen der Immunzellen mindern soll.



Der Vektor bei **Anito-cel** (Anitocabtagen-Autoleucel) ist ein replikationsdefizienter lentiviraler Vektor.

Konkret handelt es sich um einen selbstinaktivierenden lentiviralen Vektor (basierend auf dem Humanen Immundefizienz-Virus 1 / HIV-1). In der Fachliteratur wird die Vektor-Konstruktion oft als **LV-SIN-EF1α-anti-BCMA** bezeichnet.

Phase 1 Study of Anito-cel, a D-Domain BCMA CAR T Cell for Refractory or Recurrent Myeloma

Anitocabtagene autoleucel (anito-cel), a B-cell maturation antigen (BCMA)–directed autologous chimeric antigen receptor (CAR) T-cell therapy with a synthetic d-domain binder (ddBCMA), may have efficacy in patients with relapsed or refractory multiple myeloma. In a phase 1 study, we evaluated the safety and efficacy of anito-cel (dose level 1, 100×10^6 CAR+ T cells; dose level 2, 300×10^6 CAR+ T cells) in patients with relapsed or refractory multiple myeloma who had received three or more lines of therapy previously or had triple-class refractory disease. Primary end points were adverse events during the treatment period and establishment of the recommended phase 2 dose. In complementary in vitro studies, we compared the anito-cel ddBCMA binder with a dual variable heavy-chain domain of a heavy chain–only antibody (dual-VHH) binder corresponding to the published sequence for ciltacabtagene autoleucel.

Conclusions

Anito-cel therapy led to a high incidence of response among patients with heavily pretreated relapsed or refractory multiple myeloma. Cytokine release syndrome and ICANS of grade 3 or higher were rare.

B-cell maturation antigen (BCMA)–directed chimeric antigen receptor (CAR) T-cell therapies have improved outcomes in patients with relapsed or refractory multiple myeloma. Some patients remain disease-free beyond 5 years after treatment with ciltacabtagene autoleucel (cilta-cel), which suggests potential cure. However, rare but irreversible non–immune effector cell–associated neurotoxicity syndrome (ICANS) neurotoxic effects, including parkinsonism and Guillain–Barré syndrome, as well as immune effector cell–associated enterocolitis, have been reported with cilta-cel. The pathophysiological features of these toxic effects and the mechanistic differences underlying their relative absence with other BCMA-directed CAR T-cell therapies remain poorly understood.

Unlike currently approved CD19 CAR T cells for lymphoma that all share the same FMC63-based single-chain variable fragment binder, cilta-cel, idecabtagene vicleucel (ide-cel), and anitocabtagene autoleucel (anito-cel) each use different BCMA binders. Unique binder attributes, including the association–dissociation kinetics of antigen–receptor interactions, influence signal strength and downstream T-cell function, potentially contributing to the differing clinical profiles observed across products.

Methods

Study Design and Eligibility

In this phase 1 study, we evaluated anito-cel in eligible adults with relapsed or refractory multiple myeloma who had received at least three previous lines of therapy that included an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody or who had triple-class refractory disease (disease refractory to all three classes of drugs). The study included dose-escalation and dose-expansion components. Anito-cel product description, manufacturing, and dose-escalation results have been reported previously. Patients received anito-cel at a dose of 100×10^6 CAR+ T cells (dose level 1) or 300×10^6 CAR+ T cells (dose level 2) on day 0. Peripheral-blood samples were obtained at screening, on day 0, and at various postinfusion time points for correlative analyses.

A standard 3+3 design was used to identify the recommended phase 2 dose, with 6 patients in each dose-level cohort. The size of the expansion cohort reflected clinical and operational considerations rather than formal statistical power, with a cohort size of approximately 26 deemed to be adequate to characterize safety and estimate preliminary activity at the recommended dose.

End Points

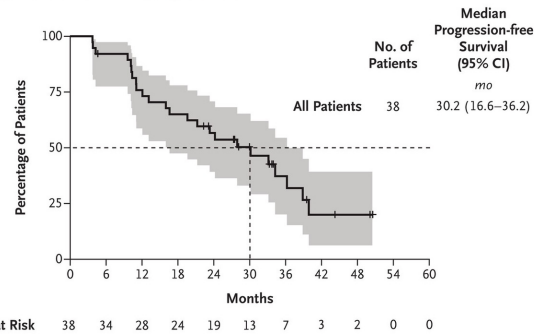
Primary end points were adverse events during the treatment period, defined as any adverse event with an onset date on or after the first anito-cel infusion until 90 days or as any adverse event occurring at any time that was assessed by the investigator as being related to anito-cel, and establishment of the recommended phase 2 dose. Secondary end points were investigator-assessed best overall response and overall response, assessed according to the International Myeloma Working Group consensus criteria, and pharmacokinetics.

Characteristic	Dose Level 1 (N = 32)	Dose Level 2 (N = 6)	Total (N = 38)
Age			
Median (range) — yr	66 (44–76)	60 (52–65)	66 (44–76)
≥65 yr — no. (%)	19 (59)	1 (17)	20 (53)
Sex — no. (%)			
Male	18 (56)	5 (83)	23 (61)
Female	14 (44)	1 (17)	15 (39)
Race — no. (%)†			
White	28 (88)	4 (67)	32 (84)
Black	3 (9)	1 (17)	4 (11)
Asian	1 (3)	0	1 (3)
Other	0	1 (17)	1 (3)
ECOG performance-status score — no. (%)‡			
0	9 (28)	3 (50)	12 (32)
1	23 (72)	3 (50)	26 (68)
High-risk prognostic features — no. (%)			
Extramedullary disease§	9 (28)	3 (50)	12 (32)
Bone marrow plasma cells ≥60%¶	8 (25)	4 (67)	12 (32)
β ₂ -microglobulin level ≥5.5 mg/liter¶	5 (16)	2 (33)	7 (18)
High-risk cytogenetic abnormality	9 (28)	2 (33)	11 (29)
High-risk cytogenetic abnormality inclusive of 1q gain	21 (66)	5 (83)	26 (68)
Median no. of previous lines of therapy (range)	5 (3–7)	4 (3–14)	4 (3–14)
Triple-class–refractory disease — no. (%)**	32 (100)	6 (100)	38 (100)
Penta-drug–refractory disease — no. (%)††	21 (66)	5 (83)	26 (68)
Previous autologous stem-cell transplantation — no. (%)	24 (75)	4 (67)	28 (74)
Previous BCMA-directed therapy — no. (%)‡‡	1 (3)	0	1 (3)
Median time since diagnosis (range) — yr	6.5 (1.5–14.9)	6.9 (1.7–11.0)	6.5 (1.5–14.9)
Bridging therapy — no. (%)	22 (69)	6 (100)	28 (74)

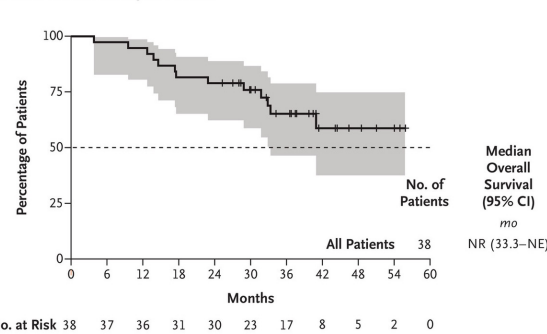
Adverse Events in 38 Patients Who Received Anito-cel at Either Dose Level.

Event	Dose Level 1 (N = 32)		Dose Level 2 (N = 6)		Total (N = 38)
	Grade 1 or 2	Grade ≥3	Grade 1 or 2	Grade ≥3	Any Grade
	<i>number of patients (percent)</i>				
Any event	1 (3)	31 (97)	0	6 (100)	38 (100)
Neutropenia	0	27 (84)	0	6 (100)	33 (87)
Thrombocytopenia	8 (25)	13 (41)	1 (17)	4 (67)	26 (68)
Anemia	2 (6)	17 (53)	1 (17)	4 (67)	24 (63)
Hypophosphatemia	13 (41)	1 (3)	4 (67)	0	18 (47)
Fatigue	16 (50)	0	1 (17)	0	17 (45)
Lymphopenia	0	11 (34)	0	4 (67)	15 (39)
Hypokalemia	10 (31)	2 (6)	1 (17)	0	13 (34)
Hypogammaglobulinemia	11 (34)	0	1 (17)	0	12 (32)
Constipation	6 (19)	0	4 (67)	0	10 (26)
Diarrhea	9 (28)	0	1 (17)	0	10 (26)
Decreased appetite	6 (19)	1 (3)	1 (17)	1 (17)	9 (24)
Dizziness	6 (19)	0	3 (50)	0	9 (24)
Headache	7 (22)	0	2 (33)	0	9 (24)
Hypocalcemia	6 (19)	0	2 (33)	0	8 (21)
Leukopenia	0	6 (19)	0	2 (33)	8 (21)
Nausea	6 (19)	0	2 (33)	0	8 (21)
Adverse events of special interest					
Cytokine release syndrome	30 (94)	0	5 (83)	1 (17)	36 (95)
ICANS	5 (16)	1 (3)	0	1 (17)	7 (18)
Grade ≥3 infection	—	5 (16)	—	1 (17)	6 (16)

A Progression-free Survival among All Patients



B Overall Survival among All Patients

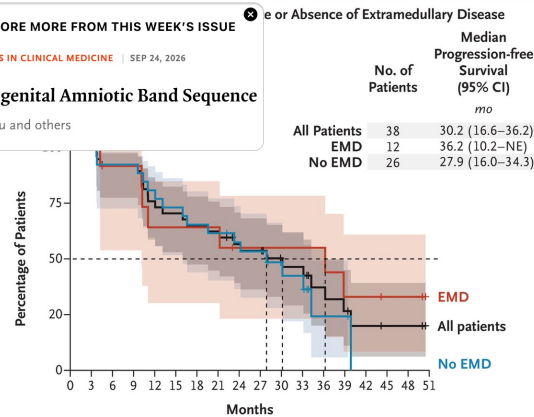


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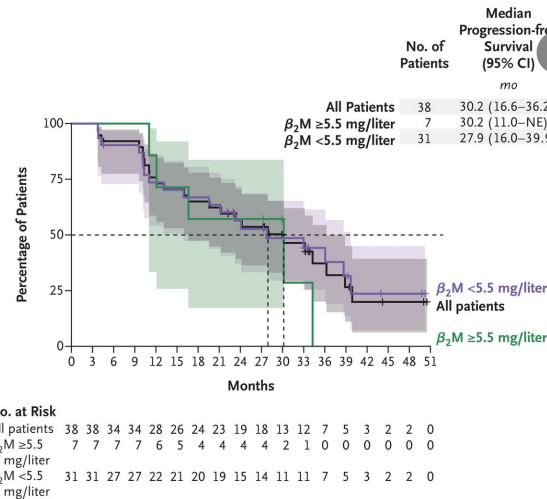
IMAGES IN CLINICAL MEDICINE | SEP 24, 2026

Congenital Amniotic Band Sequence

Yao Lu and others

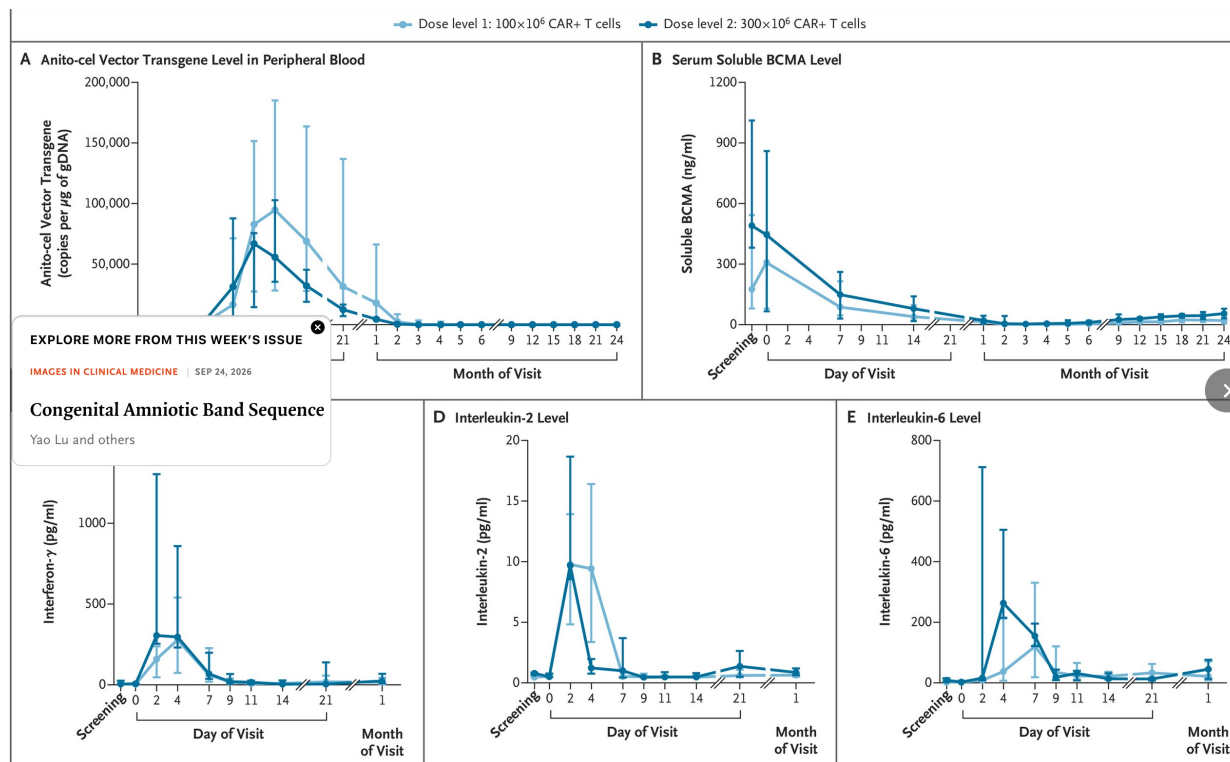


D Progression-free Survival According to β_2 -Microglobulin Level



Progression-free Survival and Overall Survival among Patients Treated with Anito-cel.

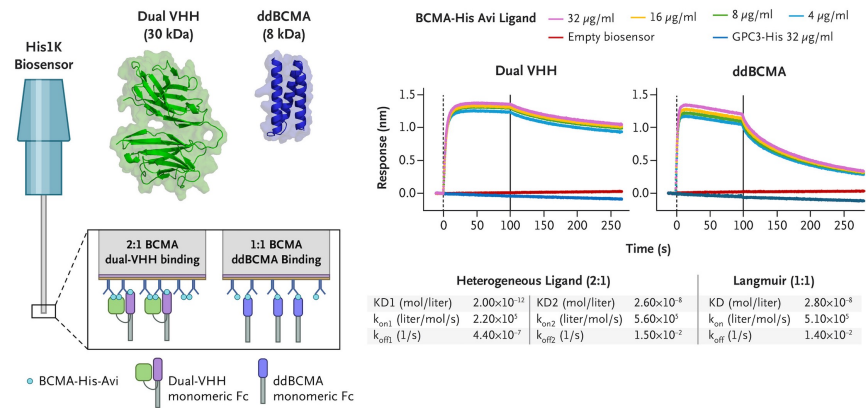
Shown are progression-free survival (Panel A) and overall survival (Panel B) among all patients who received anitocabtagene autoleucel (anito-cel), a B-cell maturation antigen (BCMA)–directed autologous chimeric antigen receptor (CAR) T-cell therapy with a synthetic D-domain binder (ddBCMA). Panels C and D show progression-free survival among patients according to the presence or absence of extramedullary disease (EMD) and according to the β_2 -microglobulin (β_2M) level (≥ 5.5 or < 5.5 mg per liter), respectively. In all panels, tick marks indicate censored data, and shaded areas 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used for hypothesis testing. NE denotes could not be estimated, and NR not reached.



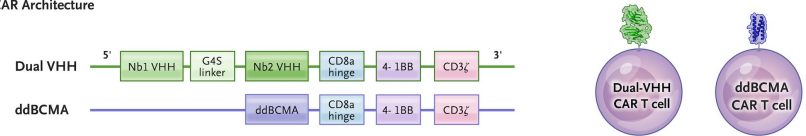
Anito-cel Pharmacokinetics and Pharmacodynamics.

Anito-cel CAR transgene levels were measured in peripheral blood and bone marrow for up to 2 years after the infusion with the use of a transgene-specific digital droplet polymerase-chain-reaction assay. Panel A shows anito-cel vector transgene levels in peripheral blood per microgram of genomic DNA (gDNA). Changes in serum soluble BCMA levels (Panel B) and in concentrations of CAR T-cell activation-associated serum analytes interferon- γ (Panel C), interleukin-2 (Panel D), and interleukin-6 (Panel E) were evaluated at baseline and after the anito-cel infusion. Data are shown as median values, and I bars indicate the interquartile range.

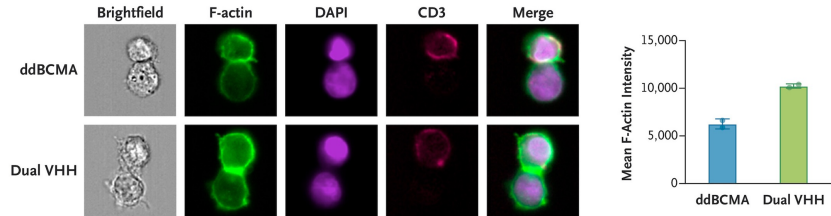
A Biophysical Characteristics of the Dual-VHH and ddBCMA Binders



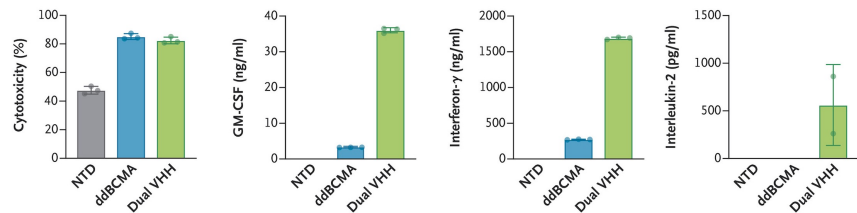
B CAR Architecture



C F-Actin Recruitment to the Immune Synapse



D CAR T-Cell Cytotoxicity and Cytokine Release in Response to Tumor Cells in Bone Marrow from Patients with Multiple Myeloma



Functional Effects of ddBCMA and Dual-VHH Binders.

Panel A shows the size and structure of the dual variable heavy-chain domain of a heavy chain-only antibody (dual-VHH) and ddBCMA binders and biolayer interferometry binding data demonstrating strong avidity effects for the dual-VHH binder, whereas no avidity effect was observed with the ddBCMA binder. The left part of Panel A was adapted from Sun et al.¹⁰

The vertical lines in the graphs on the right indicate the start of association (dashed lines) and the start of dissociation (solid lines) of the chimeric antigen receptor (CAR) binders binding BCMA. The dual VHH has two distinct binders for BCMA, so a heterogeneous ligand model that quantifies the binding kinetics for two binding events was used, whereas ddBCMA has one binder, so it can be

quantified with the Langmuir model. GPC3-His denotes human glypican 3 protein fused with a polyhistidine (His) tag. His-Avi histidine-avidin, KD dissociation constant, and Nb nanobody. Panel B shows a schematic of the research-grade CAR constructs expressed in T cells and used in subsequent experiments. Panel C shows immune synapse formation between ddBCMA CAR or dual-VHH CAR T cells and BCMA-expressing K562 cells as assessed by imaging flow cytometry; representative images of CAR T cells stained with phalloidin (F-actin stain), 4',6-diamidino-2-phenylindole (DAPI), and anti-CD3 are shown. G4S denotes poly-glycine-serine.

The graph in Panel C shows the mean fluorescence intensity of F-actin at the immune synapse of CAR T cells from two independent donors. Dots indicate mean values in CAR T cells derived from two independent donors, and I bars the standard deviation. Panel D shows cytotoxicity (the percentage of tumor cells killed) and cytokine release values (granulocyte-macrophage colony-stimulating factor [GM-CSF], interleukin-2, and interferon- γ) with primary bone marrow mononuclear cells from patients with multiple myeloma after coculture with ddBCMA CAR T cells or dual-VHH CAR T cells, with technical replicates shown as means (dots); data are representative of two independent patient bone marrow mononuclear cell samples, each with CAR T cells generated from two independent T-cell donors. I bars indicate the standard deviation. NTD denotes nontransduced (control cells).

Discussion

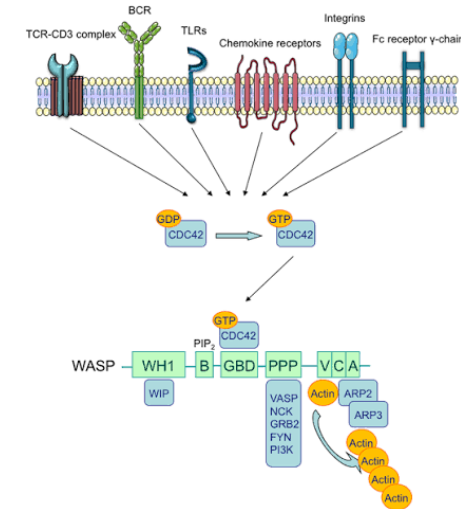
Anito-cel induced rapid, deep, and durable responses with MRD negativity (sensitivity threshold, 10^{-5}) in a population of patients with heavily pretreated relapsed or refractory multiple myeloma, with responses also observed across all high-risk subgroups. This population included patients with extramedullary disease and an elevated β_2 -microglobulin level, features generally associated with inferior outcomes in multiple myeloma, although these subgroups were small and assessed descriptively. All the patients with MRD-negative status that was sustained for at least 12 months continued to have a response at the time of data cutoff. These responses were observed with what appears to be a low incidence of immune adverse events, including no cytokine release syndrome of grade 3 or higher and only one case of grade 3 ICANS among patients who received the recommended phase 2 dose (dose level 1 cohort). The incidence of infection of grade 3 or higher was 16%, with no grade 5 infections — values that are numerically lower than rates reported with BCMA-directed bispecific antibodies in other trials.

The Wiskott-Aldrich syndrome protein (WASp) acts as a master regulator of the actin cytoskeleton—the internal protein network that gives blood and immune cells their shape, strength, and mobility

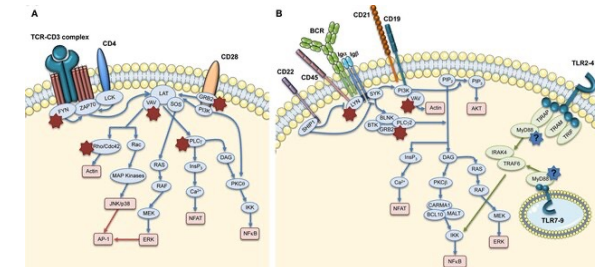
WASp is found exclusively in blood-forming (**hematopoietic**) cells, including T cells, B cells, natural killer (NK) cells, and platelets. It helps these cells perform critical survival tasks:

- **Immune defense:** Allows white blood cells to move toward infections, squeeze through tissues, and form "immunological synapses" (communication zones) to activate immune responses.
- **Platelet production:** Assists in the normal creation and stability of platelets, which control blood clotting.
- **Cell signaling:** Transmits signals from the cell surface inward to direct physical movement.

When the *WAS* gene is mutated, a lack of functional WASp causes **Wiskott-Aldrich syndrome**, a rare disorder marked by frequent infections, tiny and low-count platelets (thrombocytopenia), and eczema.



Wiskott–Aldrich syndrome structure and interacting proteins.

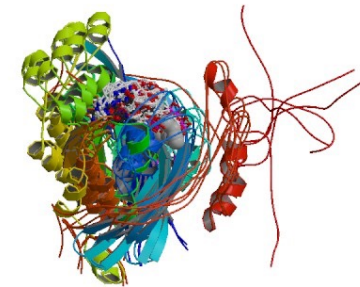


Role of WASp in TCR and BCR signaling pathways. The main signaling molecules (blue and green ovals) acting downstream of TCR (A), BCR, and TLRs (B) are depicted.

Das **Wiskott-Aldrich-Syndrom (WAS)** ist eine sehr seltene, X-chromosomal-rezessiv vererbte Immunschwächekrankheit, die fast ausschließlich Jungen betrifft. Sie führt zu einer kombinierten Störung der B- und T-Zellen sowie der Blutplättchen (Thrombozyten).

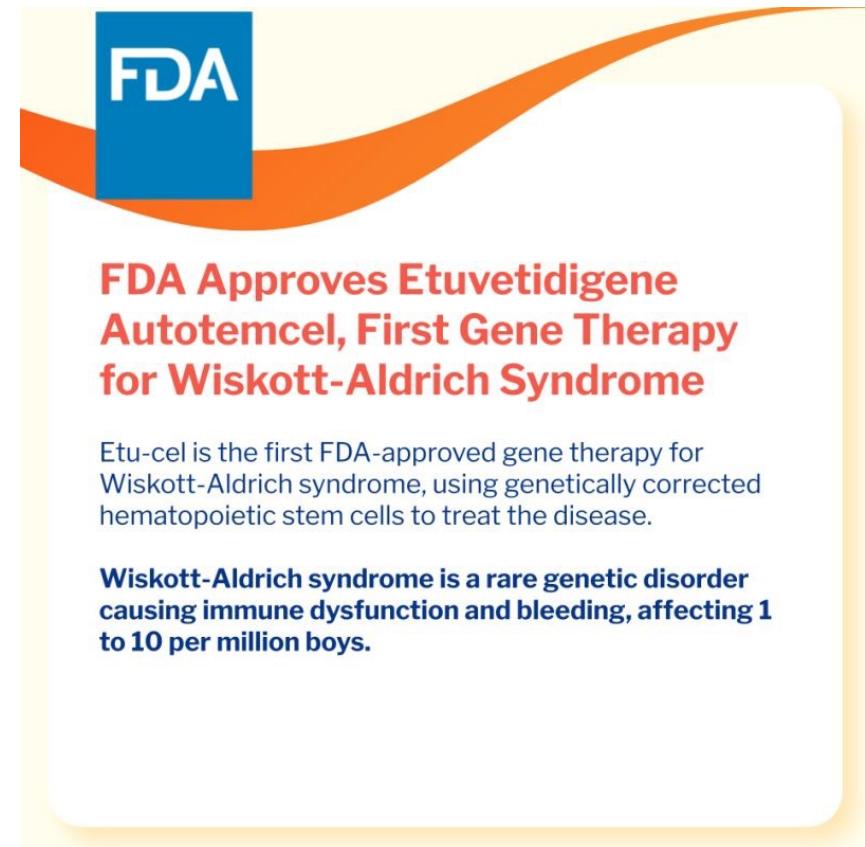
Die Erkrankung wird durch Mutationen im sogenannten **WASP-Gen** ausgelöst, welches für ein Protein verantwortlich ist, das eine zentrale Rolle beim Aufbau des Zytoskeletts (Zellgerüsts) spielt

- **Thrombozytopenie (Mikrothrombozytopenie):** Ein Mangel an kleinen Blutplättchen. Dies führt bereits im Säuglingsalter zu einer stark **erhöhten Blutungsneigung** (z. B. blutige Durchfälle, blaue Flecken, Nasenbluten).
- **Rezidivierende Infektionen:** Aufgrund des Immundefekts leiden Betroffene unter ständig wiederkehrenden Infektionen, insbesondere der Atemwege, Ohren (Mittelohrentzündung) und der Haut.
- **Ekzeme:** Es entwickeln sich chronische, schwer behandelbare Hautausschläge, die einer Neurodermitis ähneln.



Etu-cel ist das gängige medizinische Kürzel für Etuvetidigen-Autotemcel, die weltweit erste zugelassene **Gentherapie zur Behandlung des Wiskott-Aldrich-Syndroms (WAS)**.

- **Indikation:** Es wird bei Patienten ab einem Alter von 6 Monaten eingesetzt, die an der seltenen, erblichen Immun- und Blutgerinnungsstörung *Wiskott-Aldrich-Syndrom* leiden und für die kein genetisch passender (HLA-kompatibler) Stammzellspender zur Verfügung steht.
- **Wirkungsweise:** Bei dieser sogenannten *Ex-vivo*-Gentherapie werden dem Patienten eigene Blutstammzellen entnommen. Im Labor wird mithilfe eines entschärften Virus (lentiviraler Vektor) eine intakte Kopie des defekten WAS-Gens in die Zellen geschleust. Anschließend werden diese genetisch korrigierten Zellen per Infusion zurückgegeben, woraufhin der Körper wieder funktionierende Abwehr- und Blutplättchen bilden kann.
- **Zulassungen:** Die Therapie wurde im **Dezember 2025** von der US-amerikanischen Arzneimittelbehörde FDA und im **Januar 2026** in der Europäischen Union (EMA) zugelassen



Etuvetidigene Autotemcel for the Treatment of Wiskott–Aldrich Syndrome

Wiskott–Aldrich syndrome is a rare, X-linked, life-threatening inborn error of immunity and platelet disorder caused by variants in the gene *WAS*. Etuvetidigene autotemcel (etu-cel) is an autologous gene therapy consisting of hematopoietic stem and progenitor cells that have been transduced ex vivo with a lentiviral vector encoding *WAS* complementary DNA. We integrated data from two prospective open-label clinical studies (a phase 1–2 study with 8 participants and a phase 3 study with 10 participants) and an expanded-access program with 9 participants to evaluate the efficacy and safety of etu-cel in patients with Wiskott–Aldrich syndrome. The participants received a single intravenous infusion of etu-cel after rituximab administration and reduced-intensity conditioning. The primary efficacy end points were overall survival, severe infections from 6 to 18 months after gene therapy, and moderate and severe bleeding events in the first 12 months after gene therapy. Results for severe infections and moderate and severe bleeding are reported as the rate of events (number per person-year of observation), which was compared with the rate in the year before gene therapy.

Conclusions

Our results show that the effects of etu-cel are consistent with a sustained clinical benefit in persons with Wiskott–Aldrich syndrome.

Wiskott–Aldrich syndrome is a rare, X-linked, life-threatening inborn error of immunity and platelet disorder caused by variants in the Wiskott–Aldrich syndrome protein (WASP)–encoding gene. Wiskott–Aldrich syndrome is characterized by thrombocytopenia, bleeding events, recurrent and severe infections, eczema, and increased risk of immune dysregulation and malignant conditions, leading to reduced life expectancy. Genotype can be a predictive biomarker for disease severity and survival. Current treatment options consist of symptomatic and preventive management and allogeneic hematopoietic stem-cell transplantation (HSCT). Etuvetidigene autotemcel (etu-cel) is an autologous gene therapy consisting of hematopoietic stem and progenitor cells (HSPCs) that have been transduced ex vivo with a lentiviral vector encoding human *WAS* complementary DNA (cDNA) under the control of a reconstituted promoter from the endogenous locus. We had previously reported interim safety and efficacy findings from a phase 1–2 clinical study involving 8 participants with Wiskott–Aldrich syndrome who received gene therapy and were followed for a median of 3.6 years. We now report the results of an integrated analysis of the efficacy and safety of etu-cel in 27 participants with Wiskott–Aldrich syndrome who had an extended long-term follow-up.

Methods

Participants and Study Conduct

We integrated data from two prospective open-label clinical studies — a phase 1–2 study involving 8 participants (TIGET-WAS) and a two-center phase 3 study involving 10 participants (OTL-103-4) — and from an expanded-access program involving 10 participants. Of the 28 enrolled participants with Wiskott–Aldrich syndrome, 27 were treated with etu-cel.

Key eligibility criteria were a diagnosis of Wiskott–Aldrich syndrome as defined by the presence of a genetic variant, the lack of an HLA-identical related donor, and documentation of at least one of the following: a severe WAS variant known to be associated with severe disease, absence of WASP expression, and a severe clinical score (Zhu clinical score of ≥ 3 [scores range from 0.5 to 5, with higher scores indicating worse clinical conditions]).

Procedures

The participants were treated with etu-cel manufactured from autologous CD34+ HSPCs purified from harvested bone marrow (5 participants), from mobilized peripheral blood collected through apheresis (21 participants) after administration of granulocyte colony-stimulating factor with (20 participants) or without (1 participant) plerixafor, or from both sources (1 participant). CD34+ cells were transduced ex vivo with a self-inactivating lentiviral vector (LV-w1.6WAS), as previously described.

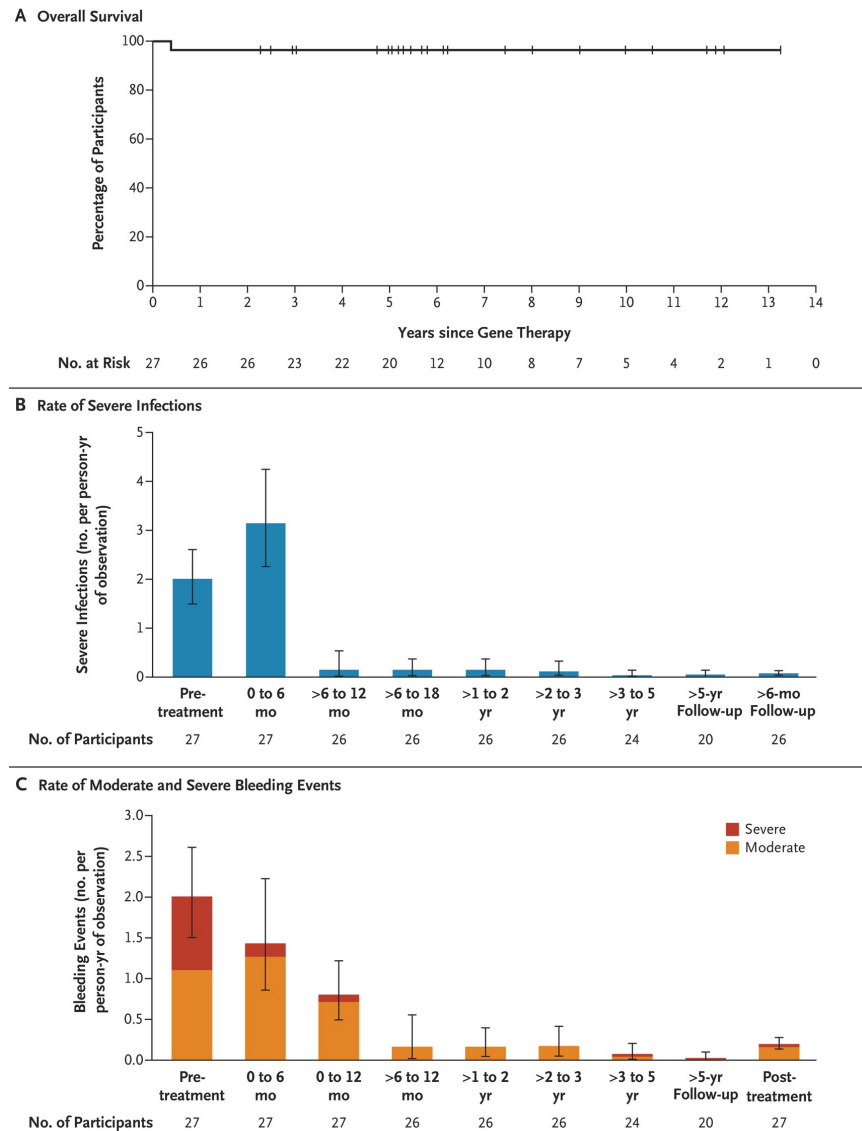
End Points

Primary efficacy end points were overall survival (i.e., the time from etu-cel administration to death from any cause), severe infections in the period beyond 6 months up to 18 months after gene therapy, and moderate and severe bleeding events in the first 12 months after gene therapy.

Characteristic	Participants (N=27)
Median age at disease onset (range) — mo	0.3 (0.0–32.3)
Median age at diagnosis (range) — yr	1.0 (0.1–12.0)
Median age at day of gene therapy (range) — yr	2.6 (1.0–35.1)
Age group at day of gene therapy — no. (%)	
<5 yr	18 (67)
≥5 yr	9 (33)
Zhu score at baseline — no. (%) [†]	
2	1 (4)
3	13 (48)
4	4 (15)
5A	8 (30)
Missing‡	1 (4)
WAS variant at baseline — no. (%)	
Class I	5 (19)
Class II	22 (81)
Race or ethnic group — no. (%)§	
American Indian or Alaska Native	1 (4)
Asian	4 (15)
Black or African American	2 (7)
White	20 (74)
Hispanic or Latino ethnic group — no. (%)§	
Yes	3 (11)
No	24 (89)
Median duration of follow-up (range) — yr¶	5.7 (0.4–13.3)
Median duration of follow-up among participants alive at data cutoff (range) — yr	5.7 (2.3–13.3)
Transduction efficiency in the drug product — no. (%)	
≤80%	6 (22)
>80%	21 (78)
Median VCN in the drug product (range) — copies per cell	2.3 (0.9–4.3)
Median no. of CD34+ cells infused (range) — ×10 ⁻⁶ cells/kg	16.9 (7.0–31.0)

Frequently Reported Adverse Events

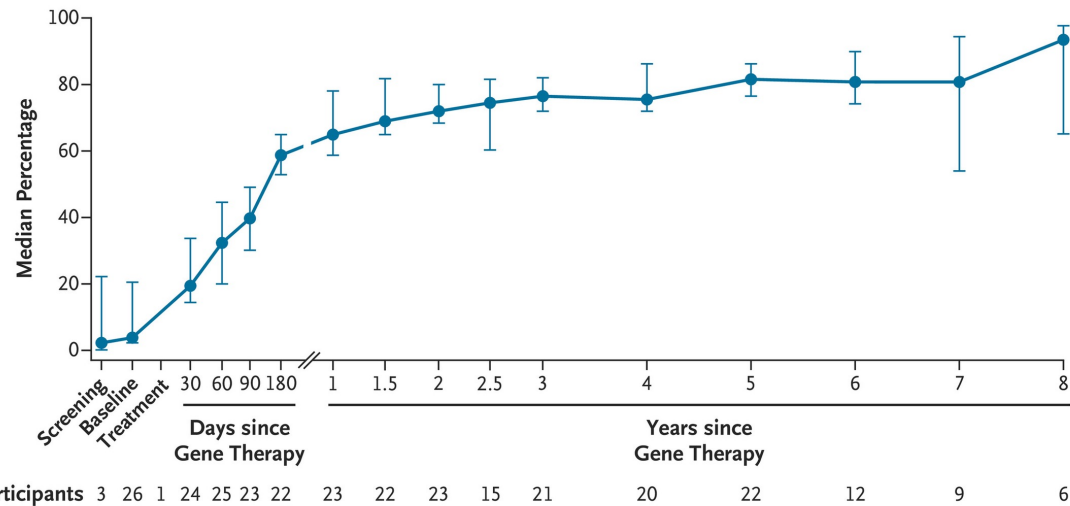
System Organ Class	Pretreatment (N=28)	Treatment (N=28)	Follow-up						Post-treatment ≥Day 2 (N=27)
			0 to 6 mo (N=27)	>6 mo to 1 yr (N=26)	>1 to 2 yr (N=26)	>2 to 3 yr (N=26)	>3 to 8 yr (N=24)	>8 yr (N=8)	
Any adverse event of grade ≥3									
Participants with event — no. (%)	17 (61)	23 (82)	23 (85)	5 (19)	6 (23)	7 (27)	7 (29)	2 (25)	24 (89)
No. of events	45	71	126	7	11	10	13	3	170
Blood and lymphatic system disorders									
Participants with event — no. (%)	5 (18)	5 (18)	12 (44)	0	0	0	1 (4)	0	12 (44)
No. of events	5	6	21	0	0	0	2	0	23
Gastrointestinal disorders									
Participants with event — no. (%)	4 (14)	5 (18)	9 (33)	1 (4)	0	2 (8)	2 (8)	0	11 (41)
No. of events	5	5	11	1	0	2	2	0	16
General disorders and administration site conditions									
Participants with event — no. (%)	2 (7)	5 (18)	7 (26)	2 (8)	1 (4)	1 (4)	0	0	9 (33)
No. of events	2	5	11	2	3	1	0	0	17
Immune system disorders									
Participants with event — no. (%)	1 (4)	3 (11)	2 (7)	0	2 (8)	1 (4)	1 (4)	0	4 (15)
No. of events	1	5	2	0	3	1	2	0	8
Infections and infestations									
Participants with event — no. (%)	7 (25)	10 (36)	16 (59)	2 (8)	4 (15)	3 (12)	2 (8)	1 (12)	20 (74)
No. of events	16	16	37	2	4	3	4	1	51
Investigations†									
Participants with event — no. (%)	2 (7)	5 (18)	9 (33)	1 (4)	0	2 (8)	0	0	9 (33)
No. of events	2	6	13	1	0	2	0	0	16
Metabolism and nutrition disorders									
Participants with event — no. (%)	2 (7)	1 (4)	3 (11)	1 (4)	1 (4)	0	0	1 (12)	4 (15)
No. of events	2	2	8	1	1	0	0	1	11
Skin and subcutaneous tissue disorders									
Participants with event — no. (%)	2 (7)	9 (32)	7 (26)	0	0	0	0	0	7 (26)
No. of events	3	12	10	0	0	0	0	0	10



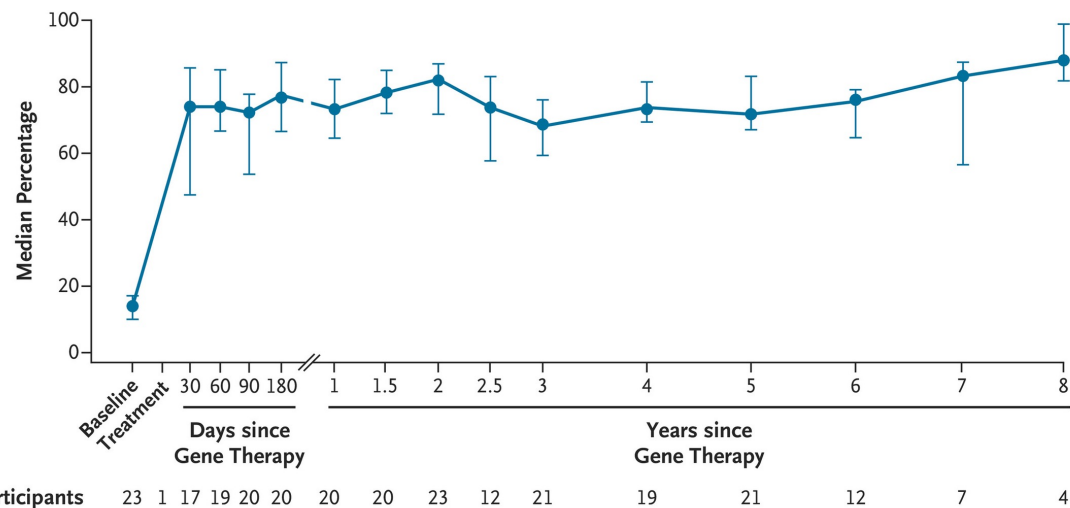
Primary Efficacy End Points (Efficacy Population).

Shown are the results in the efficacy population, which included all 27 participants who were enrolled and treated with etuvetidigene autotemcel (etu-cel) in the clinical studies or in the expanded-access program. Panel A shows a Kaplan–Meier plot of overall survival. Tick marks indicate censored data; data from the participants were censored at the latest time point for which vital status information was available (up to the data cutoff). Panel B shows the rate of severe infections according to study phase; I bars indicate the 95% confidence interval. Panel C shows the rate of moderate and severe bleeding events according to study phase; I bars indicate the 95% confidence interval for the combined rate of moderate and severe bleeding. The 95% confidence intervals were not adjusted for multiplicity and should not be used in place of hypothesis testing. The pretreatment phase was the 12-month period before the day of gene therapy (day 1). Events that occurred on day 1 were not included in the analysis. The period beyond 5 years of follow-up was from day 1827 to the end of the study (i.e., the last follow-up evaluation, up to 13.3 years). The period beyond 6 months of follow-up was from day 184 to the end of the study. The post-treatment phase was the period from day 2 to the end of the study. The exact time windows according to study days are described in the statistical analysis plan, available with the [protocol](#).

A Lymphocytes Expressing WASP in Peripheral Blood

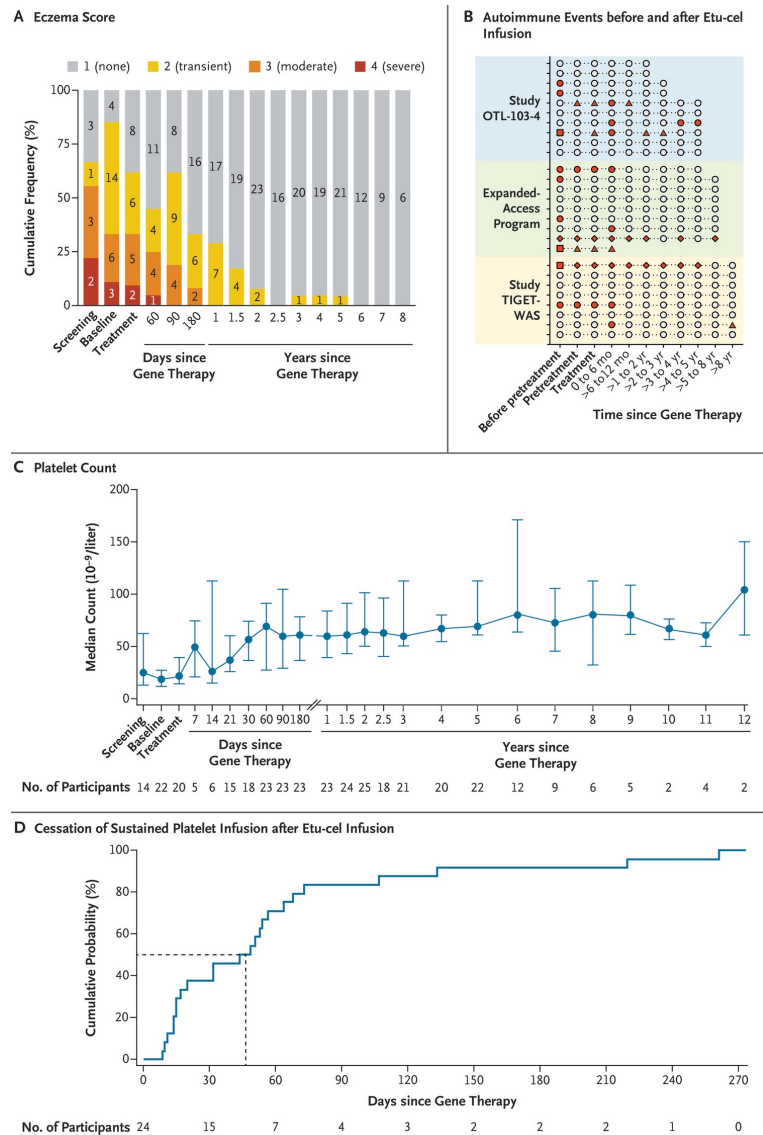


B Platelets Expressing WASP in Peripheral Blood



WASP Expression after Treatment with Etu-cel (Efficacy Population).

Shown is the percentage of lymphocytes (Panel A) and of platelets (B) in peripheral blood expressing Wiskott–Aldrich syndrome protein (WASP) after treatment with etu-cel, as assessed by flow cytometry over time. Results based on fewer than two participants were omitted. I bars indicate 95% confidence intervals, which were not adjusted for multiplicity and should not be used in place of hypothesis testing. Infusion of transduced cells (gene therapy) was performed at the treatment visit. The participant who was enrolled at the Children’s Healthcare of Atlanta site did not have WASP expression assessed in platelets or lymphocytes. The exact time windows according to study days are described in the statistical analysis plan, available with the [protocol](#).



Efficacy Population.

Panel A shows a percentage-stacked bar chart of eczema scores over time. This graph represents the cumulative percentage of participants having different eczema scores at various time points before and after treatment with etu-cel. The absolute number of participants having a certain score at a given time point is reported in the relative portion of each column. Data are for participants with an available eczema score. Gene therapy was performed at the treatment visit. Panel B shows autoimmune events before and after etu-cel infusion in the efficacy population. This graph represents the presence or absence of autoimmune clinical manifestations over time, before and after etu-cel infusion. Each row represents a participant, enrolled in either the TIGET-WAS or the OTL-103-4 clinical studies or in the expanded-access program. Gray circles represent the absence of autoimmune manifestation in the indicated time window. Red symbols show the presence of one or more autoimmune manifestations in the indicated time window: red circles represent autoimmune cytopenia, diamonds inflammatory bowel disease, triangles other types of clinical autoimmunity (including Henoch–Schonlein purpura, IgA nephropathy, psoriasis, and uveitis), and squares the simultaneous presence of multiple autoimmune manifestations. Additional details about autoimmune events before and after etu-cel infusion are described in Tables S14 and S15. “Before pretreatment” indicates the period before the start of screening, and “pretreatment” the period from the date of screening up to and including the day before the treatment phase (i.e., the period from the day of rituximab administration on day –22 [22 days before gene therapy] or the day of peripheral-blood stem-cell mobilization, if performed, up to and including day 1 [the day of gene therapy]). The exact time windows according to study days are described in the statistical analysis plan. Panel C shows the median platelet count over time. Platelet samples taken within 7 days after a platelet transfusion, 25 days after romiplostim administration, or 14 days after eltrombopag administration were excluded from the calculation of data displayed in this panel. Results based on data from fewer than two participants were omitted. I bars indicate 95% confidence intervals, which were not adjusted for multiplicity and should not be used in place of hypothesis testing. Gene therapy was performed at the treatment visit. Panel D shows a Kaplan–Meier plot of the time to cessation of sustained platelet infusions. Only participants who received platelet infusions after gene therapy were included in this analysis. The dashed line represents the median time of cessation of sustained platelet infusions.

Discussion

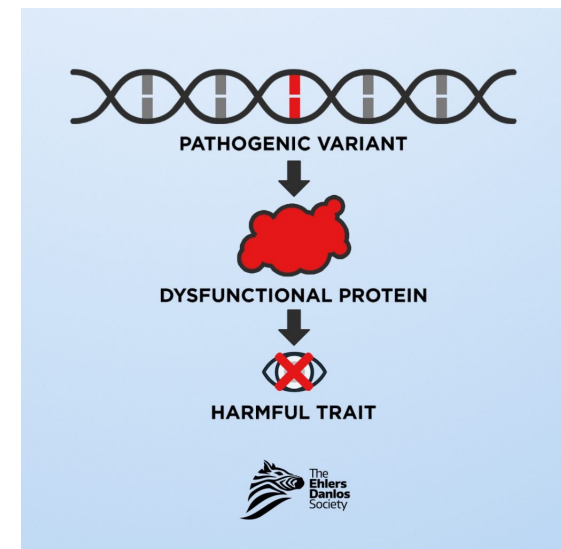
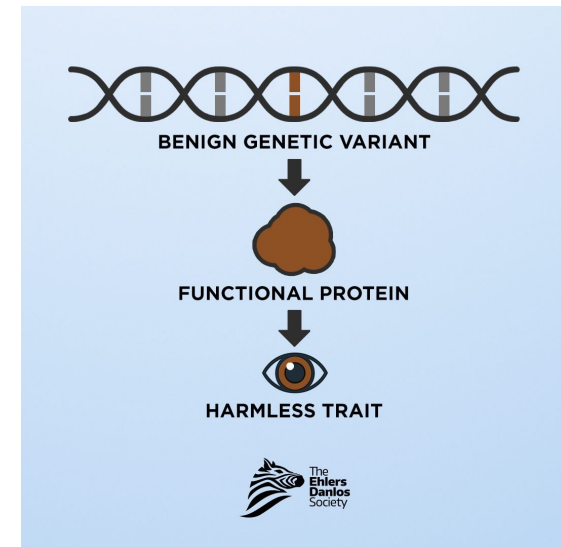
Our findings, based on data collected over 13 years after a single infusion of etu-cel (median follow-up, 5.7 years), show that the effects of this cellular drug are consistent with a durable clinical benefit in a broad spectrum of patients with Wiskott–Aldrich syndrome. More specifically, our data indicate that in patients with Wiskott–Aldrich syndrome, gene therapy can produce a sustained reduction in the risk of severe infections (a hallmark of Wiskott–Aldrich syndrome). The participants had progressive immune reconstitution, discontinued immunoglobulin replacement therapy, and — in line with the B-cell defect correction after gene therapy — had a response to vaccinations by producing protective specific antibodies against vaccine antigens. We observed a resolution of eczema and autoimmunity in most participants, as well as progressive improvement of social life and reduced morbidity. Transient autoimmune cytopenias were observed shortly after gene therapy in 19% of the participants, and autoimmune manifestations developed in 15% of the participants more than 6 months after etu-cel infusion, which resolved after short-term treatment or without intervention. Autoimmune events have been reported in 14 to 20% of patients with Wiskott–Aldrich syndrome after HSCT and were also observed in two of five patients after gene therapy in a distinct phase 1–2 study that used a similar vector backbone but did not include rituximab as preparatory conditioning. A delayed reconstitution of T or B regulatory cells or both has been suggested to contribute to slower or incomplete correction of immune dysregulation after gene therapy or HSCT.

Wichtigste Typen häufiger Genvarianten

- **SNPs (Single Nucleotide Polymorphisms):** Der Austausch einzelner Basenpaare in der DNA; sie machen den Großteil der genetischen Variation beim Menschen aus.
- **Indels:** Kleine Einfügungen (Insertionen) oder das Fehlen (Deletionen) von einem oder mehreren Basenpaaren.
- **CNVs (Copy Number Variations):** Unterschiede in der Anzahl der Kopien bestimmter DNA-Abschnitte oder Gene im Genom.

Häufige Varianten haben oft eine geringe Penetranz (sie verursachen eine Krankheit nicht direkt allein), beeinflussen aber das Risiko für Volkskrankheiten oder steuern die Medikamentenverträglichkeit (Pharmakogenetik).

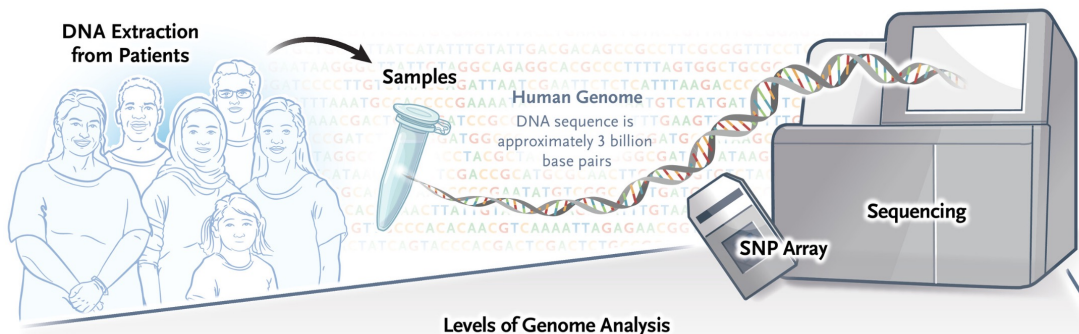
- **APOE4:** Eine Variante, die das Risiko für die **Alzheimer-Krankheit** erhöht.
- **Faktor-V-Leiden:** Eine Variante, die das Risiko für **Thrombosen** (Blutgerinnsel) steigert.
- **CFH:** Eine Variante, die mit altersbedingter **Makuladegeneration** (Augenerkrankung) zusammenhängt.



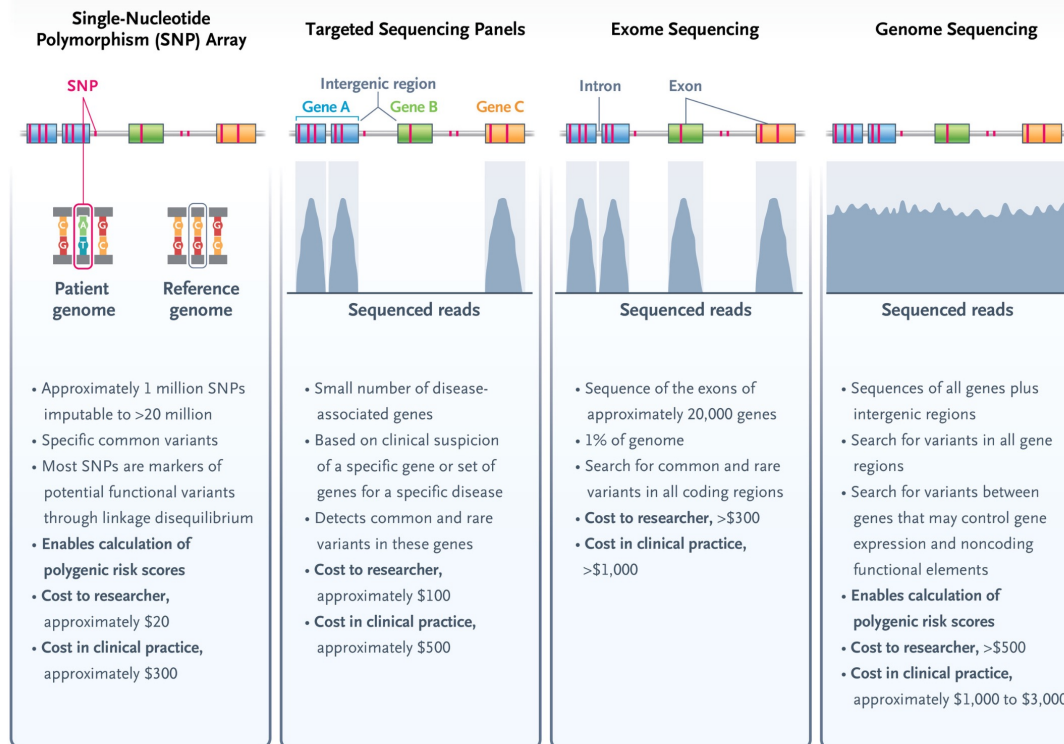
Clinical Uses of Common Genetic Variants Associated with Common Diseases

Summary

Twenty-five years after the draft of the human genome sequence, genomics has revolutionized many areas of biology, the diagnosis of familial and early-onset diseases, and the development of targeted therapies, particularly in oncology. Genomic knowledge has had little effect on the diagnosis and treatment of most common adult-onset conditions. Genomewide association studies have revealed that for these conditions, thousands of genetic variants of small effect underpin the polygenic nature of risk. When incorporated into polygenic risk scores, these variants predict risk; however, polygenic risk scores have had little effect in the clinic. In this article, we review the reasons for the slow pace of the diffusion of these methods in clinical practice. With the impending era of relatively inexpensive genome sequencing in mind, we review the ways in which polygenic risk scores, along with the related field of pharmacogenomics, may be useful in clinical practice for the prevention and treatment of common diseases.



Levels of Genome Analysis



Levels of Human Genome Analysis and Implications for Analysis of Disease Risk and Diagnosis.

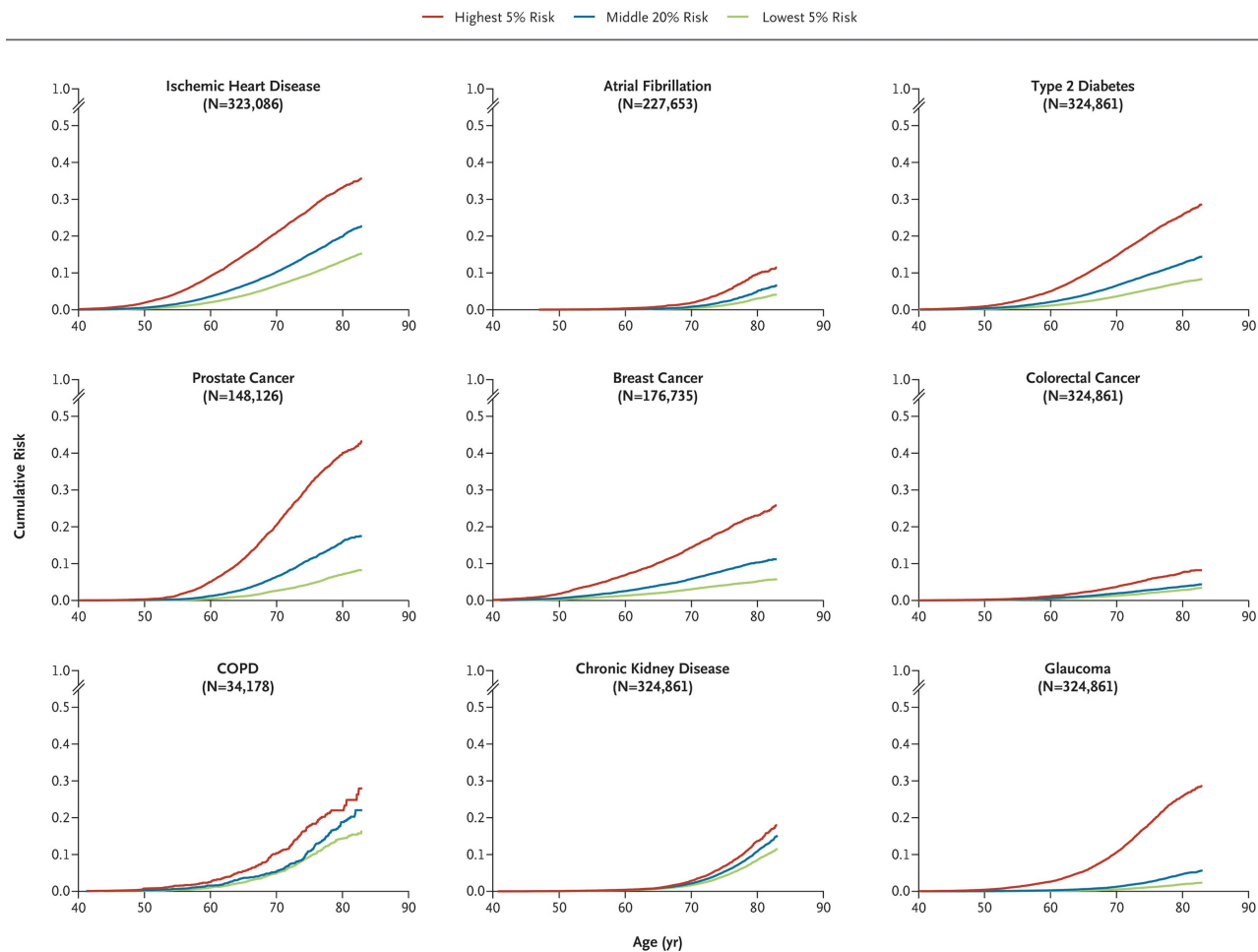
The costs to researchers and the costs in clinical practice are approximations and vary according to the scale of the samples (e.g., many thousands of samples are run for researchers) and for different clinical indications that may involve clinical specialty consultation and bioinformatics interpretation. Costs to patients also vary substantially according to the indication and insurance coverage. All costs are in U.S. dollars.

Clinical Uses of Common Genetic Variants in Common Diseases

- The field of genomics has made substantial advances in recent years; however, clinical utility has largely been reserved for the diagnosis of rare diseases in infants and children and for adults with undiagnosed disease or a strong family history of a specific disease.
- Only a limited number of common genetic variants confer relative risks of more than 1.5 for a specific disease.
- Aggregating hundreds or thousands of common genetic variants into polygenic risk scores can create highly predictive risk assessments for common diseases that are largely independent of family history and conventional risk factors.
- As genome sequencing decreases in cost and becomes the predominant technology, polygenic risk scores could be almost routinely available.
- A patient's genetic information could frequently inform the choice, or the initial dose, of a medication.
- Information needed to assess genetic risks, including clinical decision-support tools, is not readily available to physicians or patients.
- As with other technological approaches, genomic methods have been developed primarily with the use of data derived from persons of European ancestry and usually perform with less accuracy in persons of other ancestries.

Associations between Common Variants and Common Diseases.

Genetic Variant	Prevalence†	Estimated Relative Risk	Disease
European ancestry			
APOE4	0.20	3–4	Alzheimer's disease (increased risk) ⁷⁶
APOE2	0.08	0.5	Alzheimer's disease (reduced risk) ⁷⁶
CFH rs1061170	0.38	2.5	Age-related macular degeneration ⁷⁷
ARMS2 rs10490924	0.23	2.4	Age-related macular degeneration ⁷⁸
Factor V Leiden rs6025	0.03	2.3	Venous thromboembolism ⁷⁹
Prothrombin rs179963	0.01	1.5	Venous thromboembolism ⁷⁹
NOD2 rs2066843	0.27	1.5	Crohn's disease ⁸⁰
NOD2 rs2076756	0.26	1.5	Crohn's disease ⁸⁰
HFE rs1800562‡	0.08	3.4	Hemochromatosis ⁸¹
HLA region (multiple alleles)	Variable	Variable	Multiple autoimmune diseases, such as ankylosing spondylitis, rheumatoid arthritis, multiple sclerosis, and type 1 diabetes ¹¹
East Asian ancestry			
ALDH2–2 rs671§	0.23	0.2	Alcohol dependence ^{82,83}
ADH1B rs2075633	0.18	0.4	Alcohol dependence ^{82,83}
ADH1B rs1229984§	0.30	2.3	Alcohol dependence ^{82,83}
CETP rs2303790	0.03	1.7	Age-related macular degeneration ⁸⁴
African ancestry			
HBB	0.10	Pathognomonic	Sickle cell anemia in homozygotes ⁸⁵
HBA1 or HBA2	Multiple	Pathognomonic	Alpha-thalassemia in homozygotes ⁸⁶
APOL1 rs73885319	0.22	2.3	Chronic kidney disease ⁸⁷
APOL1 rs60910145	0.20	2.0	Chronic kidney disease ⁸⁷
APOL1 rs71785313	0.12	0.6	Chronic kidney disease ⁸⁷



Cumulative Risk of Diagnosis during a Hospitalization for 12 Common Diseases, Stratified According to Polygenic Risk.

Cumulative-risk curves were calculated for disease outcomes with data from unrelated participants with European ancestry in the U.K. Biobank. Only women were considered for breast cancer, only men for prostate cancer, and only current smokers (as reported by participants) for chronic obstructive pulmonary disease (COPD). Polygenic risk scores were stratified into the highest 5% risk (red), middle 20% risk (blue), and lowest 5% risk (green). The outcome definitions and specific polygenic risk scores were as follows: ischemic heart disease (phenotype code, 411; Polygenic Score Catalog ID, PGS000018), atrial fibrillation (427.21; PGS000035), type 2 diabetes (250.2; PGS000020), prostate cancer (185; PGS004872), breast cancer (174; PGS000007), colorectal cancer (153; PGS003386), COPD (496.21; PGS003862), chronic kidney disease (585.3; PGS000859), and glaucoma (365; PGS004765). Outcomes were defined with hospital episode statistics in which prevalent diagnoses are coded that may not be the indication for hospital admission, and we note that for disease incidence outcomes that are usually first diagnosed in primary care (e.g., atrial fibrillation and type 2 diabetes), the absolute cumulative-risk values are underestimates.

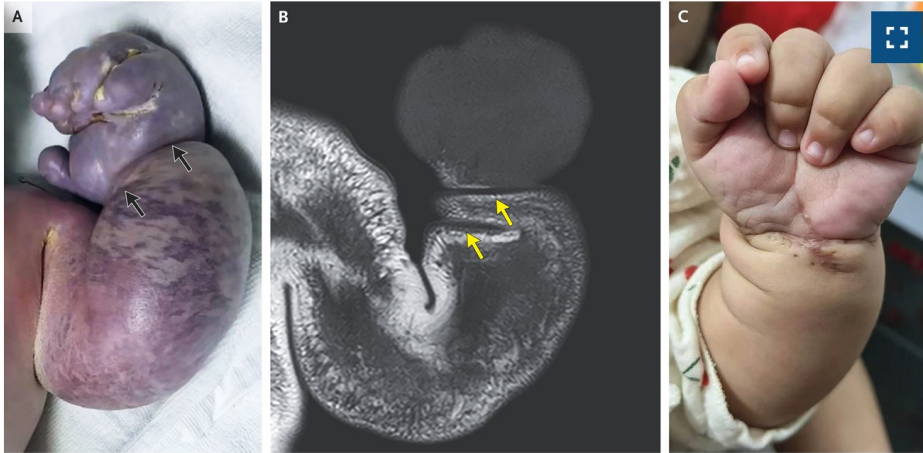
Pharmacogenetics

As far back as 1902, Archibald Garrod included “idiosyncrasies as regards drugs” in his list of interindividual differences in response to environmental agents that he speculated were inherited. Numerous reviews have documented a wide range of drugs for which differences in efficacy or adverse effects can be traced to genetic differences in specific genes. Extreme events, such as Stevens–Johnson syndrome in patients who are carriers of HLA-B1502 and are exposed to carbamazepine, could, in theory, be avoided by prescreening for such variants. The Food and Drug Administration maintains a list of warnings for drugs for which testing for germline or somatic mutations may be indicated, so that persons who are less likely to have a response or more likely to have an adverse reaction are not given a standard dose. These drugs include commonly prescribed medicines such as allopurinol, carbamazepine, clopidogrel, phenytoin, tramadol, warfarin, and several selective serotonin-reuptake inhibitors and other antidepressants. In a study involving more than 7 million U.S. veterans, 99% were estimated to carry at least one actionable pharmacogenetic variant. Polygenic risk scores for blood pressure and LDL cholesterol level also identify patients whose hypertension or hypercholesterolemia may be difficult to control.

Implications for Future Clinical Practice

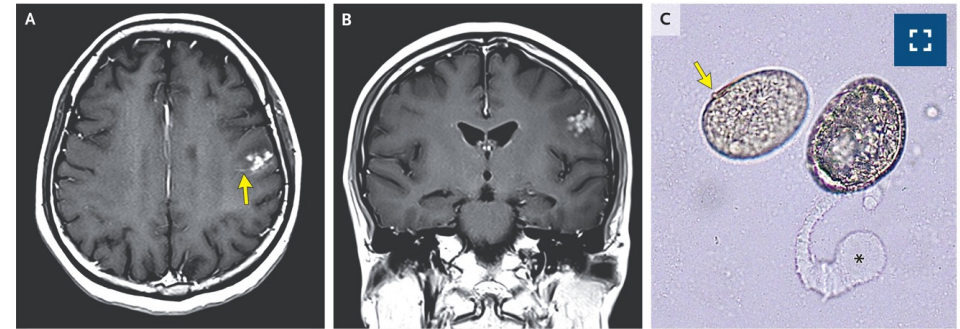
The evidence for the clinical utility of common genetic variants has slowly but steadily built over the past few decades. The U.K. government has announced that within 10 years, genome sequencing will be offered to all babies, and pharmacogenomic testing will be integrated into patients' electronic health records. The provision of polygenic risk scores combined with the results of pharmacogenomic panels and genome sequencing to identify rare disease-causing gene variants may lead to better management of relevant high-risk diseases, bringing genomic medicine to whole populations. However, substantial regulatory, decision-support, financial, and data-security barriers must be cleared before this vision can be implemented at scale.

Congenital Amniotic Band Sequence



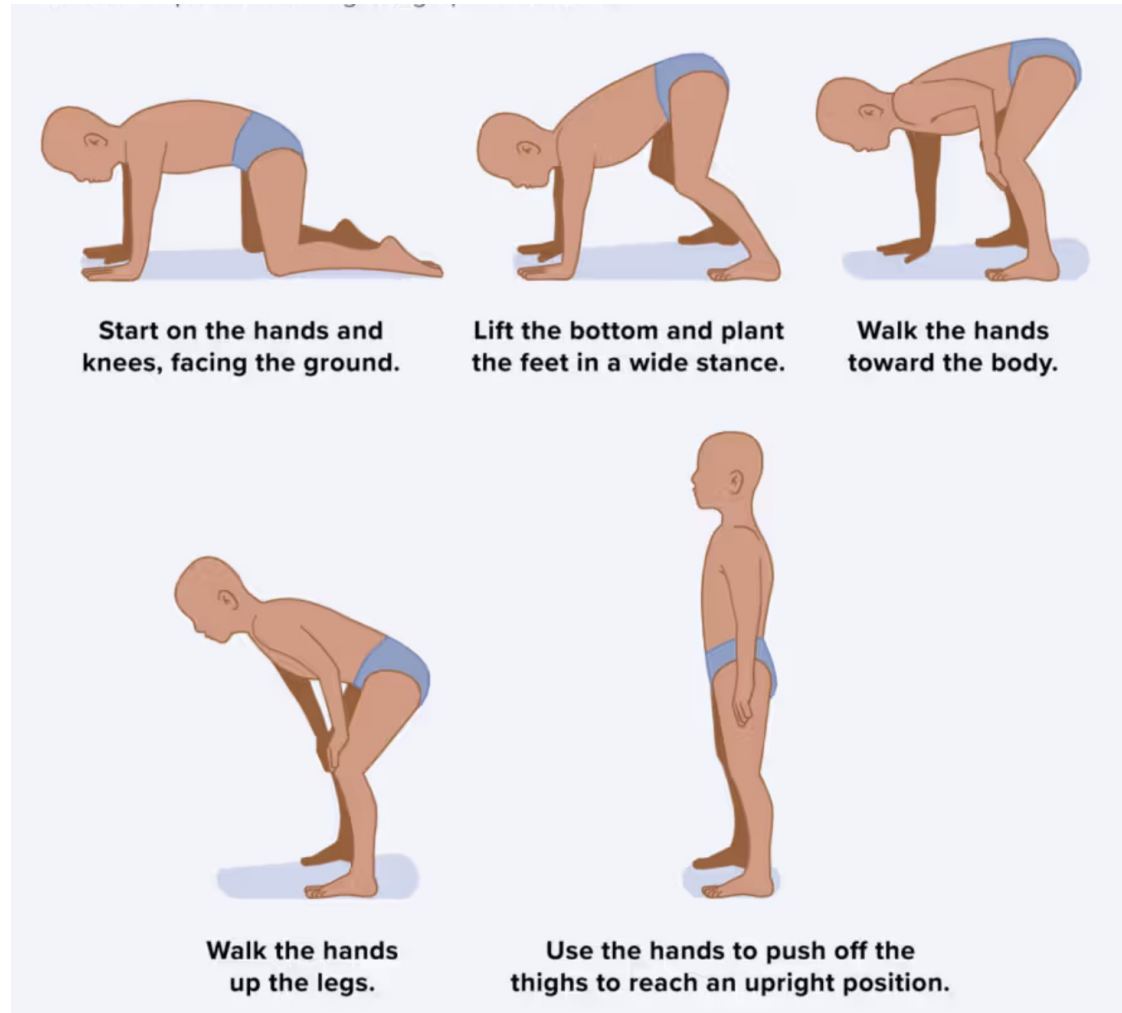
A baby girl was noted to have severe swelling and discoloration of the left arm immediately after birth by cesarean section at 38 weeks' gestation. Prenatal ultrasonography at 28 weeks' gestation had identified soft-tissue swelling of the left arm of undetermined cause. Her mother (gravida 2, para 0) had not undergone any prenatal intrauterine interventions. On physical examination, swelling, cyanosis, and limited movement of the left arm, shoulder, and chest were observed. Two areas of constriction were noted at the level of the wrist and proximal forearm (Panel A, arrows). Brachial and radial pulses were detectable by Doppler ultrasonography. Magnetic resonance imaging of the arm showed two fibrous bands penetrating the deep fascia (Panel B, arrows). A diagnosis of congenital amniotic band sequence was made. Amniotic band sequence describes the cascade of events that occurs after early rupture of the amnion in which fetal body parts project into the chorionic cavity and subsequently risk deformation, constriction by amniotic bands, or amputation. In this case, no other anatomical abnormalities were identified. Surgical release of the bands was performed, and the baby went home on postoperative day 7. At the 5-month follow-up, the left arm had healed well (Panel C) and functioned normally.

Cerebral Schistosomiasis



A previously healthy 35-year-old female rice farmer presented to the emergency department after a 1-minute episode of arm and leg shaking on the right side. She reported no preceding headache, confusion, or weakness. Physical examination was normal. Magnetic resonance imaging of the brain was performed. Axial and coronal T1-weighted images obtained after administration of contrast material (Panels A and B, respectively) showed an area of linear enhancement (arrow) associated with a cluster of enhancing nodules and surrounding edema in the left frontal lobe. This arborizing radiographic pattern may be seen in neuroschistosomiasis, with the nodules representing granulomatous inflammation around schistosome eggs. Owing to concern about schistosomiasis, a circumoval precipitin test for *Schistosoma japonicum* — which involves incubation of live *S. japonicum* eggs with patient serum — was performed. A tail-like precipitate (Panel C, asterisk) formed outside the eggs, a finding that indicates an antibody-mediated reaction against antigens secreted by the eggs (a positive result); a small knob (arrow), often seen on *S. japonicum* eggs, was also visible on eggs in the sample. A Kato–Katz stool smear was also positive for *S. japonicum* (190 eggs per gram of stool). A diagnosis of cerebral schistosomiasis resulting in a focal seizure was made. Treatment with praziquantel, glucocorticoids, and levetiracetam was initiated. At a 3-month follow-up visit, the patient reported no further seizures. Repeat imaging obtained at that time showed no abnormalities.

Gowers' sign indicates weakness in the proximal muscles of the lower limbs, specifically the hip and pelvic girdle muscles (such as the gluteus maximus and quadriceps femoris)



Case 27-2026: A 4-Year-Old Boy with Fatigue, Imbalance, and Frequent Falls

The patient had been in his usual state of health until 30 months before the current presentation, when his parents noticed that he was tripping when he walked and appeared to be imbalanced. As an infant, he was able to sit unassisted but never crawled; instead, he scooted and pulled himself along the floor. He began walking independently at 13 months of age but had persistent falls, often extending his arms to brace himself before hitting the ground. **After falling, he could not stand up using his legs and would push himself up with his hands instead.** He often walked on his toes, and his parents noticed that he used his calves to compensate for weakness in his core and hips. The patient was referred for physical therapy and occupational therapy. Owing to the coronavirus disease 2019 (Covid-19) pandemic, his in-person sessions were discontinued, and he attended sessions virtually from home. Eighteen months before the current presentation, the patient had a fall at home and began limping, favoring his left leg. He was evaluated by his primary care pediatrician at a pediatric clinic affiliated with this hospital, and radiographs of the lower legs and feet were obtained.

The parents noted that the patient appeared to have marked fatigue, **becoming exhausted after 2 hours of play** with other children and often needing to be carried upstairs at the end of the day or before his usual nap. The patient's physical therapist reported that he had **weakness in the hips, thighs, and calves during exercise**, which was associated with prominent fatigue. On examination, the oral temperature was 37°C, the blood pressure 88/49 mm Hg, the heart rate 95 beats per minute, the respiratory rate 16 breaths per minute, and the oxygen saturation 97% while the patient was breathing ambient air. The abdomen was soft, nondistended, and nontender, without organomegaly. The neurologic examination showed normal cerebellar function, normal reflexes, symmetric cranial-nerve function, and no sensory deficits. The patient was able to jump using both legs, **but only with great effort**, and he **was unable to stand on one leg**. Gait testing showed toe walking with mild waddling at higher speeds. **Mild hypertrophy was noted in the calves and deltoids.**



Radiographs of the Legs.

Radiographs of the legs were obtained 18 months before the current presentation. Anteroposterior radiographs (Panels A and B) show no fracture or dislocation. Magnified anteroposterior and lateral views of the right distal femur (Panels C and D, respectively) show a small, round lucency with a sclerotic rim at the posteromedial metaphysis (arrows). A follow-up anteroposterior radiograph of the right knee obtained 15 months after the episode of limping (Panel E) shows resolution of the lesion.

Variable	Reference Range, Children†	On Presentation
Hemoglobin (g/dl)	11.3–14.6	11.9
Hematocrit (%)	35.0–45.0	37.1
Mean corpuscular volume (fl)	77.0–95.0	76.4
White-cell count (per μ l)	5000–14,500	9250
Differential count (per μ l)		
Neutrophils	1500–8000	4620
Lymphocytes	1500–7000	3400
Monocytes	200–1600	420
Eosinophils	0–1200	120
Basophils	0–400	40
Platelet count (per μ l)	150,000–450,000	407,000
Sodium (mmol/liter)	135–145	138
Potassium (mmol/liter)	3.4–5.0	4.1
Chloride (mmol/liter)	98–108	102
Carbon dioxide (mmol/liter)	23–32	25
Urea nitrogen (mg/dl)	5–20	15
Creatinine (mg/dl)	0.30–1.00	▶ 0.20
Calcium (mg/dl)	8.5–10.5	10.1
Aspartate aminotransferase (U/liter)	10–40	▶ 423
Alanine aminotransferase (U/liter)	10–50	▶ 588
Alkaline phosphatase (U/liter)	142–335	153
γ -Glutamyltransferase (U/liter)	8–61	8
Total bilirubin (mg/dl)	0.2–0.8	0.2
Albumin (g/dl)	3.3–5.0	4.7
Globulin (g/dl)	1.9–4.1	2.0

Differential Diagnosis

This 4-year-old boy presented to his pediatrician with imbalance and frequent falls, **proximal muscle fatigue, and gross motor delay**. His parents often carried him at the end of the day because of his fatigue and were compelled to purchase a helmet, given his frequent falls. The examination was notable for toe walking, waddling gait, calf and deltoid hypertrophy, hip and thigh weakness, and an **inability to stand on one leg**. Cerebellar function, cranial-nerve function, and deep-tendon reflexes were otherwise normal. Laboratory testing revealed markedly **elevated AST and ALT levels and a low creatinine level**, despite normal bilirubin and albumin levels. On the basis of these findings, I will approach the differential diagnosis by first considering categories of disease that may cause fatigue and motor delay in a child of this age and then focusing on features that may help narrow the list of possible diagnoses.

A Subtle but Telling Sign

The patient's history included a critical but subtle detail: early in life, the patient was noted to **push himself up with his hands after falling**, given that he could not rise using his legs alone. Between 18 months and 2 years of age, he was noted to have increasing imbalance and tripping, although the assessment was limited owing to virtual care during the Covid-19 pandemic. Normal gait development progresses from a wide-based, externally rotated gait with "high guard" arm positioning at 12 to 14 months of age to heel strike with reciprocal arm swing by 15 to 18 months of age, to running by 2 years of age, to a mature gait pattern that includes the use of alternating feet on stairs by 3 years of age. Persistent waddling, intoeing, lumbar lordosis, and the inability to use alternating feet on stairs beyond 3 years of age are red flags for neuromuscular disease, many of which were present in this patient.

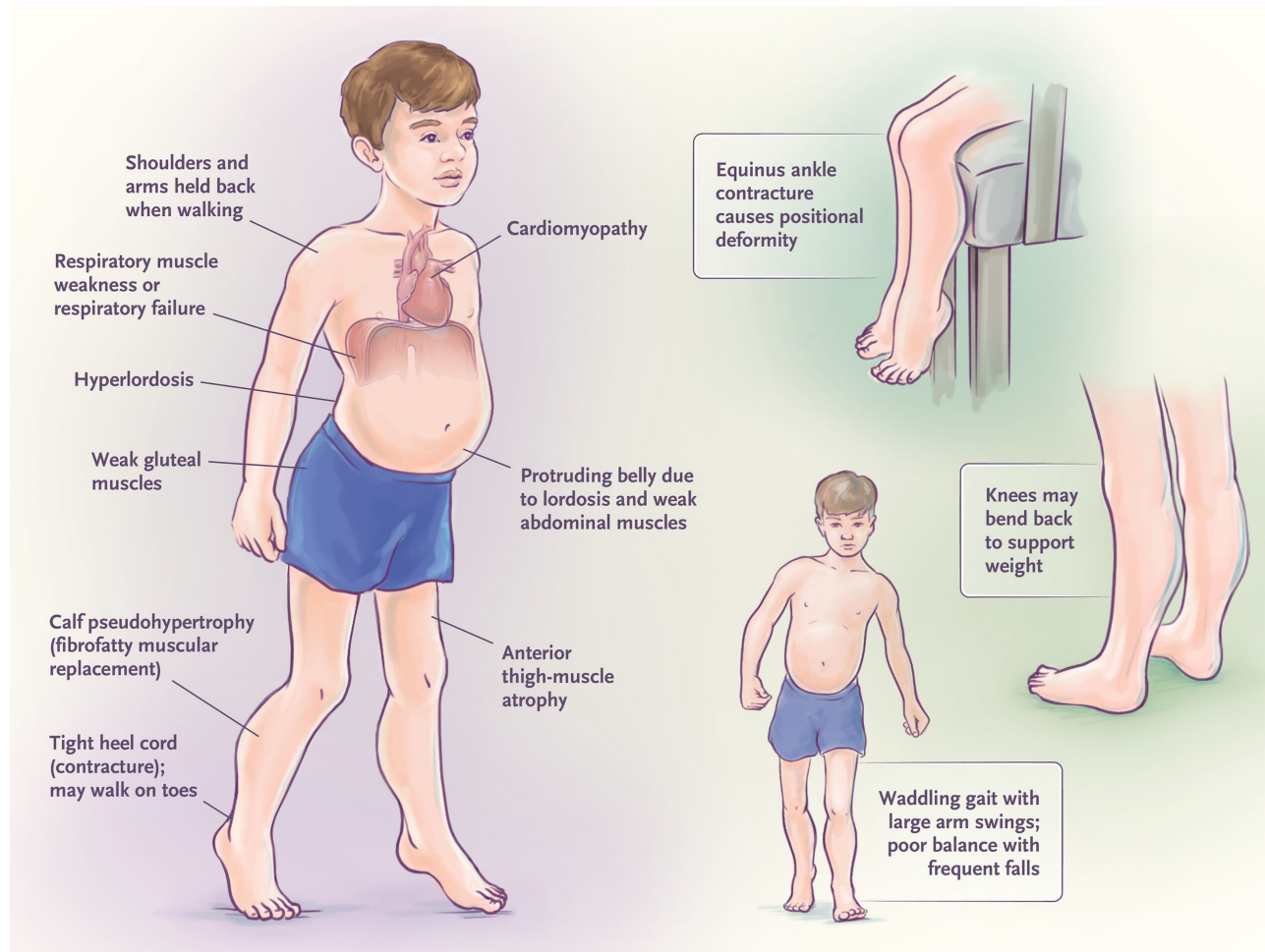
For a child with proximal muscle weakness, pseudohypertrophy, **Gowers sign**, and elevated AST and ALT levels without liver disease, guidelines suggest that an evaluation for DMD should be initiated. An appropriate initial test would be measurement of the blood level of creatine kinase. In patients with DMD, the creatine kinase level is markedly elevated, which reflects ongoing sarcolemma injury and muscle-fiber necrosis.

Diagnostic Testing

The patient's creatine kinase level was markedly elevated (>19,000 U per liter; reference range, 39 to 308). In the absence of abnormal liver function, the elevated creatine kinase level aligns with the elevated AST and ALT levels. A severe leakage of muscle enzymes, which typically results in levels 50 to 100 times the upper limit of the normal range, confirms sarcolemma permeability and strongly supports a diagnosis of DMD. The diagnosis of DMD was confirmed on subsequent genetic analysis of the patient's blood sample with detection of the c.745C→T (p.Gln249Ter) variant in exon 8 of the dystrophin gene.

Discussion of Management

DMD is the most common childhood muscular dystrophy, with an estimated prevalence of 1 in 5000 boys 5 to 9 years of age. It is a sex-linked recessive degenerative disorder caused by variants in the dystrophin gene that lead to deficiency of dystrophin, a sarcolemma protein that is critical for structural integrity in skeletal and cardiac muscle.



Multisystem Findings in Patients with Duchenne Muscular Dystrophy.

Clinical consequences and manifestations of the genetic variant are seen mostly in organ systems that express large amounts of dystrophin, including skeletal and cardiac muscle, gastrointestinal smooth muscle, and the central nervous system.

Follow-up

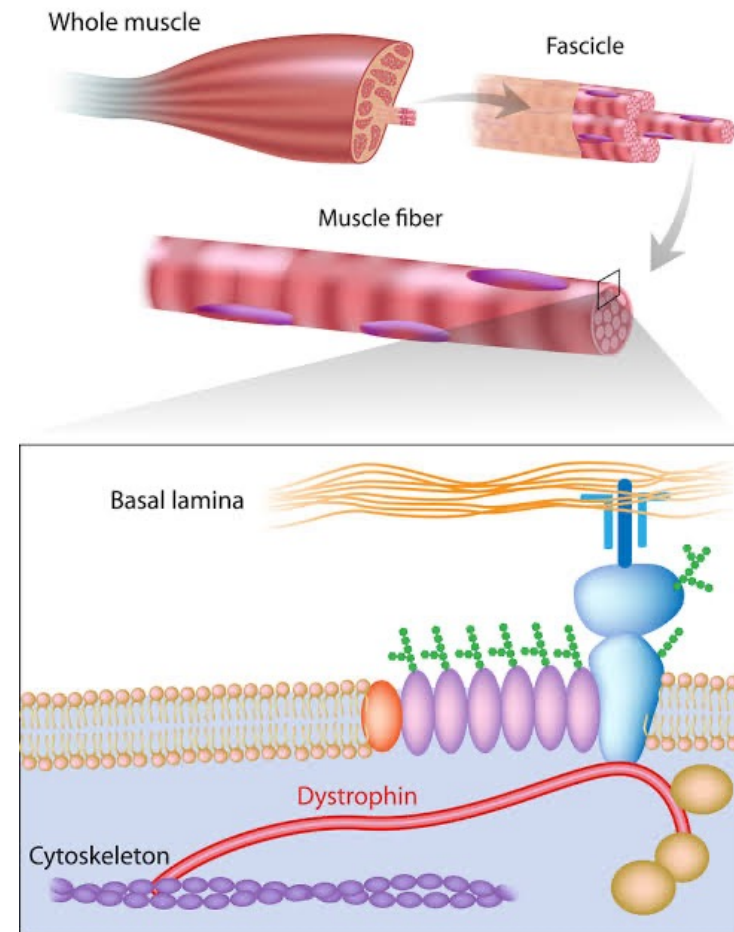
The patient had a response to deflazacort therapy, with clinical signs of improved motor function at his 6-month follow-up clinic visit. Measures of motor function had all improved, and he had developed new motor skills, including the ability to rise from a seated position on the floor to a standing position “hands free,” without using the floor or his thighs to brace himself, as well as the ability to hop on one leg. Transthoracic echocardiography showed normal left ventricular function, without signs of cardiomyopathy, and there was no evidence of pulmonary abnormalities.

The patient has had some side effects associated with 3 years of daily deflazacort therapy, including weight gain and slowing of growth in height. He has minimal facial fullness and no signs of spinal compression fractures or declining bone density on DXA studies. A neuropsychological evaluation at 6 years 3 months of age identified areas in need of monitoring and support: reading and mathematics learning disorders, attention deficit–hyperactivity disorder, generalized anxiety disorder, and obsessive–compulsive disorder. Despite these conditions, the patient is doing well in school and has a strong support system. Genetic carrier screening in the patient’s mother and two sisters was negative, which suggested a reduced risk of DMD cardiomyopathy for family members.

Dystrophin ist ein wichtiges Strukturprotein, das als molekularer Stoßdämpfer in den Muskelzellen wirkt.

Hauptfunktion von Dystrophin

- **Verbindung:** Es verbindet das innere Zytoskelett (die Aktinfilamente) einer Muskelzelle mit der umliegenden extrazellulären Matrix außerhalb der Zelle.
- **Stabilisierung:** Dieser Verbund wird als Dystrophin-Glycoprotein-Komplex (DGC) bezeichnet. Er stabilisiert die Zellmembran (das Sarkolemm) bei jeder Muskelkontraktion.
- **Schutz:** Bei der Muskularbeit fängt Dystrophin mechanische Belastungen ab und verhindert so, dass die Membran der Muskelzelle einreißt

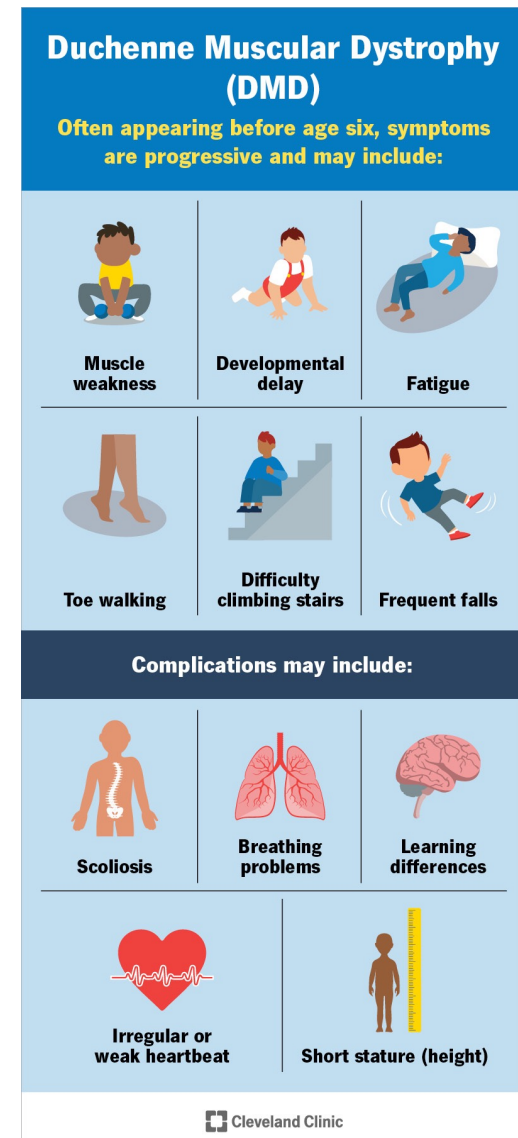


Menschen mit **Duchenne-Muskeldystrophie (DMD)** haben stark erhöhte Leberenzyme, weil diese Enzyme nicht nur in der Leber, sondern in sehr großen Mengen auch in den Skelettmuskelzellen vorkommen.

Bei der Duchenne-Dystrophie führt der genetisch bedingte Mangel des Proteins Dystrophin dazu, dass die Membranen der Muskelzellen instabil werden und reißen. Durch diesen fortschreitenden Muskelabbau und die erhöhte Membranpermeabilität treten die Enzyme aus den geschädigten Muskelzellen direkt in die Blutbahn aus. Die Erhöhung ist somit **kein Zeichen für eine Lebererkrankung**, sondern eine direkte Folge des Muskelschadens.

Folgende Enzyme, die routinemäßig im Labor als „Leberwerte“ bestimmt werden, sind davon betroffen:

- **ALT (Alanin-Aminotransferase / GPT):** Gilt klassisch als leberspezifisch, ist aber ebenfalls in der Muskulatur vorhanden. Bei DMD-Patienten ist dieser Wert oft **massiv erhöht** (teilweise um das 10- bis 20-Fache des Normalwerts).
- **AST (Aspartat-Aminotransferase / GOT):** Dieses Enzym kommt in sehr hohen Konzentrationen im Muskelgewebe vor und steigt bei Muskelzerfall entsprechend stark an.

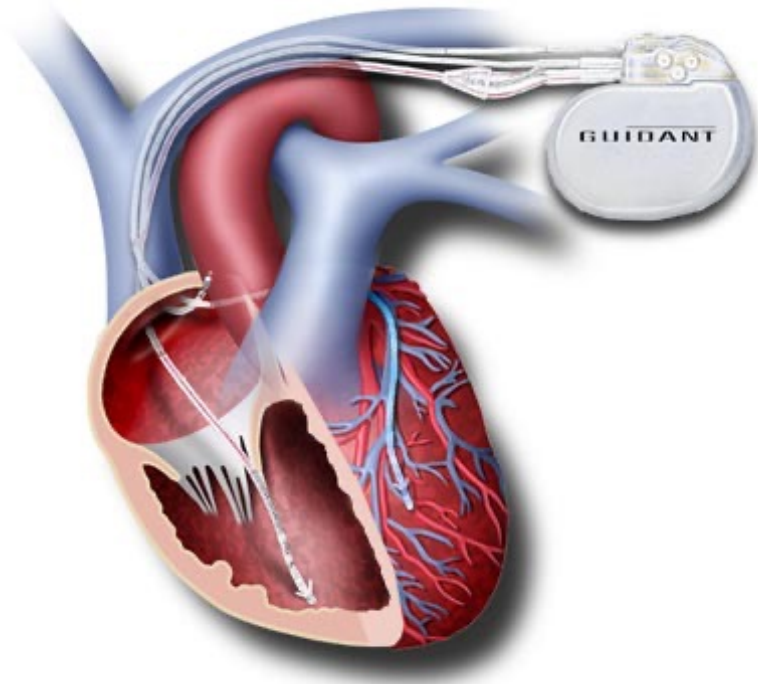


THE LANCET

Ein biventrikulärer Schrittmacher (auch als **kardiale Resynchronisationstherapie** oder **CRT** bezeichnet) verbessert die Pumpkraft des Herzens bei Herzinsuffizienz, indem er die rechte und linke Herzkammer gleichzeitig stimuliert.

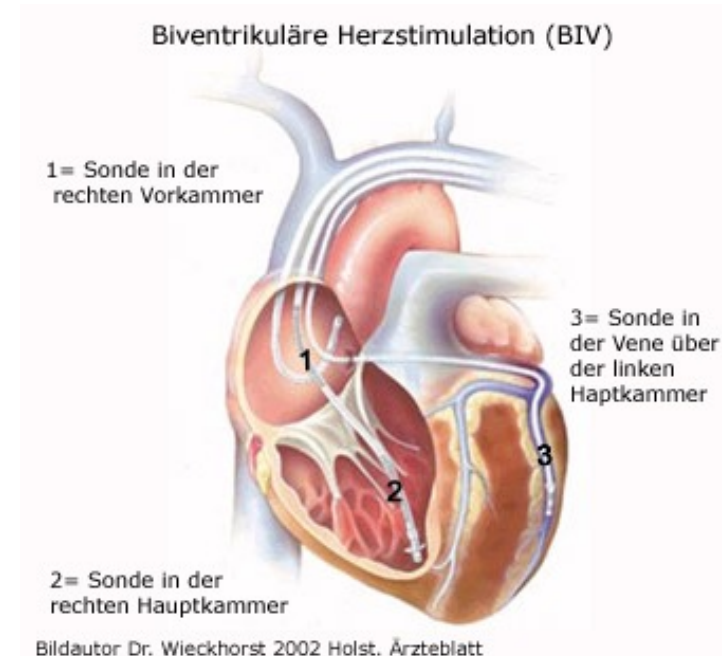
Funktion und Ablauf

- **Gleichzeitiger Takt:** Das Gerät gleicht verzögerte Erregungen (wie einen Linksschenkelblock) aus, damit beide Herzkammern wieder im gleichen Takt schlagen.
- **Drei Sonden:** Eine Sonde liegt im rechten Vorhof, eine in der rechten Herzkammer und eine dritte über den Koronarsinus an der linken Herzkammer.
- **Implantation:** Der Eingriff erfolgt meist unter lokaler Betäubung (oder leichter Sedierung) unterhalb des Schlüsselbeins.



Wo sollte die linke Elektrode optimal liegen?

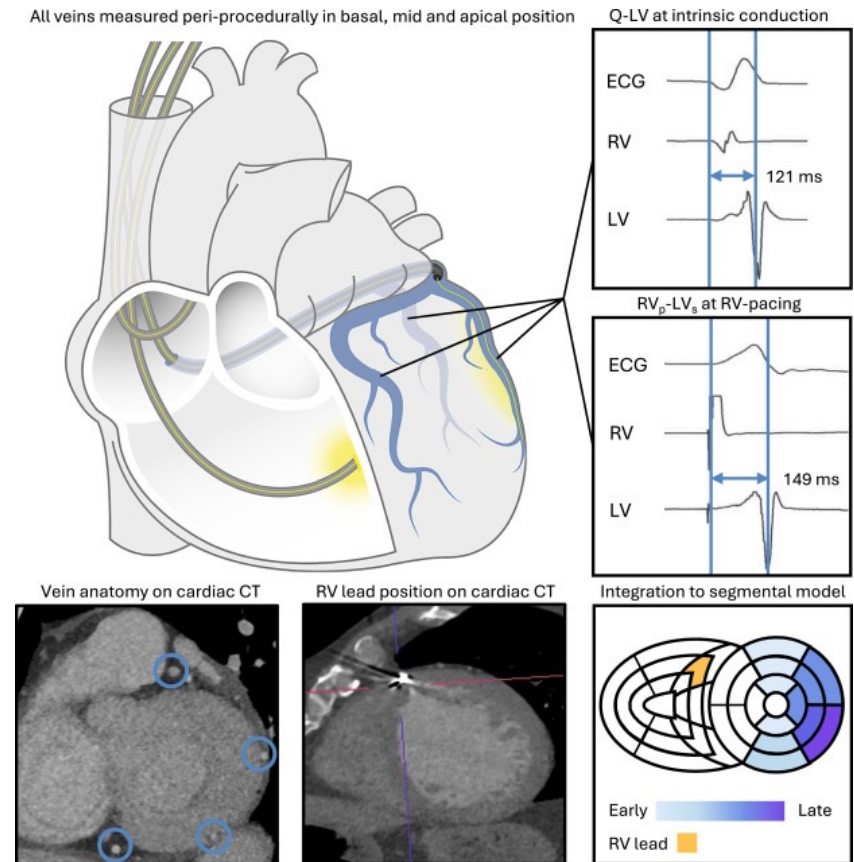
- **Die "Zielzone" (Lateral/Posterolateral):** Studien und klinische Praxis zeigen, dass die Platzierung an der **seitlichen (lateralen) oder hinteren-seitlichen (posterolateralen) Wand** der linken Herzkammer in der Regel die besten Ergebnisse liefert. Das Herz kann so das Blut wieder deutlich kraftvoller auswerfen.
- **Die Höhe (Mitte statt Spitze):** Die Elektrode sollte idealerweise im **mittleren Bereich** zwischen der Herzbasis und der Herzspitze liegen. Eine Position direkt an der Herzspitze (apikal) gilt meist als ungünstig und sollte vermieden werden.
- **Narbengewebe meiden:** Hat der Patient beispielsweise nach einem Herzinfarkt Narbengewebe in einem bestimmten Areal der linken Kammer, nützt eine Elektrode dort wenig. Totes Gewebe leitet keinen Strom. Die Elektrode muss daher in einem Bereich mit gesundem, lebendem Muskelgewebe liegen.



Die Platzierung der linksventrikulären (LV) Schrittmacherelektrode am Ort der spätesten elektrischen Aktivierung ist ein zentrales Konzept in der kardialen Resynchronisationstherapie (CRT). Ziel dieser Strategie ist es, die durch einen Linksschenkelblock verursachte Asynchronie des Herzens bestmöglich auszugleichen, indem das am spätesten kontrahierende Areal gezielt zuerst stimuliert wird.

Die im Jahr 2026 veröffentlichte, randomisierte und verblindete **DANISH-CRT-Studie** (1.001 Patienten) brachte jedoch Ernüchterung:

Die gezielte Platzierung der Elektrode am Ort der spätesten elektrischen Aktivierung senkte den kombinierten Endpunkt aus Tod oder ungeplanter Krankenhauseinweisung wegen Herzinsuffizienz **nicht** im Vergleich zur konventionellen Platzierung. Als Standardkontrolle diente die klassische, nicht-apikale Positionierung in einer posterolateralen oder lateralen Vene, welche sich im klinischen Alltag weiterhin als robust und effektiv erweist.



Targeted left ventricular lead placement in biventricular pacing for heart failure: a national, multicentre, double-blind, randomised controlled trial in Denmark

Summary

Background Left ventricular lead position is a key determinant of optimal biventricular pacing for heart failure. Observational data indicate better outcomes in patients with late myocardial activation at the left ventricular lead site. We aimed to test whether targeting the left ventricular lead at site of latest electrical activation improves outcomes.

Methods In this national, randomised, controlled, double-blinded, superiority trial we included patients from all five Danish university centres performing device implantation who had heart failure and wide QRS on guideline-directed medication, eligible for biventricular pacing. We randomly assigned (1:1) patients to either the intervention group, with left ventricular lead placement at the latest electrically activated site within the coronary sinus branches, or to control group, with left ventricular lead placement in a posterolateral non-apical branch. Primary outcome was a composite of time to death or first unplanned heart failure hospitalisation. We used block randomisation and masked patients and all study personnel (except operating room personnel) to treatment allocation. The primary outcome was a composite of time to death or first unplanned hospitalisation for heart failure. Analysis followed a modified intention-to-treat approach. Safety was assessed in all correctly assigned patients. The trial is registered at ClinicalTrials.gov (NCT03280862) and is complete.

Findings From March 20, 2018, to June 3, 2024, we included 1001 patients (255 females and 746 males); 499 were randomly assigned to the intervention group and 502 to the control group. One incorrectly enrolled patient was excluded, leaving 1000 patients for the modified intention-to-treat analysis. Electrical activation at left ventricular lead was a mean of 9 milliseconds (95% CI 5–13) later in the intervention group. Follow-up was completed on Feb 27, 2026, after a median 45·8 months (IQR 28·5–65·7). The primary endpoint occurred in 139 (28%) of 499 patients in the intervention group and 128 (26%) of 501 in control group (hazard ratio 1·10 [95% CI 0·86–1·39]; $p=0·45$). Overall complication risk was similar between groups (71 [14%] patients in the intervention group *vs* 64 [13%] in the control group), but lead-related complications were more frequent in the intervention group. One procedure-related death occurred in the intervention group.

Interpretation In patients with heart failure and prolonged QRS, targeted left ventricular lead placement at the site of latest electrical activation did not reduce the composite endpoint of death or unplanned hospitalisation for heart failure compared with conventional lead placement in a posterolateral, non-apical position.

Funding Novo Nordisk Foundation, Danish Heart Foundation, Danish Pacemaker and ICD Registry, and Independent Research Fund Denmark.

	Intervention group (n=499)	Control group (n=501)
Age, years	73 (65-78)	72 (63-77)
Sex		
Female	130 (26%)	125 (25%)
Male	369 (74%)	376 (75%)
Height*, cm	176 (169-182)	175 (169-181)
Weight*, kg	83 (74-96)	84 (74-97)
QRS duration, milliseconds	164 (158-180)	166 (158-180)
Left ventricular ejection fraction, %	27% (6)	27% (6)
Left ventricular end-diastolic volume, mL	187 (73)	190 (64)
Left ventricular end-systolic volume, mL	138 (62)	140 (54)
Estimated GFR, mL/min per 1.73m ²		
0-29	20 (4%)	21 (4%)
30-60	206 (41%)	196 (39%)
>60	269 (54%)	279 (56%)
NYHA class		
II	279 (56%)	286 (57%)
III	216 (43%)	206 (41%)
IV	2 (<1%)	9 (2%)
Heart failure causes†		
Ischaemic heart disease	221 (44%)	193 (39%)
Non-ischaemic dilated cardiomyopathy	271 (54%)	284 (57%)
Valvular heart disease	37 (7%)	44 (9%)
Hypertrophic cardiomyopathy	21 (4%)	26 (5%)
Arrhythmogenic cardiomyopathy	16 (3%)	9 (2%)
Congenital heart disease	4 (<1%)	1 (<1%)
Cardiac sarcoidosis	7 (1%)	5 (1%)
Pacing-induced heart failure	87 (17%)	87 (17%)
Pre-existing cardiac pacemaker or implantable cardioverter defibrillator	174 (35%)	174 (35%)
Indication for biventricular pacing		
Left bundle-branch block with QRS ≥130 milliseconds	336 (67%)	342 (68%)
Other bundle-branch block with QRS >150 milliseconds	43 (9%)	41 (8%)
Paced QRS and need for ventricular pacing	111 (22%)	111 (22%)
Indication for pacing and low ejection fraction	9 (2%)	7 (1%)

(Table 1 continues in next column)

	Intervention group (n=499)	Control group (n=501)
(Continued from previous column)		
Coexisting conditions		
Hypertension	294 (59%)	289 (58%)
Persistent or permanent atrial fibrillation	96 (19%)	79 (16%)
Paroxysmal atrial fibrillation	108 (22%)	119 (24%)
Chronic obstructive pulmonary disease	55 (11%)	62 (12%)
Diabetes	120 (24%)	135 (27%)
Medication		
ACE inhibitor, angiotensin 2 receptor blocker, or ARNI	465 (93%)	475 (95%)
β blocker	434 (87%)	429 (86%)
Mineralocorticoid receptor blocker	349 (70%)	337 (67%)
SGLT2 inhibitor	194 (39%)	191 (38%)
Diuretics	345 (69%)	326 (65%)
Digoxin	21 (4%)	20 (4%)
Amiodarone	58 (12%)	51 (10%)
Nt-Pro BNP†, ng/L	1259 (574-5-2672)	1260 (487-2666)

Data are median (IQR), mean (SD), or n (%). ACE=angiotensin-converting enzyme. ARNI=angiotensin receptor-neprilysin inhibitor. GFR=glomerular filtration rate. Nt-Pro BNP=N-terminal pro B-type Natriuretic Peptide. NYHA=New York Heart Association. SGLT2=sodium-glucose co-transporter 2. *Missing values for baseline characteristics were less than 2% of patients except for the variables of height (n=37; 3.7%), weight (n=50; 5.0%), and Nt-Pro BNP (n=244; 24.4%). †Some patients might have more than one cause for heart failure.

Table 1: Baseline characteristics

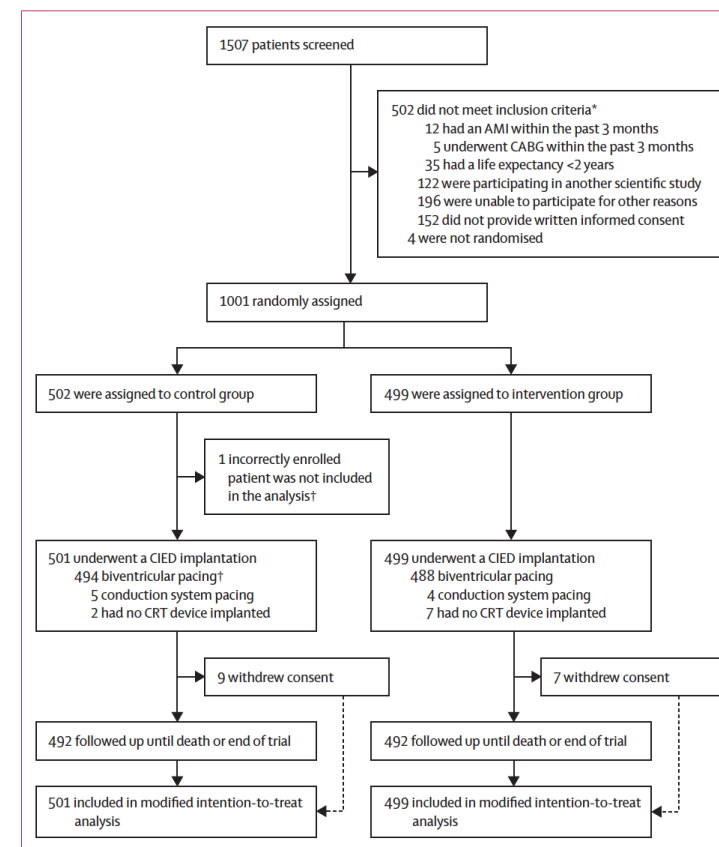


Figure 1: Patient inclusion flowchart
AMI=acute myocardial infarction. CABG=coronary artery bypass grafting. CIED=cardiac implantable electronic device. *For some patients, more than one criteria were not met. †Underwent randomisation despite not meeting the inclusion criteria (left ventricular ejection fraction >35%); no device was implanted and the participant was not followed up in the trial. ‡In one patient, implantation of a transvenous left ventricular lead was unsuccessful; instead, an epicardial left ventricular pacing lead was implanted thoracoscopically.

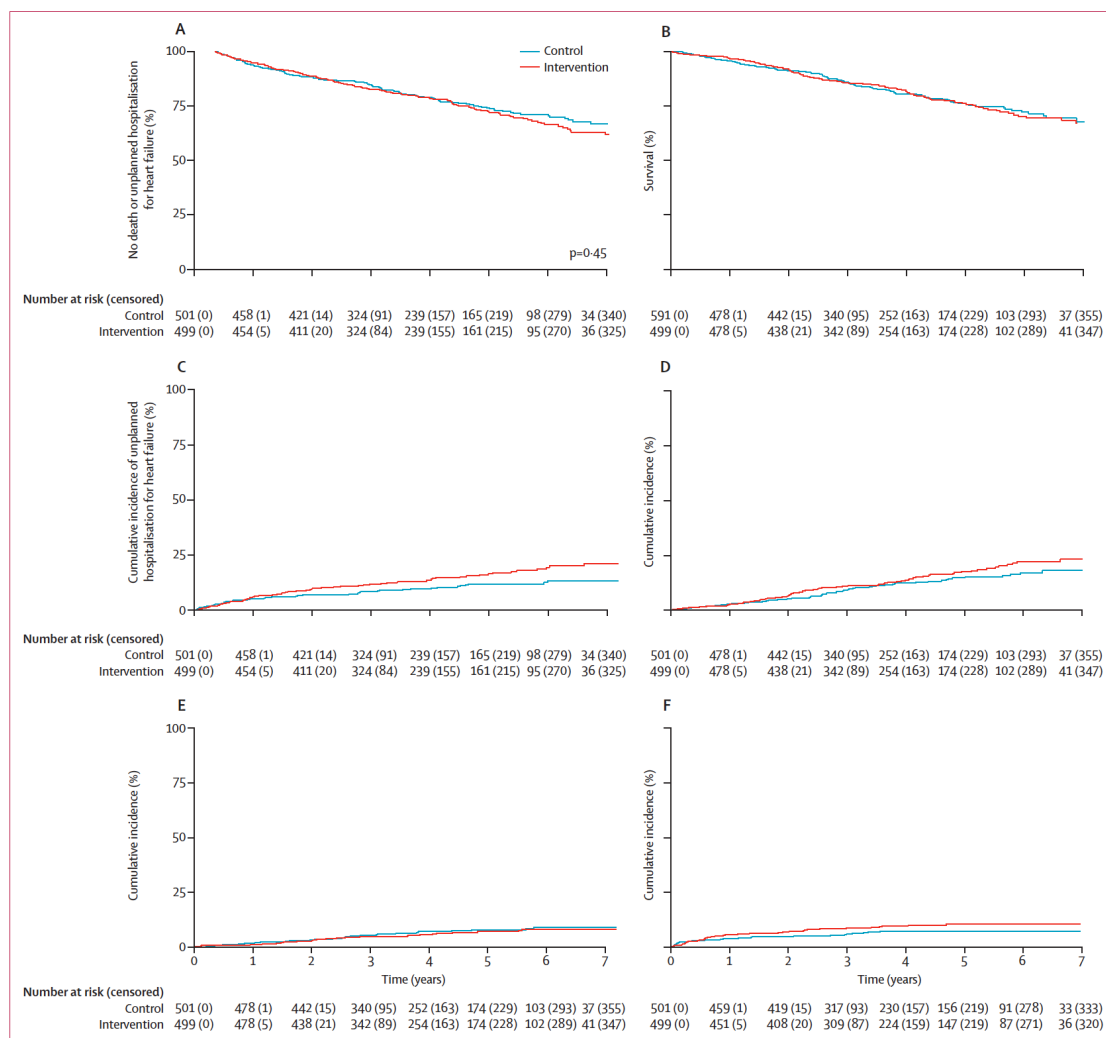


Figure 2: Time-to-event and curves for primary and secondary outcomes

Time-to-event curves as Kaplan-Meier curves for the primary composite outcome event of death or unplanned hospitalisation for heart failure (A) and for all-cause death (B). For the outcome unplanned hospitalisation for heart failure, there are cumulative incidence curves accounting for all-cause death as a competing risk (C). For the outcomes cardiovascular death (D), sudden death (E), and atrial fibrillation (Panel F), cumulative incidence curves accounting for death or other causes of death as competing risk are shown.

	Intervention group (n=499)	Control group (n=501)	Total (N=1000)
Total complications	88	75	163
Major complications	71	54	125
Lead dislodgement	29	13	42
Left ventricular lead	16	5	21
Right atrial lead	8	4	12
Right ventricular lead	3	3	6
Not available	2	1	3
High threshold not resolved by reprogramming	4	3	7
Left ventricular lead	1	1	2
Left bundle branch lead	1	0	1
Right ventricular lead	2	2	4
Lead fracture or insulation defect	3	2	5
Lead perforation	3	0	3
Pneumothorax with drainage	2	2	4
Sensing failure not resolved by reprogramming	1	2	3
Phrenic nerve capture not resolved by reprogramming	6	8	14
Haematoma requiring reintervention and/or prolonged hospitalisation	2	0	2
Bleeding requiring reintervention	1	1	2
Local device infection	7	4	11
Systemic device infection*	2	6	8
Acute decompensation	1	0	1
Tamponade	4	3	7
Ventricular arrhythmias	3	2	5
Procedure-related death	1	0	1
Coronary sinus dissection, left ventricular lead not implanted	1	2	3
Other, major†	1	6	7
Minor complications	17	21	38
Pneumothorax without drainage	1	2	3
Haematoma without reintervention or prolonged hospitalisation	3	8	11
Superficial pocket infection treated with antibiotics	3	2	5
Coronary sinus dissection, left ventricular lead implanted	9	9	18
Other, minor‡	1	0	1

Data are n (%). *One patient was treated with antibiotics without device removal. †Pain at the device site with revision (n=3), bleeding (n=1), upper extremity deep venous thrombosis (n=1), right ventricular lead not connected to generator (n=1), damage to pre-existing right ventricular lead during implantation requiring reimplantation of a new lead (n=1). ‡Upper extremity oedema due to venous congestion without deep venous thrombosis (n=1).

Table 3: Procedure-related and device-related complications

More lead-related complications

	Intervention group (n=499)	Control group (n=501)	Effect measure (95% CI)	p value
Clinical outcomes*				
Death or unplanned hospitalisation for heart failure	139 (28%)	128 (26%)	1.10 (0.86 to 1.39)	0.45
Death	113 (23%)	110 (22%)	1.03 (0.79 to 1.34)	0.82
Cardiovascular death	82 (16%)	67 (13%)	1.23 (0.89 to 1.70)	0.21
Sudden cardiac death	32 (6%)	36 (7%)	0.90 (0.56 to 1.44)	0.65
Unplanned hospitalisation for heart failure	77 (15%)	53 (11%)	1.47 (1.03 to 2.08)	0.03
Atrial fibrillation	48 (10%)	34 (7%)	1.44 (0.93 to 2.23)	0.11
Six-month outcomes†‡				
Left ventricular end-diastolic volume, mL	154 (69)	154 (58)	-0.4 (-7.7 to 8.6)	0.92
Left ventricular end-systolic volume, mL	95 (57)	94 (49)	-0.8 (-7.6 to 5.9)	0.81
Left ventricular ejection fraction, %	41% (9.9)	41% (9.8)	0.2 (-1.1 to 1.4)	0.40
Increase in LVEF from baseline, %	14% (9.1)	14.2% (8.9)	-0.1 (-1.3 to 1.0)	0.81
Six-min walk test distance, m	436 (107)	432 (113)	4.2 (-11.5 to 19.9)	0.60
NYHA class	..	..	..	0.66
I	167 (33%)	154 (31%)	..	..
II	262 (53%)	282 (56%)	..	..
III	43 (9%)	41 (8%)	..	..
IV	1 (<1%)	2 (<1%)	..	..
Change in KCCQ-12 CSS score from baseline	11.9 (17.4)	11.0 (17.5)	0.9 (-1.8 to 3.6)	0.50
Difference in KCCQ-12 CSS with multiple imputation	..	..	0.6 (-1.8 to 3.1)	0.62
Safety outcomes§				
Patients with device-related complications				
At implantation	17 (3%)	14 (3%)	..	0.58
After implantation before discharge	21 (4%)	21 (4%)	..	0.99
During follow-up	39 (8%)	35 (7%)	..	0.62
Total patients with any complication	71 (14%)	64 (13%)	1.11 (0.81 to 1.52)	0.50
Patients with major complications	59 (12%)	50 (10%)	1.18 (0.83 to 1.69)	0.35
Patients with one complication	48 (10%)	46 (9%)	..	..
Patients with two complications	10 (2%)	4 (1%)	..	..
Patients with three complications	1 (<1%)	0	..	..
Total patients with lead-related complications¶	34 (7%)	23 (5%)	1.48 (0.89 to 2.48)	0.13
Total patients with lead-related complications including perforations	39 (8%)	26 (5%)	1.51 (0.93 to 2.44)	0.09

(Table 2 continues on next page)

	Intervention group (N=499)	Control group (N=501)	Effect measure (95% CI)	p value
(Continued from previous page)				
Total patients with left ventricular lead-related complications	15 (3%)	6 (1%)	2.51 (0.98 to 6.42)	0.05
Patients with appropriate ICD therapy during follow-up**	36 (7%)	34 (7%)	1.06 (0.68 to 1.67)	0.79
Patients with inappropriate ICD-therapy during follow-up	8 (2%)	9 (2%)	0.89 (0.35 to 2.29)	0.81
Patients with inappropriate ICD-therapy caused by atrial tachyarrhythmia	5 (1%)	9 (2%)	..	..
Patients with inappropriate ICD-therapy caused by oversensing	3 (1%)	0	..	..

Data are n (%) or mean (SD), unless otherwise specified. KCCQ-12 CSS= Clinical Summary Score of the 12-item Kansas City Cardiomyopathy Score. LVEF=left ventricular ejection fraction. NYHA=New York Heart Association. ICD=implantable cardioverter defibrillator. *Effect measures for these outcomes are hazard ratios. †Effect measures for these outcomes are mean differences. ‡For the following variables, data were missing for some of the patients, because they did not survive to the 6-month follow-up or for other reasons: data were missing on LVEF for 56 (6%) patients, for left ventricular volumes for 57 (6%) patients, for six-min walk test distance for 242 (24%) patients, for NYHA-class for 48 (5%) patients, and for change in KCCQ-12 CSS for 362 (36%) patients. §Effect measures for these outcomes are risk ratios. ¶Includes lead dislodgements and high lead threshold or phrenic nerve stimulation not resolved by reprogramming. ||Includes lead dislodgements, tamponade, perforation, and high lead threshold or phrenic nerve stimulation not resolved by reprogramming. **Includes any ICD therapy, ICD shock, or anti-tachycardia pacing.

Table 2: Outcomes and adverse events

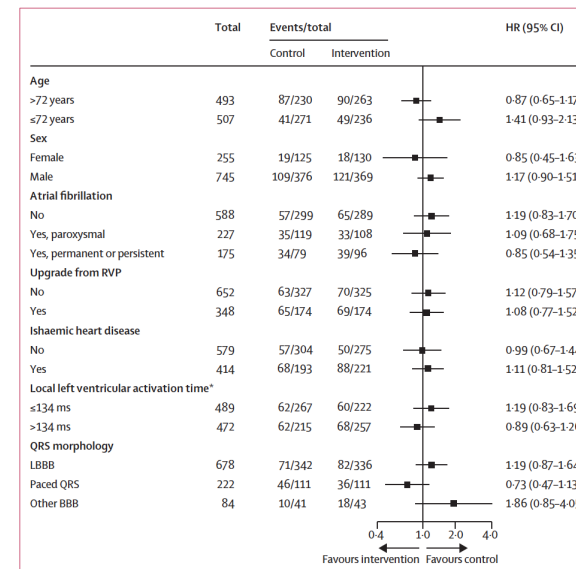


Figure 3: Forest plot of subgroup analyses
 Predefined subgroup analyses of the primary composite outcome. BBB= bundle-branch block. LBbB=left bundle-branch block. RVP=right ventricular pacing. *Local left ventricular activation time measured from right ventricular activation.

Research in context

Evidence before this study

No formal literature review was done before planning this study. Biventricular pacing for cardiac resynchronisation therapy (CRT) in patients with heart failure and broad QRS improves left ventricular ejection fraction, functional status, and quality of life; reduces heart failure hospitalisations; and prolongs longevity. However, a considerable portion of these patients have no measurable benefit from CRT. A series of observational reports indicated that the more delayed the local electrical activation was at the site of the left ventricular lead, the better the outcomes of the patients with heart failure and bundle-branch block treated with CRT. Small randomised controlled trials (RCTs) investigating targeting the left ventricular lead towards the latest activation in the left ventricle showed various results, but differences in methods and endpoints used precluded a strong meta-analysis. We did two single centre RCTs testing targeted left ventricular lead placement in CRT for heart failure, including 182 and 122 patients, respectively. Results indicated that after 6 months of follow-up, targeted placement of the left ventricular lead towards the latest activated segment of the left ventricle was associated with a higher rate of response to CRT and potentially a higher increase in left ventricular ejection fraction. We therefore joined national centres for this double-blind, long-term follow-up RCT, which was powered to show whether

targeted placement of the left ventricular lead in CRT for heart failure reduces the clinically relevant endpoint of death or unplanned hospitalisation for heart failure and thus might reduce the proportion of patients not responding to CRT.

Added value of this study

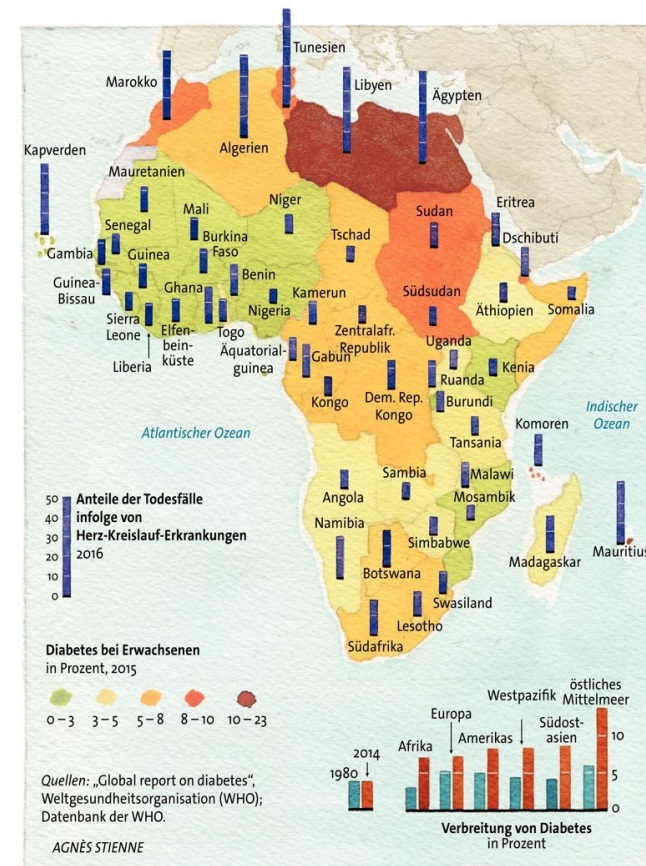
This large, double-blind RCT shows that in patients with heart failure and prolonged QRS, targeted placement of the left ventricular pacing lead at the site of latest electrical activation has no effect in reducing the risk of death or unplanned hospitalisation for heart failure compared with conventional placement of the lead in a posterolateral, non-apical position. Numerically, more lead-related complications were observed with the intervention. This was the largest trial to date on this topic.

Implications of all the available evidence

The findings in this trial, when added to current evidence, indicate that for routine implantation of CRT for heart failure, the left ventricular lead should be placed in a posterolateral, non-apical position rather than guided by electrical mapping. Placing the lead guided by electrical mapping makes no difference to outcomes, but requires longer operation time, requires longer fluoroscopy time, and results in more lead-related complications.

Akute Herzinsuffizienz in Afrika stellt eine wachsende, aber oft übersehene Gesundheitskrise dar. Während das globale Augenmerk in afrikanischen Ländern südlich der Sahara historisch auf übertragbaren Krankheiten wie HIV, Malaria und Tuberkulose liegt, breitet sich eine „stille Epidemie“ nicht-übertragbarer Erkrankungen (*Non-Communicable Diseases*, NCDs) rasant aus.

Die Sterblichkeit (*Mortalität*) infolge einer Herzinsuffizienz ist in Afrika **doppelt so hoch wie in anderen Schwellenländern** und **fünfmal so hoch wie in Industrieländern**.



Aetiology, management, and outcomes of acute heart failure in 17 African countries (THESUS-HF II): a prospective, multicentre, observational cohort study

Summary

Background Contemporary data on the aetiology, management, and outcomes of acute heart failure across Africa are scarce. We aimed to conduct a contemporary assessment of acute heart failure aetiology, treatment patterns, presentation rates, and 180-day outcomes across Africa.

Methods THESUS-HF II was a prospective, multicentre, observational cohort study in 50 hospitals across 17 African countries. Adults aged 18 years or older with acute heart failure were enrolled during seven 24 h surveillance periods within an 8-week, site-specific window. Acute heart failure was identified by acute dyspnoea and congestion, supported by electrocardiography, chest radiography, and point-of-care echocardiography. We assessed presentation rates per 10 000 people in the adult catchment population per week, treatment patterns (including medication use at discharge), readmission, and all-cause mortality through to 180 days. This study was registered with the Pan African Clinical Trial Registry (PACTR202410553810557) and is completed; however, substudies are ongoing.

Findings Between July 1, 2024, and July 31, 2025, 1741 patients were assessed for eligibility at participating hospitals and 1578 were included in the study cohort. 793 (50·5%) of 1570 participants were female, 777 (49·5%) were male, and 1533 (97·8%) of 1567 were of African descent; median age was 56·0 years (IQR 40·0–69·0). The weekly acute heart failure presentation rate was 0·03 per 10 000 people (95% CI 0·02–0·05) overall and 0·02 per 10 000 people (0·01–0·04) for de novo acute heart failure. De novo acute heart failure accounted for 1007 (64·2%) of 1568 presentations. The leading aetiologies were hypertensive heart disease (576 [36·5%] of 1578), cardiomyopathy (370 [23·4%]), and ischaemic heart disease (367 [23·3%]). Median hospital ward stay was 6·0 days (IQR 4·0–10·0), and in-hospital mortality was 8·7% (95% CI 7·3–10·2; 134 of 1542 patients). At discharge, renin–angiotensin–aldosterone system inhibitors were prescribed in 1014 (73·9%) of 1373 patients, β blockers in 1053 (76·9%) of 1369 patients, mineralocorticoid receptor antagonists in 982 (71·9%) of 1366, and SGLT2 inhibitors in 743 (54·7%) of 1359; target doses were reached in fewer than half of patients. Of 1567 patients included in time-to-event analyses, 528 (33·7%) were lost to follow-up before 180 days. All-cause mortality was 11·1% (95% CI 9·6–12·9; 160 deaths) at 30 days and 20·6% (18·4–23·0; 255 deaths) at 180 days. All-cause mortality did not differ across aetiological groups over 30 days (log-rank $p=0\cdot39$), but differed over 180 days ($p=0\cdot019$).

Interpretation Compared with THESUS-HF, THESUS-HF II suggests an evolving aetiological profile of acute heart failure in Africa, although differences in ascertainment and diagnostic capability might have contributed to the apparent aetiological shift. High mortality in this relatively young cohort highlights the importance of heart failure prevention, access to cardiac care, guideline-directed therapy, and post-discharge follow-up. These findings suggest that short-term acute heart failure outcomes are not driven by its demographic, aetiological, and echocardiographic factors.



Figure 1: Participating countries and hospital locations

Green shading shows countries with at least one participating hospital (Angola, Botswana, Cameroon, Democratic Republic of the Congo, Ethiopia, Ghana, Mauritania, Mozambique, Namibia, Nigeria, São Tomé and Príncipe, South Africa, Sudan, Tanzania, Tunisia, Uganda, and Zambia). Plus signs (+) show locations of participating hospitals.

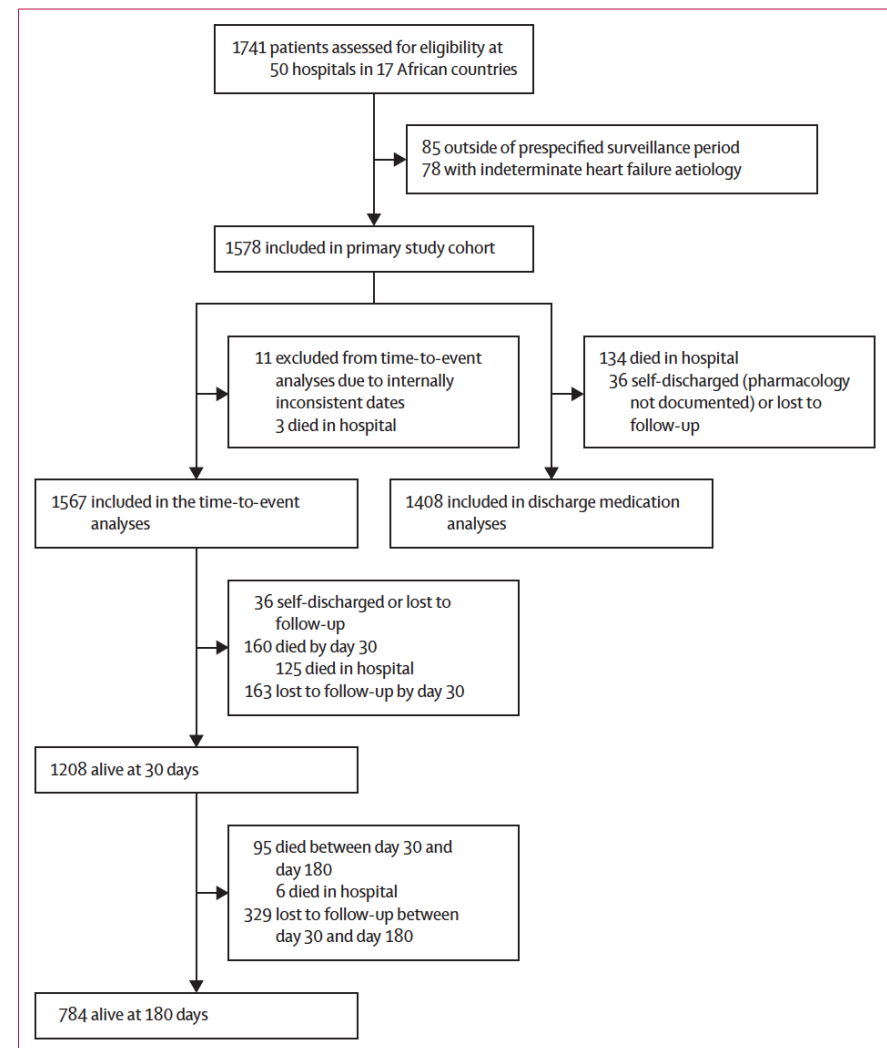


Figure 2: Patient flow diagram

The time-to-event and discharge-medication cohorts represent parallel analysis pathways.

	Overall (n=1578)	Ischaemic heart disease (n=367)	Hypertensive heart disease (n=576)	Valvular or congenital heart disease (n=168)	Cardiomyopathy (n=370)	Other (n=97)	p value
Demographics							
Age, years	56.0 (40.0-69.0)	59.0 (43.0-70.0)	61.0 (49.0-70.0)	41.0 (28.5-63.0)	46.0 (31.0-63.0)	56.0 (40.0-69.0)	<0.0001
Male	777/1570 (49.5%)	212/367 (57.8%)	286/574 (49.8%)	71/165 (43.0%)	162/367 (44.1%)	46/97 (47.4%)	0.0018
Female	793/1570 (50.5%)	155/367 (42.2%)	288/574 (50.2%)	94/165 (57.0%)	205/367 (55.9%)	51/97 (52.6%)	..
Ethnicity							
African	1533/1567 (97.8%)	339/362 (93.6%)	570/574 (99.3%)	164/168 (97.6%)	364/367 (99.2%)	96/96 (100%)	<0.0001
Other*	34/1567 (2.2%)	23/362 (6.4%)	4/574 (0.7%)	4/168 (2.4%)	3/367 (0.8%)	0	..
Cardiovascular risk factors and comorbidities							
Previous heart failure diagnosis	561/1568 (35.8%)	122/363 (33.6%)	203/572 (35.5%)	73/168 (43.5%)	136/369 (36.9%)	27/96 (28.1%)	0.10
Hypertension	988/1575 (62.7%)	220/366 (60.1%)	549/576 (95.3%)	41/168 (24.4%)	128/368 (34.8%)	50/97 (51.5%)	<0.0001
Diabetes	318/1564 (20.3%)	139/364 (38.2%)	125/569 (22.0%)	10/167 (6.0%)	29/367 (7.9%)	15/97 (15.5%)	<0.0001
Dyslipidaemia	249/1571 (15.8%)	125/365 (34.2%)	79/574 (13.8%)	11/167 (6.6%)	15/368 (4.1%)	19/97 (19.6%)	<0.0001
HIV-positive	54/1566 (3.4%)	4/363 (1.1%)	15/574 (2.6%)	5/165 (3.0%)	22/367 (6.0%)	8/97 (8.2%)	0.0003
Smoking status	..	..	..	..	..	..	<0.0001
Current	79/1552 (5.1%)	35/363 (9.6%)	21/563 (3.7%)	7/167 (4.2%)	13/363 (3.6%)	3/96 (3.1%)	..
Previous	170/1552 (11.0%)	61/363 (16.8%)	51/563 (9.1%)	8/167 (4.8%)	33/363 (9.1%)	17/96 (17.7%)	..
NYHA class at admission	..	..	..	..	..	..	<0.0001
I	65/1549 (4.2%)	33/364 (9.1%)	11/560 (2.0%)	4/165 (2.4%)	9/364 (2.5%)	8/96 (8.3%)	..
II	132/1549 (8.5%)	48/364 (13.2%)	34/560 (6.1%)	8/165 (4.8%)	26/364 (7.1%)	16/96 (16.7%)	..
III	459/1549 (29.6%)	101/364 (27.7%)	169/560 (30.2%)	44/165 (26.7%)	122/364 (33.5%)	23/96 (24.0%)	..
IV	893/1549 (57.7%)	182/364 (50.0%)	346/560 (61.8%)	109/165 (66.1%)	207/364 (56.9%)	49/96 (51.0%)	..
Clinical presentation							
BMI, kg/m ²	23.7 (21.2-27.4)	23.6 (21.5-27.5)	24.6 (21.9-28.5)	21.9 (20.0-24.6)	23.2 (20.8-26.6)	24.3 (20.8-28.7)	<0.0001
Systolic blood pressure, mm Hg	124.0 (107.0-142.0)	127.0 (110.0-140.0)	138.0 (117.0-158.5)	114.0 (100.0-130.0)	110.0 (99.5-130.0)	122.0 (108.0-140.0)	<0.0001
Diastolic blood pressure, mm Hg	80.0 (70.0-93.0)	80.0 (70.0-94.0)	87.5 (71.0-100.0)	70.0 (63.0-80.0)	75.5 (63.5-88.0)	76.0 (66.0-88.0)	<0.0001
Heart rate, bpm	96.0 (82.0-108.0)	96.0 (80.0-104.0)	93.0 (81.0-104.0)	98.0 (84.0-112.0)	98.0 (82.0-112.0)	93.5 (82.0-110.0)	0.026
Electrocardiography							
Atrial fibrillation or atrial flutter	306/1464 (20.9%)	102/353 (28.9%)	83/517 (16.1%)	58/162 (35.8%)	46/338 (13.6%)	17/94 (18.1%)	<0.0001
Echocardiography							
LVEDD, mm	58.0 (49.0-65.0)	56.0 (51.0-64.7)	58.0 (49.0-65.0)	53.0 (45.0-62.0)	61.0 (53.0-67.0)	45.0 (38.0-57.7)	<0.0001
LVEF, %	38.0 (28.0-55.0)	38.0 (30.0-50.0)	38.0 (29.0-55.0)	53.0 (35.0-60.0)	31.0 (24.0-41.0)	55.0 (40.0-63.0)	<0.0001
Laboratory investigations							
NT-proBNP, pg/mL†	1879.0 (140.0-6305.0)	423.5 (135.0-3625.0)	2610.0 (1129.0-8102.0)	2084.5 (890.0-8017.0)	4549.0 (1337.5-11 918.0)	3500.0 (1329.0-8164.0)	<0.0001
NT-proBNP (measured or BNP-converted), pg/mL‡	1993.0 (140.0-7164.0)	781.4 (136.0-4561.0)	2185.0 (518.8-7633.0)	2169.0 (904.0-8017.0)	4674.1 (1337.5-12 000.0)	3741.5 (1329.0-7150.0)	<0.0001
Data are median (IQR) or n/N (%), unless otherwise stated. Comparisons across aetiologies: Kruskal-Wallis test (continuous, ordered categorical), χ^2 , or Fisher's exact test (categorical). BNP=B-type natriuretic peptide. LVEDD=left ventricular end-diastolic diameter. LVEF=left ventricular ejection fraction. NT-proBNP=N-terminal pro-B-type natriuretic peptide. NYHA=New York Heart Association. *Other ethnicities were White, Asian, and mixed ancestry. †NT-proBNP was available for 345 patients (176 with ischaemic heart disease, 74 with hypertensive heart disease, 34 with valvular or congenital heart disease, 50 with cardiomyopathy, and 11 other). ‡For patients without a directly measured NT-proBNP but with an available BNP result, BNP was converted to an NT-proBNP-equivalent value (additional n=74: 23 with ischaemic heart disease, 20 with hypertensive heart disease, five with valvular or congenital heart disease, 20 with cardiomyopathy, and six other), giving a combined measured or BNP-converted total of n=419 (199 with ischaemic heart disease, 94 with hypertensive heart disease, 39 with valvular or congenital heart disease, 70 with cardi							

	Overall (n=1578)	Ischaemic heart disease (n=367)	Hypertensive heart disease (n=576)	Valvular or congenital heart disease (n=168)	Cardiomyopathy (n=370)	Other (n=97)	p value
Emergency department stay, h	14.0 (4.0–37.0)	12.0 (3.0–48.0)	24.0 (6.0–40.5)	10.0 (3.0–24.0)	12.0 (3.0–24.0)	12.0 (2.0–24.0)	0.0002
Intensive care unit admission	151/1461 (10.3%)	57/356 (16.0%)	24/523 (4.6%)	20/149 (13.4%)	40/341 (11.7%)	10/92 (10.9%)	<0.0001
Length of intensive care unit stay, days	3.0 (2.0–5.0)	3.0 (2.0–5.0)	5.0 (3.0–8.0)	2.0 (1.0–4.0)	3.0 (2.0–6.0)	3.0 (2.0–5.0)	0.064
Admitted to ward	1340/1499 (89.4%)	309/356 (86.8%)	496/546 (90.8%)	142/154 (92.2%)	317/352 (90.1%)	76/91 (83.5%)	0.075
Length of ward stay, days	6.0 (4.0–10.0)	5.0 (3.0–8.0)	7.0 (4.0–10.0)	6.0 (4.0–10.0)	6.0 (4.0–10.0)	7.0 (4.0–12.0)	<0.0001
In-hospital mortality	134/1542 (8.7%)	29/365 (7.9%)	48/567 (8.5%)	13/158 (8.2%)	31/356 (8.7%)	13/96 (13.5%)	0.53

Data are median (IQR) or n/N (%), unless otherwise stated. p values for continuous variables (emergency department stay, intensive care unit length of stay, and ward length of stay) were calculated using the Kruskal–Wallis test; the p value for in-hospital mortality was calculated using the χ^2 test. Discharge status was missing for 36 patients; in-hospital mortality is reported as a percentage of those with known discharge status (n=1542).

Table 2: In-hospital clinical outcomes overall and by primary heart failure aetiology

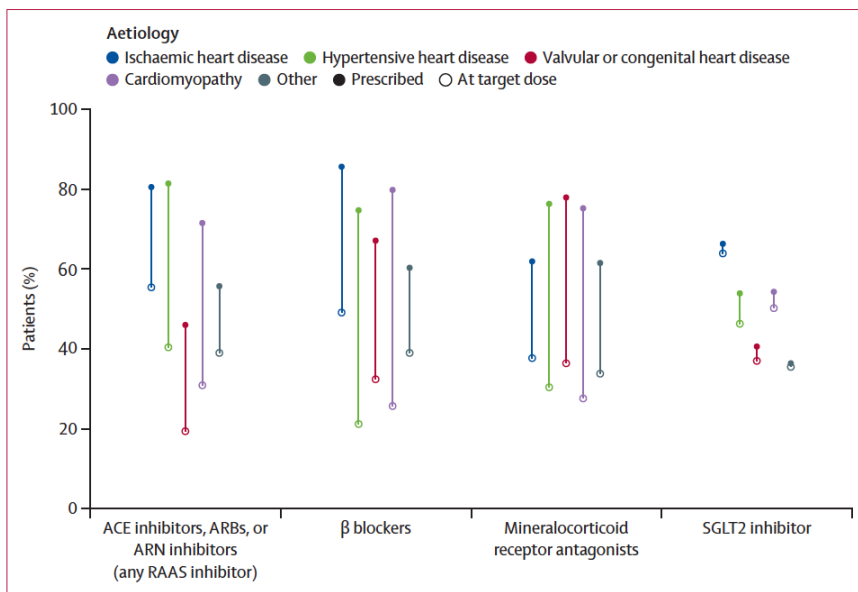


Figure 3: Medication use at discharge by heart failure aetiology and target dose
 ACE=angiotensin-converting enzyme. ARB=angiotensin-receptor blocker. ARN=angiotensin receptor-neprilysin. RAAS=renin-angiotensin-aldosterone system.

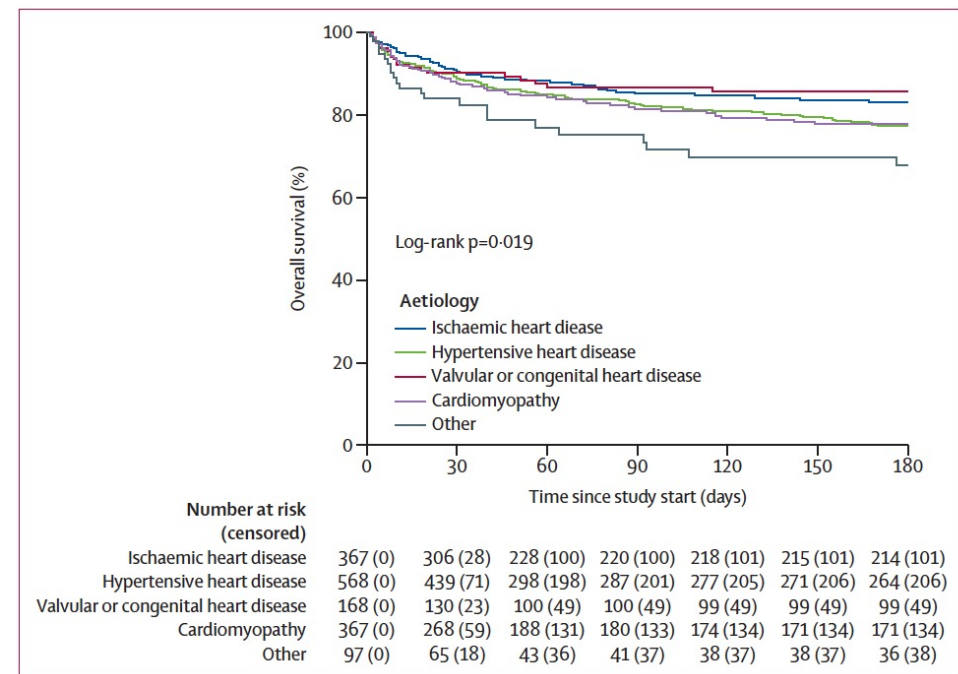


Figure 4: Kaplan-Meier estimates of 180-day overall survival by heart failure aetiology
 Numbers at risk reflect the 1567 patients included in the time-to-event analyses. 11 patients (eight with hypertensive heart disease and three with cardiomyopathy) were excluded because of internally inconsistent dates that could not be resolved with source data.

Research in context

Evidence before this study

We searched Cochrane Library, MEDLINE (PubMed), and Embase for articles published between Jan 1, 2010, and Jan 1, 2025, with the final search conducted on Jan 1, 2026. The search was restricted to articles published in English and used combinations of the terms “acute heart failure”, “de novo heart failure”, “Africa”, “sub-Saharan Africa”, “epidemiology”, “aetiology”, “management”, “treatment”, “outcomes”, “mortality”, and “readmission”. We included observational studies, registries, cohort studies, and other clinical studies reporting the epidemiology, aetiology, clinical characteristics, management, treatment, or outcomes of acute heart failure in adult African populations. We excluded studies conducted outside Africa, paediatric-only studies, studies limited to stable chronic heart failure without a separately identifiable acute heart failure population, case reports, editorials, commentaries, and publications without relevant clinical data. We primarily considered contemporary studies, while also including earlier landmark publications identified through reference screening when these were important to the historical context of acute heart failure in Africa. The original THESUS-HF registry was the principal multicountry study of acute heart failure in sub-Saharan Africa. Conducted between 2007 and 2010 in 12 university hospitals across nine countries, it showed that patients admitted with acute heart failure in Africa were substantially younger than those in high-income settings, with a near-equal distribution between men and women. Heart failure was predominantly non-ischaemic, with hypertensive heart disease and rheumatic heart disease as leading causes, whereas ischaemic heart disease was uncommon. Despite this distinct aetiological profile, short-term outcomes were poor, with high mortality by 180 days. Since that study, many African countries have experienced increasing urbanisation and a growing burden of hypertension, diabetes, and obesity, alongside wider but uneven access to contemporary heart failure therapies. However, contemporary multicountry

evidence examining whether the aetiology, management, and outcomes of acute heart failure in Africa have changed during this period remain scarce.

Added value of this study

THESUS-HF II, comprising more than 1500 patients from 17 African countries, extends the existing evidence by providing a contemporary assessment of the changing aetiological profile, management, and outcomes of acute heart failure in Africa. Hypertensive heart disease remained the leading contributor, although its proportion was lower than in the original THESUS-HF registry; the proportion attributed to ischaemic heart disease was higher, and cardiomyopathy was also common. Patients continue to present at a relatively young age, with near-equal sex distribution and a high proportion of de novo heart failure. The findings extend previous evidence by showing that guideline-directed medical therapies were commonly prescribed (although target doses were reached in fewer than half of patients), access to advanced cardiac diagnostics and interventions varied across participating hospitals, and 30-day and 180-day mortality was high in this relatively young cohort.

Implications of all the available evidence

The available evidence suggests that acute heart failure in Africa is compatible with an evolving epidemiological profile, although differences in diagnostic ascertainment over time mean that the extent of any true transition remains uncertain. The findings support continued emphasis on heart failure prevention, including detection and management of hypertension, alongside improved access to appropriate diagnostic services, guideline-directed medical therapy, specialist cardiac care where indicated, and post-discharge follow-up. Future research should move beyond broad continental estimates towards regional and country-specific analyses that can inform pragmatic, resource-sensitive strategies to improve heart failure care and outcomes in Africa.

Erwachsene mit [Down-Syndrom](#) (Trisomie 21) erreichen heute dank besserer medizinischer Versorgung und Förderung eine durchschnittliche Lebenserwartung von rund 60 Jahren und älter.

Gesundheitliche Herausforderungen im Alter

- **Alzheimer-Demenz:** Erwachsene mit Down-Syndrom haben ein stark erhöhtes Risiko, im Laufe ihres Lebens (oft früher als die Allgemeinbevölkerung) an Alzheimer zu erkranken. Dies gilt heute als eine der häufigsten gesundheitlichen Herausforderungen im höheren Alter.
- **Weitere Risiken:** Häufiger treten auch Schilddrüsenunterfunktionen, Seh- und Hördefizite, Schlafapnoe oder Gelenkprobleme auf.
- **Lebenslange Förderung:** Auch im Erwachsenenalter sind medizinische Vorsorge, gezielte kognitive Förderung und soziale Teilhabe essenziell für die Lebensqualität.



Natural history and clinical impact of epilepsy in adults with Down syndrome: a multicentre clinical study

Late-onset
myoclonic
epilepsy in
Downs (LOMED)

Unappreciated,
difficult to
diagnose,
associated with
Alzheimer's
disease.

Summary

Background As individuals with Down syndrome age, they face high risks of Alzheimer's disease and epilepsy. With symptomatic Alzheimer's disease, late-onset myoclonic epilepsy in Down syndrome (LOMEDS) often emerges. We aimed to examine how epilepsy develops in Down syndrome, its timing relative to Alzheimer's disease symptom onset, and its effect on prognosis.

Methods We conducted a multicentre, observational, longitudinal study across seven international cohorts with an aggregate observation window from Oct 24, 2012, to July 28, 2025. We included adults with Down syndrome aged at least 18 years and with at least one longitudinal clinical assessment. Alzheimer's disease staging was done by clinical consensus. Active epilepsy required an epilepsy diagnosis plus ongoing antiseizure medication or at least one seizure within the past 5 years. We analysed active epilepsy prevalence, incidence and cumulative incidence, its timing with respect to symptomatic Alzheimer's disease, and its effect on survival and cognitive trajectories as well as electroencephalogram (EEG) abnormalities.

Findings We included 4804 adults with Down syndrome (mean age 43 years [SD 13]): 3238 (67·4%) were cognitively stable, 267 (5·6%) had non-degenerative cognitive decline, 321 (6·7%) had prodromal Alzheimer's disease, and 978 (20·3%) had Alzheimer's disease dementia. Intellectual disability was mild in 1020 (24·6%) participants, moderate in 2352 (56·7%), and severe to profound in 779 (18·8%). Active epilepsy prevalence was 145·2 per 1000 adults with Down syndrome overall but significantly increased with age, particularly with symptomatic Alzheimer's disease, when epilepsy manifested mostly as myoclonic or tonic-clonic seizures. Cumulative incidence of epilepsy increased linearly after symptomatic Alzheimer's disease, from 9·5% (95% CI 7·8–11·3) at diagnosis to 56·9% (51·7–61·7) after 9 years. Risk of epilepsy increased with time since Alzheimer's disease diagnosis (adjusted odds ratio 1·33 per year [95% CI 1·22–1·45]; $p<0·0001$), severe-to-profound intellectual disability (2·14 per year [1·25–3·70]; $p=0·0057$), and APOE $\epsilon 4$ carriership (1·61 per year [1·04–2·49]; $p=0·034$), independent of age. LOMEDS was associated with increased mortality (hazard ratio 2·10 [95% CI 1·57–2·82]; $p<0·0001$), and faster cognitive decline. Interictal EEG abnormalities showed little diagnostic utility.

Interpretation Epilepsy increases sharply after symptomatic Alzheimer's disease onset in people with Down syndrome. The association of epilepsy with reduced survival and accelerated cognitive decline underscores the need for targeted preventive and therapeutic strategies against Alzheimer's disease-related epileptogenesis and hyperexcitability.

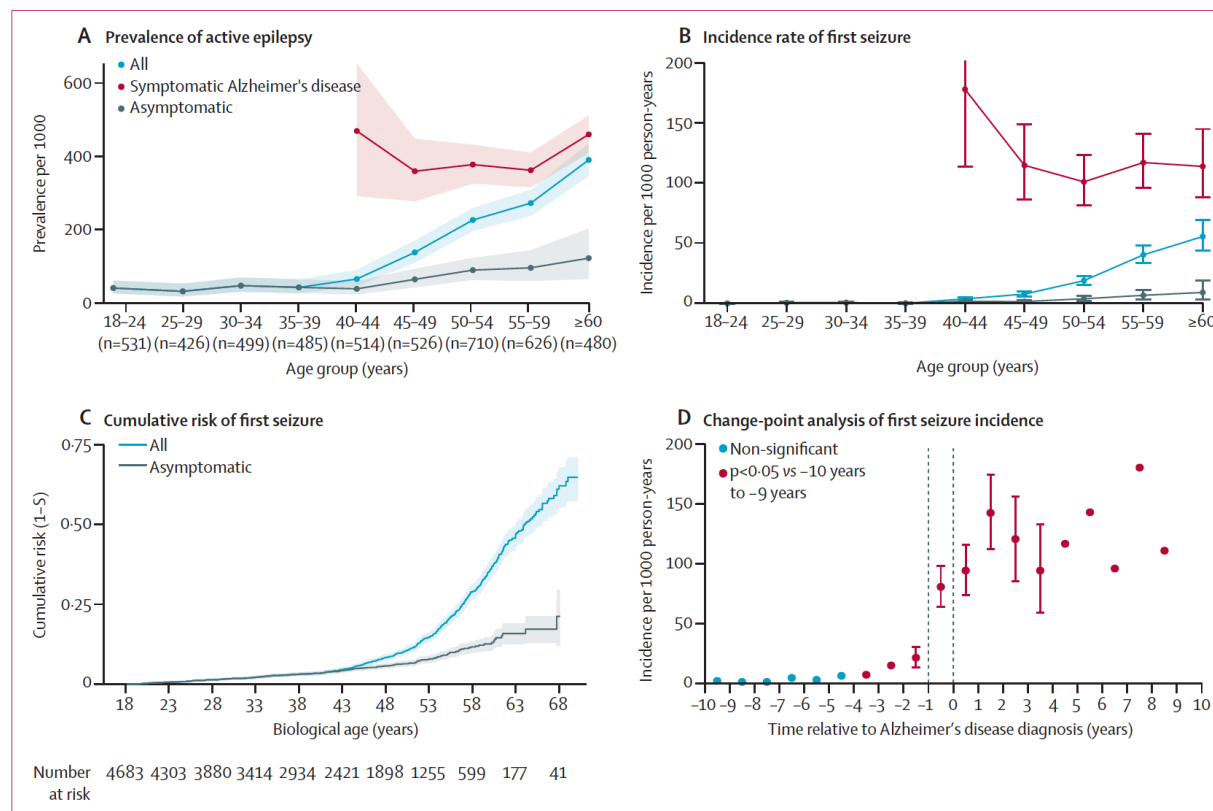


Figure 1: Epilepsy across the adult Down syndrome lifespan

(A) Cross-sectional age-specific prevalence of active epilepsy at last visit, per 1000 individuals with Down syndrome with exact Clopper-Pearson 95% CIs by age group. Symptomatic Alzheimer's disease includes prodromal or dementia-stage Alzheimer's disease at last visit; asymptomatic includes cognitively stable or uncertain non-neurodegenerative. (B) Incidence rate of first seizure per 1000 person-years by age group with exact Poisson 95% CIs. Symptomatic Alzheimer's disease includes participants whose first seizure occurred from 1 year before Alzheimer's disease diagnosis onwards; asymptomatic includes participants whose first seizure occurred more than 1 year before Alzheimer's disease diagnosis or in individuals never diagnosed with Alzheimer's disease. (C) Kaplan-Meier cumulative risk of first seizure from age 18 years. All indicates complete follow-up; asymptomatic includes participants censored from 1 year before Alzheimer's disease diagnosis onwards or end of follow-up if no Alzheimer's disease diagnosis. (D) Change-point analysis of first seizure incidence using annual intervals from -10 years to +10 years relative to Alzheimer's disease diagnosis; reference interval -10 years to -9 years; red points indicate $p < 0.05$ versus reference; blue dotted line marks the operative threshold of 1 year before Alzheimer's disease diagnosis onwards; points are omitted when fewer than 20 person-years at risk and CIs are omitted when fewer than 20 events are recorded. Shaded areas and error bars show 95% CIs.

	Overall (n=4804)	Cognitively stable (n=3238)	Non-neurodegenerative cognitive decline (n=267)	Prodromal Alzheimer's disease (n=321)	Alzheimer's disease dementia (n=978)	p value	q value	Effect size
Age at visit, years	44.42 (32.42–54.19)	37.31 (28.42–46.34)	48.89 (39.71–54.72)	54.67 (51.75–58.78)	57.37 (53.08–61.18)	<0.0001	<0.0001	$\eta^2=0.424$
Sex								
Male	2489/4804 (52%)	1740/3238 (54%)	144/267 (54%)	172/321 (54%)	433/978 (44%)	<0.0001	<0.0001	V=0.077
Female	2315/4804 (48%)	1498/3238 (46%)	123/267 (46%)	149/321 (46%)	545/978 (56%)	..	..	..
Intellectual disability								
Mild	1020/4151 (25%)	804/2742 (29%)	22/236 (9%)	57/276 (21%)	137/897 (15%)	<0.0001	<0.0001	V=0.135
Moderate	2352/4151 (57%)	1529/2742 (56%)	141/236 (60%)	160/276 (58%)	522/897 (58%)	..	..	..
Severe or profound	779/4151 (19%)	409/2742 (15%)	73/236 (31%)	59/276 (21%)	238/897 (27%)	..	..	..
Active epilepsy at last visit	699/4804 (15%)	157/3238 (5%)	28/267 (10%)	55/321 (17%)	459/978 (47%)	<0.0001	<0.0001	V=0.473
History of febrile seizures	45/1358 (3%)	24/724 (3%)	2/77 (3%)	5/100 (5%)	14/457 (3%)	0.76	>0.99	V=0.028
History of CNS infection	18/1324 (1%)	10/699 (1%)	0	2/97 (2%)	6/451 (1%)	0.75	>0.99	V=0.033
History of traumatic brain injury	24/1324 (2%)	10/698 (1%)	2/76 (3%)	3/97 (3%)	9/453 (2%)	0.41	>0.99	V=0.037
Data are median (IQR) for age and n/N (%) for categorical variables. Demographic and clinical characteristics by cognitive status of all participants (tables stratified by cohort are available in appendix pp 13–16). Multiplicity was controlled using Bonferroni-adjusted q-values. Effect sizes are reported for all participants: η^2 for age at visit (Kruskal-Wallis) and Cramér's V for categorical variables (interpretation: <0.10 small, 0.10–0.30 moderate, and >0.30 large). Holm-adjusted pairwise comparisons (Wilcoxon rank-sum for age; Fisher's exact for binary variables; Fisher's exact on R $\times$ 2 for multi-category intellectual disability) for variables with q<0.05 are reported in the appendix (p 12). Active epilepsy refers to status at the last visit.								
Table: Participant demographics								

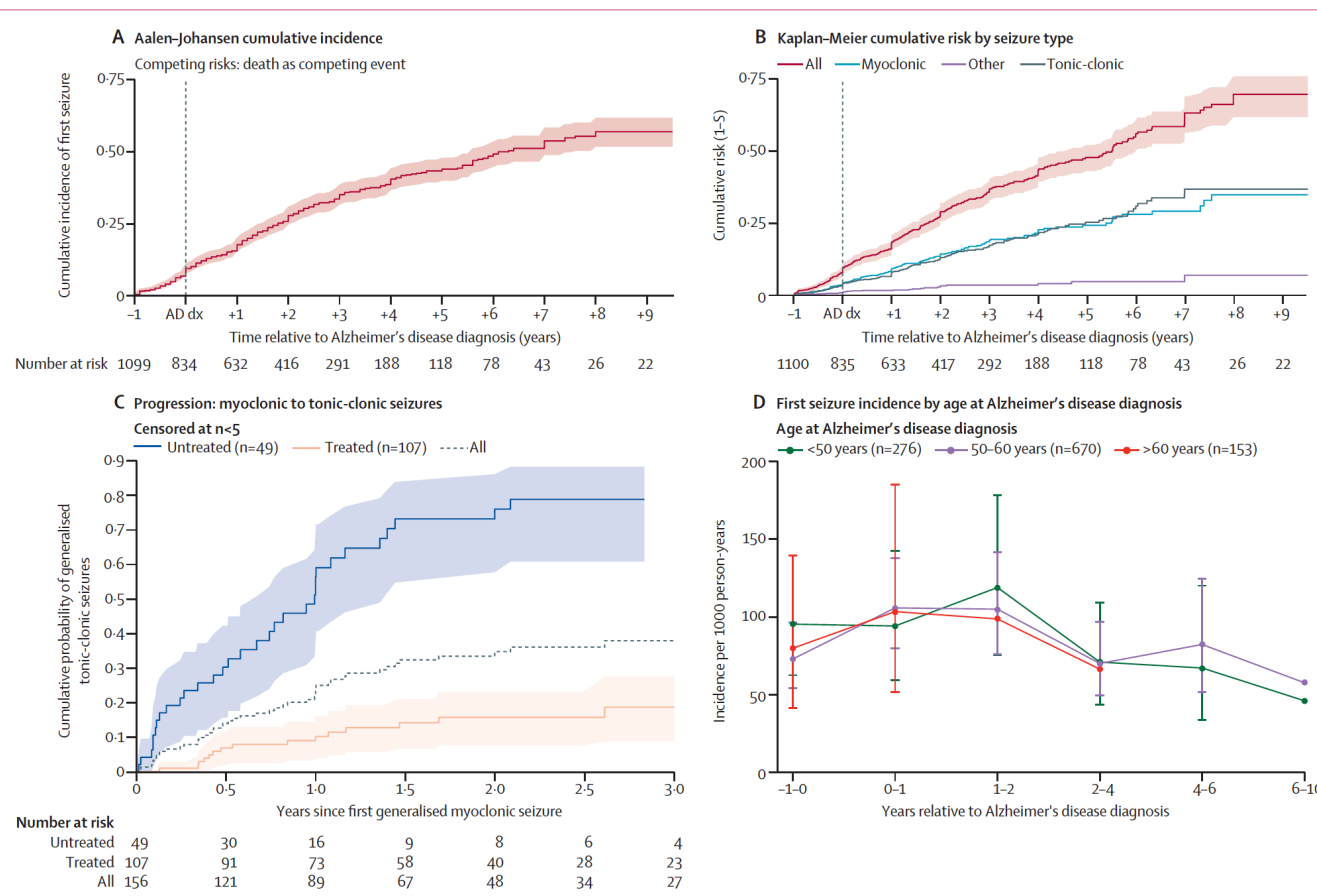


Figure 2: Natural history and semiology of epilepsy arising in parallel to symptomatic Alzheimer's disease (LOMEDS)

All analyses use a symptomatic Alzheimer's disease window defined as 1 year before Alzheimer's disease onwards. Time 0 indicates date of Alzheimer's disease diagnosis and curves are shown until fewer than 20 individuals remain at risk (except for panel C). (A) Aalen-Johansen cumulative incidence of first seizure from 1 year before Alzheimer's disease onwards, treating death as a competing event. Numbers at risk refer to individuals entering the symptomatic window without a previous seizure. (B) Kaplan-Meier cumulative risk of first seizure from 1 year before Alzheimer's disease onwards, overall (red) and stratified by seizure type at first event: generalised myoclonic (blue), tonic-clonic (grey), and other (purple). Numbers at risk refer to the overall cohort. (C) Kaplan-Meier cumulative probability of progression from a first generalised myoclonic seizure to a generalised tonic-clonic seizure, in treated (orange) and untreated (blue) individuals, with overall curve (dashed). Censored when fewer than five individuals remain at risk, given the smaller subset analysed in this panel. (D) Incidence rate of first seizure per 1000 person-years by time interval relative to Alzheimer's disease diagnosis, stratified by age at Alzheimer's disease diagnosis (<50 years, 50-60 years, >60 years). Points are shown only when at least three events are recorded and CIs when at least ten events. LOMEDS=late-onset myoclonic epilepsy in Down syndrome. Shaded areas and error bars show 95% CIs. AD dx=Alzheimer's disease diagnosis.

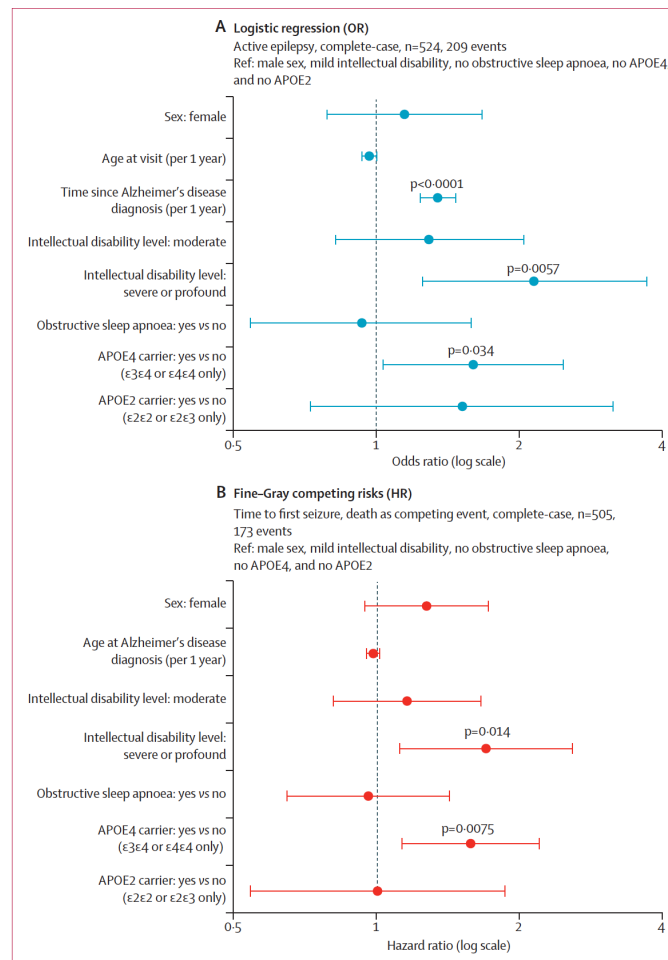


Figure 3: Predictors of active epilepsy in Down syndrome with symptomatic Alzheimer's disease
(A) Multivariable logistic regression showing adjusted ORs for active epilepsy. (B) Multivariable Fine-Gray competing risks model showing adjusted sub-distribution HRs for time to first seizure from 1 year before Alzheimer's disease diagnosis onwards, with death as a competing event. Both models include sex, age at Alzheimer's disease diagnosis (per 1 year), intellectual disability level, time since Alzheimer's disease diagnosis (per 1 year), obstructive sleep apnoea, and APOE4 carrier status ($\epsilon 3\epsilon 4$ or $\epsilon 4\epsilon 4$ vs remainder). Obstructive sleep apnoea was coded as positive only when confirmed by polysomnography. Dashed line marks an OR or HR of 1, the x-axis is on a log scale, and error bars show 95% CIs. HR=hazard ratio. OR=odds ratio.

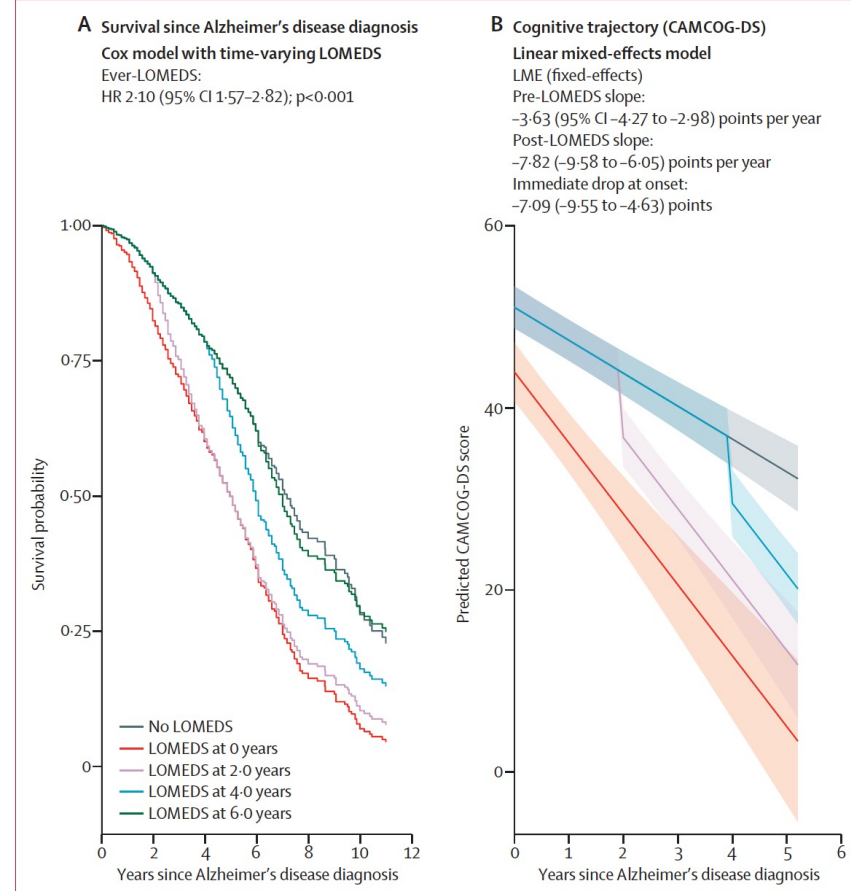


Figure 4: Survival after Alzheimer's disease diagnosis and cognitive trajectory around LOMEDS in adults with Down syndrome

(A) Predicted survival curves from a Cox proportional hazards model with time-varying LOMEDS exposure, showing five scenarios defined by timing of first seizure onset relative to Alzheimer's disease diagnosis (0–6 years); LOMEDS window: 1 year before Alzheimer's disease diagnosis onwards. (B) Predicted CAMCOG-DS trajectories from a linear mixed-effects broken-stick model, showing the pre-LOMEDS slope, immediate drop at seizure onset, and accelerated post-LOMEDS decline for four onset scenarios; ribbons represent 95% CIs around fixed-effect means. CAMCOG-DS=Cambridge Cognitive Examination for Older Adults with Down Syndrome. HR=hazard ratio. LOMEDS=late-onset myoclonic epilepsy in Down syndrome.

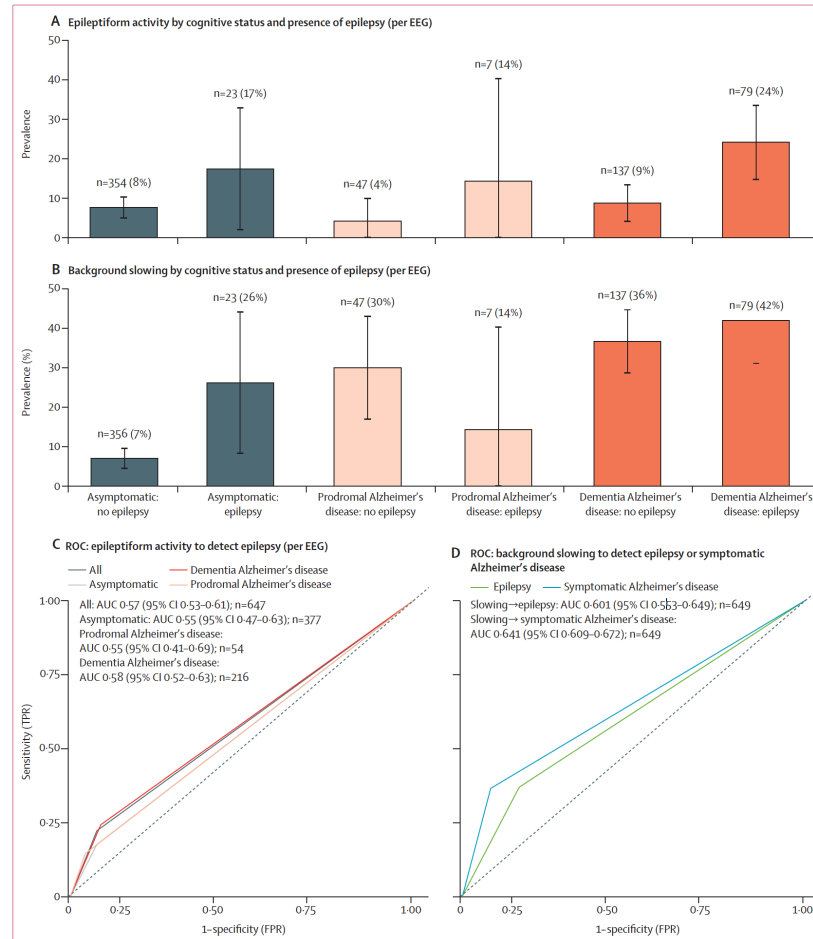


Figure 5: EEG markers by Alzheimer's disease stage and diagnostic performance (per EEG)

(A) IED prevalence. Proportion of EEGs with IEDs across cognitive strata (asymptomatic, prodromal Alzheimer's disease, and Alzheimer's disease dementia) and by epilepsy status at the EEG (yes indicates EEG performed on or after the date of first seizure if present, and no indicates otherwise); bars show point estimates with two-sided 95% Wald CIs, with N as the total EEGs per bar (denominator). (B) Background slowing prevalence (95% Wald CIs, with N as the total EEGs per bar [denominator] annotated). The y-axis is capped at 50% where indicated. (C) IED as a classifier of epilepsy. ROC curves (overall and by cognitive stratum) showing the ability of IED presence to discriminate EEGs of individuals with epilepsy (performed on or after the first seizure) from those of individuals without epilepsy (performed before the first seizure or in patients who never had a seizure). AUCs with 95% CIs are shown; the diagonal represents no discrimination (AUC=0.5). (D) Background slowing performance. ROC curves for background slowing predicting epilepsy (overall) and symptomatic Alzheimer's disease (prodromal Alzheimer's disease or Alzheimer's disease dementia vs asymptomatic). Figure shows AUCs with 95% CIs; diagonal reference shown. AUC=area under the ROC curve. EEG=electroencephalogram. FPR=false positive rate. IED=interictal epileptiform discharge. LOMEDS=late-onset myoclonic epilepsy in Down syndrome. ROC=receiver operating characteristic. TPR=true positive rate (sensitivity).

Late-onset myoclonic epilepsy in Downs (LOMED)

Research in context

Evidence before this study

We searched MEDLINE (PubMed; from inception to Oct 1, 2025); abstracts from the International League Against Epilepsy, the Alzheimer's Association, and Trisomy 21 Research Society; hand searched reference lists; and performed forward citation tracking. No language limits were applied; non-English articles were translated as needed. Search terms combined controlled vocabulary and free text for three concepts: population ("Down syndrome", "Down's syndrome", "trisomy 21"; epilepsy ("epilepsy", "seizure*", "myoclon*", "late-onset myoclonic epilepsy of Down syndrome", "LOMEDS"), and epidemiology or clinical impact ("prevalence", "incidence", "risk", "age of onset", "hazard*", "survival", "mortality", "cognit*", "functional decline"), with Alzheimer's modifiers ("Alzheimer*", "dementia", "amyloid", "Down syndrome-associated Alzheimer*", "DSAD"). We included observational studies reporting epilepsy prevalence, incidence, or age-specific risk in adults with Down syndrome; studies on the temporal relation between symptomatic Alzheimer's disease and epilepsy; and studies reporting clinical consequences. We excluded single case reports or series (<10 participants) and paediatric-only reports.

Previous work suggested a high overall epilepsy burden with a late-adult peak, but was constrained by small samples, few older adults, and non-standard Alzheimer's disease ascertainment. Consequently, the nature and timing of epilepsy relative to Alzheimer's disease, its clinical and prognostic effect, and its potential as a disease activity marker or therapeutic target remain unclear.

Added value of this study

We report the largest multicentre characterisation of adult epilepsy in Down syndrome (n=4804), with standardised symptomatic Alzheimer's disease assessment (n=1299 with symptomatic Alzheimer's disease), spanning the full adult life

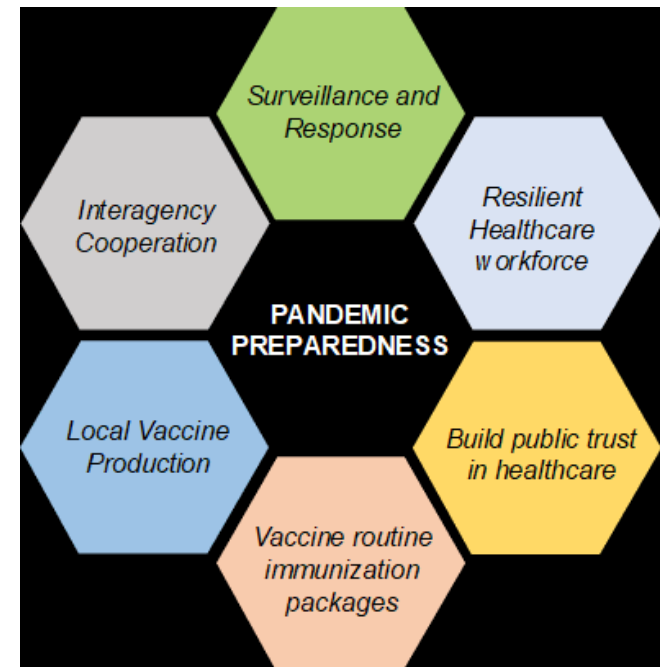
course using time-to-event analyses. We deliver granular, age-specific, and Alzheimer's disease-specific estimates of epilepsy burden and the timing of seizure emergence.

We show that while baseline epilepsy burden in early adulthood is higher than in the general population, it rises sharply with symptomatic Alzheimer's disease when late-onset myoclonic epilepsy in Down syndrome (LOMEDS) emerges. LOMEDS is driven by time since Alzheimer's disease symptom onset rather than chronological age and predicts worse cognition and earlier mortality (hazard ratio 2.10 [95% CI 1.57–2.82]). Scalp electroencephalography has low diagnostic accuracy (area under the curve 0.57).

Implications of all the available evidence

This study establishes LOMEDS as a dominant, clinically distinctive, and prognostically meaningful comorbidity of Alzheimer's disease in Down syndrome. The tight temporal coupling to symptomatic onset, characteristic semiology, and strong associations with survival and cognitive decline identify LOMEDS as both a marker of disease activity and a potentially modifiable mediator of progression. Clinically, adult Down syndrome services should implement systematic seizure surveillance across adulthood and adopt age-specific and Alzheimer's disease stage-informed management pathways. Scientifically, the findings extend evidence from sporadic and autosomal-dominant Alzheimer's disease and position Down syndrome-associated Alzheimer's disease as a uniquely informative model of Alzheimer's disease-related epileptogenesis. Our findings offer concrete parameters for trial design (enrichment around the Alzheimer's disease clinical transition and seizure-related endpoints) and should encourage prospective, biomarker-integrated cohort studies to detect network hyperexcitability before overt seizures and test targeted anti-hyperexcitability interventions, transforming a high-risk marker into a targetable pathway for disease modification.

Pandemic Readiness (Pandemievorsorge) beschreibt die strategische Vorbereitung auf weltweite Krankheitsausbrüche, um Infektionswellen frühzeitig zu erkennen, abzuflachen und die kritische Infrastruktur zu schützen. Nach den Erfahrungen mit COVID-19 hat sich der globale Fokus grundlegend verändert: Der Schwerpunkt liegt heute auf **globaler Chancengleichheit (Equity)**, digitaler Echtzeit-Überwachung und der Vernetzung von Human-, Tier- und Umweltgesundheit (One-Health-Ansatz)



The NUS–Lancet PRIME Commission: transforming pandemic readiness for equity

Positioning statement

The National University of Singapore (NUS)–Lancet Pandemic Readiness through Institutions, Mobilising Communities, and Equity (PRIME) Commission redefines pandemic readiness and offers a practical blueprint for whole-of-society pandemic planning and implementation. Drawing on the hard lessons of the COVID-19 pandemic, the Commission brings together evidence from 20 countries, including interviews with members of diverse communities and groups, future scenarios, and epidemiological modelling. By integrating lived experience with systems analysis and forward-looking evidence, the Commission sets out how governments, institutions, and communities can move from formal plans to people-centred protection across all stages of a health crisis.

PRIME turns the often-invoked whole-of-society idea into a structured framework for action across sectors and levels of governance. Applying PRIME's recommendations has the potential not only to save lives, but also to strengthen institutions and community trust for future health emergencies and other 21st-century crises.

Recommendations organised by foundational blocks

Centre protection on people and communities

- 1 Resource and embed community participation and inclusion. Establish funded participation mechanisms, engage trusted community actors, and remove legal, administrative, and digital barriers that prevent equitable protection.
 - Lead actors: national and subnational governments, civil society, and communities
 - Implementation marker: funded participation platform operating and informing readiness decisions

Prevent, anticipate, and detect

- 2 Operationalise One Health and multihazard readiness. Create crossgovernment coordination mechanisms linking human, animal, environmental, and disaster-risk systems. Strengthen surveillance and cross-border cooperation.
 - Lead actors: ministries of health, agriculture, and environment, and regional bodies
 - Implementation marker: operational One Health coordination platform and routine joint risk assessment
- 3 Embed readiness in the social conditions that enable protection. Integrate social protection, essential services, and health promotion into preparedness planning.
 - Lead actors: ministries of health and social protection
 - Implementation marker: preparedness plans include funded social protection measures and delivery triggers

Governance for trust and system function

- 4 Strengthen crossgovernment leadership, universal health coverage, health system resilience, and legal frameworks. Establish permanent whole-of-government readiness structures, strengthen universal health coverage through resilient primary care and workforce capacity, and update rights-based emergency laws.
 - Lead actors: heads of government and ministries of health, finance, and justice
 - Implementation marker: operational cross-government readiness mechanism
- 5 Build trust through continuous communication and action against misinformation. Institutionalise two-way communication and coordinated responses to misinformation.
 - Lead actors: governments, public health institutes and civil society
 - Implementation marker: permanent risk communication and misinformation response systems established

Invest, learn, and adapt

- 6 Secure stable, accountable, and predictable financing. Protect and sustain investments in health, social protection, and readiness through transparent financing and accountability mechanisms.
 - Lead actors: ministries of finance and health
 - Implementation marker: funded readiness plan and public financing accountability mechanism in operation
- 7 Measure effectiveness and adapt in real time. Strengthen independent scientific advice, monitor protection in practice, and establish mechanisms for rapid course correction.
 - Lead actors: governments, national public health institutes, and scientific advisory bodies
 - Implementation marker: revised indicators adopted and used to inform policy adjustments

Recover and plan for a better future

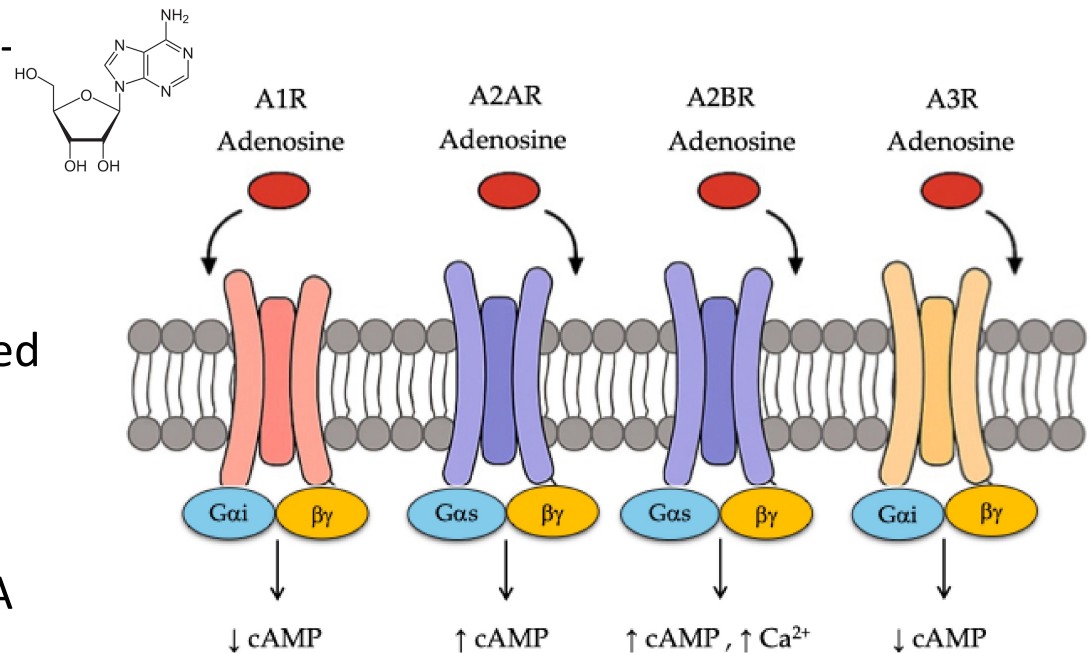
- 8 Recover through transformation and community participation. Institutionalise postcrisis learning, restore essential services, strengthen mental health and workforce wellbeing, and support long-term recovery for those most affected by harm.
 - Lead actors: governments across health, education, social protection, and finance sectors
 - Implementation marker: recovery mechanism established with public reporting and funded implementation plans

Recalibrate regional and global governance

- 9 Strengthen regional countermeasure ecosystems. Expand regional manufacturing, diversify supply chains, strengthen regulatory cooperation, and improve equitable access to vaccines, diagnostics, and therapeutics.
 - Lead actors: regional organisations, development banks, manufacturers, and regulatory authorities
 - Implementation marker: financed regional manufacturing or procurement initiative underway
- 10 Recalibrate regional and global governance around subsidiarity, equity, and accountable leadership. Clarify responsibilities across levels of governance, strengthen equitable access arrangements, and establish independent monitoring and accountability for pandemic readiness and equity.
 - Lead actors: WHO, WHO member states, regional organisations, and global financing institutions
 - Implementation marker: agreed monitoring mechanism and implementation roadmap in place

Adenosine receptors (ARs) are G protein-coupled receptors that are widely expressed across tissues, traditionally associated with cardiovascular, neurological, and immune regulation. Recent studies, however, have highlighted their non-canonical functions, revealing critical roles in metabolism, immunometabolism, and epigenetic regulation. AR subtypes, particularly A2A and A2B, modulate glucose and lipid metabolism, mitochondrial activity, and energy homeostasis.

In immune cells, AR signaling influences metabolic reprogramming and polarization through key regulators such as mTOR, AMPK, and HIF-1 α , contributing to immune tolerance or activation depending on the context. Additionally, ARs have been implicated in epigenetic modulation, affecting DNA methylation, histone acetylation, and non-coding RNA expression via metabolite-sensitive mechanisms.



Der **G $\beta\gamma$ -Komplex** (G-Beta-Gamma-Komplex) ist eine eng gebundene, dimere Proteineinheit, die als essenzieller Bestandteil von **heterotrimeren G-Proteinen** eine zentrale Rolle in der zellulären Signaltransduktion einnimmt. Zusammen mit der Alpha-Untereinheit (G α) vermittelt er die Signalweiterleitung von **G-Protein-gekoppelten Rezeptoren (GPCRs)** ins Innere der Zelle.

Aktivierungsmechanismus

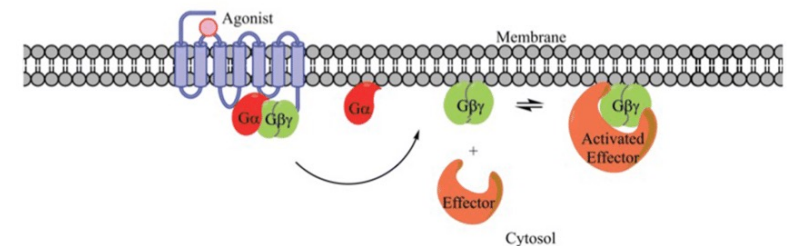
Ruhezustand: Im inaktiven Zustand liegt das G-Protein als Heterotrimer (bestehend aus G α , G β und G γ) vor, wobei G α an GDP gebunden ist.

Aktivierung: Bindet ein extrazellulärer Ligand an den GPCR, fungiert der Rezeptor als Guaninnukleotid-Austauschfaktor (GEF). Er veranlasst G α , GDP gegen GTP auszutauschen.

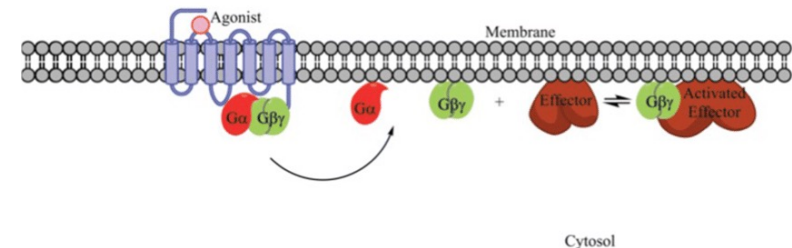
Dissoziation: Durch die Konformationsänderung **dissoziiert die GTP-gebundene G α -Untereinheit vom G $\beta\gamma$ -Komplex**. Beide Einheiten liegen nun frei vor und können unabhängig voneinander oder gemeinsam spezifische nachgeschaltete Effektormoleküle regulieren.

Mechanisms of G $\beta\gamma$ activation of effectors

Membrane Recruitment:



Allosteric Activation:



Der G $\beta\gamma$ -Komplex kann sowohl kanonische als auch nicht-kanonische Signalwege vermitteln.



Targeting an atypical G protein–coupled receptor signaling pathway for cardiac fibrosis therapy

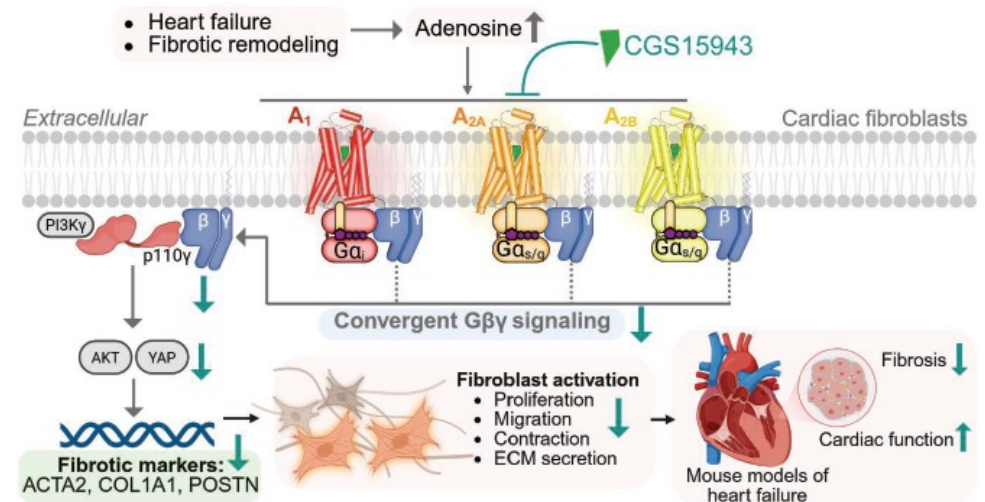
INTRODUCTION: Cardiac fibrosis contributes to the progression of diverse heart diseases and independently predicts mortality. Yet no approved therapy directly targets fibrotic remodeling in the heart. Animal models remain essential for validation but cannot support compound screening at scale, and primary human cardiac fibroblasts are available only in limited quantities. These constraints create a need for scalable phenotypic screening platforms built on human cells.

RATIONALE: We developed a multidimensional drug discovery platform based on human induced pluripotent stem cells (iPSCs). Reporter iPSC-derived cardiac fibroblasts, in which fluorescence tracks myofibroblast activation, provided the efficacy readout, whereas iPSC-derived cardiomyocytes and endothelial cells served as counterscreens for toxicity. Screening ~4000 bioactive compounds at seven doses identified CGS15943 (CGS), a nonselective antagonist of adenosine receptors (ARs), as the leading antifibrotic compound without overt cardiotoxicity. ARs are G protein–coupled receptors (GPCRs), and three subtypes are expressed in cardiac fibroblasts. These subtypes couple to distinct and sometimes opposing G α proteins, so canonical signaling did not readily explain the antifibrotic activity of CGS. Resolving this required measuring G protein activity directly in primary human cardiac fibroblasts, where conventional assays lack the sensitivity to detect signaling induced by endogenous receptors. We therefore applied biosensors that overcome this limitation together with pharmacological and genetic perturbations as well as multiomic profiling to define how CGS acts.

RESULTS: CGS suppressed fibroblast activation induced by multiple profibrotic stimuli in iPSC-derived and primary human cardiac fibroblasts, activated fibroblasts from patients with cardiomyopathy, and engineered human heart tissues. The endogenous AR ligand adenosine, which is elevated in patients with heart failure, accumulated in the plasma of mice with pressure overload and in the supernatant of activated fibroblasts. All three AR subtypes were also up-regulated in mouse hearts and human cardiac fibroblasts during fibrotic remodeling.

We therefore asked how the individual subtypes contribute. Combined pharmacological or genetic blockade of all three suppressed fibroblast activation more effectively than blockade of any single subtype. Biosensor measurements showed that all three receptors converged on the release of free G $\beta\gamma$ (the $\beta\gamma$ subunits of heterotrimeric GTP-binding proteins) and that CGS blocked this shared response. Fibroblast-directed sequestration of G $\beta\gamma$ reduced cardiac fibrosis and improved function in vivo, establishing G $\beta\gamma$ as a functional mediator of the profibrotic response. Accordingly, CGS reduced fibrotic remodeling in the preventive mouse model and limited further fibrosis progression and functional decline in the therapeutic mouse model, and single-nucleus transcriptomics confirmed suppression of activated fibroblast states in the heart.

Mechanism of CGS15943 action in cardiac fibrosis. During heart failure progression, extracellular adenosine levels are elevated and promote cardiac fibrosis. CGS15943 simultaneously antagonizes multiple AR subtypes, which converge on G $\beta\gamma$ signaling, thereby down-regulating phosphoinositide 3-kinase γ (PI3K γ)–AKT and yes-associated protein (YAP) activity, reducing fibrotic gene expression and fibroblast activation, and ultimately attenuating fibrotic remodeling and improving cardiac function in mouse models of heart failure. ECM, extracellular matrix.



CONCLUSION: Individual AR subtypes have been reported to exert conflicting effects on fibrosis, and subtype-selective antagonism has produced inconsistent results. Our findings reconcile these observations by identifying $G\beta\gamma$, rather than the divergent canonical $G\alpha$ pathways of individual subtypes, as their shared profibrotic signal. Convergence of multiple ARs on $G\beta\gamma$ explains why simultaneous blockade is more effective than subtype-selective antagonism. The AR- $G\beta\gamma$ signaling axis therefore represents a druggable target for cardiac fibrosis and potentially for fibrosis in other organs.

Scientists heard a knock at the door. It was a pelican in need of help.



A recent quiet morning at a Florida marine research facility was interrupted by tapping at the back door.

A biologist walked over to investigate and found a brown pelican standing on the stoop and pecking at the glass with its long beak. It stood there patiently, as if waiting for help. A quick inspection revealed the pelican was injured.

Fishing line was wrapped around the pelican's right wing, and a double-barbed treble hook was stuck in the wing, restricting the bird's ability to fly. About a dozen cactus spines were lodged in its left foot.

When Annsli Hilton, a University of Miami research associate who works at the National Oceanic and Atmospheric Administration (NOAA) research facility, heard the commotion, she figured someone had brought in the injured bird. She was shocked to hear the pelican came on its own to the lab in Panama City.



While another biologist held the pelican's right wing, Hilton cut the roughly 6-foot-long fishing line with scissors. Her co-worker then snapped the fish hook with wire cutters. The hook's small barb was still lodged in the pelican's bone; Hilton carefully removed it with forceps.

She also removed the cactus spines, which she said the pelican probably picked up from cacti near the facility.

Hilton, 26, said she had never treated a pelican before but relied on techniques she uses while inserting tags into smalltooth sawfish, the fish she primarily studies. The pelican was calm throughout the procedure, which Hilton said took about five minutes but felt like an hour because of the unusual nature of the situation.

Her co-worker then carried the pelican to the basin, where the bird stretched and flapped its wings for a few minutes before flying away.