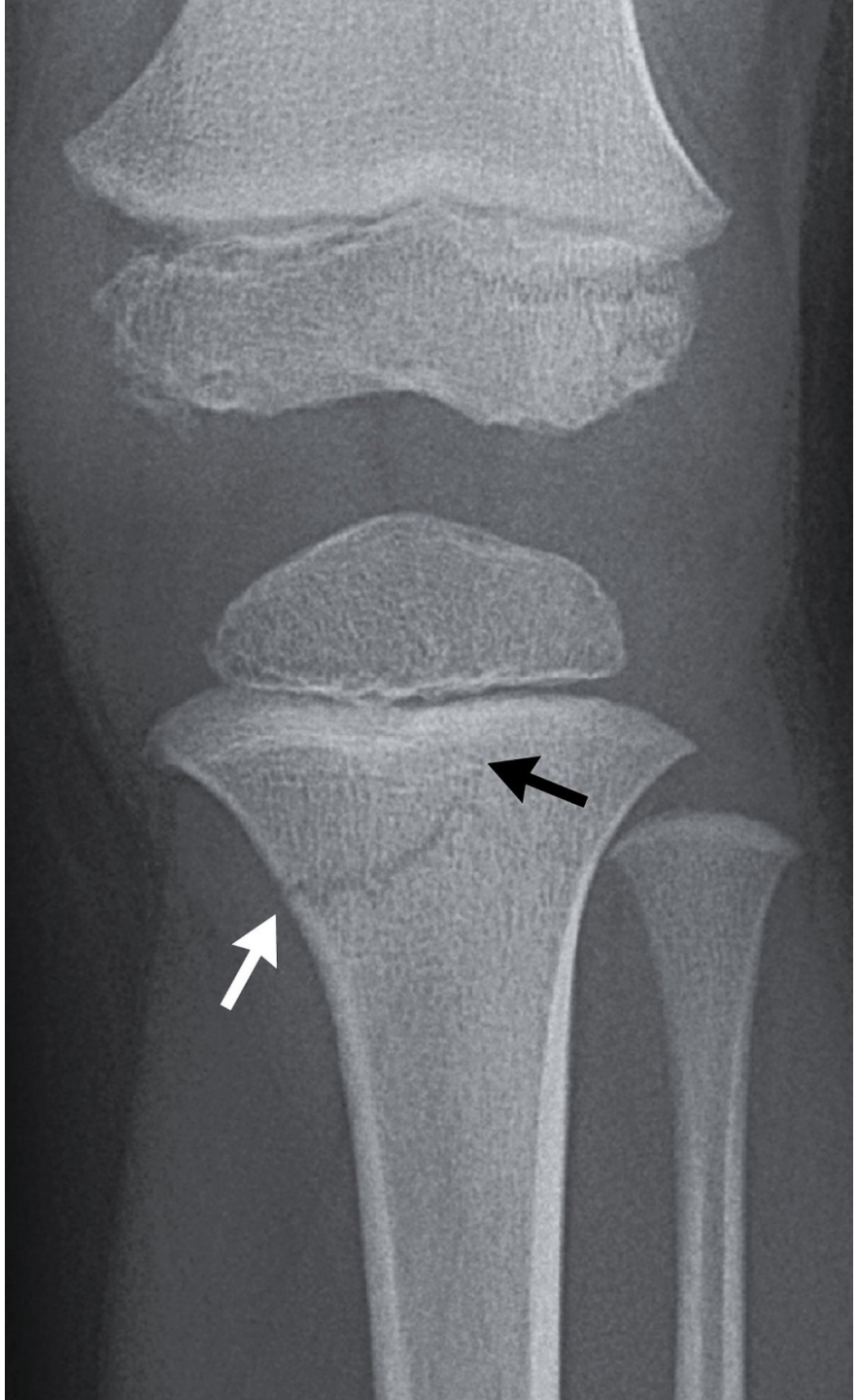
https://www.mdc-berlin.de/de/veroeffentlichungstypen/clinical-journal-club

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



The radiograph showed a nondisplaced fracture of the proximal tibial metaphysis extending up to the growth plate. A diagnosis of a trampoline fracture was made. Trampoline fractures in children typically manifest as transverse, proximal tibial fractures owing to compressive axial forces on the bone while bouncing. The risk of these injuries increases when a heavier person is also jumping and generating increased recoil of the trampoline. Growth-plate involvement in these fractures may result in altered limb growth.

Twisting around a planted foot

A previously healthy 4-year-old boy presented to the emergency department with leg pain and an inability to bear weight on his left side. While jumping on a trampoline with his father at home, he had leaped higher than usual, landed on his feet, and then felt the leg pain. Physical examination was notable for knee swelling and tenderness to palpation on the left side. Radiographs of the left tibia and fibula are shown. What is the most likely mechanism of this injury?

Avulsion of the patellar tendon

Bending of the bone

Blunt trauma

Compressive axial forces on the bone

Twisting around a planted foot

Chronic Hepatitis B: The Global Challenge & The Goal of Functional Cure

GLOBAL HEALTH CHALLENGE

Over 250 Million People
Affected Worldwide

Leading Cause of Liver Cancer

CURRENT STANDARD OF CARE (SOC)

Nucleos(t)ide Analogues

Often Requires Lifelong Therapy

Low Functional Cure Rate
(Typically ~1%)

THE GOAL: FUNCTIONAL CURE

Functional Cure:
Sustained **Undetectable HBsAg** (Viral Protein)
& Undetectable HBV DNA in Blood

At least **24 Weeks**
After Finite Course
of Treatment

- **HBsAg** (Undetectable)
- **HBV DNA** (Undetectable)

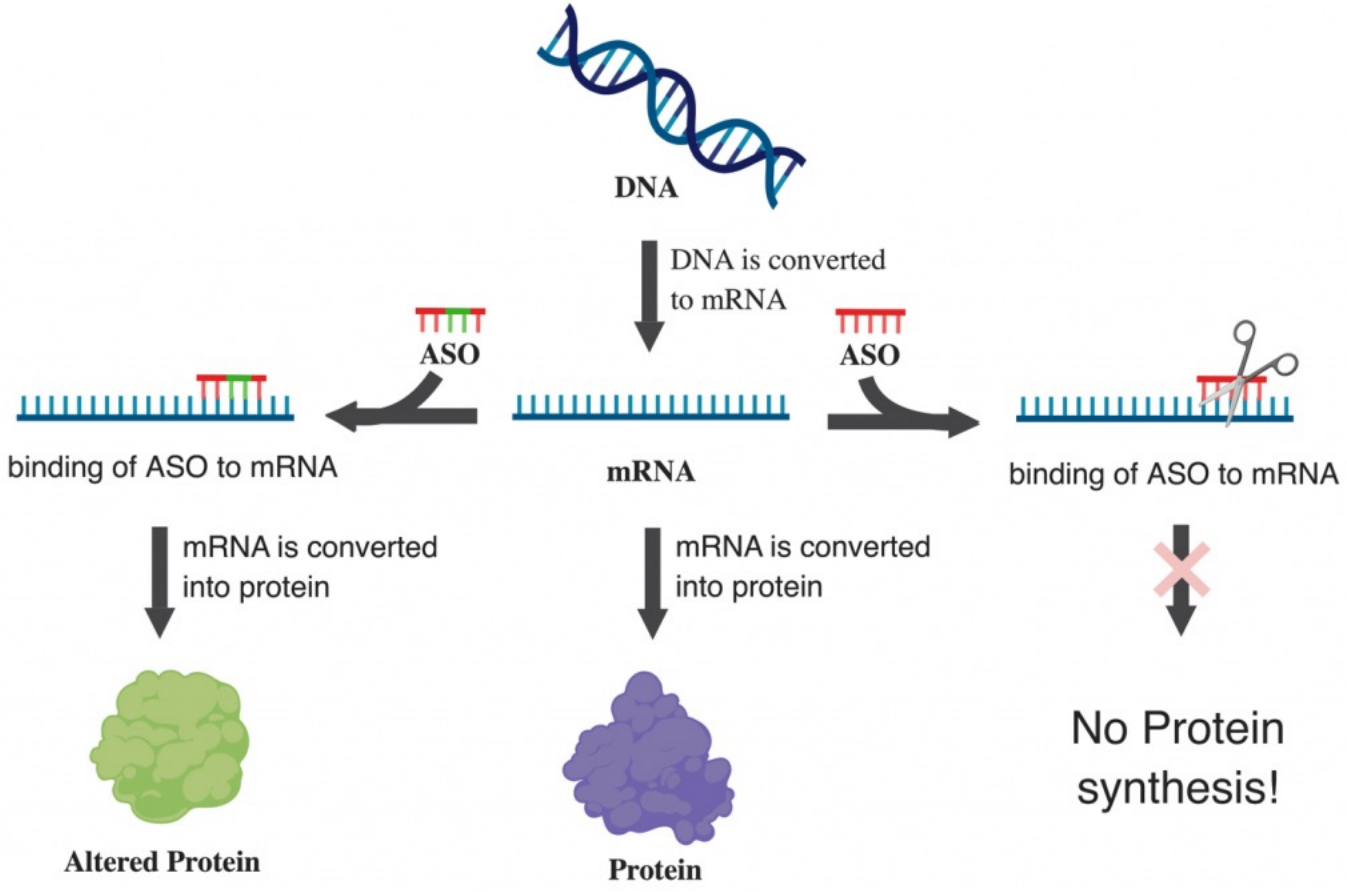
BENEFITS OF FUNCTIONAL CURE

Significant Reduction in Long-Term Liver Complications
(Including Liver Cancer)

Significant Reduction in All-Cause Mortality

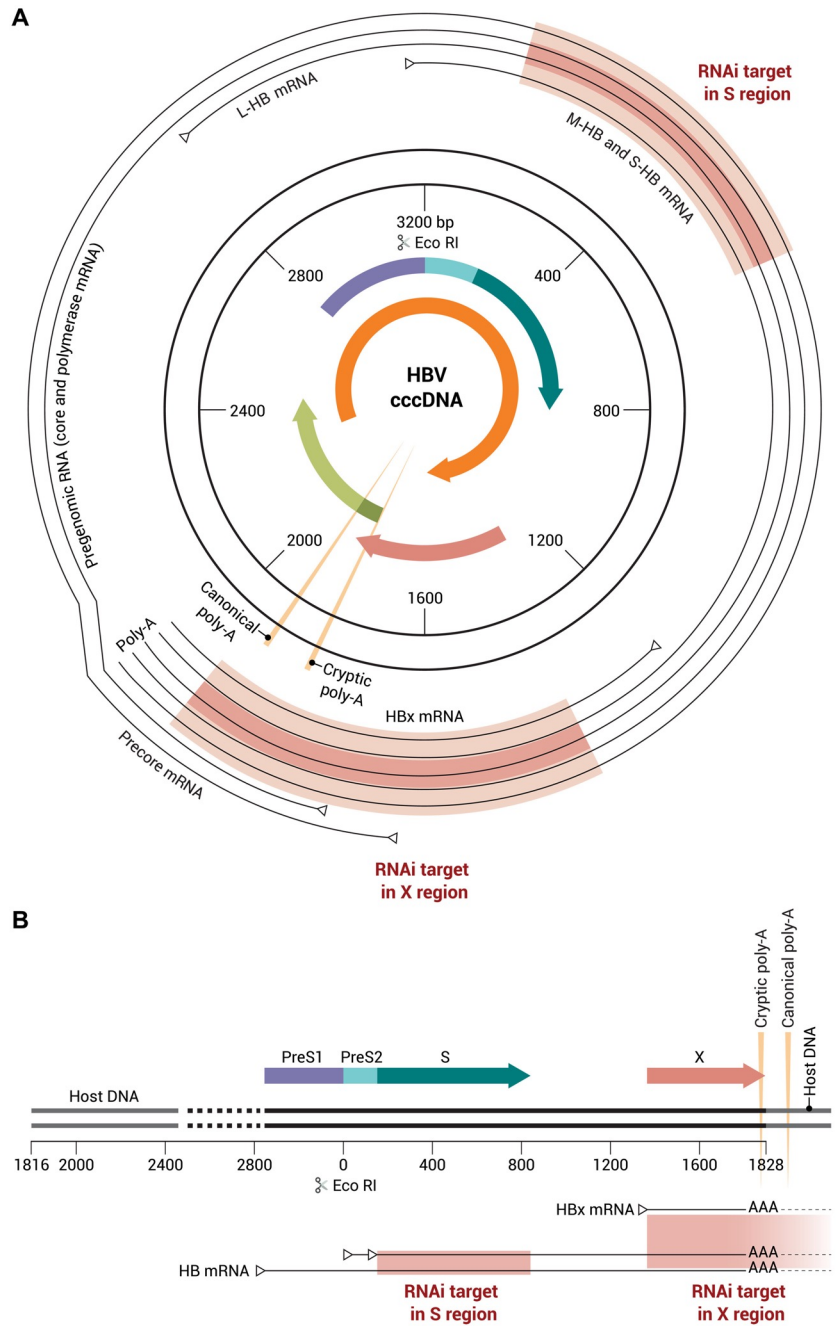
Improved Long-Term Health Outcomes

ASOs are short single stranded pieces of DNA that match the complementary sequence of a specific mRNA. Based on the type of chemical modifications, the ASO can have two different effects on the mRNA. Some modifications of ASOs trigger the destruction of the mRNA. This will result in the loss of the corresponding protein. Other modifications can mask only certain parts of the mRNA leading to a modified version of the protein.



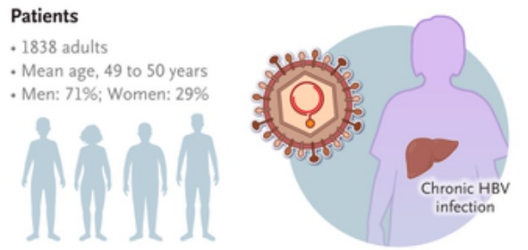
Bepirovirsen ist ein experimentelles Antisense-Oligonukleotid, das von GSK (GlaxoSmithKline) zur Behandlung von chronischer Hepatitis B (HBV) entwickelt wird. Es zielt darauf ab, virale RNAs abzubauen, um so das Hepatitis-B-Oberflächenantigen (HBsAg) zu senken.

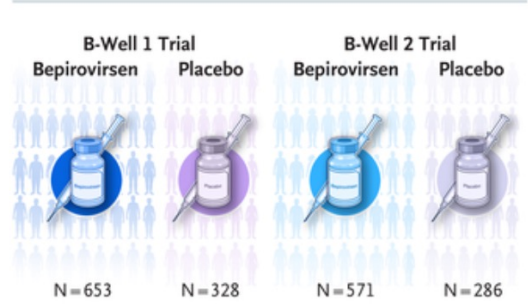
Wirksamkeit & "Funktionelle Heilung": In den globalen Phase-3-Studien (*B-Well 1* und *B-Well 2*) führte eine 24-wöchige subkutane Behandlung bei etwa 20 % der Patienten zu einer funktionellen Heilung. Dies bedeutet, dass sowohl die HBV-DNA als auch das Oberflächenantigen HBsAg auch Monate nach dem Absetzen aller Therapien nicht mehr nachweisbar waren.
Wirkmechanismus: Es ist das erste in der klinischen Erprobung befindliche Medikament, das nach einer zeitlich begrenzten Anwendung hohe Erfolgsquoten bei der Beseitigung des Oberflächenantigens erzielt. Dies könnte die bisher nötige, oftmals lebenslange Einnahme von Virustatika ablösen.
Zulassungsstatus: Bepirovirsen hat von der FDA den Status „Breakthrough Therapy“ und „Fast Track“ erhalten und befindet sich in der EU, Japan und China im Prüfverfahren.
Verträglichkeit: Zu den häufigsten Nebenwirkungen zählen Reaktionen an der Injektionsstelle, Hautrötungen und ein vorübergehender Anstieg von Leberwerten, der während des Abbaus viraler Proteine auftritt.

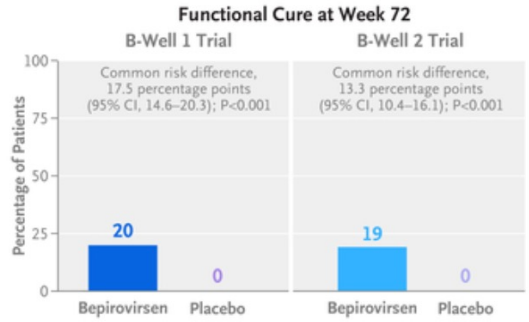


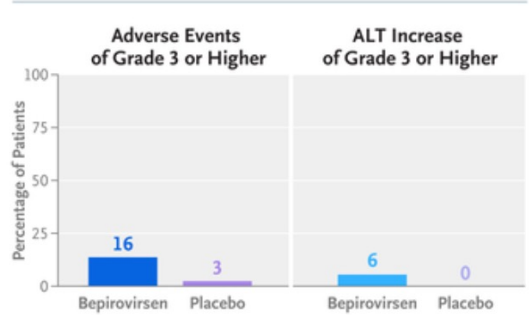
Phase 3 Results of Bepirovirsen Treatment for Chronic Hepatitis B Virus Infection

Treatment with bepirovirsen, an antisense oligonucleotide targeting hepatitis B virus (HBV) transcripts, has the potential to result in a functional cure, defined by at least 24 weeks of a sustained HBV DNA level below the lower limit of quantification (LLOQ) and hepatitis B surface antigen (HBsAg) loss after fixed-duration therapy. In two replicate, double-blind trials (B-Well 1 and B-Well 2), we randomly assigned adults with noncirrhotic chronic HBV infection in a 2:1 ratio to receive subcutaneous bepirovirsen (at a weekly dose of 300 mg) or placebo for 24 weeks. All the patients were receiving stable nucleoside or nucleotide analogue (NA) therapy and had an HBsAg level of more than 100 to 3000 IU per milliliter. Eligible patients discontinued NA therapy at 48 weeks. The primary outcome was a functional cure at week 72.





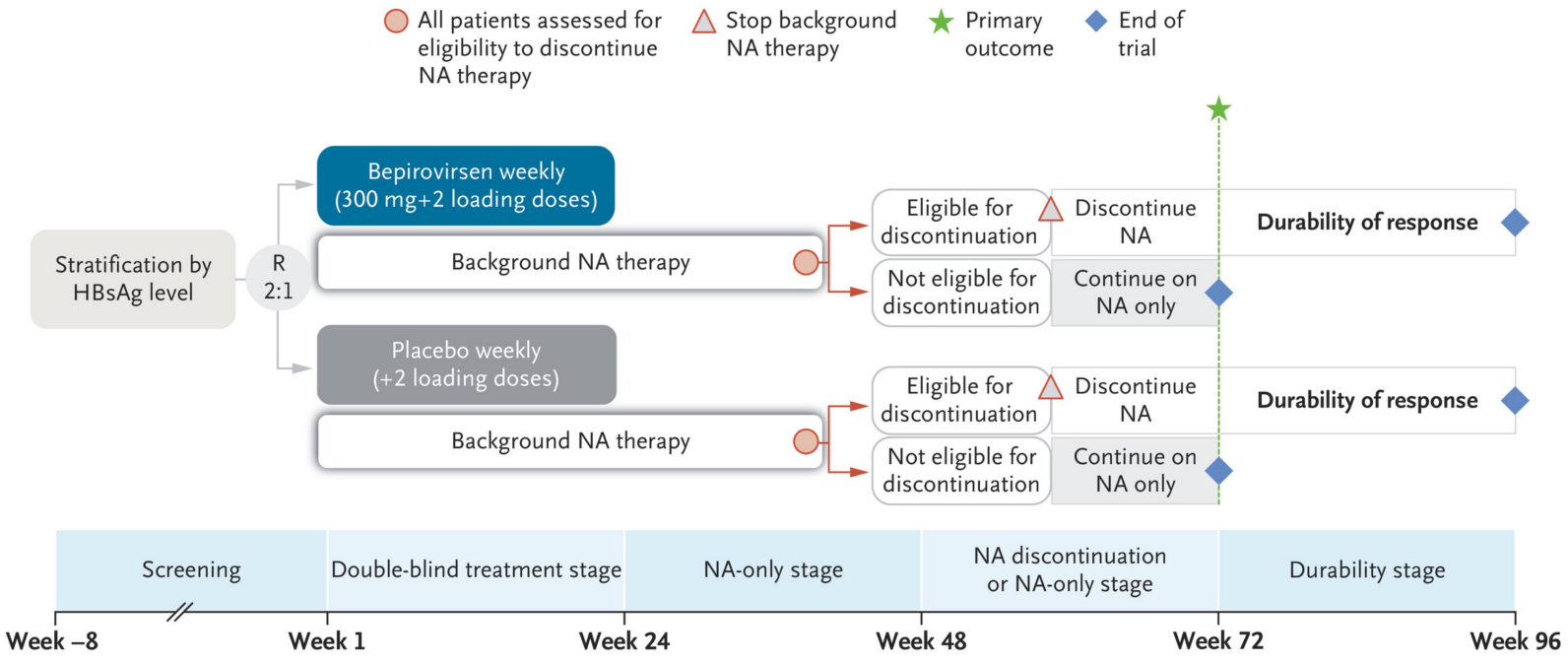




A functional cure, defined as an HBV DNA level below the lower limit of quantification (LLOQ) and hepatitis B surface antigen (HBsAg) loss (i.e., a level of <0.05 IU per milliliter) for at least 24 weeks after finite (fixed-duration) therapy — with or without a positive test for hepatitis B surface antibody — is the treatment goal for patients with chronic HBV infection and the recommended end point for new finite HBV therapies. Bepirovirsen is an unconjugated antisense oligonucleotide that targets all HBV transcripts, thereby reducing levels of HBV DNA and HBsAg. In addition to its direct antiviral effects, bepirovirsen also stimulates the immune response, with evidence of cytokine induction and immune-cell activation. Extended follow-up of the phase 2 bepirovirsen studies showed that some patients with a baseline HBsAg level of 3000 IU per milliliter or less who received a course of bepirovirsen were able to discontinue NA therapy and have a durable functional cure. Here, we present the key efficacy and safety results of the phase 3 B-Well 1 and B-Well 2 trials involving patients with NA-suppressed chronic HBV infection. In these trials, we assessed the percentage of patients who had a functional cure with 24 weeks of bepirovirsen therapy, as compared with placebo.

Patients

We enrolled adults with documented chronic HBV infection who had been receiving stable NA therapy for at least 6 months before screening and had no planned regimen changes during the trial. All the patients had an HBsAg level ranging from 100 to 3000 IU per milliliter, an HBV DNA level of less than 90 IU per milliliter, and an alanine aminotransferase (ALT) level of no more than two times the upper limit of the normal range.



B-Well 1 and B-Well 2 Trial Design.

The B-Well 1 and 2 trials were designed to have an identical format for replication purposes, with the exception of an optional exit interview in B-Well 1 (not reported in this article). After a screening window of 45 days, randomization could extend to 60 days with a medical monitoring agreement (e.g., waiting for retesting results). Patients were stratified according to the hepatitis B surface antigen (HBsAg) level (>100 to ≤1000 IU per milliliter [lower HBsAg stratum] or >1000 to ≤3000 IU per milliliter [higher HBsAg stratum]). Trial treatments were two subcutaneous injections administered once weekly, except during weeks 1 and 2, which had additional loading doses on days 4 and 11. All the patients were receiving stable nucleoside or nucleotide analogue (NA) therapy at baseline. To be eligible for NA discontinuation at week 48, a hepatitis B virus (HBV) DNA level below the lower limit of quantification (LLOQ; <20 IU per milliliter or not detected) was required, along with HBsAg loss (qualitative assay, <0.05 IU per milliliter) from week 24 to week 46; an alanine aminotransferase value that was no more than two times the upper limit of the normal range at week 46; and negative results on testing for hepatitis B e antigen at week 46. The evaluation of findings obtained in the durability stage is ongoing.

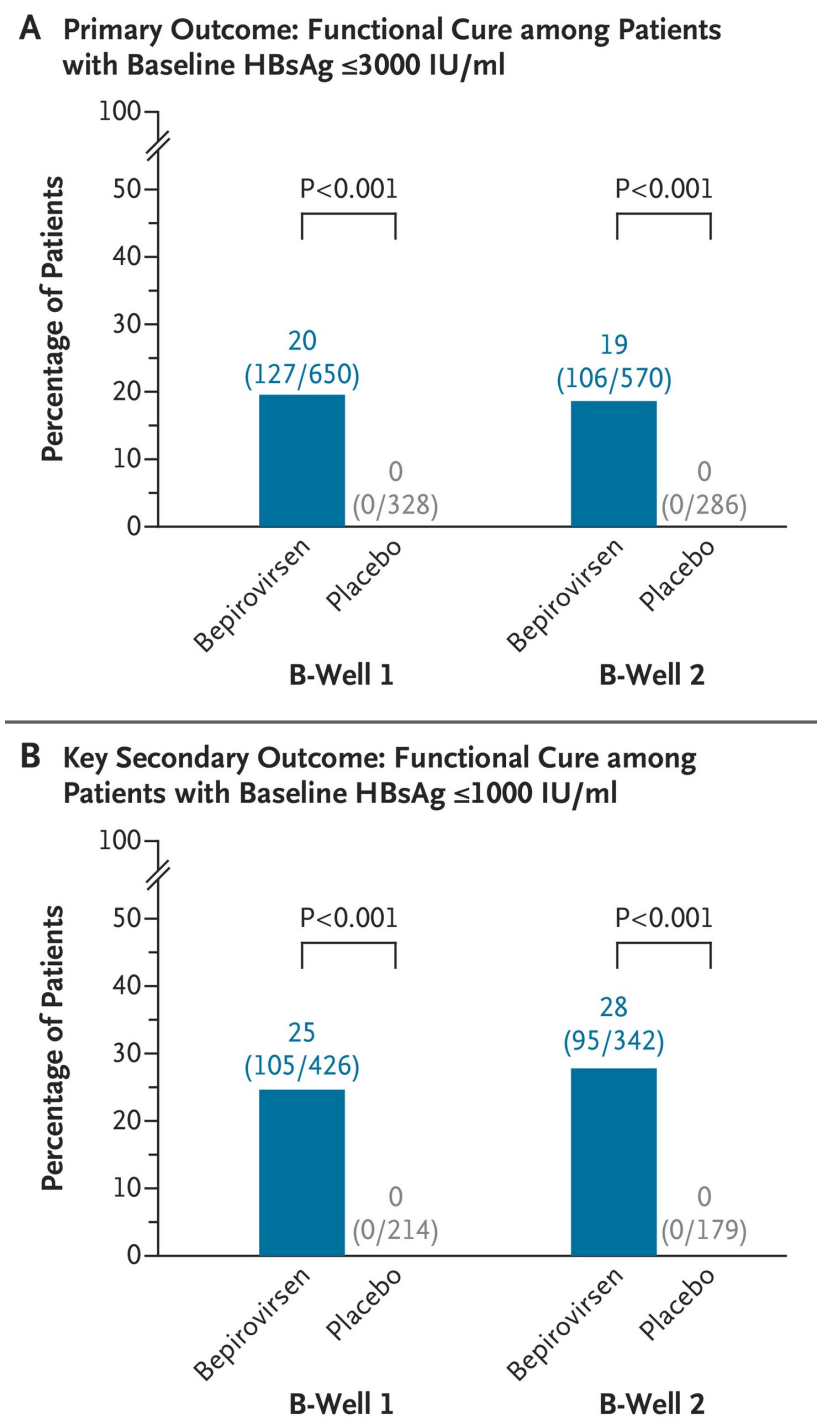
Safety Summary

Characteristic	B-Well 1		B-Well 2	
	Bepirovirsen (N=653)	Placebo (N=328)	Bepirovirsen (N=571)	Placebo (N=286)
Age — yr	50.2±11.8	49.2±10.6	48.7±10.4	49.2±11.4
Male sex — no. (%)	461 (71)	227 (69)	414 (73)	202 (71)
Race or ethnic group — no. (%)†				
Asian	440 (67)	229 (70)	388 (68)	195 (68)
White	168 (26)	78 (24)	149 (26)	78 (27)
Black	31 (5)	18 (5)	25 (4)	11 (4)
Multiple	7 (1)	2 (1)	1 (<1)	2 (1)
American or Alaskan First Nations	7 (1)	1 (<1)	1 (<1)	0
Native Hawaiian or other Pacific Islander	0	0	7 (1)	0
Hispanic or Latino ethnic group — no. (%)†				
Yes	81 (12)	25 (8)	27 (5)	20 (7)
No	561 (86)	296 (90)	542 (95)	264 (92)
Not reported or unknown	11 (2)	7 (2)	2 (<1)	2 (1)
Hepatitis B surface antigen‡				
Mean — IU/ml	952±1047	914±760	955±741	919±691
Distribution — no. (%)				
≤1000 IU/ml	427 (65)	214 (65)	343 (60)	179 (63)
>1000 to ≤3000 IU/ml	226 (35)	114 (35)	228 (40)	107 (37)
Log_{10} — IU/ml	2.80±0.41	2.79±0.45	2.83±0.39	2.82±0.37
Hepatitis B virus DNA <20 IU/ml — no. (%)§	641 (98)	322 (98)	564 (99)	283 (99)
Hepatitis B e antigen–negative status — no. (%)	598 (92)	300 (91)	528 (92)	260 (91)
Alanine aminotransferase				
Mean — IU/liter	22.1±11.4	23.1±11.6	21.9±10.5	22.9±12.1
≤ULN — no. (%)	599 (92)	296 (90)	535 (94)	263 (92)
Current NA — no. (%)‡¶				
Entecavir	261 (40)	139 (42)	252 (44)	117 (41)
TAF, TDF, tenofovir, or TMF‖	395 (60)	189 (58)	324 (57)	169 (59)
Other NAs**	13 (2)	2 (1)	6 (1)	5 (2)

Event	B-Well 1		B-Well 2		Pooled Data	
	Bepirovirsen (N=652)	Placebo (N=326)	Bepirovirsen (N=571)	Placebo (N=285)	Bepirovirsen (N=1223)	Placebo (N=611)
	number of patients (percent)					
Any adverse event	575 (88)	210 (64)	512 (90)	189 (66)	1,087 (89)	399 (65)
Leading to permanent dose discontinuation	26 (4)	0	15 (3)	2 (<1)	41 (3)	2 (<1)
Leading to dose reduction	13 (2)	0	11 (2)	0	24 (2)	0
Leading to dose interruption or delay	100 (15)	10 (3)	93 (16)	3 (1)	193 (16)	13 (2)
Adverse event of grade ≥3 severity†	96 (15)	8 (2)	101 (18)	8 (3)	197 (16)	16 (3)
Adverse event related to bepirovirsen or placebo‡	512 (79)	111 (34)	469 (82)	104 (36)	981 (80)	215 (35)
Any serious adverse event	25 (4)	5 (2)	23 (4)	3 (1)	48 (4)	8 (1)
Related to bepirovirsen or placebo‡	12 (2)	0	11 (2)	0	23 (2)	0
Fatal§	0	0	1 (<1)	0	1 (<1)	0

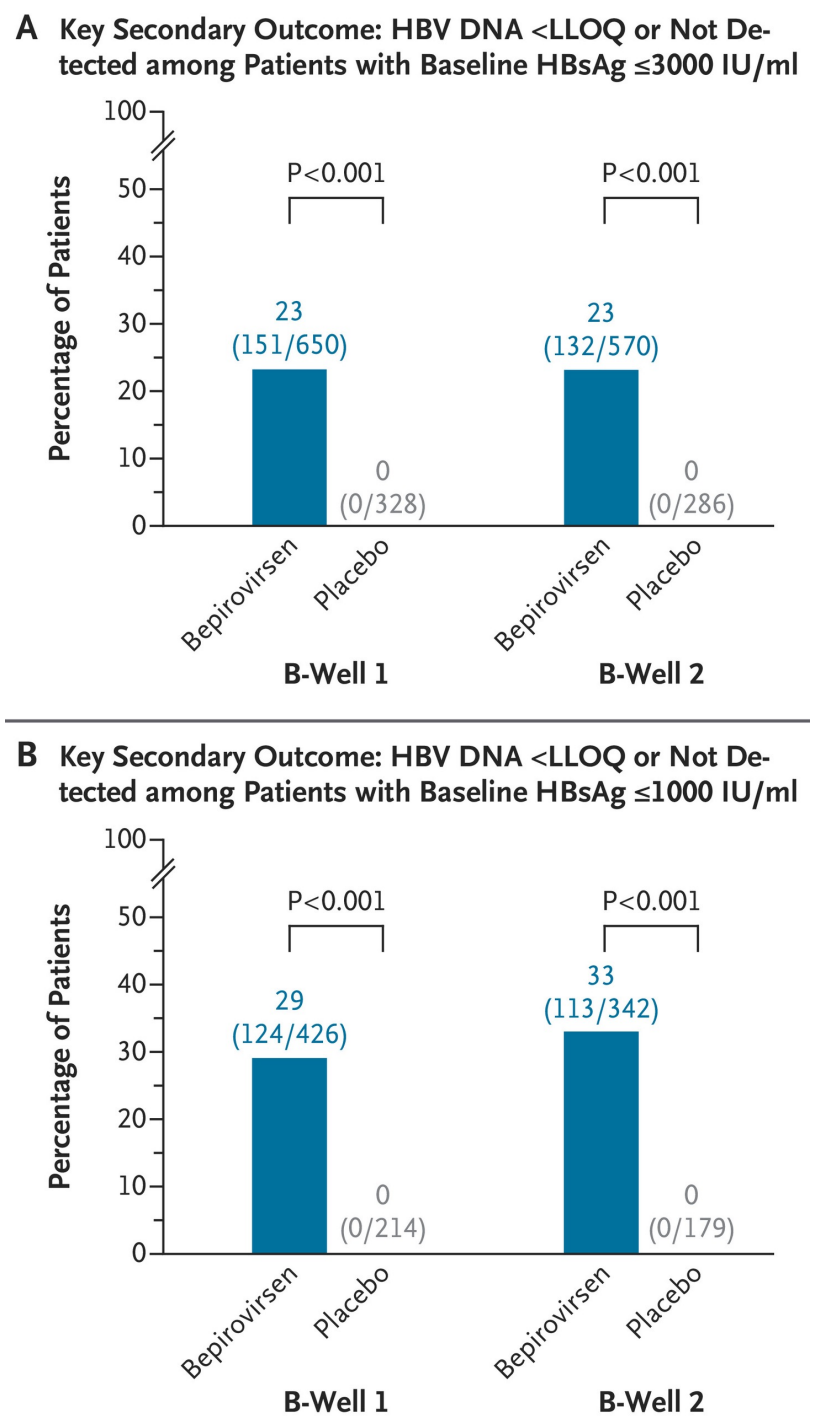
Adverse Events

Event or Abnormality	Pooled Data from B-Well 1 and B-Well 2			
	Weeks 1 to 24		Weeks 25 to 48	
	Bepirovirsen	Placebo	Bepirovirsen	Placebo
	number of patients/total number (percent)			
Injection-site reaction	648/1223 (53)	84/611 (14)	45/1173 (4)	1/566 (<1)
Laboratory abnormality				
Hepatobiliary: alanine aminotransferase level ≥3× ULN	292/1221 (24)	2/609 (<1)	11/1170 (1)	1/564 (<1)
Hematologic: platelet count of <100,000 per mm^3	100/1223 (8)	3/611 (<1)	53/1223 (4)	1/611 (<1)
Renal				
Change from baseline of >0.5 mg/dl in serum creatinine level†	31/1223 (3)	9/611 (1)	11/1223 (1)	4/611 (1)
Urinary albumin:creatinine ratio of >300‡	18/1223 (1)	7/611 (1)	13/1223 (1)	6/611 (1)



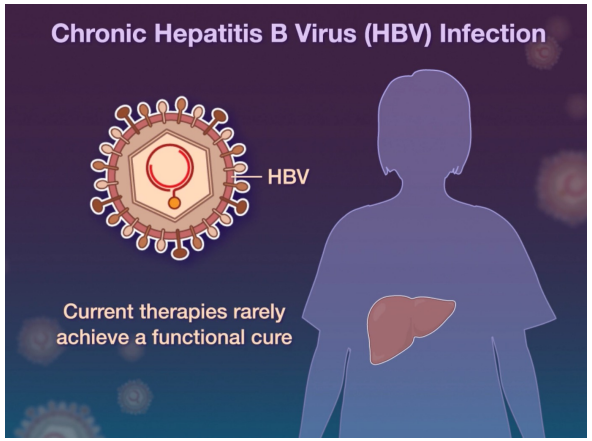
Functional Cure at Week 72 and Key Secondary Outcome, According to Baseline HBsAg Level.

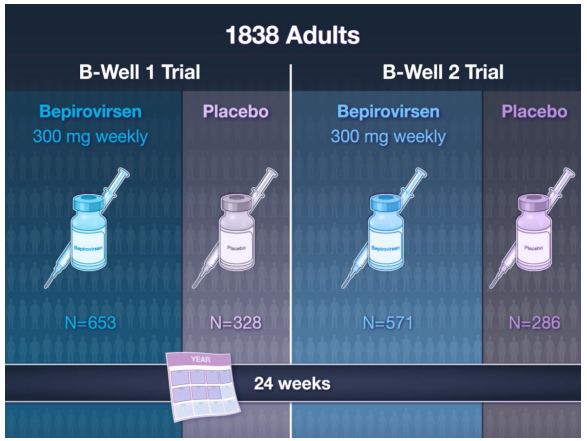
Panel A shows the percentage of patients who had a functional cure (the primary outcome), which was defined as 24 weeks or more of a sustained HBV DNA level below the LLOQ (<20 IU per milliliter or not detected) and HBsAg loss (qualitative assay, <0.05 IU per milliliter). The common risk difference between the groups (calculated with the Miettinen–Nurminen method) was 17.5 percentage points (95% CI, 14.6 to 20.3) in the B-Well 1 trial and 13.3 percentage points (95% CI, 10.4 to 16.1) in the B-Well 2 trial. Panel B shows the percentage of patients who had a functional cure in those with a baseline HBsAg value of 1000 IU per milliliter or less (lower HBsAg stratum) — a key secondary outcome — for a difference of 24.6 percentage points (95% CI, 20.8 to 29.0) in B-Well 1 and 27.8 percentage points (95% CI, 23.3 to 32.8) in B-Well 2.

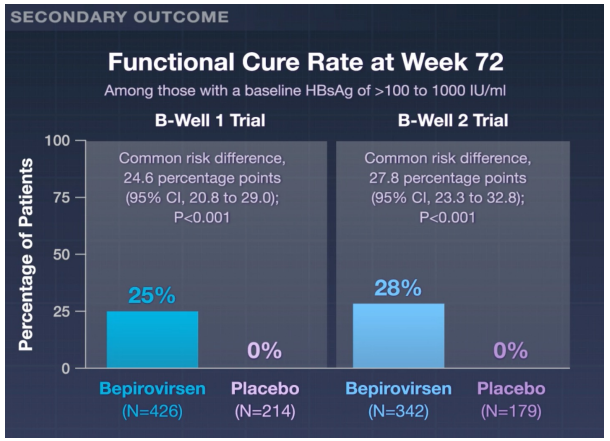


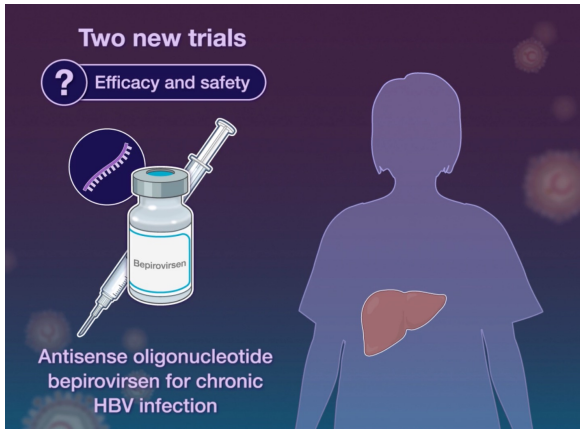
Discontinuation of NA and HBV DNA below LLOQ or Not Detected at Week 72, According to Baseline HBsAg Level.

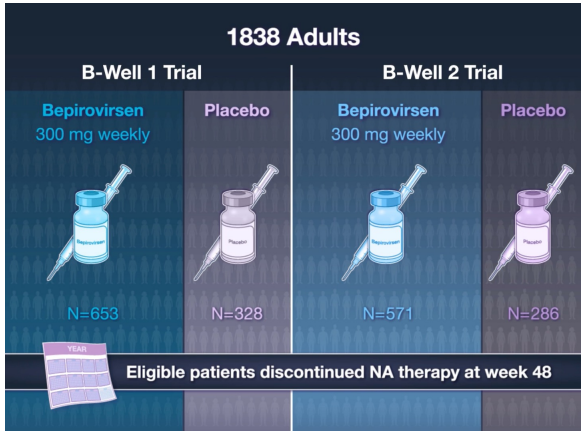
Shown is the percentage of patients who had an HBV DNA value that was below the LLOQ (<20 IU per milliliter or not detected) at week 72, according to whether they had a baseline HBsAg level of 3000 IU per milliliter or less (Panel A) or a baseline level of 1000 IU per milliliter or less (Panel B) (two key secondary outcomes). In Panel A, the common risk difference was 21.0 percentage points (95% CI, 17.9 to 24.0) in B-Well 1 and 18.2 percentage points (95% CI, 15.1 to 21.3) in B-Well 2. In Panel B, the risk difference was 29.1 percentage points (95% CI, 25.0 to 33.6) in B-Well 1 and 33.0 percentage points (95% CI, 28.3 to 38.2) in B-Well 2.

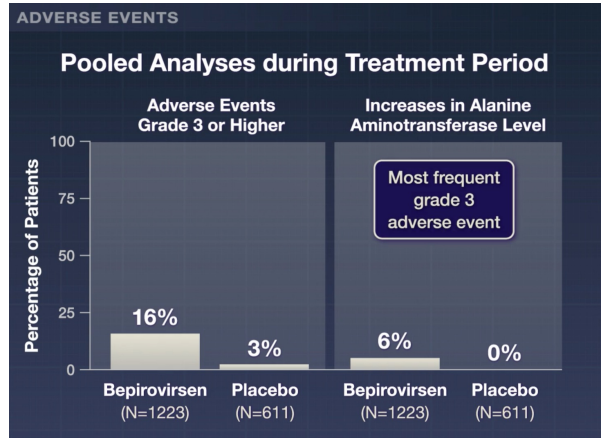

Chronic Hepatitis B Virus (HBV) Infection
HBV
Current therapies rarely achieve a functional cure

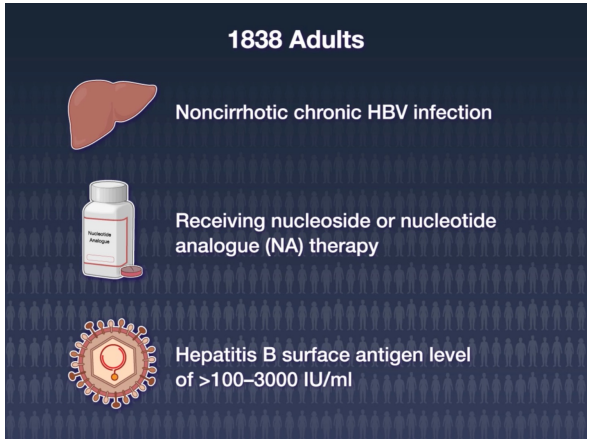

1838 Adults
B-Well 1 Trial
B-Well 2 Trial
Bepirovirsen 300 mg weekly
Placebo
Bepirovirsen 300 mg weekly
Placebo
N=653
N=328
N=571
N=286
24 weeks

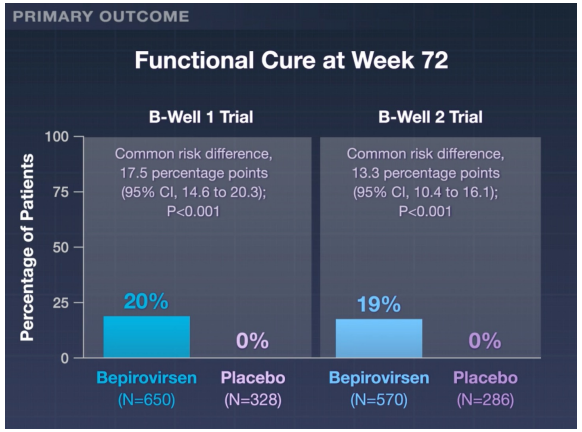

SECONDARY OUTCOME
Functional Cure Rate at Week 72
Among those with a baseline HBsAg of >100 to 1000 IU/ml
B-Well 1 Trial
B-Well 2 Trial
Percentage of Patients
Common risk difference, 24.6 percentage points (95% CI, 20.8 to 29.0); P<0.001
Common risk difference, 27.8 percentage points (95% CI, 23.3 to 32.8); P<0.001
25%
0%
28%
0%
Bepirovirsen (N=426)
Placebo (N=214)
Bepirovirsen (N=342)
Placebo (N=179)

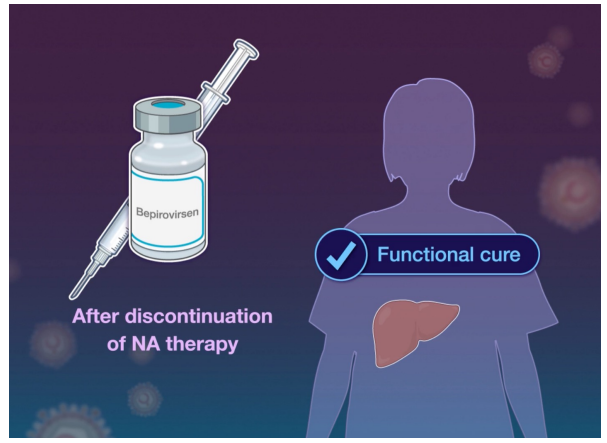

Two new trials
Efficacy and safety
Antisense oligonucleotide bepirovirsen for chronic HBV infection

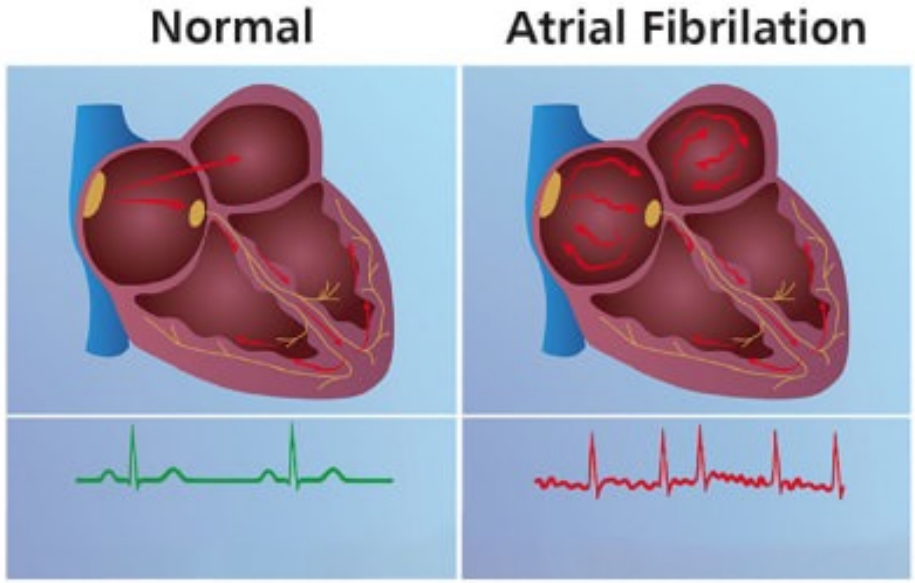

1838 Adults
B-Well 1 Trial
B-Well 2 Trial
Bepirovirsen 300 mg weekly
Placebo
Bepirovirsen 300 mg weekly
Placebo
N=653
N=328
N=571
N=286
Eligible patients discontinued NA therapy at week 48

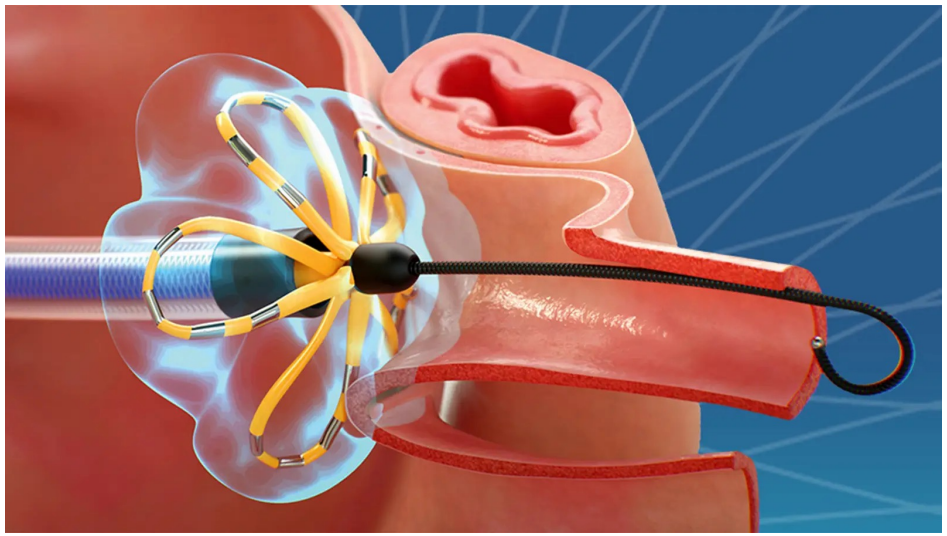

ADVERSE EVENTS
Pooled Analyses during Treatment Period
Adverse Events Grade 3 or Higher
Increases in Alanine Aminotransferase Level
Most frequent grade 3 adverse event
Percentage of Patients
16%
3%
6%
0%
Bepirovirsen (N=1223)
Placebo (N=611)
Bepirovirsen (N=1223)
Placebo (N=611)


1838 Adults
Noncirrhotic chronic HBV infection
Receiving nucleoside or nucleotide analogue (NA) therapy
Hepatitis B surface antigen level of >100–3000 IU/ml


PRIMARY OUTCOME
Functional Cure at Week 72
B-Well 1 Trial
B-Well 2 Trial
Percentage of Patients
Common risk difference, 17.5 percentage points (95% CI, 14.6 to 20.3); P<0.001
Common risk difference, 13.3 percentage points (95% CI, 10.4 to 16.1); P<0.001
20%
0%
19%
0%
Bepirovirsen (N=650)
Placebo (N=328)
Bepirovirsen (N=570)
Placebo (N=286)


Functional cure
After discontinuation of NA therapy





Die **Pulsed Field Ablation (PFA)** ist ein modernes, minimalinvasives Katheterverfahren zur Behandlung von **Vorhofflimmern (Atrial Fibrillation, AF)**. Im Gegensatz zu traditionellen thermischen Verfahren (wie der Radiofrequenzablation, die Hitze nutzt, oder der Kryoablation, die Kälte nutzt) arbeitet die PFA völlig **ohne extreme Temperaturen**. Stattdessen gibt das System ultrakurze, hochenergetische elektrische Impulse ab. Diese Impulse erzeugen winzige Poren in den Zellmembranen der fehlerhaften Herzmuskelzellen (**irreversible Elektroporation**), wodurch diese gezielt absterben und die störenden elektrischen Fehlsignale blockiert werden.

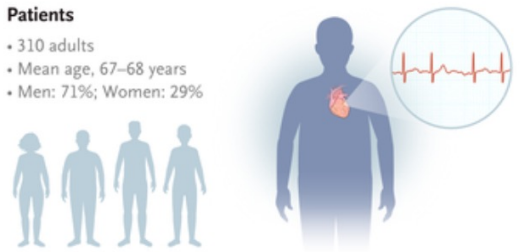
Schnellere Prozedur: Das Abgeben der eigentlichen elektrischen Pulse dauert oft weniger als eine Minute. Die gesamte Prozedur ist in der Regel in ein bis zwei Stunden abgeschlossen, was die Narkosezeit für Patienten deutlich verkürzt.

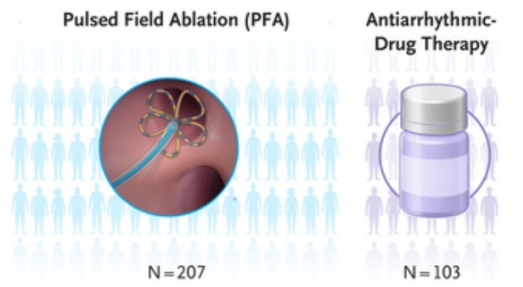
Rasche Erholung: Patienten verspüren nach dem Eingriff oft weniger Entzündungen und Gewebereizungen, was zu einer schnelleren Mobilisierung und häufig zu einer Entlassung noch am selben Tag führt.

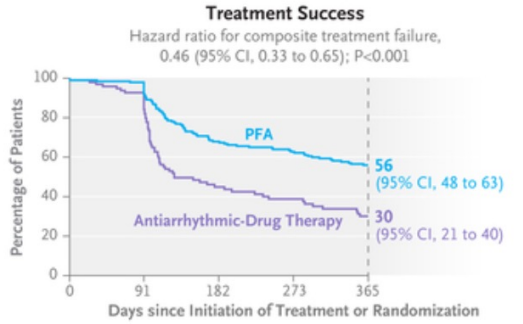
Pulsed Field Ablation as Initial Therapy for Persistent Atrial Fibrillation

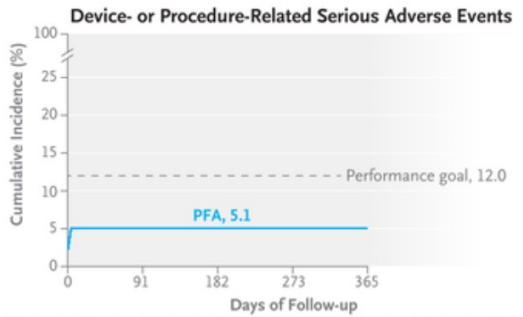
Guidelines recommend a trial of antiarrhythmic drugs before catheter ablation for persistent atrial fibrillation. Whether pulsed field ablation (PFA) may be a preferred initial treatment is unclear.

We conducted an international, randomized trial involving patients with previously untreated persistent atrial fibrillation. The patients were randomly assigned in a 2:1 ratio to receive PFA performed with a pentaspline catheter or to receive antiarrhythmic-drug therapy. An additional group of patients (PFA-assigned) underwent PFA for the analysis of the primary safety end point alone. All the patients received an insertable cardiac monitor. The primary effectiveness end point was the short-term and long-term success of treatment through 12 months. Short-term success was defined as procedural success in the PFA group and the absence of ablation during the blanking period (90 days after treatment initiation) in the antiarrhythmic-drug group. Long-term success was defined as freedom from recurrence of atrial arrhythmias, repeat ablation, or need for antiarrhythmic drugs from 90 days through 12 months (in the PFA group) and freedom from amiodarone use at any time. The primary safety end point was device- and procedure-related serious adverse events.









Catheter ablation has been shown to be superior to antiarrhythmic-drug therapy in maintaining sinus rhythm, improving quality of life, and reducing health care use in patients in whom drug therapies have already failed. For patients with paroxysmal atrial fibrillation, catheter ablation is established as a safe and superior alternative to antiarrhythmic drugs as a first-line therapy. However, patients with persistent atrial fibrillation often have substantial electrical and structural remodeling, which leads to worse procedural outcomes with thermal-based ablation techniques than in patients with paroxysmal atrial fibrillation.

We conducted the Pulsed Field Ablation (PFA) vs. Antiarrhythmic Drug Therapy as a First Line Treatment for Persistent Atrial Fibrillation (AVANT GUARD) trial to evaluate initial rhythm control with PFA as compared with antiarrhythmic drugs to prevent the recurrence of clinically relevant atrial tachyarrhythmias, as assessed by an insertable continuous rhythm monitor.

Patients and Randomization

We enrolled adults (≥18 years of age) with symptomatic, persistent atrial fibrillation (i.e., continuous atrial fibrillation for 7 days to 365 days) with at least one electrocardiographically documented episode within 180 days before randomization. Patients were excluded if they had a history of the receipt of a class I or III antiarrhythmic drug for more than 7 consecutive days or the receipt of more than 24 hours of amiodarone within 6 months before enrollment.

Trial Procedures

Patients received an insertable cardiac monitor (LUX-Dx, Boston Scientific) that was programmed to standardized settings. An atrial arrhythmia detection algorithm (BeatLogic, Boston Scientific) determined the timing of arrhythmia occurrence and quantified the atrial arrhythmia burden (percentage of time that the patient was in atrial fibrillation, flutter, or tachyarrhythmia). Patients recorded symptomatic arrhythmia episodes with the patient-controlled activator.

Trial Pause

Following the recommendation of the data and safety monitoring committee, the trial was temporarily paused on October 18, 2024, after six neurologic events had been observed.

End Points

The primary effectiveness outcome consisted of metrics of short-term and long-term success.

Anticoagulation

Anticoagulation was required prior to ablation for all patients undergoing pulsed field ablation (PFA). Oral anticoagulants were required for a minimum of 4 weeks prior to the ablation procedure regardless of the CHA_2DS_2-VASc score. Uninterrupted oral anticoagulants is part of the modified workflow post-pause. Patients were maintained on oral anticoagulation for at least 2 months following ablation. All patients, regardless of treatment arm with a CHA_2DS_2-VASc score ≥2 (men) and ≥3 (women) were recommended to continue to receive oral anticoagulants for the duration of the study.

Antiarrhythmic Drug Therapy – Initiation and Titration

Patients randomized to antiarrhythmic drugs (AADs) (Class I or III, excluding amiodarone) as the initial treatment were prescribed and monitored in accordance with local clinical practice and established guideline-directed therapy for patients with persistent AF. Amiodarone use was excluded from this trial. Although low doses of amiodarone are considered reasonable treatment, in view of its adverse effects, it should be reserved only for patients in whom other rhythm control strategies are not effective. Clinical inefficacy during the blanking period was defined as the recurrence of atrial fibrillation (AF), atrial flutter (AFL), or atrial tachycardia (AT) lasting ≥1hr if asymptomatic and ≥30s if symptomatic despite the use of a maximally tolerated therapeutic dose of AAD or the recurrence is deemed by the investigator to be of sufficient clinical severity to warrant a change in therapy. If there was a lack of clinical efficacy during the 90-day blanking period, the AAD dose was up-titrated to the maximum tolerated dose. If still ineffective, alternative AADs could be started if the patient was still within the blanking period. The goal with AAD optimization and titration was to completely suppress AF episodes ≥30s. It was recommended that during these AAD initiation and optimization visits the patient be cardioverted if still not in sinus rhythm.

Characteristic	Pulsed Field Ablation		Antiarrhythmic-Drug Group (N=102)
	Randomized Group (N=207)	PFA-Assigned Group (N=78)	
Age — yr	68.1±8.5	67.2±9.6	67.4±8.7
Female sex — no. (%)	65 (31)	23 (29)	26 (25)
Body-mass index†	31.0±5.6	30.6±5.6	31.9±5.3
Race or ethnic group — no. (%)‡			
American Indian or Alaska Native	1 (<1)	3 (4)	2 (2)
Asian	11 (5)	1 (1)	4 (4)
Black	3 (1)	1 (1)	3 (3)
White	187 (90)	71 (91)	89 (87)
Unknown or declined to disclose	6 (3)	4 (5)	5 (5)
Left ventricular ejection fraction — %	56.3±7.4	56.0±7.5	56.3±7.4
Left arterial diameter — cm	4.3±0.6	4.3±0.6	4.3±0.6
New York Heart Association class — no./total no. (%)			
Class I	59/207 (29)	22/78 (28)	17/101 (17)
Class II	59/207 (29)	24/78 (31)	37/101 (37)
Class III	6/207 (3)	0	3/101 (3)
CHA_2DS_2-VASc score§	2.6±1.5	2.3±1.0	2.5±1.2
Atrial flutter — no. (%)	12 (6)	3 (4)	6 (6)
Medical history — no. (%)¶			
Acute myocardial infarction	7 (3)	3 (4)	2 (2)
Coronary artery disease	43 (21)	14 (18)	18 (18)
Diabetes	47 (23)	11 (14)	19 (19)
Dyslipidemia	103 (50)	43 (55)	56 (55)
Hypertension	135 (65)	44 (56)	63 (62)
Stroke	5 (2)	0	2 (2)
Transient ischemia attack	5 (2)	0	2 (2)
Sleep apnea	49 (24)	18 (23)	26 (25)
First diagnosis of persistent atrial fibrillation			
No. of years before enrollment	0.5±1.4	0.7±1.1	0.7±2.6
<1 Yr before enrollment — no./total no. (%)	164/206 (80)	37/78 (47)	76/101 (75)

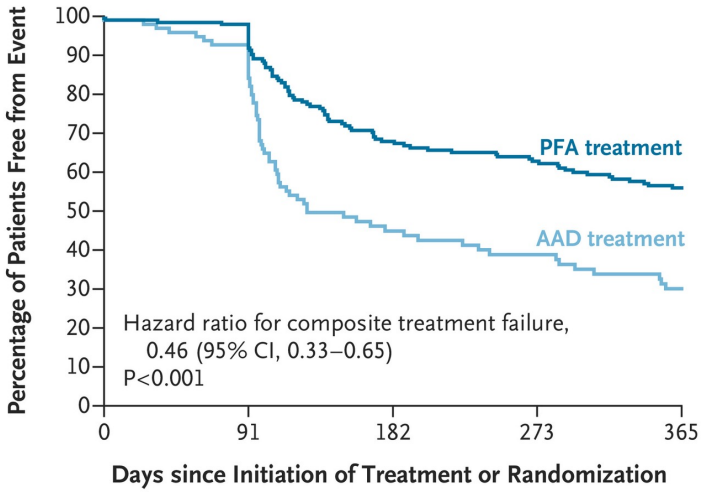
Primary, Secondary, and Other End Points.

End Point	Pulsed Field Ablation	Antiarrhythmic Drug	Difference (95% CI)†
Intention-to-treat population			
Total no. of patients in population	207	103	
Treatment success — no. (%)‡	128 (56)	40 (30)	26 (14 to 38)
Mode of first failure of primary effectiveness end point — no. (%)§			
Any failure: amiodarone use	3 (1)	3 (3)	−2 (−5 to 2)
Short-term failure: nonprotocol ablation	1 (<1)	6 (6)	NA
Long-term failure			
Detected arrhythmia recurrence	67 (32)	50 (49)	−16 (−28 to −5)
Symptomatic atrial fibrillation, flutter, or tachycardia ≥30 sec after blanking	4 (2)	3 (3)	−1 (−5 to 3)
Asymptomatic atrial fibrillation, flutter, or tachycardia ≥1 hr after blanking	63 (30)	47 (46)	−15 (−27 to −4)
Use of class I or III AAD in PFA group	8 (4)	NA	NA
Catheter ablation at any time in AAD group	NA	4 (4)	NA
Secondary effectiveness end point: atrial burden¶			
No. of patients	178	90	
Postblanking burden at 12 mo — %			
Median value (IQR)	0.0 (0.0 to 0.4)	0.3 (0.0 to 4.5)	−0.2 (−0.3 to 0.0)
Mean value	3.4±11.8	9.9±23.4	−6.5 (−10.7 to −2.3)
Burden category — no. (%)			
0 to 0.1%	116 (65)	42 (47)	18.7 (6.2 to 31.1)
>0.1%	62 (35)	48 (53)	−18.1 (−30.5 to −5.7)
Additional effectiveness end points — no. (%)‡			
Freedom from symptomatic recurrence at ≥30 sec	189 (90)	92 (87)	3 (−6 to 11)
Freedom from asymptomatic recurrence at ≥1 hr	136 (60)	50 (40)	20 (8 to 33)
Freedom from symptomatic recurrence at ≥30 sec or asymptomatic recurrence at ≥1 hr	134 (59)	49 (39)	20 (8 to 33)
As-treated population			
Total no. of patients in population	179	95	
Serious adverse events at 12 mo‖			
No. of patients with event — no. (%)	45 (25)	20 (21)	4 (−6 to 14)
No. of events	61	29	
Any adverse event at 12 mo**			
No. of patients with event — no. (%)	53 (30)	29 (31)	−1 (−12 to 10)
No. of events	77	42	

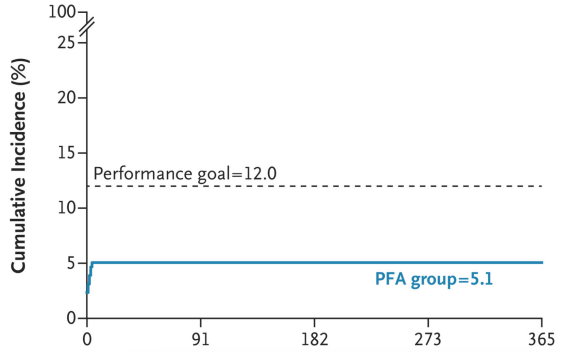
Primary Safety End Points in the PFA Group, before and after Trial Pause.

Safety End Point†	Pulsed Field Ablation		
	Randomized plus PFA-Assigned Group (N=257)	Before Pause (N=183)	After Pause (N=74)
	number of patients (percent)		
Any safety event	13 (5)	11 (6)	2 (3)
Composite primary safety events			
Stroke	6 (2)	6 (3)	0
Vascular access complication	2 (1)	2 (1)	0
Heart block	1 (<1)	0	1 (1)
Cardiovascular or pulmonary adverse event	2 (1)‡	2 (1)	0
Pulmonary edema	3 (1)	2 (1)	1 (1)

A Primary Efficacy End Point in Randomized Groups

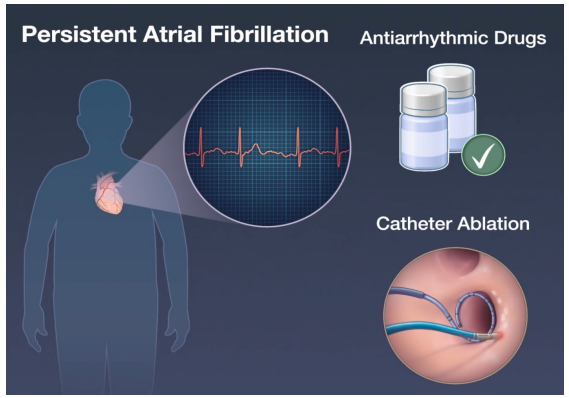


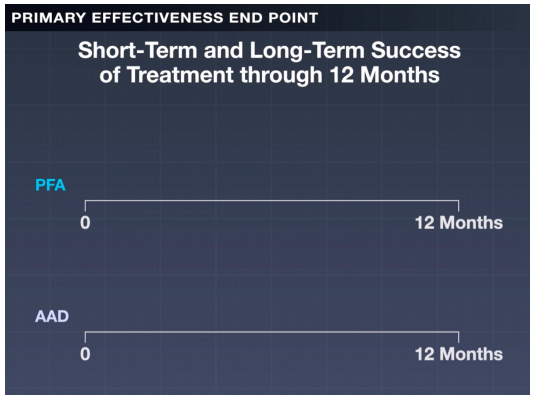
B Primary Safety End Point in PFA Group

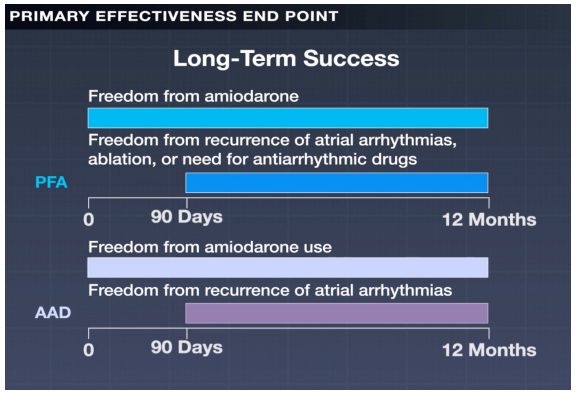


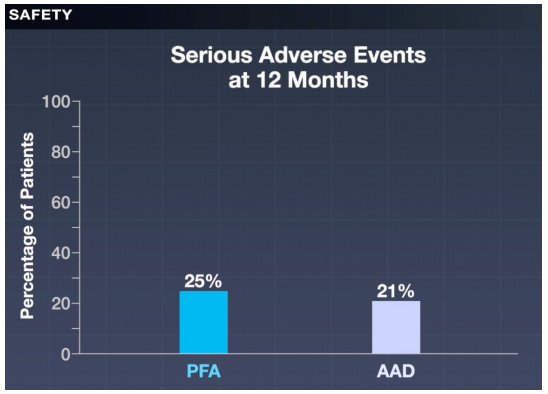
Efficacy Outcomes and Safety.

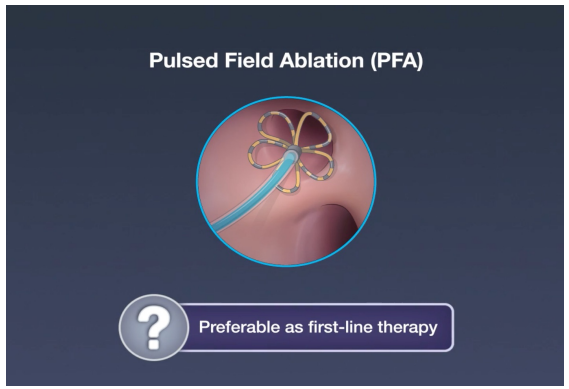
Panel A shows Kaplan–Meier survival curves for freedom from a primary efficacy event in the pulsed-field-ablation (PFA) group and the antiarrhythmic-drug group (AAD). The hazard ratio for composite treatment failure (a lack of short- and long-term success) was estimated with a univariate Cox regression model. Proportional hazards were met and assessed visually. Panel B shows the primary safety end point — device- or procedure-related serious adverse events among patients in both the randomized PFA group and the PFA-assigned group — at 12 months. A primary safety end-point event occurred in 13 of 257 patients (5.1%) in the PFA combined group. The performance goal of 12% was determined on the basis of event rates and performance goals obtained from trials of ablation involving patients with persistent atrial fibrillation.

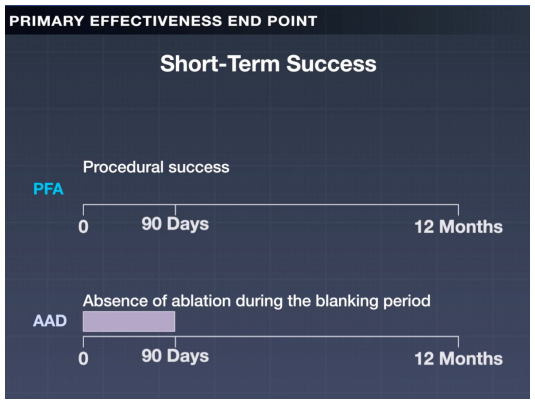

Persistent Atrial Fibrillation
Antiarrhythmic Drugs
Catheter Ablation

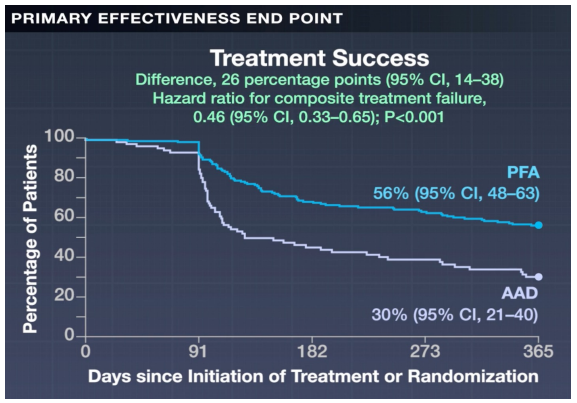

PRIMARY EFFECTIVENESS END POINT
Short-Term and Long-Term Success of Treatment through 12 Months
PFA
0
12 Months
AAD
0
12 Months

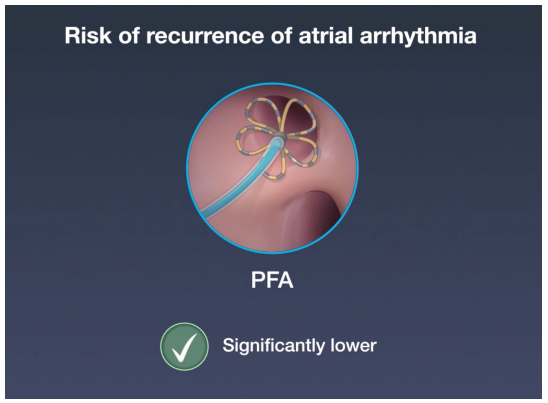

PRIMARY EFFECTIVENESS END POINT
Long-Term Success
Freedom from amiodarone
Freedom from recurrence of atrial arrhythmias, ablation, or need for antiarrhythmic drugs
PFA
0
90 Days
12 Months
Freedom from amiodarone use
Freedom from recurrence of atrial arrhythmias
AAD
0
90 Days
12 Months

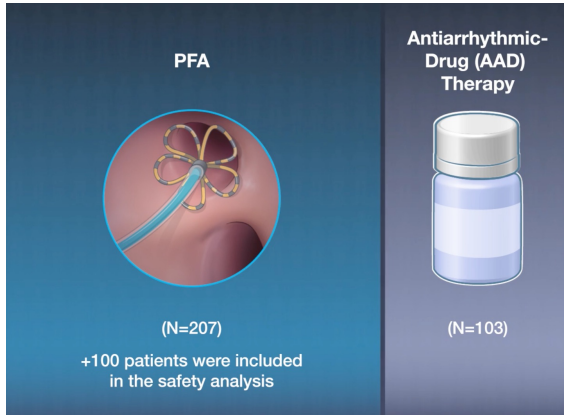

SAFETY
Serious Adverse Events at 12 Months
Percentage of Patients
100
80
60
40
20
0
25%
21%
PFA
AAD

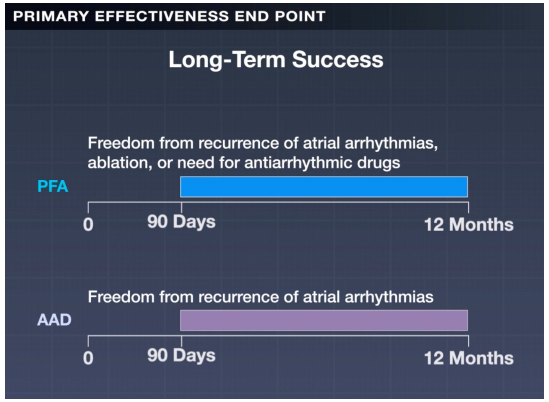

Pulsed Field Ablation (PFA)
Preferable as first-line therapy

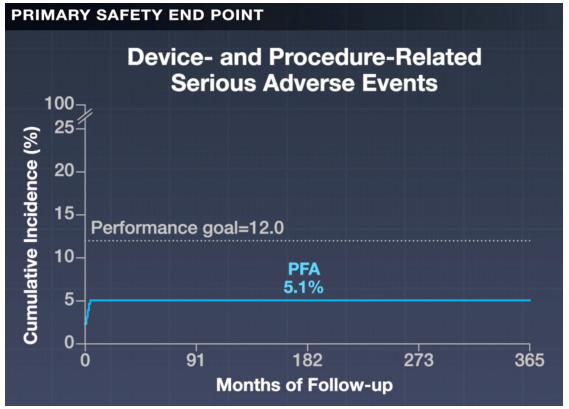

PRIMARY EFFECTIVENESS END POINT
Short-Term Success
Procedural success
PFA
0
90 Days
12 Months
Absence of ablation during the blanking period
AAD
0
90 Days
12 Months


PRIMARY EFFECTIVENESS END POINT
Treatment Success
Difference, 26 percentage points (95% CI, 14–38)
Hazard ratio for composite treatment failure, 0.46 (95% CI, 0.33–0.65); P<0.001
Percentage of Patients
100
80
60
40
20
0
PFA
56% (95% CI, 48–63)
AAD
30% (95% CI, 21–40)
0
91
182
273
365
Days since Initiation of Treatment or Randomization

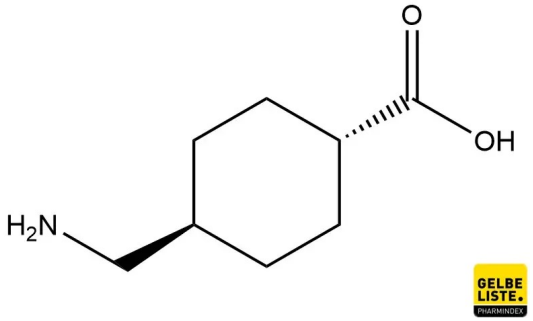

Risk of recurrence of atrial arrhythmia
PFA
Significantly lower


PFA
Antiarrhythmic-Drug (AAD) Therapy
(N=207)
+100 patients were included in the safety analysis
(N=103)


PRIMARY EFFECTIVENESS END POINT
Long-Term Success
Freedom from recurrence of atrial arrhythmias, ablation, or need for antiarrhythmic drugs
PFA
0
90 Days
12 Months
Freedom from recurrence of atrial arrhythmias
AAD
0
90 Days
12 Months

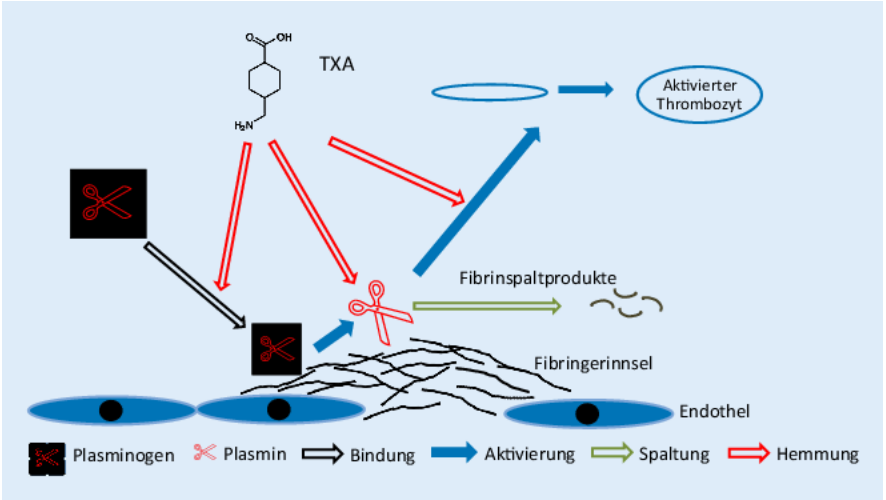

PRIMARY SAFETY END POINT
Device- and Procedure-Related Serious Adverse Events
Cumulative Incidence (%)
100
25
20
15
10
5
0
Performance goal=12.0
PFA
5.1%
0
91
182
273
365
Months of Follow-up

Tranexamsäure ist ein hochwirksames Medikament zur Blutstillung (Antifibrinolytikum). Sie verhindert die Auflösung bereits gebildeter Blutgerinnsel (Fibrinolyse) und wird in der Notfallmedizin bei schweren Verletzungen, bei starken Regelblutungen sowie bei oder nach Operationen eingesetzt, um Blutverluste zu minimieren.



Wirkungsweise

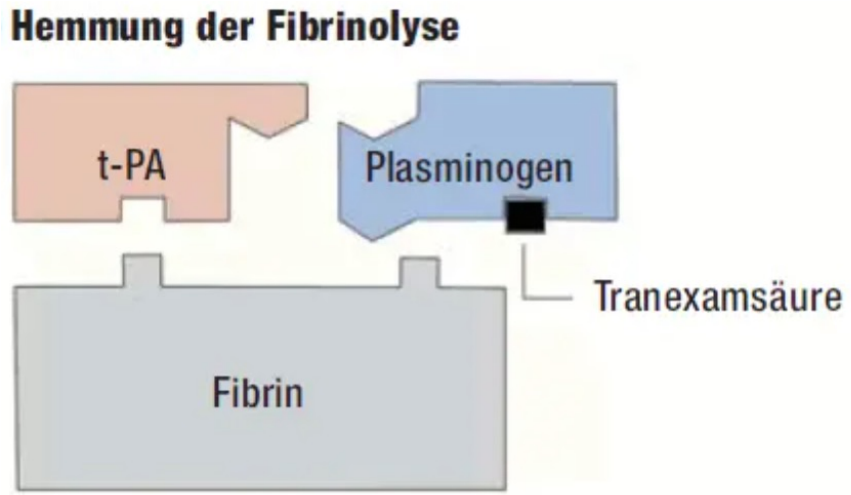
Der körpereigene Körper löst Blutgerinnsel normalerweise durch das Protein Plasmin auf. Tranexamsäure (TXA) blockiert die Aktivierungsstellen dieses Enzyms. Dadurch bleibt das Gerinnsel stabil und die Blutung wird schneller gestoppt.



Häufige Anwendungsgebiete

•**Notfallmedizin & Chirurgie:** Bei schweren Traumata (Unfällen) oder großen Operationen zur Vermeidung von Bluttransfusionen (Patient Blood Management).

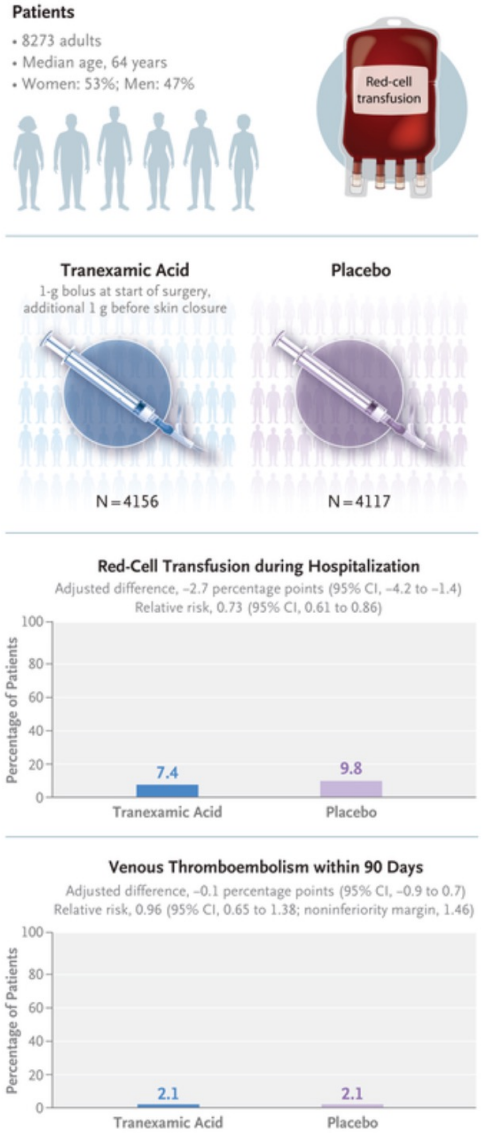
Gynäkologie: Zur Behandlung starker Menstruationsblutungen (Hypermenorrhö). **HNO & Zahnmedizin:** Bei Nasenbluten oder lokalen Blutungen (z. B. nach Zahnextraktionen), oftmals als Spülung.
Dermatologie: In der Hautpflege wird Tranexamsäure zunehmend zur Behandlung von Pigmentflecken (Melasma) eingesetzt, da sie die Melaninproduktion hemmt.



Hospital Policy of Tranexamic Acid to Reduce Transfusion in Major Noncardiac Surgery

Whether a hospital policy of tranexamic acid administration for patients undergoing major noncardiac surgery safely reduces the need for red-cell transfusion is uncertain.

We conducted a multicenter, double-blind, cluster-randomized, placebo-controlled trial involving patients undergoing noncardiac surgery who were at high risk for red-cell transfusion. Hospitals were randomly assigned at 4-week intervals to a hospital-wide policy of intraoperative tranexamic acid or placebo. The coprimary effectiveness and safety outcomes were transfusion of red cells during the index hospitalization and diagnosis of venous thromboembolism within 90 days, respectively. The safety outcome was assessed for noninferiority, with a prespecified noninferiority margin defined as an upper boundary of 1.46 for the 95% confidence interval of the relative risk. Analyses used mixed-effects models that accounted for the cluster-crossover design.



Perioperative bleeding is a leading indication for red-cell transfusion among hospitalized patients. The supply of blood components is increasingly constrained owing to rising demand and declining donor pools, which underscores the need for strategies that reduce the demand for transfusion. Tranexamic acid is an inexpensive and widely available antifibrinolytic medication that reduces blood loss and the incidence of red-cell transfusion in cardiac and orthopedic surgeries.

In the Perioperative Ischemic Evaluation–3 (POISE-3) trial that evaluated tranexamic acid in a selected population of adult patients undergoing noncardiac surgery who were at risk for bleeding or cardiovascular complications, the incidence of a composite of life-threatening bleeding, major bleeding, or bleeding into a critical organ at 30 days was significantly lower with tranexamic acid than with placebo. Noninferiority was not established for the primary safety outcome of 30-day major cardiovascular complications. Adoption of tranexamic acid across and within hospitals has been variable, in part because of unresolved concerns about potential thrombotic complications, particularly in patients with cancer or other prothrombotic conditions.

Patients

We recruited patients from 10 hospitals (clusters) in Canada. Hospitals were included if the site performed at least 100 noncardiac surgeries per month and if anesthesia, surgical, and hospital leadership agreed to manage the care of patients according to the policy implemented and evaluated in the trial.

Procedures

Participating sites were randomly assigned in a 1:1 ratio at 4-week intervals to provide either tranexamic acid or matching placebo (0.9% sodium chloride) to patients undergoing surgery who were at high risk for transfusion. Randomization was performed with the use of a central, secure, Web-based randomization system. Tranexamic acid was administered as a 1-g bolus (2-g bolus for patients with a weight of >100 kg) intravenously at the start of surgery, followed by 1 additional gram before skin closure, with the timing of the additional dose at the discretion of the anesthesiologist.

Outcome Measures

The coprimary outcomes evaluated effectiveness in the context of safety. The coprimary outcomes were transfusion of red cells during the index hospitalization (effectiveness) and diagnosis of deep-vein thrombosis or pulmonary embolism, collectively referred to as venous thromboembolism, within 90 days after surgery (safety).

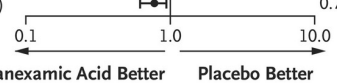
Characteristic	Tranexamic Acid (N=4156)	Placebo (N=4117)
Median age (IQR) — yr	64 (54–72)	64 (54–73)
Male sex — no. (%)	1985 (47.8)	1908 (46.3)
Median weight (IQR) — kg	80 (68–95)	80 (68–94)
Median Charlson Comorbidity Index score (IQR)†	2 (0–2)	2 (0–2)
Type of surgery — no./total no. (%)		
General surgery	1358/4107 (33.1)	1384/4058 (34.1)
Orthopedic surgery	87/4107 (2.1)	78/4058 (1.9)
Spine surgery	244/4107 (5.9)	217/4058 (5.3)
Otolaryngologic surgery	16/4107 (0.4)	21/4058 (0.5)
Thoracic surgery	451/4107 (11.0)	466/4058 (11.5)
Vascular surgery	286/4107 (7.0)	296/4058 (7.3)
Gynecologic surgery	799/4107 (19.5)	741/4058 (18.3)
Urologic surgery	735/4107 (17.9)	699/4058 (17.2)
Neurosurgery	126/4107 (3.1)	140/4058 (3.4)
Other	5/4107 (0.1)	16/4058 (0.4)
Surgical urgency — no./total no. (%)	4093/4156 (98.5)	4052/4117 (98.4)
Elective	3806/4093 (93.0)	3753/4052 (92.6)
Urgent or emergency	287/4093 (7.0)	299/4052 (7.4)
Surgical indication — no./total no. (%)	4072/4156 (98.0)	4027/4117 (97.8)
Oncologic	2536/4072 (62.3)	2466/4027 (61.2)
Nononcologic	1536/4072 (37.7)	1561/4027 (38.8)
Surgical method — no./total no. (%)	3583/4156 (86.2)	3402/4117 (82.6)
Open	1969/3583 (55.0)	1848/3402 (54.3)
Laparoscopic or endoscopic	1614/3583 (45.0)	1554/3402 (45.7)
Preoperative red-cell transfusion — no. (%)	56 (1.3)	64 (1.6)
Preoperative investigations‡		
Median hemoglobin level (IQR) — g/dl	13.4 (12.1–14.5)	13.4 (12.2–14.5)
Median platelet count (IQR) — $\times 10^{-9}$/liter	248 (205–303)	255 (205–311)
Median creatinine level (IQR) — mg/dl	0.96 (0.81–1.18)	0.96 (0.81–1.15)
Median international normalized ratio (IQR)	1 (1–1)	1 (1–1)

Primary and Secondary Outcomes.

Outcome	Tranexamic Acid (N=4156)	Placebo (N=4117)	Effect Estimate (95% CI)
Primary effectiveness outcome: red-cell transfusion during index hospitalization — no. (%)	306 (7.4)	403 (9.8)	0.73 (0.61 to 0.86)†‡
Primary safety outcome: diagnosis of venous thromboembolism within 90 days — no./total no. (%)			
Per-protocol population	86/4128 (2.1)	85/4052 (2.1)	0.96 (0.65 to 1.38)†§
Intention-to-treat population	86/4156 (2.1)	90/4117 (2.2)	0.92 (0.62 to 1.30)†
Secondary outcomes¶			
Red-cell units transfused			
Patient level per 100 patients	24.7±3.6	34.2±2.6	−9.5 (−19.2 to −0.2)‖
Hospital level per 100 patients	23.5±27.2	39.6±80.6	−16.2 (−33.5 to 1.1)‖
Myocardial infarction — no. (%)	29 (0.7)	34 (0.8)	NA
Stroke — no. (%)	9 (0.2)	9 (0.2)	NA
Deep-vein thrombosis — no.	<6**	<6**	NA
Pulmonary embolism — no. (%)	8 (0.2)	6 (0.1)	NA
Hospital length of stay — days	6.20±8.89	6.26±9.42	−0.15 (−0.69 to 0.29)‖
Intensive care unit admission — no. (%)	693 (16.7)	721 (17.5)	−0.01 (−0.03 to 0.02)††
Hospital survival — no. (%)	4112 (98.9)	4076 (99.0)	NA
Overall survival at 90 days — no. (%)	4066 (97.8)	4017 (97.6)	0.95 (0.71 to 1.28)‡‡
Median days alive and out of hospital to day 30 (IQR)	26 (22 to 27)	26 (22 to 27)	0.03 (−0.33 to 0.39)‖

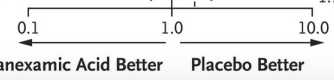
A Red-Cell Transfusion during Hospitalization

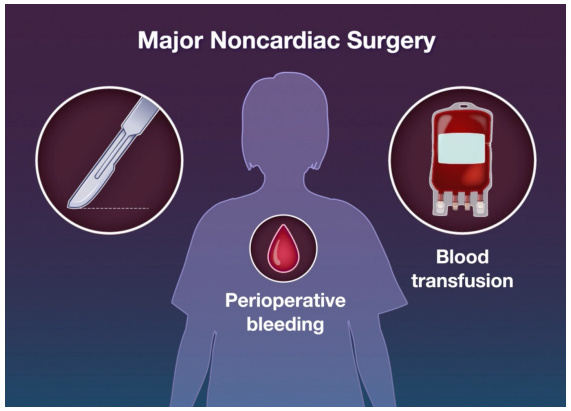
Subgroup	Tranexamic Acid	Placebo	Relative Risk (95% CI)
	no. of patients with event/total no. (%)		
Overall	306/4156 (7.4)	403/4117 (9.8)	0.73 (0.61–0.86)
Age			
<40 yr	15/287 (5.2)	21/289 (7.3)	0.73 (0.31–1.39)
40–64 yr	111/1821 (6.1)	153/1814 (8.4)	0.69 (0.50–0.88)
65–74 yr	87/1282 (6.8)	125/1226 (10.2)	0.64 (0.47–0.83)
≥75 yr	93/766 (12.1)	104/788 (13.2)	0.86 (0.63–1.12)
Surgical specialty			
General surgery	102/1358 (7.5)	155/1384 (11.2)	0.65 (0.48–0.81)
Orthopedic surgery	10/87 (11.5)	9/78 (11.5)	0.85 (0.35–1.91)
Spine surgery	22/244 (9.0)	27/217 (12.4)	0.74 (0.34–1.49)
Neurosurgery	<6/126	11/140 (7.9)	0.47 (0.09–1.31)
Thoracic surgery	14/451 (3.1)	20/466 (4.3)	0.71 (0.30–1.47)
Vascular surgery	68/286 (23.8)	53/296 (17.9)	1.28 (0.83–1.95)
Gynecologic surgery	31/799 (3.9)	55/741 (7.4)	0.50 (0.25–0.84)
Urologic surgery	51/735 (6.9)	64/699 (9.2)	0.73 (0.48–1.09)
Surgical urgency			
Elective	243/3806 (6.4)	329/3753 (8.8)	0.70 (0.56–0.82)
Urgent or emergency	61/287 (21.3)	71/299 (23.7)	0.85 (0.61–1.16)
Surgical indication			
Oncologic	161/2536 (6.3)	241/2466 (9.8)	0.63 (0.49–0.77)
Nononcologic	139/1536 (9.0)	154/1561 (9.9)	0.87 (0.64–1.13)
Risk of red-cell transfusion			
<10%	98/2583 (3.8)	144/2523 (5.7)	0.64 (0.48–0.84)
≥10%	208/1573 (13.2)	259/1594 (16.2)	0.78 (0.62–0.95)



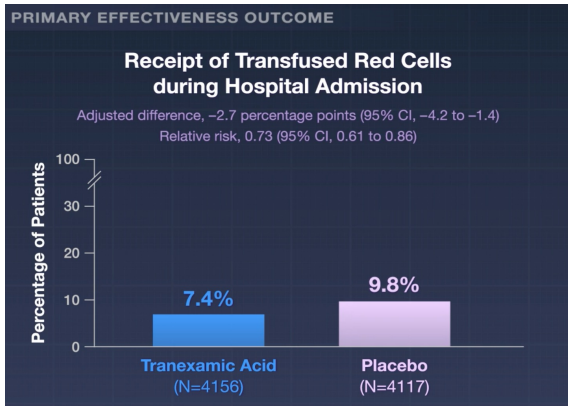
B Diagnosis of Venous Thromboembolism within 90 Days

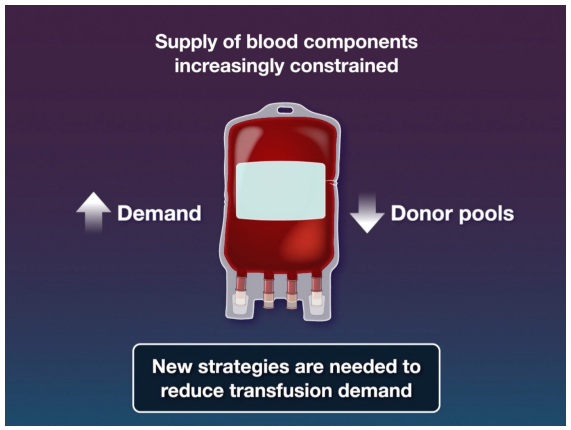
Subgroup	Tranexamic Acid	Placebo	Relative Risk (95% CI)
	no. of patients with event/total no. (%)		
Overall	86/4128 (2.08)	85/4052 (2.10)	0.96 (0.65–1.38)
Age			
<40 yr	<6/286	<6/286	5.08 (0.44–8.37)
40–64 yr	41/1808 (2.3)	34/1792 (1.9)	1.21 (0.73–2.05)
65–74 yr	22/1271 (1.7)	27/1204 (2.2)	0.77 (0.45–1.58)
≥75 yr	18/763 (2.4)	23/770 (3.0)	0.79 (0.47–1.59)
Surgical specialty			
General surgery	32/1351 (2.4)	26/1367 (1.9)	1.24 (0.77–1.86)
Orthopedic surgery	<6/86	<6/77	2.76 (0.33–4.95)
Spine surgery	<6/242	<6/217	0.92 (0.21–3.67)
Neurosurgery	<6/126	6/135 (4.4)	0.84 (0.16–2.25)
Thoracic surgery	8/449 (1.8)	16/455 (3.5)	0.52 (0.28–2.04)
Vascular surgery	<6/284	<6/286	1.83 (0.50–10.75)
Gynecologic surgery	12/789 (1.5)	12/729 (1.6)	0.84 (0.42–1.83)
Urologic surgery	14/731 (1.9)	15/691 (2.2)	0.90 (0.39–1.92)
Surgical urgency			
Elective	70/3782 (1.9)	74/3692 (2.0)	0.93 (0.68–1.42)
Urgent or emergency	15/283 (5.3)	11/295 (3.7)	1.31 (0.71–2.59)
Surgical indication			
Oncologic	60/2526 (2.4)	64/2421 (2.6)	0.92 (0.68–1.48)
Nononcologic	25/1527 (1.6)	20/1541 (1.3)	1.26 (0.71–2.07)
Risk of red-cell transfusion			
<10%	45/2564 (1.8)	49/2482 (2.0)	0.89 (0.61–1.37)
≥10%	41/1564 (2.6)	36/1570 (2.3)	1.15 (0.73–1.95)

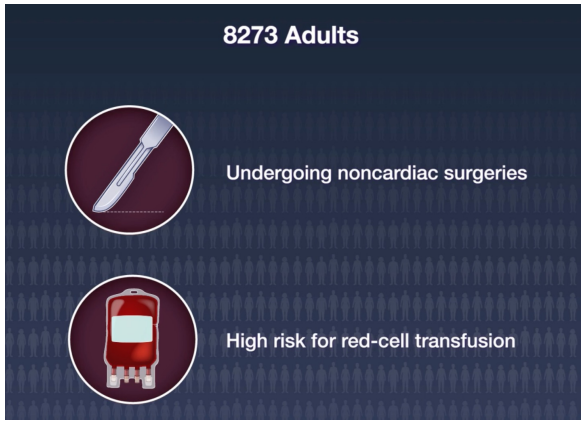


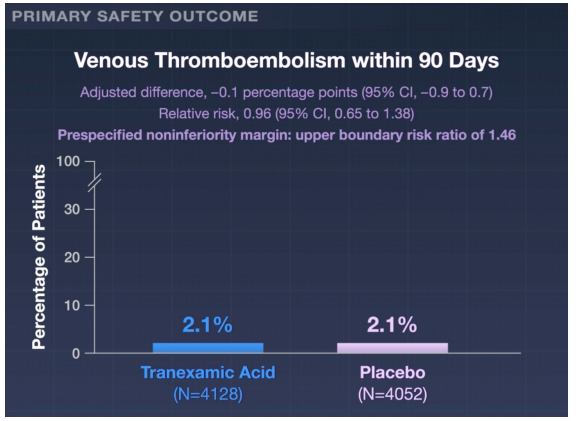

Major Noncardiac Surgery
Perioperative bleeding
Blood transfusion

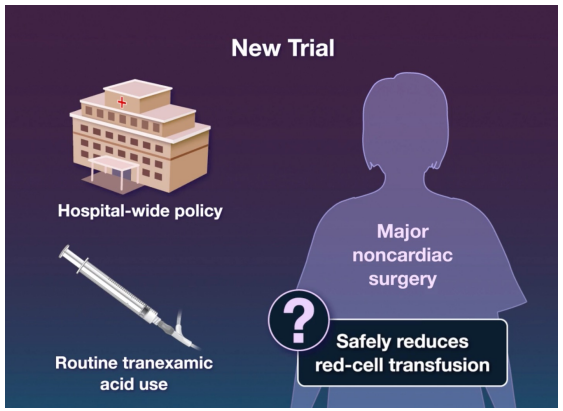

TRACTION Trial
• Randomized
• Multicenter
• Double-blind
• Cluster-crossover
• Placebo-controlled

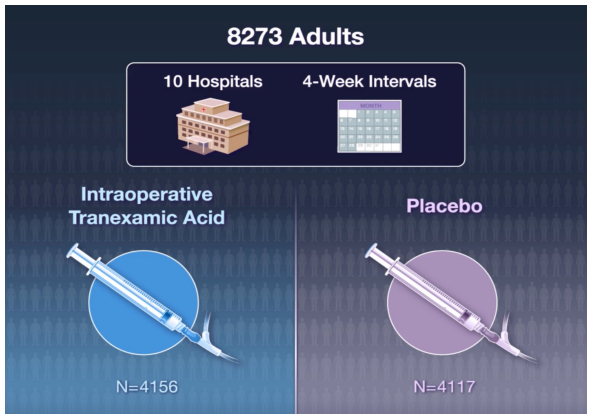

PRIMARY EFFECTIVENESS OUTCOME
Receipt of Transfused Red Cells during Hospital Admission
Adjusted difference, −2.7 percentage points (95% CI, −4.2 to −1.4)
Relative risk, 0.73 (95% CI, 0.61 to 0.86)
Percentage of Patients
100
30
20
10
0
7.4%
9.8%
Tranexamic Acid (N=4156)
Placebo (N=4117)

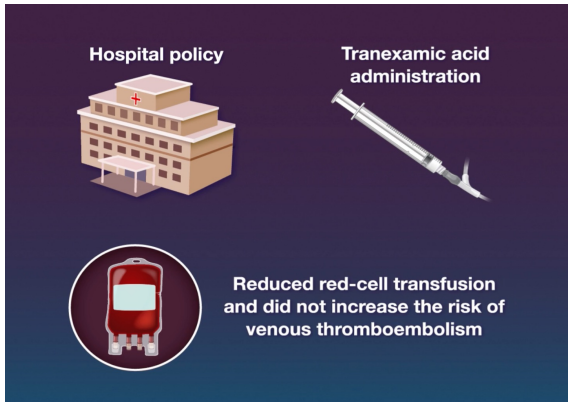

Supply of blood components increasingly constrained
Demand
Donor pools
New strategies are needed to reduce transfusion demand


8273 Adults
Undergoing noncardiac surgeries
High risk for red-cell transfusion


PRIMARY SAFETY OUTCOME
Venous Thromboembolism within 90 Days
Adjusted difference, −0.1 percentage points (95% CI, −0.9 to 0.7)
Relative risk, 0.96 (95% CI, 0.65 to 1.38)
Prespecified noninferiority margin: upper boundary risk ratio of 1.46
Percentage of Patients
100
30
20
10
0
2.1%
2.1%
Tranexamic Acid (N=4128)
Placebo (N=4052)


New Trial
Hospital-wide policy
Routine tranexamic acid use
Major noncardiac surgery
Safely reduces red-cell transfusion


8273 Adults
10 Hospitals
4-Week Intervals
Intraoperative Tranexamic Acid
Placebo
N=4156
N=4117


Hospital policy
Tranexamic acid administration
Reduced red-cell transfusion and did not increase the risk of venous thromboembolism

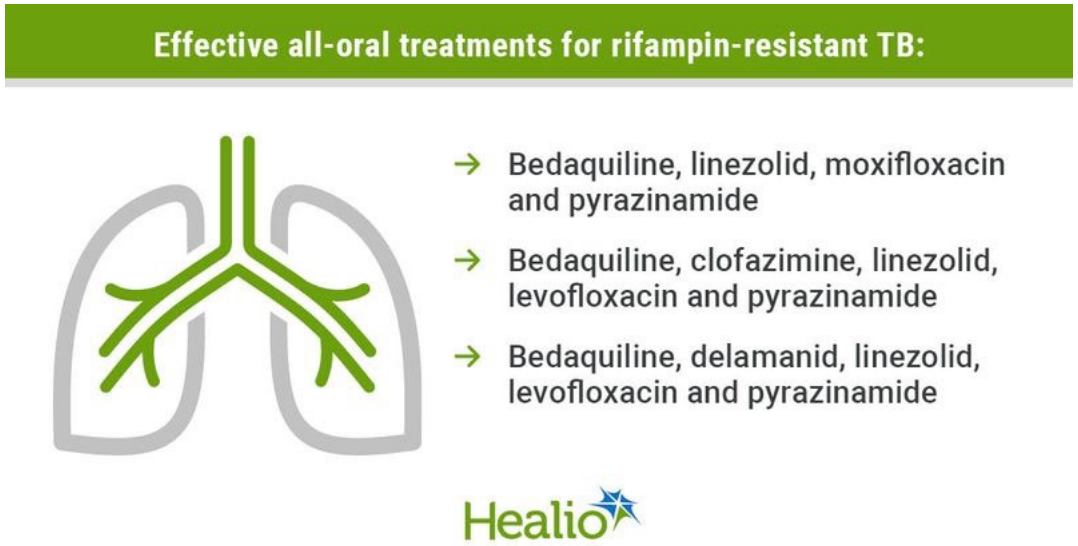
Eine **Rifampicin-resistente Tuberkulose (RR-TB)** liegt vor, wenn die auslösenden Bakterien (*Mycobacterium tuberculosis*) nicht mehr auf das extrem wichtige Erstlinien-Medikament Rifampicin ansprechen. Da Rifampicin das Fundament der Standardtherapie ist, gilt eine RR-TB klinisch und epidemiologisch als ebenso kritisch wie eine multiresistente Tuberkulose (MDR-TB) und erfordert völlig andere, spezialisierte Behandlungsstrategien.

Wichtige Fakten im Überblick

•**Definition**: Nachweis einer Resistenz gegen Rifampicin mittels genotypischer (molekularbiologischer) oder phänotypischer Labortests. Es ist dabei unabhängig, ob gleichzeitig eine Resistenz gegen Isoniazid (MDR-TB) oder andere Medikamente vorliegt.

•**Globale Relevanz**: Jährlich erkranken weltweit rund **410.000 Menschen** an einer MDR/RR-TB. Sie stellt eine erhebliche Bedrohung für die öffentliche Gesundheit dar.

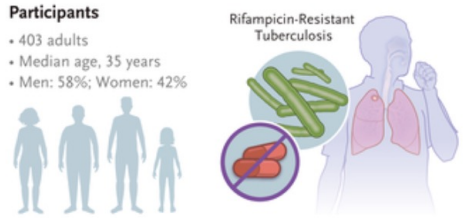
•**Ursachen**: Häufig entsteht die Resistenz durch unregelmäßige Medikamenteneinnahme, vorzeitigen Behandlungsabbruch oder die direkte Übertragung bereits resistenter Bakterienstämme von Mensch zu Mensch

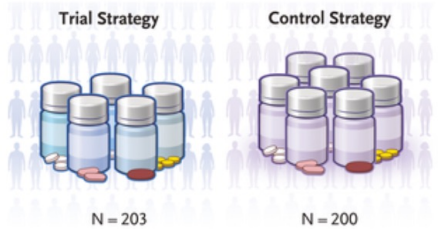


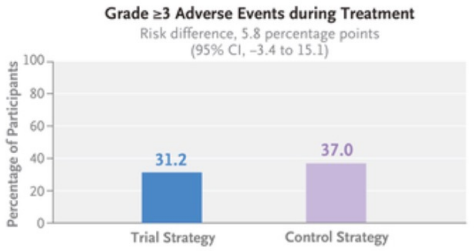
bedaquiline, linezolid, delamanid, and levofloxacin or clofazimine (or both)

A Pragmatic Trial of a 6-Month Strategy for Rifampicin-Resistant Tuberculosis

Safer, more effective treatment regimens for rifampicin-resistant tuberculosis are needed. We conducted a phase 3, open-label, pragmatic, randomized, controlled noninferiority trial in South Africa to assess a 6-month treatment strategy for pulmonary rifampicin-resistant tuberculosis. Participants with pulmonary rifampicin-resistant tuberculosis who were 6 years of age or older were randomly assigned to a regimen consisting of bedaquiline, linezolid, delamanid, and levofloxacin or clofazimine or both for 6 months (trial-strategy group) or the 9-month standard-of-care treatment regimen that was current in South Africa (control group). Persons who were pregnant or breastfeeding and those who had fluoroquinolone-resistant tuberculosis were included in the trial population. Treatment in both groups was adjusted on the basis of results of second-line drug susceptibility testing. The primary efficacy end point was a successful outcome (cure or completion of treatment) at the end of treatment and at 76 weeks after randomization. The noninferiority margin was 10 percentage points. The primary safety end point was an adverse event of grade 3 or higher.







The World Health Organization (WHO) estimated that tuberculosis that is resistant to rifampin (also known as rifampicin) developed in 400,000 persons in 2023. Until recently, treatment regimens for rifampicin-resistant tuberculosis included up to seven medications and were administered for 9 to 18 months. The pill burden and complexity of these regimens, coupled with associated adverse events, resulted in poor treatment outcomes.

Since 2012, three new drugs for rifampicin-resistant tuberculosis — bedaquiline, pretomanid, and delamanid — have been approved by at least one stringent regulatory authority as well as the South African Health Products Regulatory Authority. In addition, treatment with repurposed medications such as linezolid, levofloxacin, moxifloxacin, and clofazimine has shown improved outcomes in patients with rifampicin-resistant tuberculosis.

Trial Design and Participants

In this phase 3, open-label, pragmatic, randomized, controlled noninferiority trial, we enrolled a broad group of participants with pulmonary rifampicin-resistant tuberculosis from two urban sites in South Africa. Eligible participants had pulmonary tuberculosis with resistance to rifampicin with or without resistance to isoniazid or fluoroquinolones (or both).

Enrollment and Interventions

Participants were randomly assigned to receive bedaquiline, linezolid, delamanid, and levofloxacin or clofazimine or both for 6 months (trial-strategy group) or the 9-month standard-of-care treatment for rifampicin-resistant tuberculosis (control group). Randomization was performed with the use of a Web-based system, in blocks of varying sizes, with concealed assignment and with stratification according to trial site and human immunodeficiency virus (HIV) status.

End Points

The primary efficacy end point was a successful outcome (cure or completion of treatment) at the end of treatment and at 76 weeks after randomization. The definition was derived from WHO definitions.

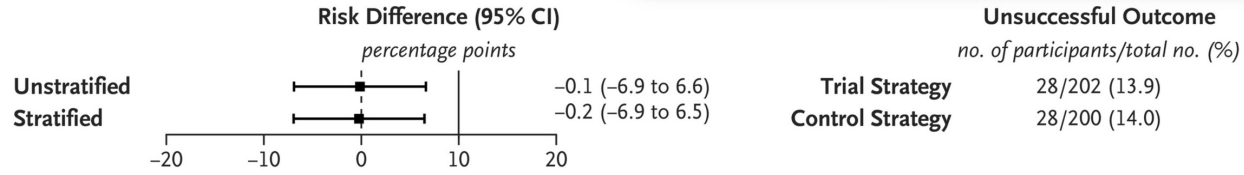
Characteristic	Trial Strategy (N=203)	Control Strategy (N=200)	Total (N=403)
Site of enrollment — no. (%)			
Gqeberha	184 (90.6)	182 (91.0)	366 (90.8)
Durban	19 (9.4)	18 (9.0)	37 (9.2)
Age			
Median (IQR) — yr	35.0 (28.0–43.0)	34.5 (27.0–44.0)	35.0 (28.0–43.0)
<18 yr — no. (%)	13 (6.4)	17 (8.5)	30 (7.4)
Female sex — no. (%)	85 (41.9)	85 (42.5)	170 (42.2)
Race — no. (%)†			
Black	150 (73.9)	160 (80.0)	310 (76.9)
Mixed	50 (24.6)	40 (20.0)	90 (22.3)
White	3 (1.5)	0	3 (0.7)
Body-mass index			
Median (IQR)	19.1 (17.0–22.0)	19.3 (17.2–22.4)	19.2 (17.1–22.2)
<18.5 — no. (%)	85 (41.9)	82 (41.0)	167 (41.4)
HIV status — no. (%)			
Positive	105 (51.7)	100 (50.0)	205 (50.9)
Negative	98 (48.3)	100 (50.0)	198 (49.1)
CD4 count			
Median (IQR) — cells/mm^3	168.0 (85.0–298.5)	229.0 (87.0–395.0)	194.0 (87.0–362.0)
<200 cells/mm^3 — no. (%)	50 (24.6)	38 (19.0)	88 (21.8)
Missing data — no. (%)	17 (8.4)	19 (9.5)	36 (8.9)
Highest level of education — no. (%)			
No schooling	1 (0.5)	0	1 (0.2)
Primary school not completed	20 (9.9)	16 (8.0)	36 (8.9)
Primary school completed	12 (5.9)	11 (5.5)	23 (5.7)
High school not completed	125 (61.6)	126 (63.0)	251 (62.3)
High school completed	32 (15.8)	45 (22.5)	77 (19.1)
Tertiary education not completed	6 (3.0)	2 (1.0)	8 (2.0)
Tertiary education completed	7 (3.4)	0	7 (1.7)
Previous diagnosis of tuberculosis — no. (%)			
None	92 (45.3)	98 (49.0)	190 (47.1)
Drug-susceptible tuberculosis	105 (51.7)	99 (49.5)	204 (50.6)
Rifampicin-resistant tuberculosis	6 (3.0)	3 (1.5)	9 (2.2)
Cavities on chest radiography — no. (%)			
No	55 (27.1)	58 (29.0)	113 (28.0)
Yes	37 (18.2)	40 (20.0)	77 (19.1)
Missing data	111 (54.7)	102 (51.0)	213 (52.9)
Drug resistance profile — no. (%)			
Susceptible to fluoroquinolones, no susceptibility testing for bedaquiline performed	123 (60.6)	123 (61.5)	246 (61.0)
Resistant to fluoroquinolones, no susceptibility testing for bedaquiline performed	7 (3.4)	15 (7.5)	22 (5.5)
Resistant to fluoroquinolones and susceptible to bedaquiline	35 (17.2)	24 (12.0)	59 (14.6)
Resistant to fluoroquinolones and bedaquiline	0	4 (2.0)	4 (1.0)
No susceptibility testing for fluoroquinolones or bedaquiline performed	38 (18.7)	34 (17.0)	72 (17.9)
Susceptible to linezolid	35 (17.2)	28 (14.0)	63 (15.6)

Primary Efficacy Analysis (Intention-to-Treat Population).

Variable	Trial Strategy (N=202)	Control Strategy (N=200)	Total (N=402)
		number (percent)	
Primary end point: successful outcome at end of treatment and at end of follow-up	174 (86.1)	172 (86.0)	346 (86.1)
Cure at end of treatment and at end of follow-up	160 (79.2)	162 (81.0)	322 (80.1)
Cure at end of treatment and negative culture at last visit	14 (6.9)	10 (5.0)	24 (6.0)
Unsuccessful outcome at end of treatment	14 (6.9)	22 (11.0)	36 (9.0)
Treatment failure	7 (3.5)	10 (5.0)	17 (4.2)
Lost to follow-up during treatment	2 (1.0)	4 (2.0)	6 (1.5)
Died during treatment	4 (2.0)	7 (3.5)	11 (2.7)
Not evaluated because of withdrawn consent	1 (0.5)	1 (0.5)	2 (0.5)
Unsuccessful outcome at end of follow-up	14 (6.9)	6 (3.0)	20 (5.0)
Recurrence after cure at end of treatment	10 (5.0)	4 (2.0)	14 (3.5)
Died after cure at end of treatment	4 (2.0)	2 (1.0)	6 (1.5)

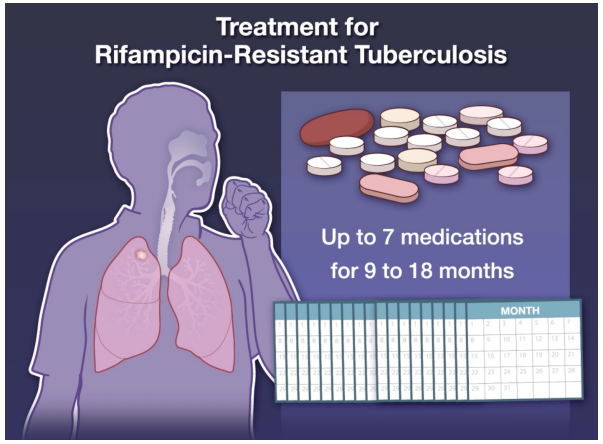
Safety (Safety Population).

Adverse Event	Trial Strategy (N=202)	Control Strategy (N=200)	Total (N=402)	Risk Difference (95% CI)†
Grade ≥3 event	69 (34.2)	76 (38.0)	145 (36.1)	3.8 (−5.5 to 13.2)
Grade ≥3 event during treatment	63 (31.2)	74 (37.0)	137 (34.1)	5.8 (−3.4 to 15.1)
Treatment-related grade ≥3 event‡	52 (25.7)	56 (28.0)	108 (26.9)	2.3 (−6.4 to 10.9)
Serious adverse event at any time	45 (22.3)	44 (22.0)	89 (22.1)	−0.3 (−8.4 to 7.8)
Serious adverse event during treatment	38 (18.8)	42 (21.0)	80 (19.9)	2.2 (−5.6 to 10.0)
Notable event§	36 (17.8)	31 (15.5)	67 (16.7)	−2.3 (−9.6 to 5.0)
Death at any time	10 (5.0)	10 (5.0)	20 (5.0)	0.0 (−4.2 to 4.3)
Death during treatment	6 (3.0)	8 (4.0)	14 (3.5)	1.0 (−2.6 to 4.6)
Death after treatment	4 (2.0)	2 (1.0)	6 (1.5)	−1.0 (−3.3 to 1.4)
Anemia leading to treatment discontinuation	10 (5.0)	8 (4.0)	18 (4.5)	−1.0 (−5.0 to 3.1)
Anemia leading to blood transfusion	20 (9.9)	11 (5.5)	31 (7.7)	−4.4 (−9.6 to 0.8)
Grade ≥3 liver abnormality	4 (2.0)	9 (4.5)	13 (3.2)	2.5 (−0.9 to 6.0)
Peripheral neuropathy leading to treatment discontinuation	10 (5.0)	7 (3.5)	17 (4.2)	−1.5 (−5.4 to 2.5)
Optic neuropathy leading to treatment discontinuation	7 (3.5)	2 (1.0)	9 (2.2)	−2.5 (−5.3 to 0.4)
QTcF ≥480 msec	12 (5.9)	19 (9.5)	31 (7.7)	3.6 (−1.7 to 8.8)
QTcF ≥500 msec	5 (2.5)	7 (3.5)	12 (3.0)	1.0 (−2.3 to 4.4)
Treatment-related serious adverse events‡				
Related to linezolid	20 (9.9)	16 (8.0)	36 (9.0)	−1.9 (−7.5 to 3.7)
Related to bedaquiline	4 (2.0)	7 (3.5)	11 (2.7)	1.5 (−1.7 to 4.7)
Related to levofloxacin	3 (1.5)	4 (2.0)	7 (1.7)	0.5 (−2.0 to 3.1)
Related to clofazimine	6 (3.0)	7 (3.5)	13 (3.2)	0.5 (−2.9 to 4.0)
Related to delamanid	2 (1.0)	2 (1.0)	4 (1.0)	0.0 (−1.9 to 2.0)

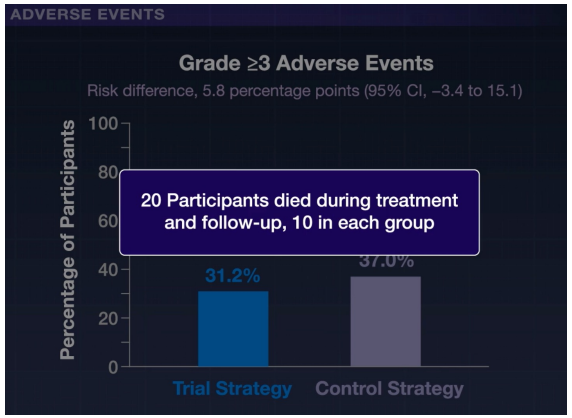


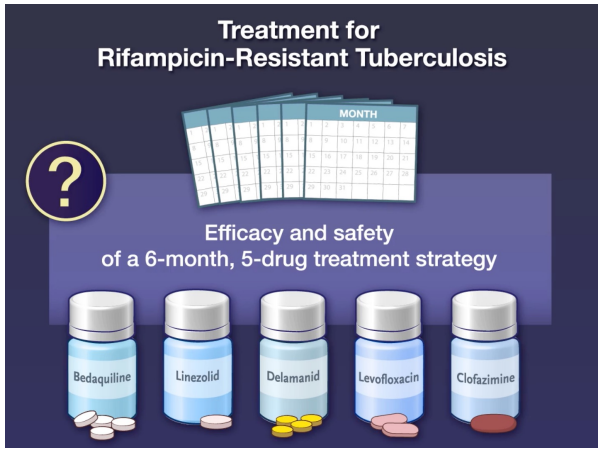
Primary Efficacy Analysis (Intention-to-Treat Population).

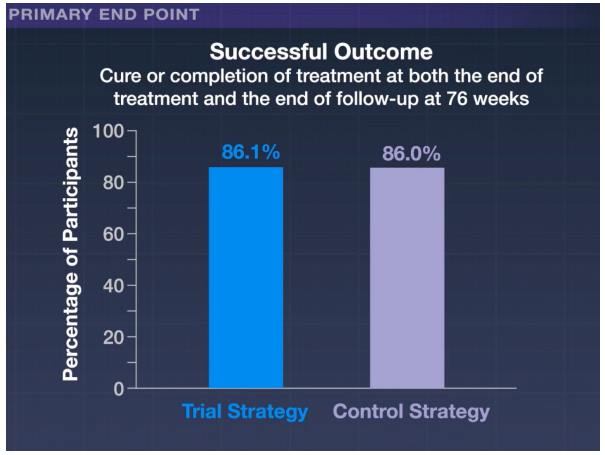
The intention-to-treat population included all the participants who had undergone randomization, with the exception of one participant in the trial-strategy group, who underwent randomization in error and was excluded from the analyses. The primary efficacy end point was a successful outcome (cure or completion of treatment) at the end of treatment and at 76 weeks after randomization. An unsuccessful outcome was defined as treatment failure, loss to follow-up, death, or no evaluation. The risk difference is the between-group difference in the percentage of participants who met the criteria for the primary end point. The solid vertical line indicates the noninferiority margin of 10 percentage points. The primary efficacy analysis was stratified according to human immunodeficiency virus status and trial site.


Treatment for
Rifampicin-Resistant Tuberculosis
Up to 7 medications
for 9 to 18 months
MONTH

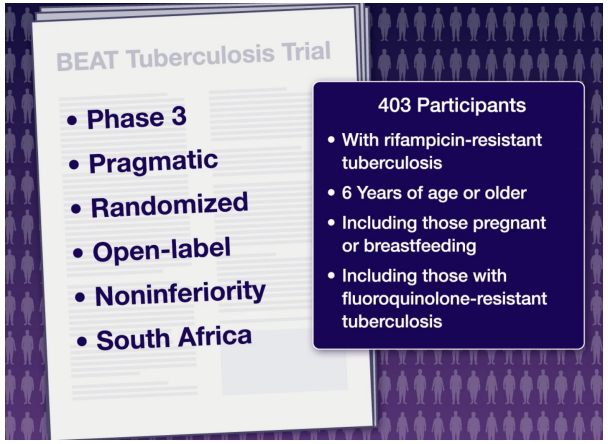

Trial Strategy
Bedaquiline, linezolid, delamanid, and levofloxacin or clofazimine or both
Bedaquiline
Linezolid
Delamanid
Levofloxacin
Clofazimine
6 months
N=203
Control Strategy
Standard treatment at time of enrollment
9 months or longer
N=200

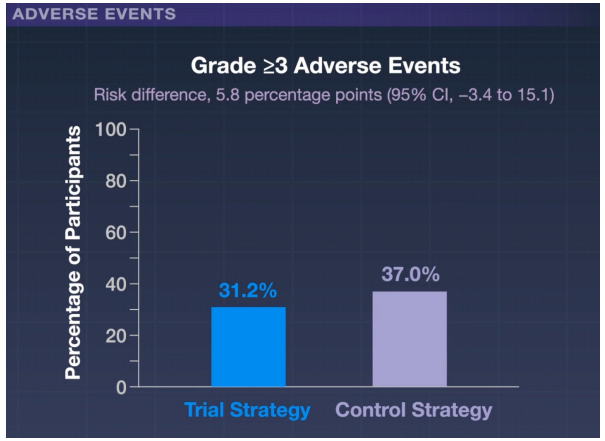

ADVERSE EVENTS
Grade ≥3 Adverse Events
Risk difference, 5.8 percentage points (95% CI, −3.4 to 15.1)
Percentage of Participants
100
80
60
40
20
0
20 Participants died during treatment and follow-up, 10 in each group
31.2%
37.0%
Trial Strategy
Control Strategy


Treatment for
Rifampicin-Resistant Tuberculosis
?
MONTH
Efficacy and safety
of a 6-month, 5-drug treatment strategy
Bedaquiline
Linezolid
Delamanid
Levofloxacin
Clofazimine


PRIMARY END POINT
Successful Outcome
Cure or completion of treatment at both the end of treatment and the end of follow-up at 76 weeks
Percentage of Participants
100
80
60
40
20
0
86.1%
86.0%
Trial Strategy
Control Strategy


Rifampicin-Resistant Tuberculosis
Bedaquiline
Linezolid
Delamanid
Levofloxacin
Clofazimine
A 6-month strategy of bedaquiline, linezolid, and delamanid with levofloxacin or clofazimine or both
was noninferior to the
standard-of-care strategy in South Africa


BEAT Tuberculosis Trial
• Phase 3
• Pragmatic
• Randomized
• Open-label
• Noninferiority
• South Africa
403 Participants
• With rifampicin-resistant tuberculosis
• 6 Years of age or older
• Including those pregnant or breastfeeding
• Including those with fluoroquinolone-resistant tuberculosis


ADVERSE EVENTS
Grade ≥3 Adverse Events
Risk difference, 5.8 percentage points (95% CI, −3.4 to 15.1)
Percentage of Participants
100
80
60
40
20
0
31.2%
37.0%
Trial Strategy
Control Strategy

Bei der **CAR-T-Zell-Therapie** (T-Zellen mit chimärem Antigenrezeptor) werden körpereigene weiße Blutkörperchen im Labor genetisch so umprogrammiert, dass sie zielgenau Krebszellen oder fehlgeleitete Immunzellen (bei Autoimmunerkrankungen) erkennen und zerstören. Sie gilt als hochwirksame, personalisierte Immuntherapie.

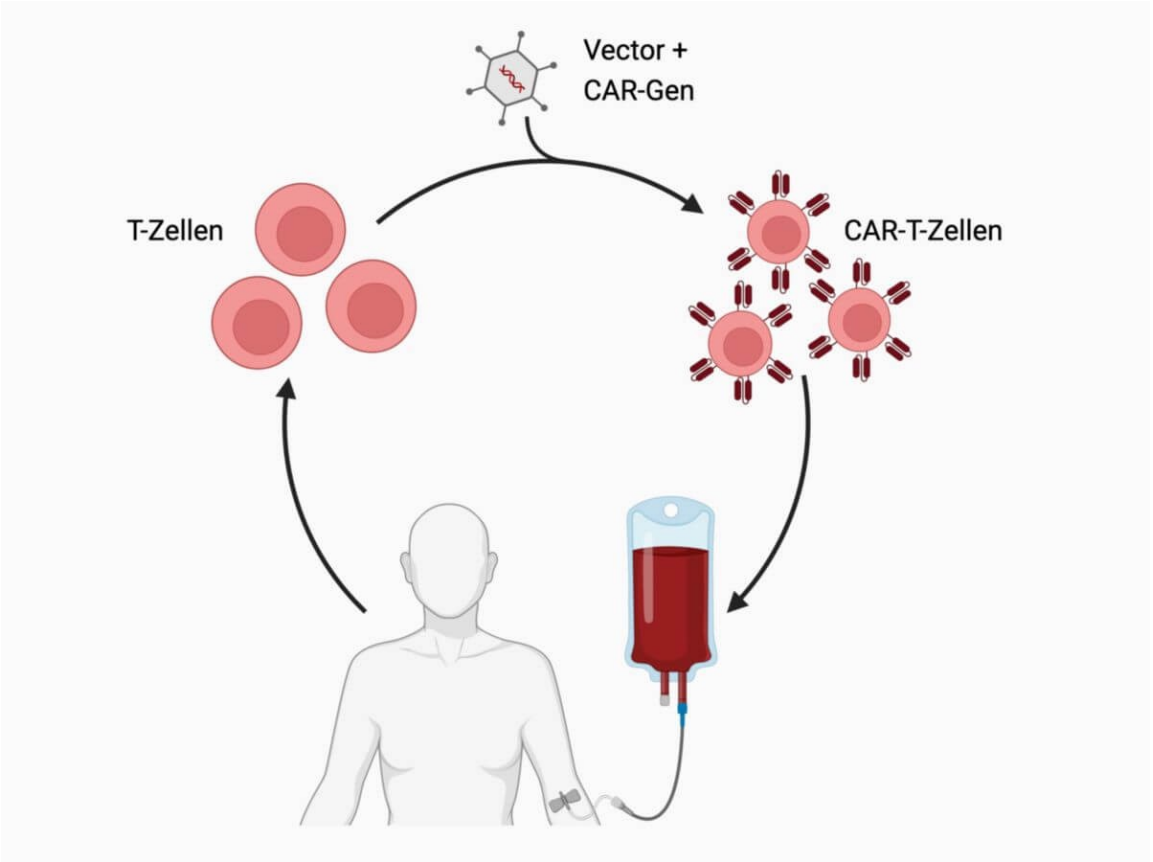
Wie die Therapie funktioniert

1.Entnahme (Leukapherese): Dem Patienten werden in einer etwa 3- bis 4-stündigen Sitzung körpereigene T-Zellen aus dem Blut entnommen.

2.Umprogrammierung: Im Labor werden die Zellen mit einem künstlichen Rezeptor (dem CAR) ausgestattet, der als „Schlüssel“ für die spezifischen Antigene der Krankheitszellen dient.

3.Vermehrung: Die gentechnisch veränderten Zellen werden millionenfach vermehrt .

4.Infusion: Über eine Infusion gelangen die Zellen zurück in den Körper des Patienten . Meist geht dem eine milde Chemotherapie (Lymphodepletion) voraus, um Platz im Immunsystem zu schaffen.



Ten-Year Outcomes after CAR T-Cell Therapy for B-Cell Lymphomas

Anti-CD19 chimeric antigen receptor (CAR) T-cell therapy is a standard treatment for relapsed or refractory B-cell non-Hodgkin lymphomas. Long-term results and curative potential remain uncertain.

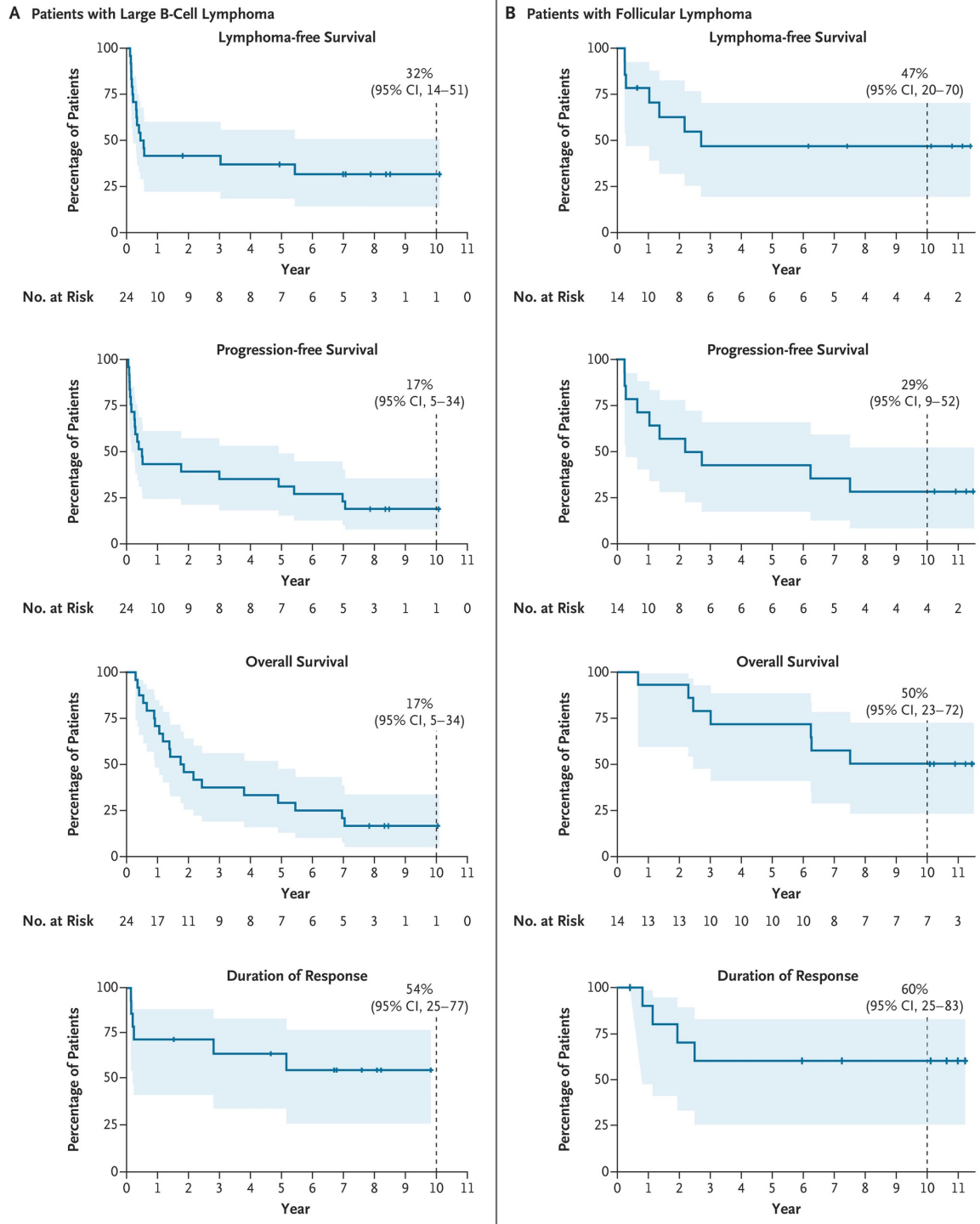
We evaluated long-term outcomes in 38 patients with relapsed or refractory B-cell non-Hodgkin lymphomas (24 patients with large B-cell lymphoma and 14 with follicular lymphoma) who had been treated with CTL019 (now called tisagenlecleucel) — autologous T cells expressing CD19-directed, 4-1BB–costimulated chimeric receptors. Lymphoma-free survival was defined as the time from the tisagenlecleucel infusion to relapse or lymphoma-related death. The incidence of non–relapse-related death and second primary cancer was estimated with the Aalen–Johansen method. The data-cutoff date was October 1, 2025.

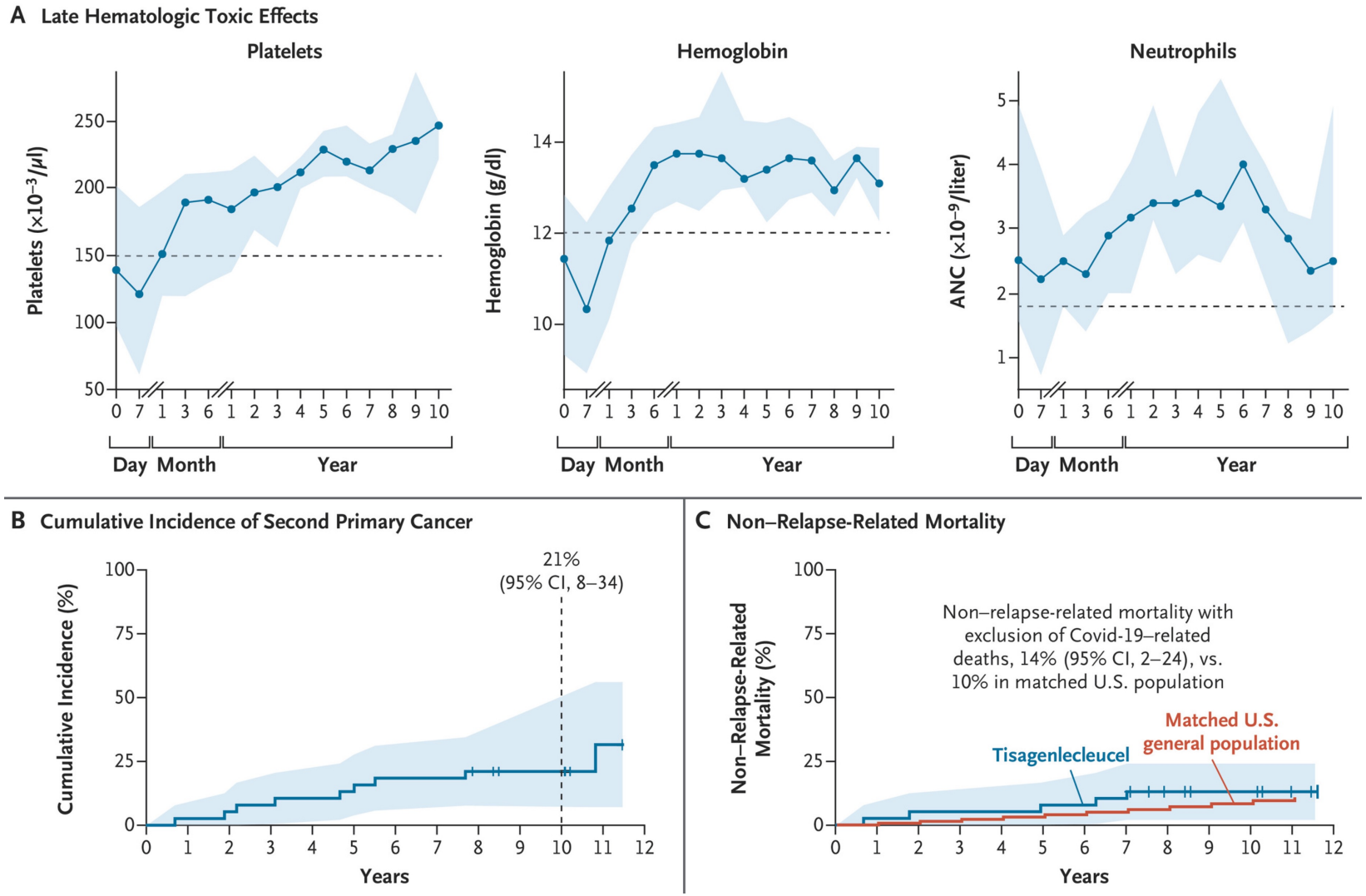
Conclusions

Among patients with heavily pretreated B-cell non-Hodgkin lymphoma, a single infusion of tisagenlecleucel led to decade-long remissions (lymphoma-free survival) in approximately one third of the patients with large B-cell lymphomas and in nearly one half of those with follicular lymphoma.

Long-term surveillance is essential to determine whether CAR T-cell therapies can result in lifelong remission; late recurrences after chemoimmunotherapy are well recognized. Extended follow-up also provides an opportunity to characterize late adverse events, including non–relapse-related death and second primary cancers. Persistent cytopenias, prolonged B-cell aplasia, and hypogammaglobulinemia may increase the risk of infection for years after the infusion. The frequency and clinical consequences of these effects over an extended period remain unclear. Here, we report the 10-year follow-up of patients with refractory or multiply relapsed B-cell non-Hodgkin lymphoma who had been treated with CD19-directed CAR T cells in a single-center, phase 2 clinical trial, providing a decade-long evaluation of efficacy, toxic effects, immune reconstitution, and survival.

Characteristic	Patients (N=12)
Median age (range) — yr	57 (49–71)
Sex — no. (%)	
Female	9 (75)
Male	3 (25)
Diagnosis — no. (%)	
Follicular lymphoma	6 (50)
Diffuse large B-cell lymphoma, not otherwise specified	2 (17)
T-cell histiocyte-rich large B-cell lymphoma	1 (8)
Transformed follicular lymphoma	3 (25)
Stage IV disease at enrollment — no. (%)	6 (50)
Median no. of previous therapies (range)	4 (2–9)
Previous autologous stem-cell transplantation — no. (%)	6 (50)
Previous allogeneic stem-cell transplantation — no. (%)	0
Lactate dehydrogenase level ≥ULN at infusion — no. (%)	5 (42)





Long-Term Safety Profile.

Panel A shows longitudinal platelet counts (left), hemoglobin levels (center), and absolute neutrophil counts (ANC; right). In these three graphs, the line indicates the median, the shaded area the interquartile range, and the dashed line the lower limit of the normal range. Panel B shows the cumulative incidence of second primary cancer, with the use of the Aalen–Johansen estimator with death as a competing risk. Panel C shows the cumulative incidence of non–relapse-related death among patients who received CTL019 (now called tisagenlecleucel) with the exclusion of deaths due to coronavirus disease 2019 (Covid-19), as assessed by the Aalen–Johansen method and as compared with the matched U.S. mortality curve (red), which was derived from the 2022 National Institutes of Health life table.[23] In Panels B and C, tick marks indicate censored data, and the shaded area the 95% confidence interval for the study data.

Discussion

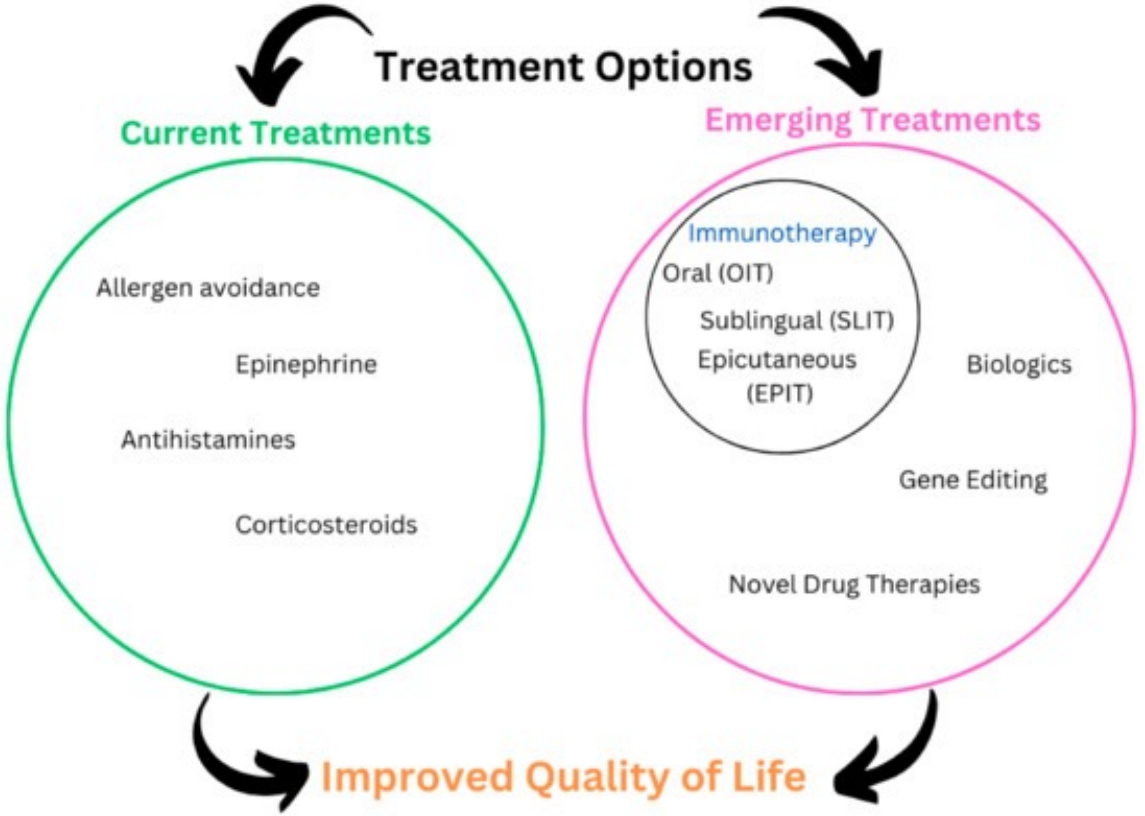
In this 10-year follow-up study of CD19-directed CAR T-cell therapy for relapsed or refractory B-cell non-Hodgkin lymphoma, we found that most treatment failures or relapses occurred within the first year after the infusion, a result that is consistent with previous reports.

The 10-year cumulative incidence of second primary cancer was 21%. No cases of CAR T-cell–related lymphomas were observed. The observed incidence of second cancer exceeds the 6% incidence that was reported by Tix et al. in a large meta-analysis, a finding that possibly reflects the longer observation period or extensive pretreatment (or both) in our study cohort.

Nearly half the patients with a long-term response had persistent B-cell aplasia, and 42% were continuing to receive intravenous immune globulin at 10 years. These findings are in line with previous reports and support the use of infection prophylaxis and immune globulin supplementation as indicated by immunologic recovery.

This study is limited by its single-center design, modest sample size, and the lack of systematically collected correlative data at late time points, which precludes a conclusive, detailed characterization of immune-cell subset reconstitution and mechanisms underlying specific second primary cancers. Nevertheless, the study establishes that CD19-directed CAR T-cell therapy can lead to exceptionally long remissions and possibly cure some patients with relapsed or refractory non-Hodgkin lymphoma.

Eine Erdnussallergie ist eine der häufigsten und gefährlichsten Nahrungsmittelallergien.



Erdnuss-Immuntherapie ist eine medizinische Behandlung, die darauf abzielt, die Toleranz gegenüber Erdnussproteinen schrittweise zu erhöhen, um schwere allergische Reaktionen bei versehentlichem Verzehr zu verhindern. Es handelt sich hierbei um eine Desensibilisierung und ausdrücklich **nicht um eine Heilung** der Erdnussallergie. Ziel ist es, den Körper "bissfest" (*bite-proof*) zu machen, sodass minimale Spuren im Alltag keine lebensbedrohliche Anaphylaxie mehr auslösen.

Behandlungsformen der Immuntherapie

•**Orale Immuntherapie (OIT)**: Der Patient nimmt täglich winzige, exakt dosierte Mengen an Erdnussprotein (z. B. Erdnussmehl) über den Mund ein. Die Dosis wird in einer Fachklinik schrittweise gesteigert.

•**Sublinguale Immuntherapie (SLIT)**: Hierbei werden flüssige Erdnussextrakte unter die Zunge getropft. Sie gilt als potenziell nebenwirkungsärmer, ist im Vergleich zur OIT jedoch seltener verbreitet.

•**Epikutane Immuntherapie (EPIT)**: Ein Hautpflaster (*Peanut Patch*) gibt täglich mikroskopische Mengen Erdnussprotein über die Haut ab. Diese Methode befindet sich primär in der klinischen Anwendung und Entwicklung.

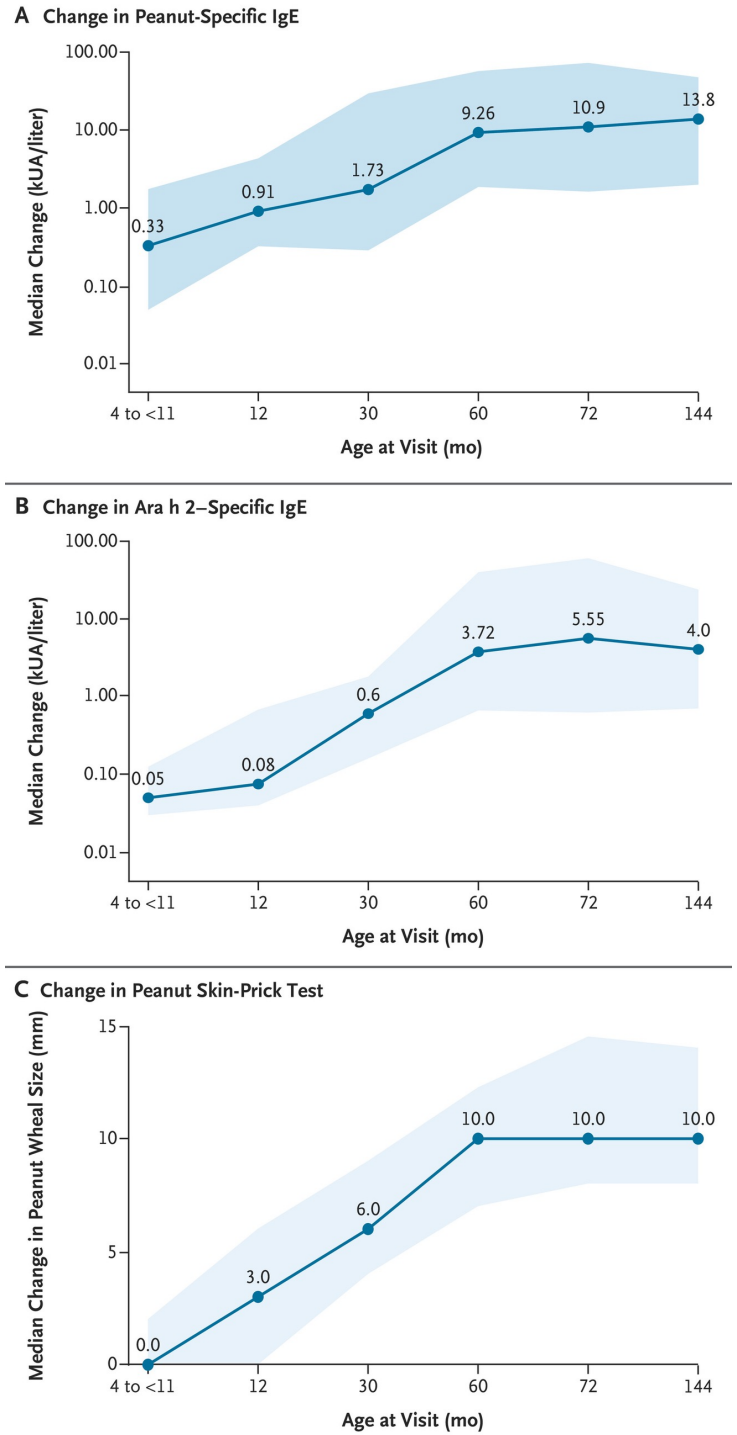
Prevention and Treatment of Peanut Allergy

A 4-month-old infant of East Asian heritage had been brought to the clinic for routine care. The infant had severe, generalized atopic dermatitis that developed at 6 weeks of age and had been treated with topical glucocorticoid agents. The infant was exclusively breast-fed, and there was a plan to continue breast-feeding until the child reached 6 months of age. The parents asked about introducing solid foods and preventing food allergies. The pediatrician recommended including smooth peanut butter in the infant's diet when weaning to prevent peanut allergy. Now, 3 months later, the family returns and reports that hives and vomiting had developed after the first introduction of peanut butter at 7 months of age. Allergy tests are performed, and a diagnosis of peanut allergy is confirmed by a positive skin-prick test (wheal diameter, 6 mm) and peanut-specific IgE level of 1.8 kU per liter. How would you counsel parents about reducing the risk of peanut allergy, and how would you manage this child's peanut allergy?

KEY POINTS

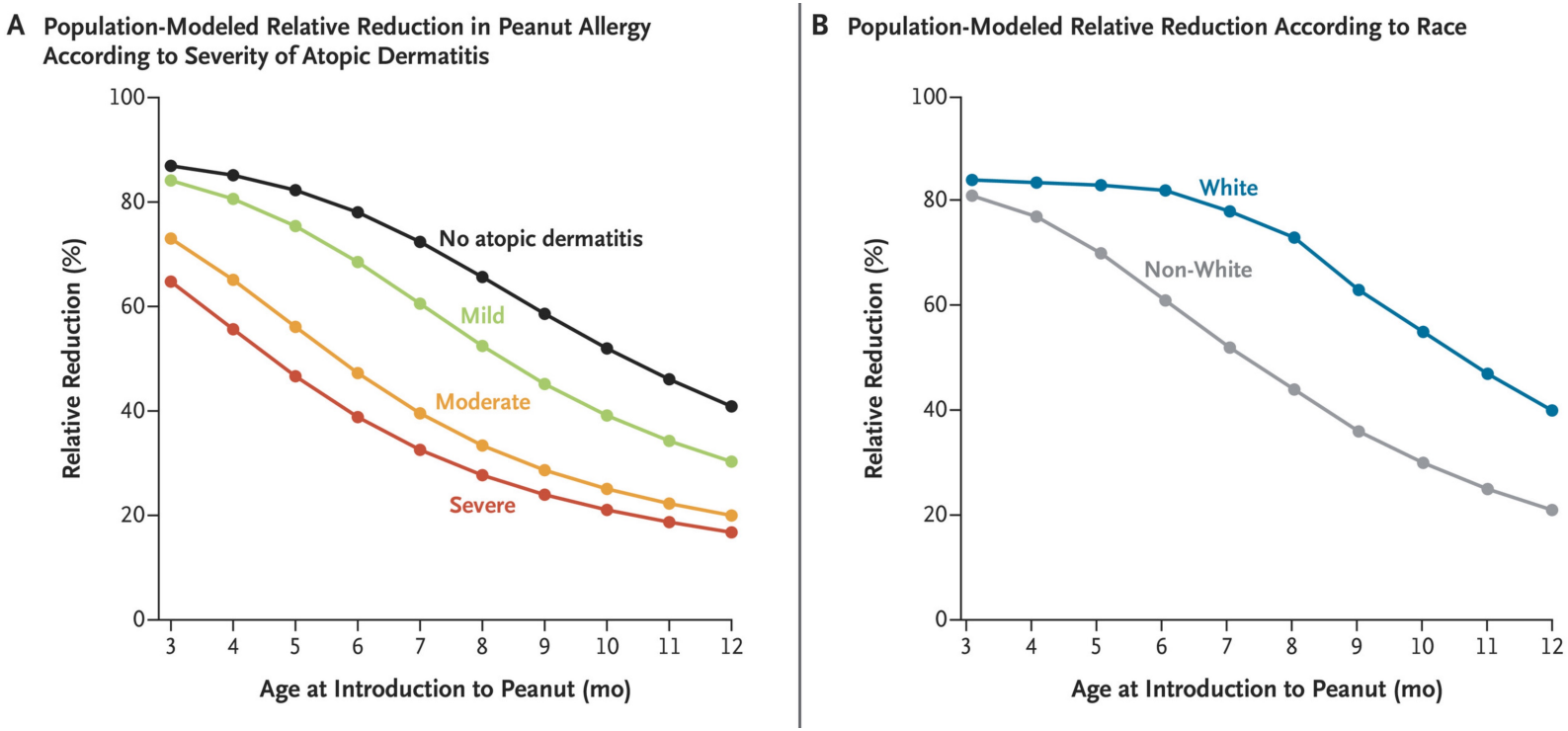
Prevention and Treatment of Peanut Allergy

- Peanuts should be introduced at 4 to 6 months of age in infants at high risk for allergy and at approximately 6 months of age in other infants.
- The window of opportunity for prevention is narrow, and every month of delayed introduction increases risk, particularly for infants who have severe atopic dermatitis or who are of non-White race.
- Appropriate prevention involves the ingestion of approximately 2 g of peanut protein weekly for infants at low risk, whereas infants at high risk should receive higher doses (4 to 6 g per week).
- Peanut immunotherapy is more effective, safer, and more likely to induce clinical remission in children in whom it was initiated at an early age than in children who began immunotherapy later.
- The natural history of peanut allergy follows a trajectory of increased allergic immune responses to peanut and increased clinical reactivity over time.
- Public health interventions that involve the early introduction of peanuts for all infants are likely to prevent peanut allergy in most infants and to enable earlier diagnosis and treatment in those who have peanut allergy; this approach is expected to lead to earlier and better treatment outcomes.



Change in Median Biomarker Levels in the LEAP, LEAP-On, and LEAP-Trio Cohorts.

Shown are changes in biomarker levels in the trial cohorts over the duration of the Learning Early About Peanut Allergy (LEAP) trial and two extensions of the LEAP trial: the Persistence of Oral Tolerance to Peanut (LEAP-On) trial and the Follow-up of LEAP Participants and Their Families (LEAP-Trio) trial.[7,11,24] Shading represents interquartile ranges.



Modeled Effect of Delayed Peanut Introduction on the Development of Peanut Allergy.

Shown is the relative reduction in the burden of peanut allergy normalized to the age at introduction in a population stratified according to atopic-dermatitis severity (Panel A) and race (Panel B). The relative reductions estimate the treatment effect of early peanut introduction and avoidance. Figure modified and adapted (under a Creative Commons Attribution license) from Roberts et al.[6]

Data Regarding Peanut Allergy from Major Trials on the Prevention of Food Allergy.

Trial	No. of Participants	Atopic Dermatitis	Intervention	Race or Ethnic Group	Outcome Measures	Results for Avoidance vs. Consumption	
						Intention-to-Treat Population	Per-Protocol Population
LEAP[7]							
Overall	640 infants at high risk	Severe	Early peanut introduction vs. avoidance Goal of 6 g peanut protein per wk	467 White (73%) 77 South Asian (12%) 64 Black (10%) 32 Other (5%)	Peanut allergy prevalence at age 5 yr	Allergy prevalence: 17% vs. 3% (difference, 81%)	Allergy prevalence: 15.2% vs. 1.9% (difference, 87.5%)
Negative skin-prick test at baseline	542					13.7% vs. 1.9% (difference, 86%)	12.0% vs. 0.4% (difference, 96.6%)
Positive skin-prick test at baseline	98					35.3% vs. 10.6% (difference, 70%)	8.1% vs. 6.8% (difference, 75.8%)
EAT[20]	1303, general population	Included infants with or without atopic dermatitis	Early introduction of 6 allergenic foods: milk, peanut, sesame, fish, egg, wheat Treatment group: goal of 4 g of peanut protein per wk Control group: avoided peanut	1029 White (79%) 104 South Asian (8%) 91 Black (7%) 78 Other (6%)	Food allergy prevalence at age 3 yr	2.5% vs. 1.2% (P=0.11)	2.5% vs. 0% (P=0.003)
PreventADALL[21]	2397, general population	Included infants with mild-to-moderate atopic dermatitis	Food-intervention groups: 1 lick of peanut butter 4–7 times per wk* Control groups: no consumption of peanut butter*	2037 White (85%) 144 South Asian (6%) 120 Black (5%) 96 Other (4%)	Allergy prevalence at 36 mo, severity of atopic dermatitis	2.0% vs. 0.9%	2.0% vs. 0.7%

Guidelines

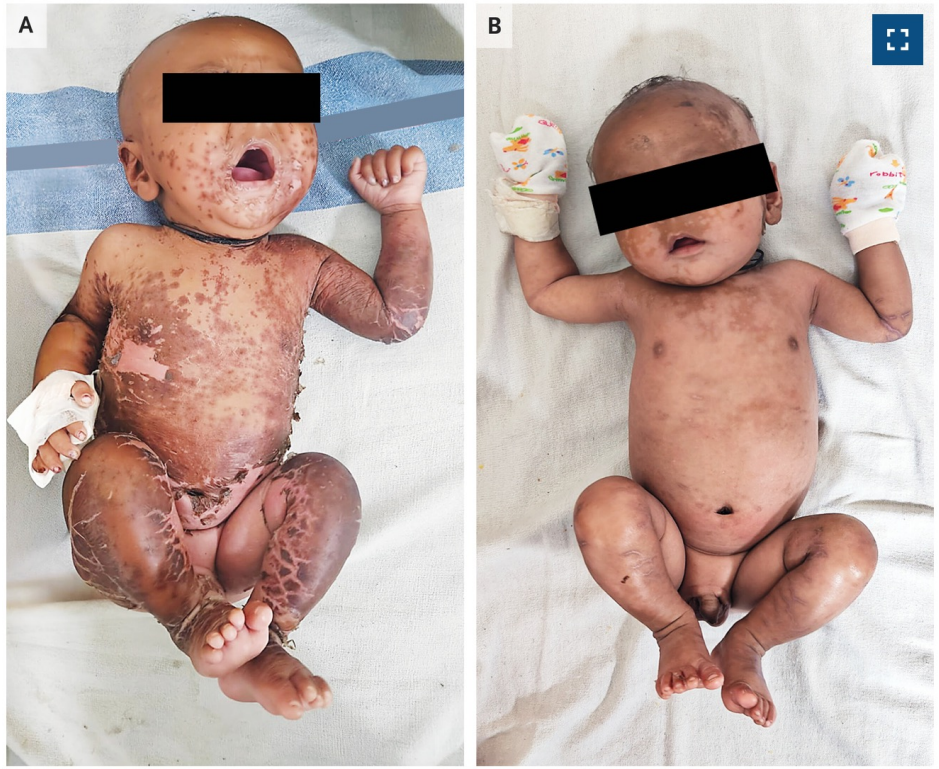
Previous guidelines for the prevention of allergy have recommended that infants should not be exposed to peanuts before specific ages (in the first year of life in the United Kingdom and not until 3 years of age in the United States). Current recommendations by national and professional societies in the United States and by the European Academy of Allergy and Clinical Immunology (EAACI) state that peanuts should be introduced at 4 to 6 months of age in at-risk infants and at approximately 6 months of age in other infants. The 2021 North American Consensus guidelines recommend early introduction of peanut, egg, and other food allergens during early weaning to prevent food allergies. This approach is also reflected in the recent Department of Agriculture and Department of Health and Human Services Dietary Guidelines for Americans. The introduction of peanut and other food allergens at 4 to 6 months of age conflicts with the World Health Organization (WHO) recommendations for exclusive breast-feeding until 6 months of age, which aim to maximize nutrition and reduce infectious-disease burden in low-income countries (where rates of food allergy are generally very low). Strict adherence to WHO guidelines may be contributing to the continued rise in food allergies in high-income countries.

Conclusions and Recommendations

The infant described in the case vignette was of East Asian heritage but was born and living in the United States, had early-onset severe atopic dermatitis, and had consumed peanuts for the first time at 7 months of age — an age that is too late in an infant who is at such a high risk for peanut allergy. Earlier introduction of peanut — at 3 to 4 months of age — and frequent consumption would have been necessary to affect the development of peanut allergy. Even in children at lower risk for peanut allergy, a delay in the introduction of peanut reduces the efficacy of this prevention strategy, and early consumption should be encouraged in all infants.

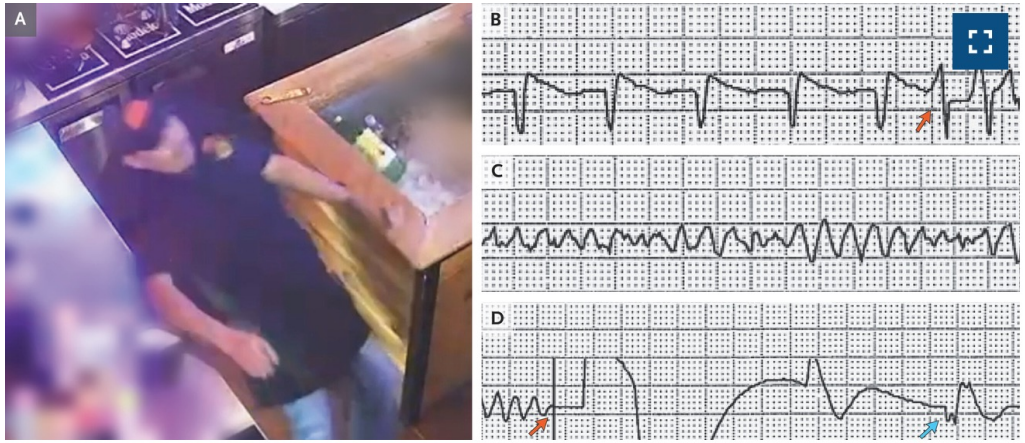
In the past, the default management strategy for an infant with peanut allergy was to advise strict avoidance of peanuts and constant availability of emergency medications, typically including an epinephrine autoinjector, as part of a bespoke emergency plan. Given that immunotherapy is more likely to be effective and result in greater tolerance at an early age, we would recommend oral immunotherapy for this infant. We would also encourage the frequent ingestion of other common food allergens relevant to the family's diet to ensure allergy prevention and ongoing tolerance. Although current therapies have a positive effect on quality of life for persons with peanut allergy, there is as yet no cure that permits an end to ongoing treatment.

Kwashiorkor



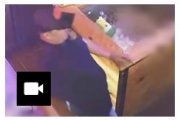
A 5-month-old full-term baby boy was brought to the outpatient clinic with a 3-week history of a rash. He had consumed breast milk exclusively until 20 days before presentation, when he had been switched to diluted formula owing to his mother's ongoing challenges with limited breast-milk supply. His weight-for-age z score was −3.4, and his length-for-age z score was −5.6. On physical examination, the baby was irritable, with sparse, wispy, hypopigmented hair and pitting edema of the arms and legs. Desquamation of hyperpigmented patches was seen on the legs, arms, and trunk; the underlying skin was hypopigmented (Panel A). A serum albumin level was 1.9 g per deciliter (reference range, 3.5 to 5.0). A diagnosis of kwashiorkor — also known as edematous malnutrition or severe acute malnutrition with pitting edema of the arms and legs — was made. Kwashiorkor may be diagnosed in malnourished children on the basis of the presence of pitting edema, regardless of height and weight values. The typical dermatosis, as seen in this baby, resembles flaking paint. Inpatient treatment with a therapeutic milk formula (F-75) was initiated. On day 7 of the admission, the baby was more active, with resolving skin lesions (Panel B). At a follow-up visit 2 weeks after discharge, the rash had abated and weight gain had normalized.

Unheralded Syncope from Ventricular Arrhythmia



A 47-year-old man with ischemic cardiomyopathy, heart failure with a reduced ejection fraction, and an implantable cardioverter–defibrillator (ICD) for the primary prevention of sudden cardiac death presented to the emergency department with a first-time episode of syncope. During the event (which had been captured by video surveillance at work), he had suddenly collapsed backward without prodromal symptoms and had had a myoclonic jerk (Panel A and video). A few seconds later, he had regained consciousness. On presentation, physical examination showed only a scalp laceration. Computed tomography of the head showed no intracranial hemorrhage. Interrogation of the ICD identified a premature ventricular contraction during ventricular repolarization — known as the R-on-T phenomenon (Panel B, arrow) — with a normal QT interval; this event had precipitated polymorphic ventricular tachycardia (Panel C). The arrhythmia progressed to ventricular fibrillation, after which a shock was delivered (Panel D, red arrow) and spontaneous electrical activity (blue arrow) returned. A diagnosis of unheralded syncope from ventricular arrhythmia was made. Coronary angiography showed patent stents in the left main and left anterior descending arteries and a known chronic total occlusion of the left circumflex artery. Transthoracic echocardiography showed a stable ejection fraction of 25% with no new wall-motion abnormalities. Treatment with amiodarone was initiated, and beta-blocker therapy was continued. On long-term follow-up, ventricular arrhythmia had not recurred.

VIDEO

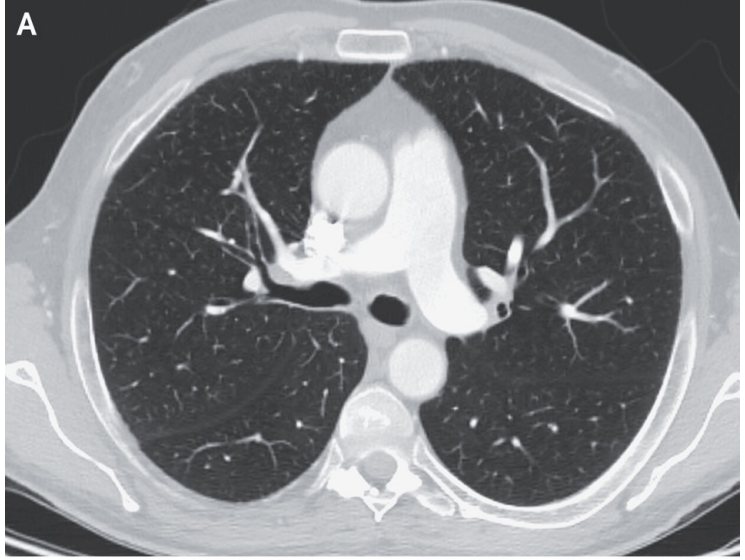


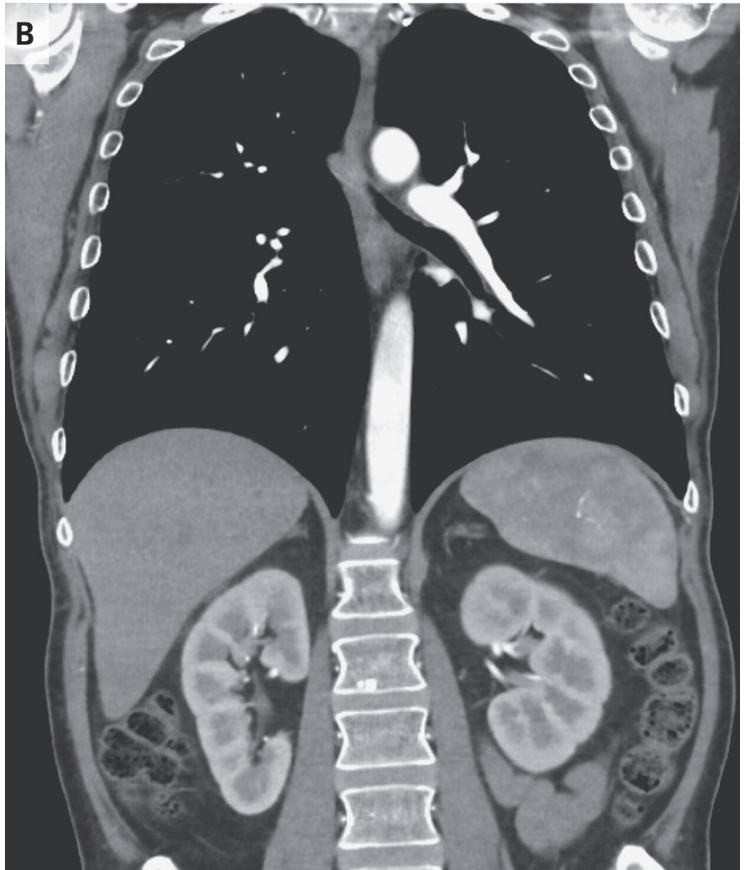
Unheralded Syncopal Event
0m 10s

Case 18-2026: A 53-Year-Old Man with Leg Weakness, Pain, and Weight Loss

Five months before the current presentation, the patient began to have profound thirst, frequent urination, and fatigue. He established care with a local primary care clinic for evaluation of these symptoms. At that time, the patient also reported atraumatic pain in the left hip that radiated to the thigh. The pain was most prominent when he ascended stairs. He had had an 11-kg weight loss during the preceding year, which he had ascribed to a poor appetite. A physical examination, including neurologic examination, was reportedly normal. The glycated hemoglobin level was greater than 14.0% (reference range, 4.3 to 5.6). Results of additional laboratory testing, including blood levels of electrolytes, aspartate aminotransferase, alanine aminotransferase, albumin, and bilirubin, along with results of kidney-function tests and a complete blood count, were normal. Treatment with metformin and dulaglutide was initiated.

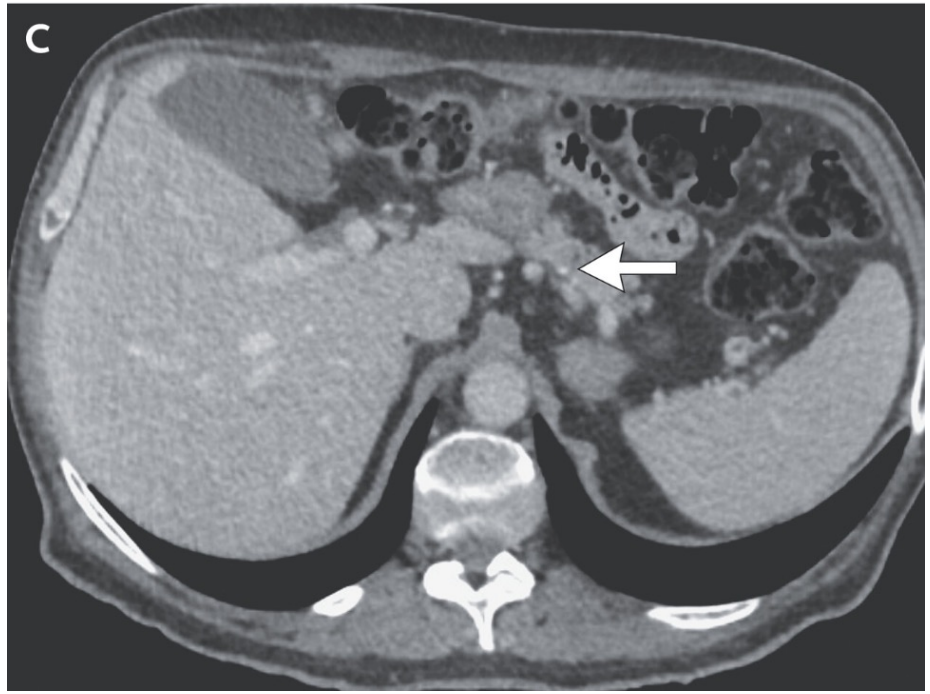
Three months before the current presentation, the patient sustained a fall while trying to stand up from his bed. As a result, he sought care at the emergency department of this hospital. At that time, he noted new weakness and pain in both legs that worsened with ambulation and was accompanied by diminished sensation in both legs.
On examination, the temperature was 36.0°C, the heart rate 90 beats per minute, the blood pressure 126/68 mm Hg, the respiratory rate 16 breaths per minute, and the oxygen saturation 100% while the patient was breathing ambient air. Neurologic examination revealed pain in the left leg during the straight-leg-raising maneuver and preserved distal strength in both legs; however, owing to pain, he was unable to lift the left leg against gravity. There was focal tenderness on palpation over the left greater trochanter and hip joint. Laboratory testing was notable for mild hyperglycemia, with a blood glucose level of 139 mg per deciliter (reference range, 70 to 99). The blood levels of thyrotropin, electrolytes, albumin, bilirubin, aspartate aminotransferase, and alanine aminotransferase were normal, as were the results of kidney-function tests.





CT Images of the Chest, Abdomen, and Pelvis.

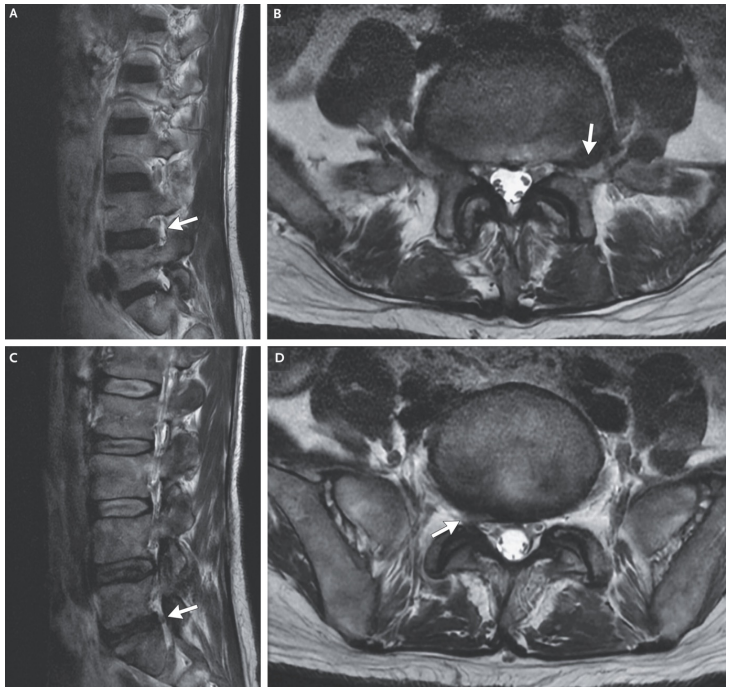
Contrast-enhanced CT was performed 3 months before the current presentation. An axial image of the chest (Panel A) and a coronal image of the abdomen (Panel B) show no mass or other substantial abnormality; an image of the pelvis (not shown) also showed no such abnormalities. An axial image of the upper abdomen (Panel C) shows a tiny focus of hyperattenuation in the pancreas (arrow) that appears to be consistent with a vascular microcalcification. Otherwise, no mass or other pancreatic abnormality is seen.



On admission, the patient noted progressive weakness, even with a walker, that caused sporadic buckling of the legs. He was no longer able to climb stairs in an upright position; instead, he had to push himself up each stair while in a seated position. The patient noted an additional 18 kg of weight loss during the preceding 5 months. A review of systems was negative for night sweats, hematochezia, melena, diarrhea, rigors, rash, dyspnea, cough, saddle anesthesia, incontinence, urinary retention, headache, or bulbar symptoms. His medical history was notable for alcohol use disorder, which had been in remission for more than a decade, as well as generalized anxiety disorder. He had not had a colonoscopy as part of age-appropriate cancer screening. Medications included sertraline, gabapentin, glargine, and metformin. The patient resided alone in a suburban area of New England and worked as an administrative assistant. He did not use recreational drugs but had smoked one pack of cigarettes per day for 35 years. The patient had sex with men; he had had no sexual partners in the preceding 2 years and had no history of sexually transmitted infections.

On examination, the temporal temperature was 36.7°C, the heart rate 94 beats per minute, the blood pressure 128/87 mm Hg, the respiratory rate 16 breaths per minute, and the oxygen saturation 100% while the patient was breathing ambient air. The weight was 73.5 kg, and the body-mass index (the weight in kilograms divided by the square of the height in meters) was 20.8. He appeared tired. No abnormalities were noted on cardiopulmonary auscultation, and the abdomen was soft and nontender. The arms and legs were warm and without edema. Neurologic examination showed symmetric cranial-nerve function with preserved strength and normal sensation in the arms. Strength on hip flexion and knee extension was diminished to 2/5 on the left side and to 3/5 on the right side. Distal leg strength was preserved in the feet, and a mild loss of sensation to touch was noted in the toes. The reflexes in the legs were absent. Asymmetric muscle atrophy was seen in the thighs, with the left leg affected to a greater extent than the right leg; sporadic fasciculations were noted in the left thigh muscle.

Blood levels of vitamin B_{12}, folate, creatine kinase, and C-reactive protein were normal, as was the erythrocyte sedimentation rate. Tests for human immunodeficiency virus, *Treponema pallidum*, and *Borrelia burgdorferi* were negative. Serum protein electrophoresis showed no monoclonal protein, and a serum free light-chain assay showed a normal light-chain ratio (ratio of kappa to lambda light chains); quantitative serum IgG and IgM levels were 466 mg per deciliter (reference range, 700 to 1600) and 36 mg per deciliter (reference range, 40 to 230), respectively.



MRI of the Lumbar Spine.

MRI of the lumbar spine was performed at the time of the current presentation. Sagittal (Panel A) and axial (Panel B) T2-weighted images show a small extraforaminal disk protrusion at the L4–L5 level on the left side (arrows) that is causing minimal contact with the exiting left L4 nerve root, without radiologically significant foraminal stenosis. Sagittal (Panel C) and axial (Panel D) T2-weighted images obtained at a different level show a small subarticular disk protrusion at the L5–S1 level on the right side (arrows) that is causing minimal contact with the descending right S1 nerve root, without radiologically significant spinal-canal stenosis.

Differential Diagnosis

This 53-year-old man presented with a subacute syndrome characterized by progressive, asymmetric weakness and marked weight loss against a backdrop of newly diagnosed diabetes. Beyond the patient's notable neurologic abnormalities and hyperglycemia, the clinical laboratory and imaging evaluations were strikingly unrevealing, showing only hypogammaglobulinemia.

Variable	Reference Range, Adults†	3 Mo before Presentation, Emergency Department, This Hospital	On Current Presentation, This Hospital
Hemoglobin (g/dl)	13.5–17.5	16.0	14.8
Hematocrit (%)	41.0–53.0	47.5	42.3
White-cell count (per μl)	4000–11,000	7010	4400
Platelet count (per μl)	150,000–400,000	240,000	273,000
Sodium (mmol/liter)	135–145	138	140
Potassium (mmol/liter)	3.4–5.0	4.2	3.5
Chloride (mmol/liter)	98–108	101	102
Carbon dioxide (mmol/liter)	20–31	24	25
Urea nitrogen (mg/dl)	6–23	9	10
Creatinine (mg/dl)	0.60–1.30	0.58	0.56
Calcium (mg/dl)	8.5–10.5	10.5	9.6
Glucose (mg/dl)	70–99	139	120
Aspartate aminotransferase (U/liter)	10–40	11	14
Alanine aminotransferase (U/liter)	10–55	8	7
Alkaline phosphatase (U/liter)	45–115	99	57
Total bilirubin (mg/dl)	0.0–1.2	0.5	0.6
Albumin (g/dl)	3.3–5.2	4.8	4.3
Globulin (g/dl)	1.9–4.1	2.3	2.2
Vitamin B_{12} (pg/ml)	232–1245	—	662
Folate (ng/ml)	>4.7	—	12.5
Creatine kinase (U/liter)	39–308	—	47
C-reactive protein (mg/liter)	<10.0	—	0.2
Erythrocyte sedimentation rate (mm/hr)	0–20	—	9
IgG (mg/dl)	700–1600	—	466
IgA (mg/dl)	70–400	—	253
IgM (mg/dl)	40–230	—	36
Free kappa light chain (mg/liter)	3.3–19.4	—	11.5
Free lambda light chain (mg/liter)	5.7–26.3	—	15.7
Ratio of kappa to lambda free light chains	0.26–1.65	—	0.73
Serum protein electrophoresis	Negative for monoclonal component	—	Negative for monoclonal component

Diabetic Lumbosacral Radiculoplexus Neuropathy

DLRPN, also known as diabetic amyotrophy, is a rare complication of diabetes mellitus that is often diagnosed at the time of, or shortly after, diagnosis of type 2 diabetes mellitus. This patient's clinical course is typical of the syndrome, which begins with painful, predominantly proximal weakness in one leg and then spreads to the distal legs during the ensuing months. The severity of pain and weakness results in substantial disability, as was seen in this patient. In parallel, marked weight loss occurs, which leaves the patient in visible decline with pain, weakness, and muscle wasting. Paradoxically, notable laboratory and imaging findings are often absent. This discrepancy is not a contradiction but rather a signature of the disease and helps to rule out alternative diagnoses. Electrodiagnostic studies are necessary to provide further diagnostic support for this diagnosis, and therefore, I would recommend performing electromyography and nerve conduction studies.

A Sensory Nerve Conduction Studies

Nerve	Site	Distance	Peak Latency	Amplitude	Temperature
		cm	*msec*	*μV*	°C
Left ulnar	Fifth digit	11	No response	No response	30.6
Left radial–snuff box	Forearm	10	2.7	10.9	33.6
Right sural–lateral malleolus	Calf	14	4.7	4.5	32.4
Left sural–lateral malleolus	Calf	14	No response	No response	29.3
Right superficial peroneal	Lateral leg	14	No response	No response	31.7
Left superficial peroneal	Lateral leg	14	No response	No response	31.3

- Mildly prolonged peak latencies could suggest mild myelin dysfunction (common in patients with diabetes), although process is predominantly axonal
- All sensory response amplitudes are reduced to varying degrees → generalized or multifocal, postganglionic, axonal neurogenic process, with a non–length-dependent pattern
- Absent ulnar response could be result of unrelated ulnar mononeuropathy (common in patients with diabetes)
- Marked asymmetry in the legs

B Motor Nerve Conduction Studies

Nerve	Site	Distance	Latency	Amplitude	Velocity	Temperature
		cm	*msec*	*mV*	*m/sec*	°C
Left ulnar–ADM	Wrist	6	2.8	7.4		33.5
	Below elbow	25	7.7	5.9	50.4	33.5
	Above elbow	10	10.0	5.8	44.9	33.5
Right peroneal–EDB	Ankle	9	5.5	0.9		
Left peroneal–EDB	Ankle	9	5.5	0.2		32.1
	Below fibular head	43	14.4	0.1	48.3	32.1
	Above fibular head	13	17.7	0.1	39.2	31.9
Right tibial–AH	Ankle	10	5.4	0.5		32.7
Left tibial–AH	Ankle	10	6.0	0.4		31.7
	Popliteal fossa	47	20.8	0.4	31.8	31.6

- Low motor response amplitudes with essentially unaffected distal latencies and conduction velocities suggest predominantly axonal process
- Asymmetry in the legs but both clearly affected
- Low-amplitude right tibial motor response despite relatively preserved right sural sensory response suggests preganglionic component (e.g., radiculopathy)
  Low-amplitude left tibial and bilateral peroneal motor responses, together with absent corresponding sensory responses, suggest postganglionic component (e.g., lumbosacral plexopathy vs. polyneuropathy vs. mononeuropathies)
- Mild slowing of conduction velocity suggests mild myelin dysfunction (from diabetes vs. ulnar neuropathy at the elbow)

C Needle Electromyography

Muscle	Spontaneous			Motor-Unit Action Potential			Recruitment		
	Fib or PSW	Fasc	Misc	Duration	Amplitude	Polyphasic	No. of MUs	Rate	Effort
Right deltoid	None	None	None	Normal	Normal	Normal	Normal	Normal	Full
Right first dorsal interosseous muscle	None	None	None	Normal	Normal	Normal	Normal	Normal	Full
Right vastus medialis	2+	None	None	Normal	Normal	Normal	Severe reduction	Rapid	Full
Right tibialis anterior	None	None	None	Long	High	Normal	Mild reduction	Rapid	Full
Right gastrocnemius muscle	3+	None	None	—	—	—	None	—	Submax

- Presence of Fibs or PSWs suggests active denervation or incomplete reinnervation, process longer than 4–6 wk
  Abnormalities despite relatively spared right sural sensory response suggest preganglionic component
- Normal MUAP morphologic features despite severely reduced recruitment in right vastus medialis suggest duration of less than 6 mo
  Mild chronic reinnervation changes in right tibialis anterior muscle may be unrelated to current presentation
- Reduced recruitment pattern confirms neurogenic process

Nerve Conduction Studies and Electromyography.

The sensory nerve conduction studies (Panel A) show reduced amplitudes in multiple nerves, which suggests a generalized or multifocal, asymmetric, predominantly axonal, postganglionic neurogenic process that is more severe in the left leg than in the right leg. The motor nerve conduction studies (Panel B) confirm an asymmetric, predominantly axonal, neurogenic process in both legs but also show a pattern that suggests a superimposed preganglionic process in the right leg. Needle electromyography (EMG) of the right leg (Panel C) shows a relatively severe subacute neurogenic process with incomplete reinnervation. The overall electrophysiological findings are consistent with a severe, subacute, asymmetric bilateral lumbosacral radiculoplexus neuropathy with incomplete reinnervation. A mild superimposed generalized, axonal sensory polyneuropathy and a mild nonlocalizing, left ulnar sensory mononeuropathy are also present; these findings were identified incidentally. ADM denotes abductor digiti minimi, AH abductor hallucis, EDB extensor digitorum brevis, Fasc fasciculation potential, Fib fibrillation potential, Misc miscellaneous, MU motor unit, MUAP motor-unit action potential, PSW positive sharp wave, and Submax submaximal.

Electrophysiological Diagnosis

Diabetic lumbosacral radiculoplexus neuropathy.

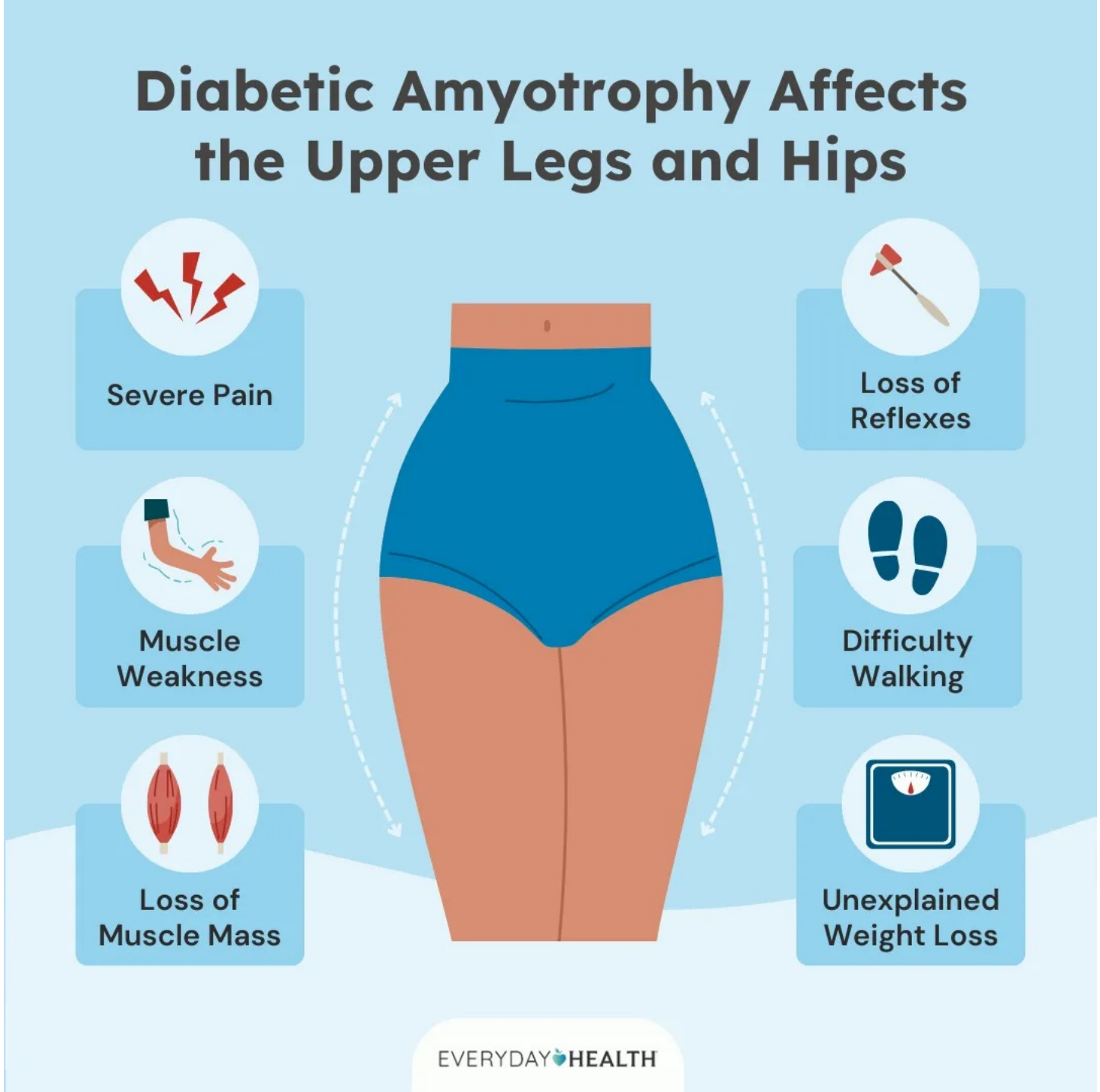
Final Diagnosis

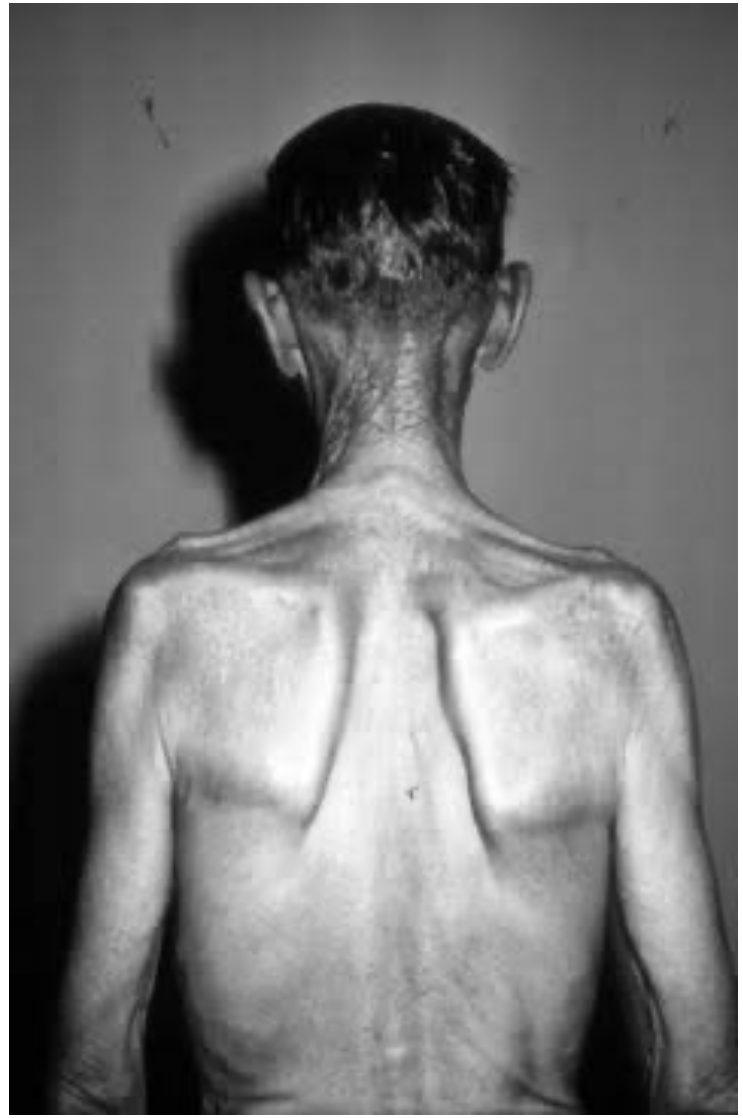
Diabetic lumbosacral radiculoplexus neuropathy.

Case Records Editors' Note — Lessons Learned

1. A rare complication of diabetes mellitus is lumbosacral plexopathy, which often extends to the nerve roots and peripheral nerves — a condition known as diabetic lumbosacral radiculoplexus neuropathy (DLRPN, also known as diabetic amyotrophy).
2. Diagnosis of DLRPN often occurs at the time of, or shortly after, diagnosis of type 2 diabetes mellitus.
3. The typical clinical syndrome begins with painful, predominantly proximal weakness in one leg and then spreads to the distal legs during the ensuing months. Profound weight loss may be a prominent clinical feature.
4. Imaging findings in persons with DLRPN may be normal, and electromyography and nerve conduction studies can help support the diagnosis.
5. DLRPN is typically a self-limited complication of diabetes mellitus, and management is primarily supportive. Glycemic control does not appear to be a disease-modifying factor.

Diabetic Amyotrophy Affects the Upper Legs and Hips





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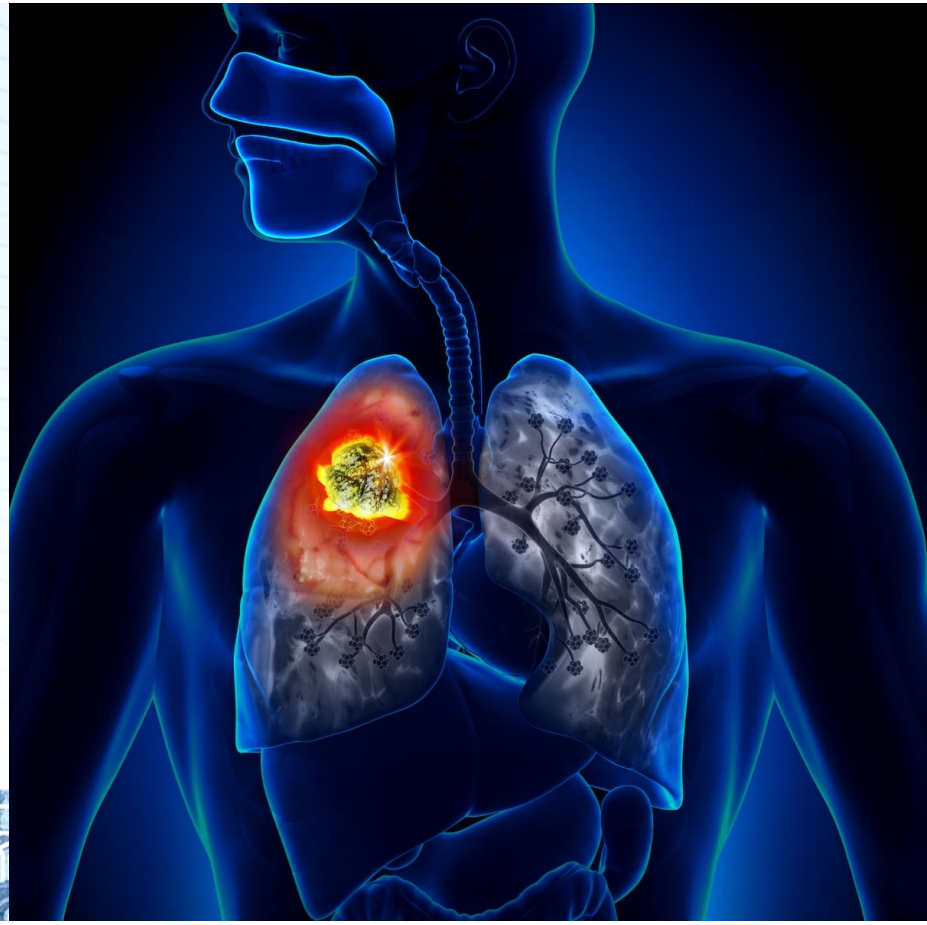
OptiTROP-Lung04

Sac-TMT Improves Survival Over Chemotherapy in EGFRm NSCLC

Berlin / 2025



Sac-TMT (Sacituzumab-Tirumotecan oder MK-2870) ist ein zielgerichtetes Antikörper-Wirkstoff-Konjugat (ADC), das sich in der klinischen Prüfung zur Krebstherapie befindet. Es zielt auf das TROP2-Protein ab und schleust einen Wirkstoff direkt in die Tumorzelle.

Wichtige Details im Überblick:

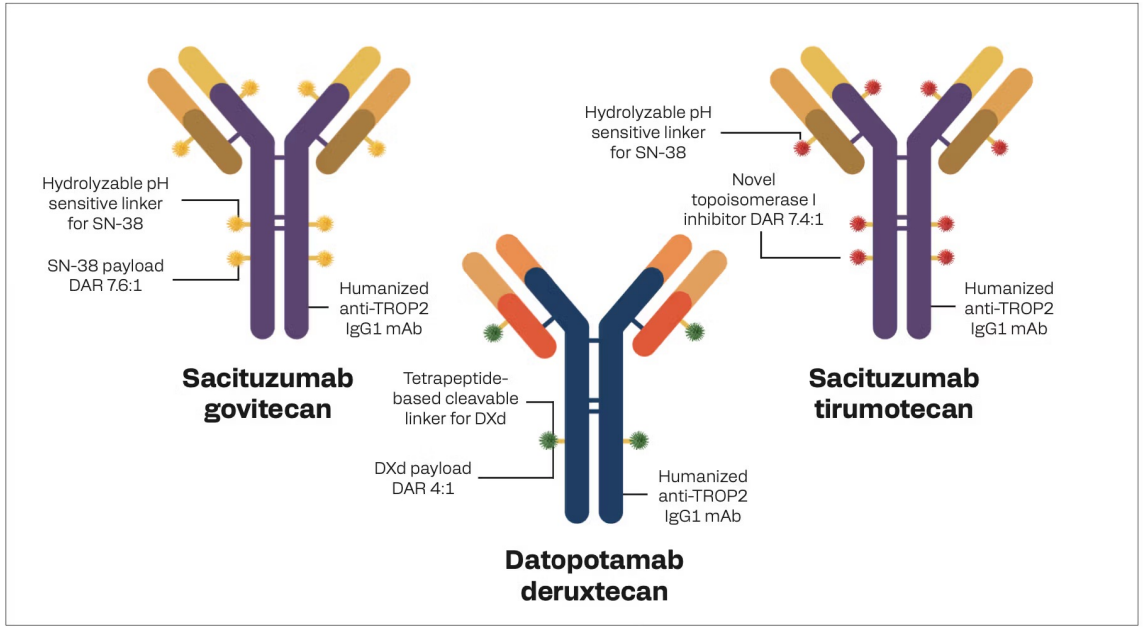
•**Wirkungsweise:** Es handelt sich um ein TROP2-gerichtetes ADC mit einem Topoisomerase-1-Inhibitor als Nutzlast.

•**Anwendungsgebiete:** Es wird in klinischen Studien für verschiedene Krebserkrankungen getestet, darunter Lungenkrebs (NSCLC), dreifach negativer Brustkrebs (TNBC) und Gebärmutterhalskrebs.

•**Klinische Erfolge:** In Studien zum EGFR-mutierten NSCLC zeigte Sac-TMT eine signifikante Verlängerung des Gesamtüberlebens. Die FDA hat ihm für bestimmte Lungenkrebsarten bereits den Status als "Breakthrough Therapy" verliehen.

Entwicklung: Es wird von Merck in Zusammenarbeit mit Kelun-Biotech entwickelt und häufig in Kombination mit Immuntherapien wie Pembrolizumab untersucht

FIGURE 1. **TROP2-Targeting ADCs Under Investigation in TNBC**



ADC, antibody-drug conjugate; DAR, drug-antibody ratio; DXd, deruxtecan; IgG, immunoglobulin G; mAb, monoclonal antibody; TNBC, triple-negative breast cancer.

Trop2 (Trophoblast-Zelloberflächenantigen-2) ist ein **Transmembranprotein**, das in gesundem Gewebe die Zellregeneration und Signalübertragung reguliert. Bei vielen Krebserkrankungen ist es jedoch stark **überexprimiert**, was das Krebswachstum und die Metastasierung fördert. Es dient heute als wichtiger Angriffspunkt für zielgerichtete Krebstherapien

Sacituzumab tirumotecan plus pembrolizumab versus pembrolizumab in PD-L1-positive advanced non-small-cell lung cancer (OptiTROP-Lung05): interim analysis of a randomised, open-label, phase 3 trial

Does sac-TMT+ checkpoint improve progression-free survival compared to checkpoint?

Summary

Background Sacituzumab tirumotecan (sac-TMT), a trophoblast cell-surface antigen 2-targeting antibody-drug conjugate, combined with programmed death 1 (PD-1) or programmed death ligand 1 (PD-L1) inhibitors, has shown promising antitumour activity as first-line therapy for non-small-cell lung cancer (NSCLC) in early-phase studies. Our aim was to evaluate the efficacy and safety of sac-TMT plus pembrolizumab as first-line treatment for patients with PD-L1-positive advanced NSCLC without targetable genomic alterations.

Methods In this randomised, open-label, phase 3 trial (OptiTROP-Lung05) conducted across 68 hospitals in China, eligible patients had locally advanced or metastatic NSCLC without targetable genomic alterations and a PD-L1 tumour proportion score (TPS) of 1% or greater. Patients were randomly assigned (1:1) to receive sac-TMT (4 mg/kg on days 1, 15, and 29) plus pembrolizumab (400 mg fixed dose on day 1), or pembrolizumab alone, administered intravenously every 6 weeks. The primary endpoint was progression-free survival, as assessed by blinded independent central review in the intention-to-treat population. This trial was registered with ClinicalTrials.gov (NCT06448312). Recruitment is complete, with the trial ongoing and the final analysis to be reported later.

Findings Between June 7, 2024, and March 27, 2025, 741 patients were screened and 413 eligible patients were randomly assigned to receive sac-TMT plus pembrolizumab (n=208) or pembrolizumab alone (n=205). At the prespecified interim analysis, conducted after a median follow-up of 10·5 months (IQR 8·7–12·5), median progression-free survival was significantly longer with sac-TMT plus pembrolizumab than with pembrolizumab alone (not reached *vs* 5·7 months; stratified hazard ratio [HR] 0·35 [95% CI 0·26–0·47]; p<0·0001). The progression-free survival benefit was broadly consistent across subgroups, including patients with PD-L1 TPS of 1–49% (HR 0·28 [95% CI 0·19–0·41]) and those with PD-L1 TPS of 50% or greater (HR 0·47 [0·29–0·77]). Grade 3 or higher treatment-emergent adverse events occurred in 115 (55%) of 208 patients in the sac-TMT plus pembrolizumab group and 64 (31%) of 204 patients in the pembrolizumab group.

Interpretation Among patients with PD-L1-positive advanced NSCLC without targetable genomic alterations, first-line treatment with sac-TMT plus pembrolizumab significantly prolonged progression-free survival compared with pembrolizumab alone. Therefore, sac-TMT plus pembrolizumab has the potential to redefine first-line treatment for patients with PD-L1-positive advanced NSCLC without targetable genomic alterations.

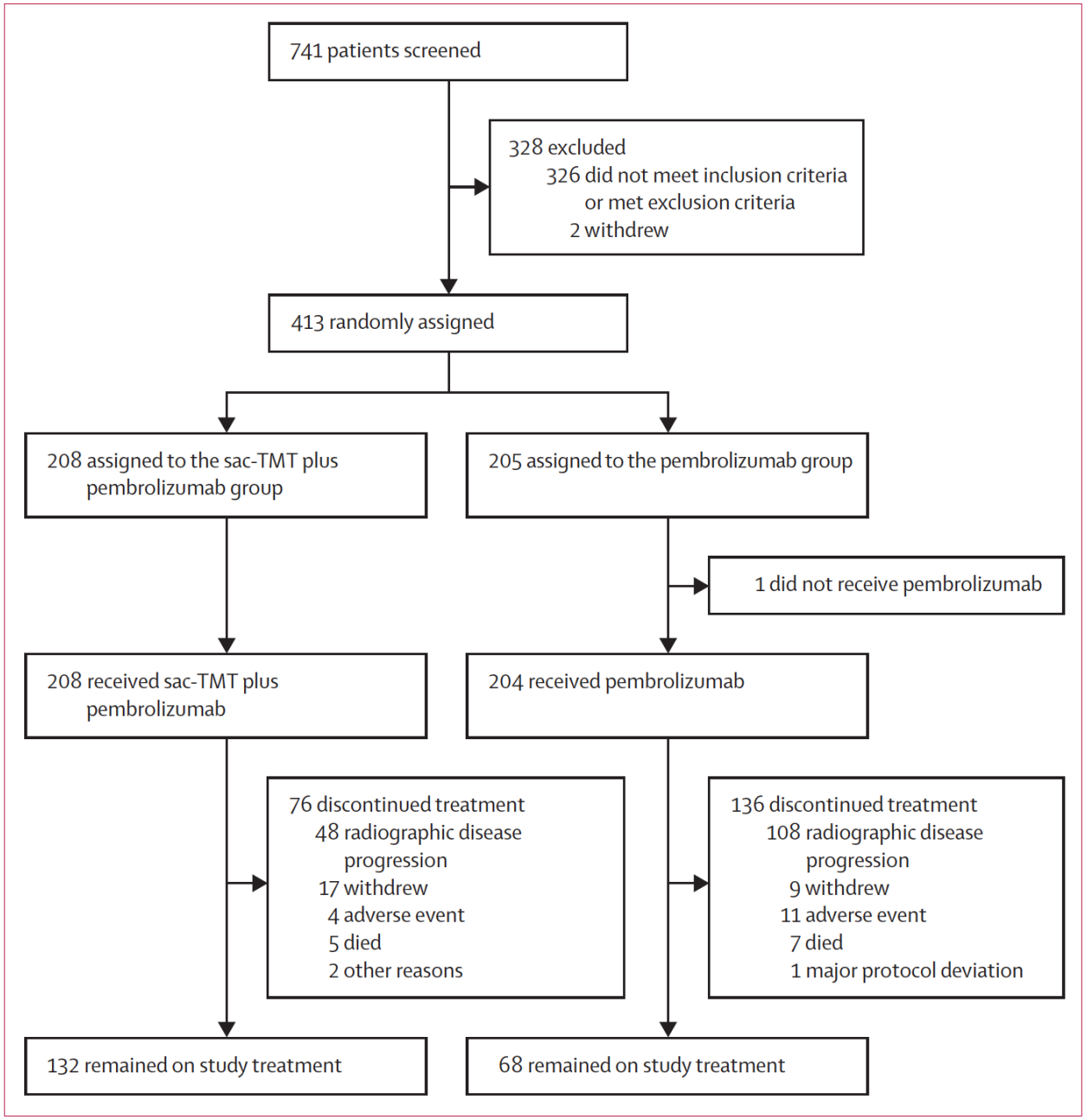


Figure 1: **Trial profile**

Among the screened patients, 104 were ineligible for a PD-L1 tumour proportion score of less than 1%, and 49 for harbouring targetable genomic alterations. Sac-TMT=sacituzumab tirumotecan.

	Sac-TMT plus pembrolizumab (n=208)	Pembrolizumab (n=205)
Age, years		
Median (IQR)	64 (58·5–69·0)	65 (60·0–70·0)
≥65	101 (49%)	108 (53%)
Sex		
Male	166 (80%)	174 (85%)
Female	42 (20%)	31 (15%)
Ethnicity		
Asian	208 (100%)	205 (100%)
ECOG performance-status score*		
0	32 (15%)	32 (16%)
1	176 (85%)	173 (84%)
Smoking history		
Current or former smoker	166 (80%)	176 (86%)
Histological type		
Squamous-cell carcinoma	85 (41%)	80 (39%)
Adenocarcinoma	122 (59%)	123 (60%)
Other†	1 (<1%)	2 (1%)
Disease stage‡		
IIIB or IIIC	14 (7%)	13 (6%)
IV	194 (93%)	192 (94%)
Liver metastases	21 (10%)	23 (11%)
Brain metastases	7 (3%)	6 (3%)
Lung metastases	91 (44%)	100 (49%)
Bone metastases	67 (32%)	66 (32%)
Lymph node metastases	54 (26%)	57 (28%)
Three or more distant metastatic sites	60 (29%)	55 (27%)
PD-L1 tumour proportion score		
1–49%	125 (60%)	123 (60%)
≥50%	83 (40%)	82 (40%)

‡§||Data are n (%), unless otherwise stated. ECOG= Eastern Cooperative Oncology Group. Sac-TMT=sacituzumab tirumotecan. PD-L1=programmed death ligand 1. The intention-to-treat population included all patients who were randomly assigned. *ECOG performance-status scores range from 0 to 5, with higher scores indicating greater disability. †Other histologic types included one non-small-cell lung cancer (not otherwise specified) in the sac-TMT plus pembrolizumab group, and one mucoepidermoid carcinoma and one thymoma in the pembrolizumab group. ‡Disease stage was determined according to the American Joint Committee on Cancer, 8th edition, tumour-node-metastasis staging system.

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

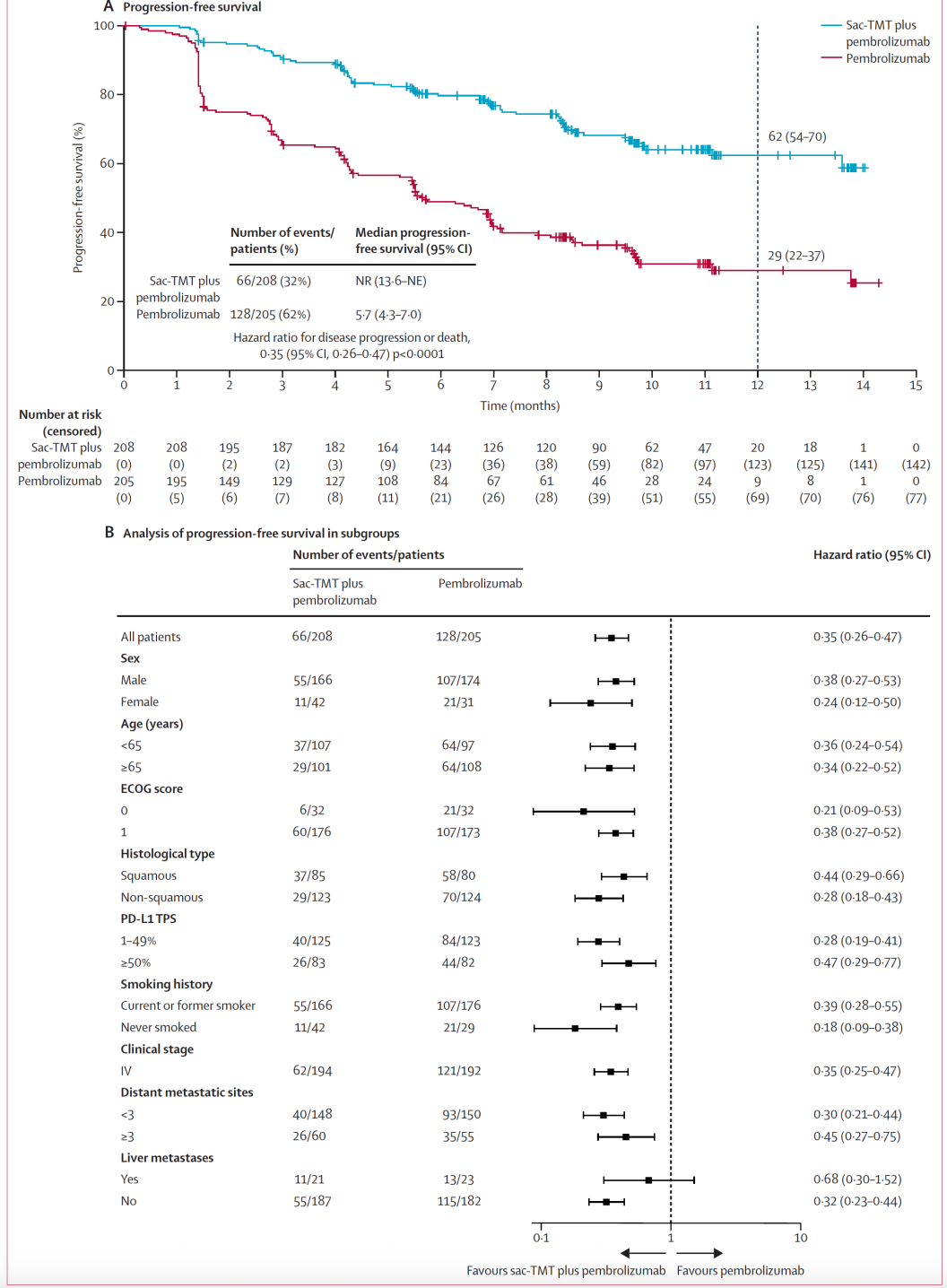
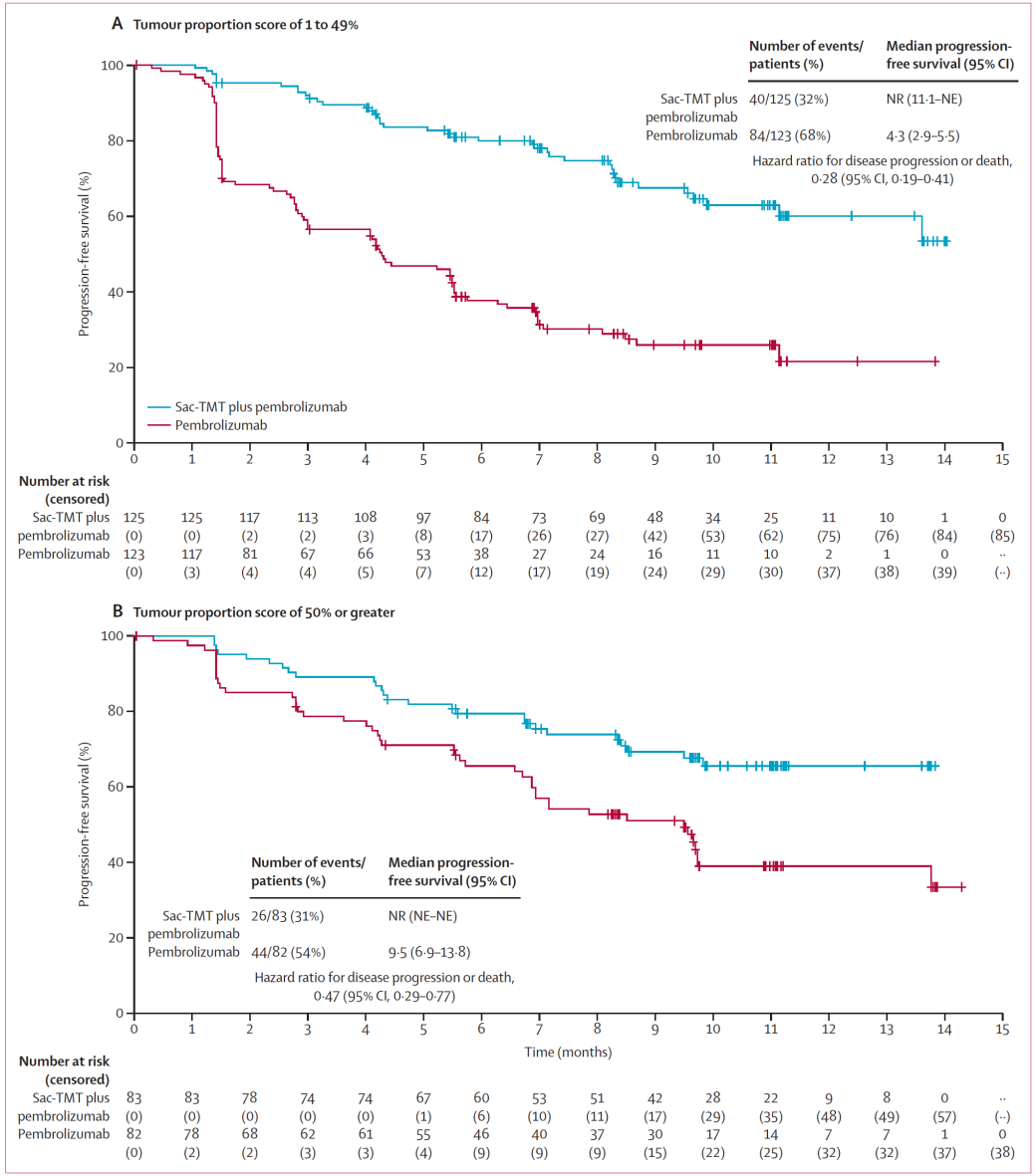


Figure 2: **Progression-free survival as assessed by blinded independent central review**

(A) Kaplan–Meier estimates of progression-free survival as assessed by blinded independent central review. (B) Forest plot of progression-free survival in subgroups. One patient with thymoma was excluded from the pembrolizumab group in the subgroup analysis of histologic type. Subgroup analyses will not be presented for any subgroup variable in which one or more levels account for less than 10% of the total analysis population. Confidence intervals have not been adjusted for multiplicity and should not be used to infer statistical significance. Sac-TMT=sacituzumab tirumotecan. PD-L1=programmed death ligand 1. TPS=tumour proportion score. NR=not reached. NE=not estimable.



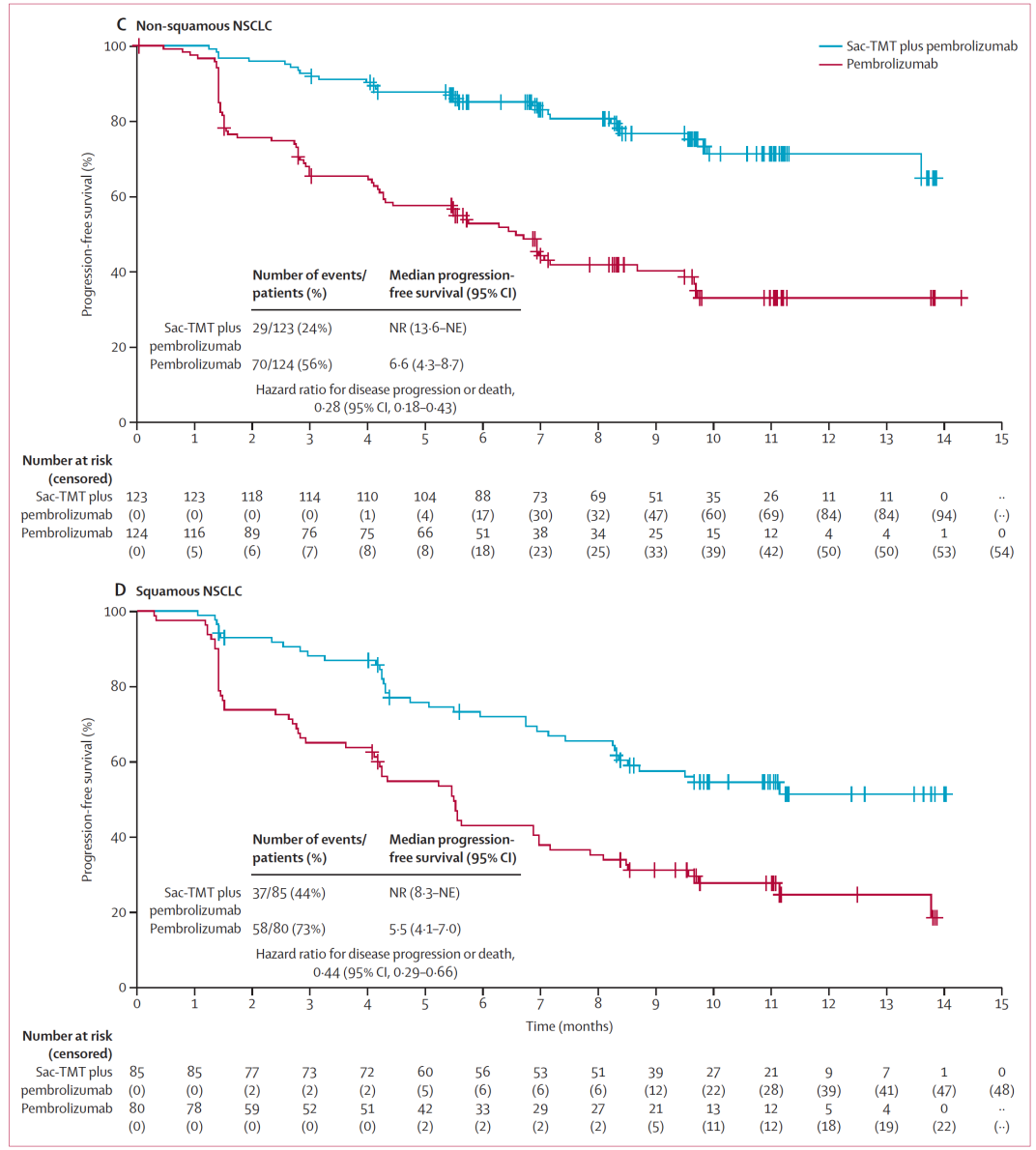


Figure 3: **Progression-free survival as assessed by blinded independent central review, according to PD-L1 expression and histological type**
Kaplan–Meier estimates of progression-free survival in patients with a PD-L1 TPS of 1–49% (A), in patients with a PD-L1 TPS of 50% or greater (B), in patients with non-squamous NSCLC (C), and in patients with squamous NSCLC (D). One patient with thymoma was excluded from the pembrolizumab group in the subgroup analysis of histological type. Sac-TMT=sacituzumab tirumotecan. PD-L1=programmed death ligand 1. NSCLC=non-small-cell lung cancer. TPS=tumour proportion score. NR=not reached. NE=not estimable. HR=hazard ratio.

	Sac-TMT plus pembrolizumab (n=208)	Pembrolizumab (n=205)	Difference (95% CI)
Best overall response			
Partial response	146 (70%)	86 (42%)	..
Stable disease	50 (24%)	61 (30%)	..
Progressive disease	8 (4%)	48 (23%)	..
Not evaluable*	4 (2%)	10 (5%)	..
Objective response†	146 (70%; 63–76)	86 (42%; 35–49)	28 (19–37)
Disease control‡	196 (94%; 90–97)	147 (72%; 65–78)	22 (16–29)
Median duration of response (95% CI), months§	NR (NE)	NR (8·3–NE)	..
Response duration ≥12 months (%; 95% CI)§	78% (68–85)	59% (45–71)	..

Data are n (%) or n (%; 95% CI), unless otherwise stated. Tumour response was evaluated by a masked independent central review according to Response Evaluation Criteria in Solid Tumors version 1.1. The intention-to-treat population included all the patients who were randomly assigned. Confidence intervals have not been adjusted for multiplicity and should not be used to infer statistical significance. The between-group difference was estimated with the Cochran–Mantel–Haenszel test. Sac-TMT=sacituzumab tirumotecan. PD-L1=programmed death ligand 1. NR=Not reached. NE=Not estimable. *Patients who had no post-baseline tumour imaging assessments or whose imaging could not be evaluated. †Objective response was defined as a complete or partial response. ‡Disease control was defined as a complete response, partial response, or stable disease. §Duration of response was defined as the time from the first documentation of a complete or partial response to disease progression or death from any cause, whichever occurred first. The percentages of patients with a response duration of at least 12 months were estimated with the Kaplan–Meier method, with corresponding 95% CIs calculated with the exponential Greenwood formula.

Table 2: **Efficacy endpoints as assessed by a masked independent central review (intention-to-treat population)**

	Sac-TMT plus pembrolizumab (n=208)		Pembrolizumab (n=204)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any treatment-emergent adverse event	207 (99%)*	115 (55%)	178 (87%)	64 (31%)
Any treatment-emergent serious adverse event	81 (39%)	..	59 (29%)	..
Treatment-emergent adverse event with an incidence of ≥5% in either group				
Anaemia	182 (88%)	19 (9%)	55 (27%)	2 (1%)
Alopecia	137 (66%)	0	6 (3%)	0
White blood cell count decreased	96 (46%)	18 (9%)	5 (2%)	1 (<1%)
Neutrophil count decreased	93 (45%)	36 (17%)	3 (1%)	1 (<1%)
Stomatitis	84 (40%)	11 (5%)	3 (1%)	0
Decreased appetite	73 (35%)	2 (1%)	27 (13%)	0
Weakness	71 (34%)	8 (4%)	23 (11%)	2 (1%)
Nausea	70 (34%)	0	11 (5%)	0
Hypoalbuminaemia	61 (29%)	0	35 (17%)	0
Weight decreased	56 (27%)	1 (<1%)	19 (9%)	1 (<1%)
Alanine aminotransferase increased	55 (26%)	1 (<1%)	33 (16%)	0
Rash	50 (24%)	6 (3%)	33 (16%)	1 (<1%)
Constipation	41 (20%)	0	19 (9%)	0
Weight increased	41 (20%)	1 (<1%)	39 (19%)	1 (<1%)
Aspartate aminotransferase increased	40 (19%)	2 (1%)	33 (16%)	0
Hyperuricaemia	38 (18%)	0	17 (8%)	0
Platelet count decreased	32 (15%)	0	10 (5%)	1 (<1%)
Hyponatraemia	32 (15%)	5 (2%)	22 (11%)	1 (<1%)
Vomiting	31 (15%)	1 (<1%)	7 (3%)	0
Pneumonia	30 (14%)	17 (8%)	19 (9%)	10 (5%)
Hyperglycaemia	30 (14%)	2 (1%)	9 (4%)	1 (<1%)
Insomnia	27 (13%)	0	16 (8%)	0
Cough	27 (13%)	1 (<1%)	16 (8%)	0
Hypothyroidism	27 (13%)	0	21 (10%)	0
Pyrexia	26 (13%)	0	15 (7%)	0
Diarrhoea	26 (13%)	3 (1%)	16 (8%)	1 (<1%)
Hypertriglyceridaemia	24 (12%)	3 (1%)	11 (5%)	2 (1%)
Blood alkaline phosphatase increased	21 (10%)	1 (<1%)	8 (4%)	0
Lymphocyte count decreased	20 (10%)	5 (2%)	10 (5%)	2 (1%)
Upper respiratory tract infection	19 (9%)	5 (2%)	9 (4%)	3 (1%)
Hypokalaemia	18 (9%)	5 (2%)	9 (4%)	0
Blood creatinine increased	18 (9%)	0	7 (3%)	0
Gamma-glutamyltransferase increased	18 (9%)	1 (<1%)	6 (3%)	0
Haemoptysis	17 (8%)	2 (1%)	11 (5%)	2 (1%)
Proteinuria	15 (7%)	0	12 (6%)	0
Blood lactate dehydrogenase increased	15 (7%)	0	8 (4%)	0
Hyperthyroidism	15 (7%)	0	10 (5%)	0
Tachypnoea	14 (7%)	2 (1%)	7 (3%)	0
Supraventricular extrasystoles	14 (7%)	0	3 (1%)	0
Electrocardiogram QT prolonged	14 (7%)	3 (1%)	4 (2%)	0
Mouth ulceration	14 (7%)	2 (1%)	3 (1%)	0
Hypocalcaemia	14 (7%)	0	7 (3%)	1 (<1%)
Conjunctivitis	12 (6%)	0	1 (<1%)	0
Urinary tract infection	12 (6%)	2 (1%)	7 (3%)	0
Back pain	12 (6%)	0	14 (7%)	1 (<1%)
Xerophthalmia	12 (6%)	0	0	0

(Table 3 continues on next page)

	Sac-TMT plus pembrolizumab (n=208)		Pembrolizumab (n=204)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
(Continued from previous page)				
Infusion related reaction	12 (6%)	0	2 (1%)	0
Pneumonitis	12 (6%)	2 (1%)	6 (3%)	0
Pain	11 (5%)	0	2 (1%)	0
Sinus tachycardia	11 (5%)	0	12 (6%)	0
Hypercholesterolaemia	11 (5%)	0	11 (5%)	0
Urinary occult blood positive	11 (5%)	0	6 (3%)	0
Influenza-like illness	11 (5%)	0	2 (1%)	0
Pruritus	11 (5%)	0	9 (4%)	1 (<1%)
Hypochloraemia	7 (3%)	0	11 (5%)	0

Data are n (%). The safety population included all the patients who received at least one dose of the assigned trial treatment and underwent a safety assessment. Adverse events were coded according to the Medical Dictionary for Regulatory Activities version 27.0, and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. Sac-TMT=sacituzumab tirumotecan. *Percentages are rounded to whole numbers; the value reported as 99% corresponds to an actual proportion of 99·5%, to distinguish it from a true 100%.

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

Implications of all the available evidence

This study provides evidence that first-line treatment with sac-TMT plus pembrolizumab significantly prolonged progression-free survival as compared with pembrolizumab alone among patients with PD-L1-positive advanced NSCLC without targetable genomic alterations. The magnitude of benefit observed in this study suggests the potential to redefine first-line treatment for a broad population of patients with PD-L1-positive NSCLC without targetable genomic alterations. Together with the biologic rationale, previous phase 2 data, and the established phase 3 activity of sac-TMT in NSCLC, these findings strengthen the evidence base for combining sac-TMT, a TROP2-directed ADC with a differentiated linker-payload platform, with pembrolizumab in PD-L1-positive advanced NSCLC.

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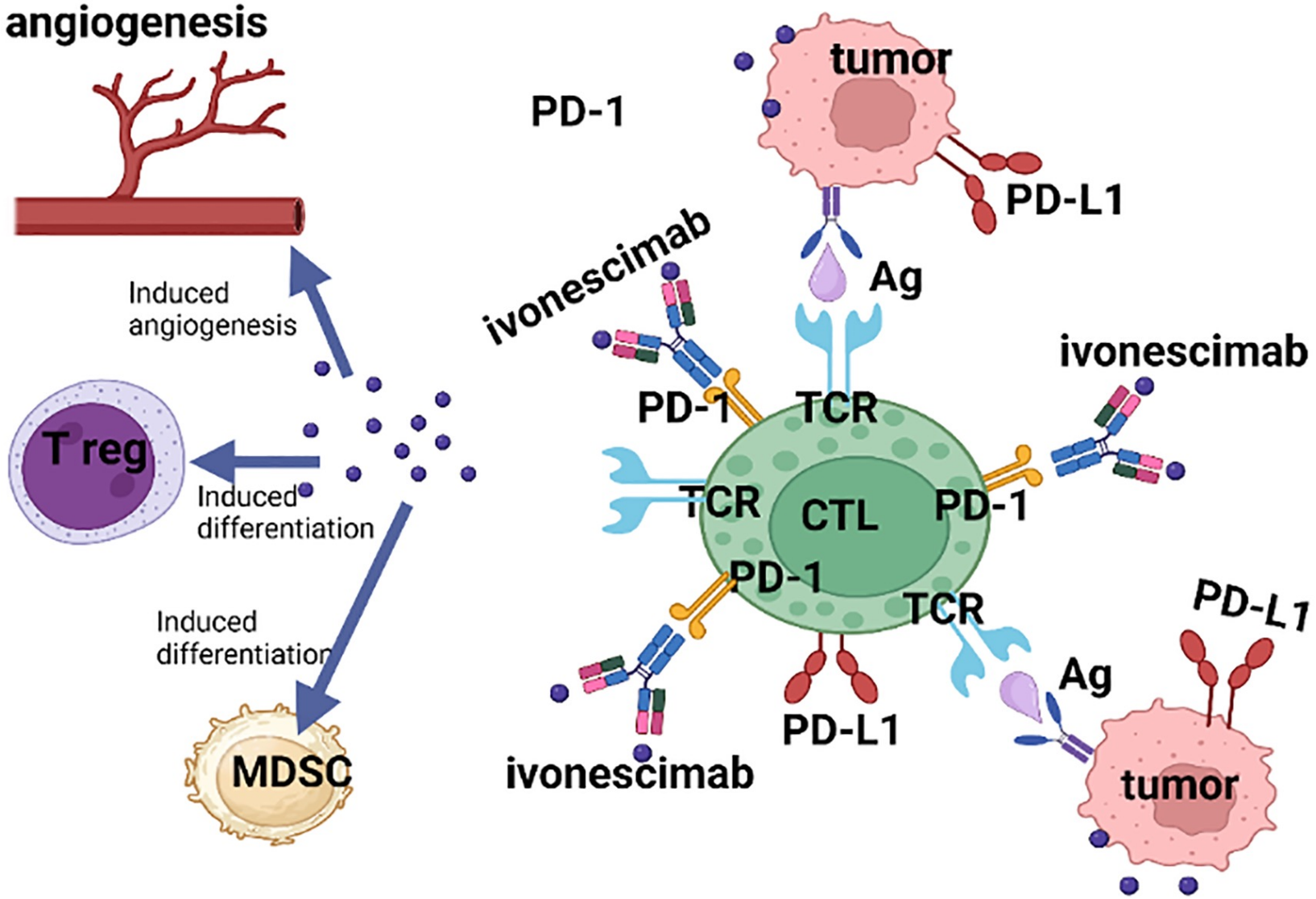
HARMONi-6 Trial

Ivonescimab Plus Chemotherapy Extends PFS in Squamous NSCLC

Berlin

Ivonescimab also interacts with VEGF-R



Ivonescimab plus chemotherapy versus tislelizumab plus chemotherapy in advanced squamous non-small-cell lung cancer (HARMONi-6): interim overall survival analysis of a randomised, double-blind, phase 3 trial in China

Ivonescimab ist ein neuartiger bispezifischer Antikörper, der gleichzeitig den PD-1-Signalweg blockiert und VEGF hemmt.

Tislelizumab ist ein Immun-Checkpoint-Inhibitor und humanisierter monoklonaler Antikörper, der den PD-1-Rezeptor auf T-Zellen blockiert.

Summary

Background Bispecific antibodies targeting programmed death 1 (PD-1) and vascular endothelial growth factor (PD1–VEGF) have shown promising efficacy in non-small-cell lung cancer (NSCLC). In our previous report of the HARMONi-6 study, we aimed to evaluate the efficacy and safety of ivonescimab plus chemotherapy versus tislelizumab plus chemotherapy as a first-line therapy for patients with advanced squamous NSCLC. Ivonescimab combined with chemotherapy significantly prolonged progression-free survival compared with tislelizumab plus chemotherapy. Here we report the prespecified interim overall survival analysis.

Methods HARMONi-6 is a double-blind, randomised, phase 3 trial, which was conducted at 50 hospitals across China. Patients aged 18–75 years with previously untreated, pathologically confirmed, unresectable stage IIIB, IIIC, or stage IV squamous NSCLC and an Eastern Cooperative Oncology Group performance status score of 0 or 1 were eligible for inclusion. Eligible patients were randomly assigned in a 1:1 ratio to receive ivonescimab or tislelizumab, in combination with paclitaxel and carboplatin for four cycles, followed by maintenance ivonescimab or tislelizumab monotherapy. The primary endpoint was progression-free survival assessed by the independent radiographic review committee as per Response Evaluation Criteria in Solid Tumours guidelines (version 1.1) in all randomly assigned patients. Overall survival was a key secondary endpoint; an interim analysis was planned when approximately 225 overall survival events were observed, but it was triggered after 204 overall survival events to meet regulatory deadlines. Safety, defined as adverse events and serious adverse events related to treatment, as well as adverse events related to immunity or VEGF blockade, were analysed in all randomly assigned patients who received at least one dose of the assigned study treatment. This study is registered at ClinicalTrials.gov (NCT05840016), has completed enrolment, and is ongoing for treatment and follow-up.

Findings From Aug 17, 2023, to Jan 21, 2025, 761 patients were assessed for eligibility, and after 229 exclusions a total of 532 patients were randomly allocated (266 per group). 494 (93%) of patients were male and 38 (7%) of patients were female. The median age was 64 years (IQR 59–69). At data cutoff (Feb 27, 2026), 204 deaths had occurred: 84 (32%) patients in the ivonescimab plus chemotherapy group and 120 (45%) in the tislelizumab plus chemotherapy group. With a median follow-up of 21·4 months (95% CI 20·27–21·91), the median overall survival was 27·9 months (95% CI 27·89–not evaluable [NE]) with ivonescimab versus 23·7 months (20·11–NE) with tislelizumab (hazard ratio for death 0·66 [95% CI 0·50–0·87]; $p_{one\text{-}sided}$=0·0017), meeting the prespecified boundary (p<0·0049). The overall survival benefit with ivonescimab plus chemotherapy was consistent across key subgroups. Treatment-related adverse events of grade 3 or higher occurred in 184 (69%) of 266 patients in the ivonescimab group and 156 (59%) of 265 patients in the tislelizumab group. The incidence of grade 3 or higher haemorrhage was seven (3%) of 266 and two (1%) of 265, respectively.

Interpretation Ivonescimab plus chemotherapy demonstrated a statistically significant and clinically meaningful improvement in overall survival compared with tislelizumab plus chemotherapy in previously untreated patients with advanced squamous NSCLC. This regimen could provide a novel treatment option as first-line treatment in this patient group.

Funding Akeso Biopharma.

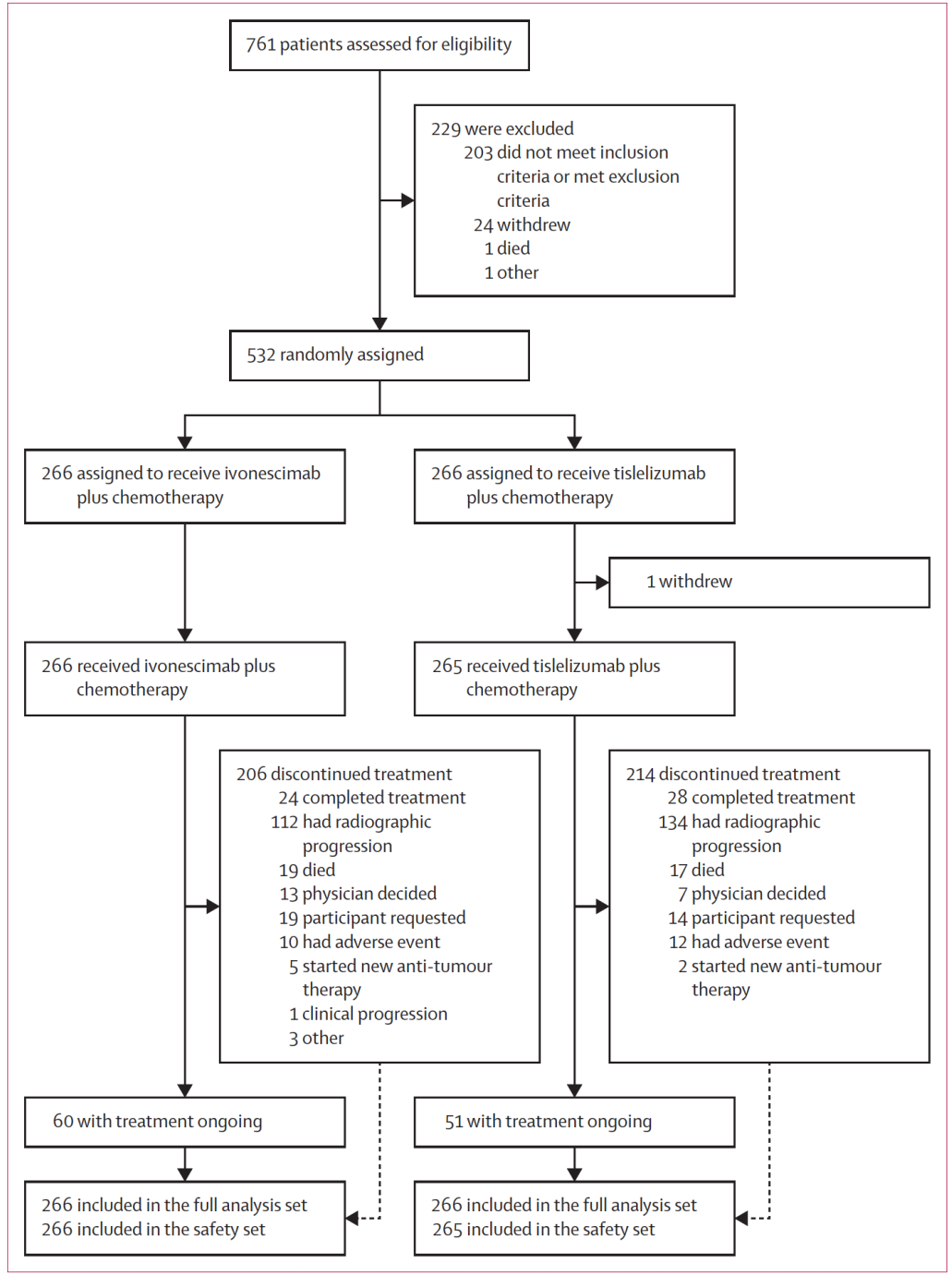


Figure 1: **Trial profile**

	Ivonescimab plus chemotherapy (n=266)	Tislelizumab plus chemotherapy (n=266)
Age, years		
Median (IQR)	64 (59–69)	64 (59–69)
≥65	131 (49%)	127 (48%)
Sex		
Male	256 (96%)	238 (89%)
Female	10 (4%)	28 (11%)
ECOG performance status score*		
0	42 (16%)	42 (16%)
1	224 (84%)	222 (83%)
Tobacco smoke exposure status		
Never exposed to tobacco smoke	21 (8%)	37 (14%)
Current or former tobacco smoke exposure	245 (92%)	229 (86%)
Disease stage		
IIIB or IIIC	21 (8%)	20 (8%)
IV	245 (92%)	246 (92%)
PD-L1 tumour proportion score		
<1%	105 (39%)	105 (39%)
1–49%	112 (42%)	99 (37%)
≥50%	49 (18%)	62 (23%)
History of haemoptysis		
Yes	86 (32%)	79 (30%)
No	180 (68%)	187 (70%)
Anatomical types		
Central	178 (67%)	158 (59%)
Peripheral	88 (33%)	108 (41%)
Major blood vessel encasement		
Yes	49 (18%)	44 (17%)
No	217 (82%)	222 (83%)
Presence of cavity in the tumour		
Yes	24 (9%)	23 (9%)
No	242 (91%)	243 (91%)

Data are n (%) unless otherwise stated. ECOG=Eastern Cooperative Oncology Group.
*ECOG performance status score ranges from 0 to 5, with higher scores indicating greater disability, and two patients had no ECOG performance status score.

Table 1: **Baseline demographics and disease characteristics**

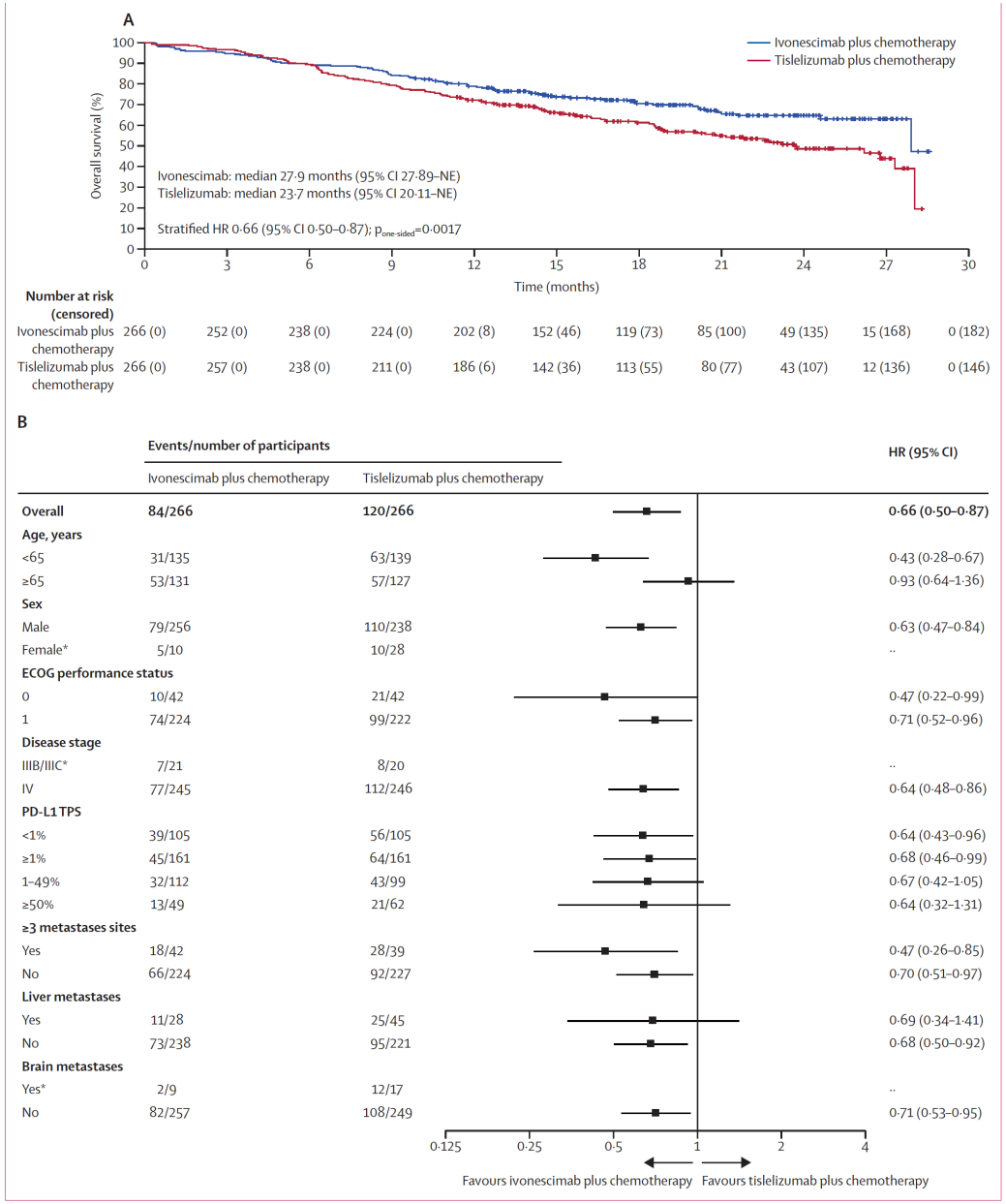


***Figure 2*: Overall survival in the full analysis set**
Kaplan–Meier estimates of overall survival in the two groups (A) and subgroup analysis of overall survival in key prespecified subgroups (B). ECOG=Eastern Cooperative Oncology Group. HR=hazard ratio. NE=not evaluable. PD-L1=programmed death-ligand 1. TPS=tumour proportion score. *If the number of events at a subgroup level is less than ten, the median overall survival and corresponding HR (95% CI) are not provided.

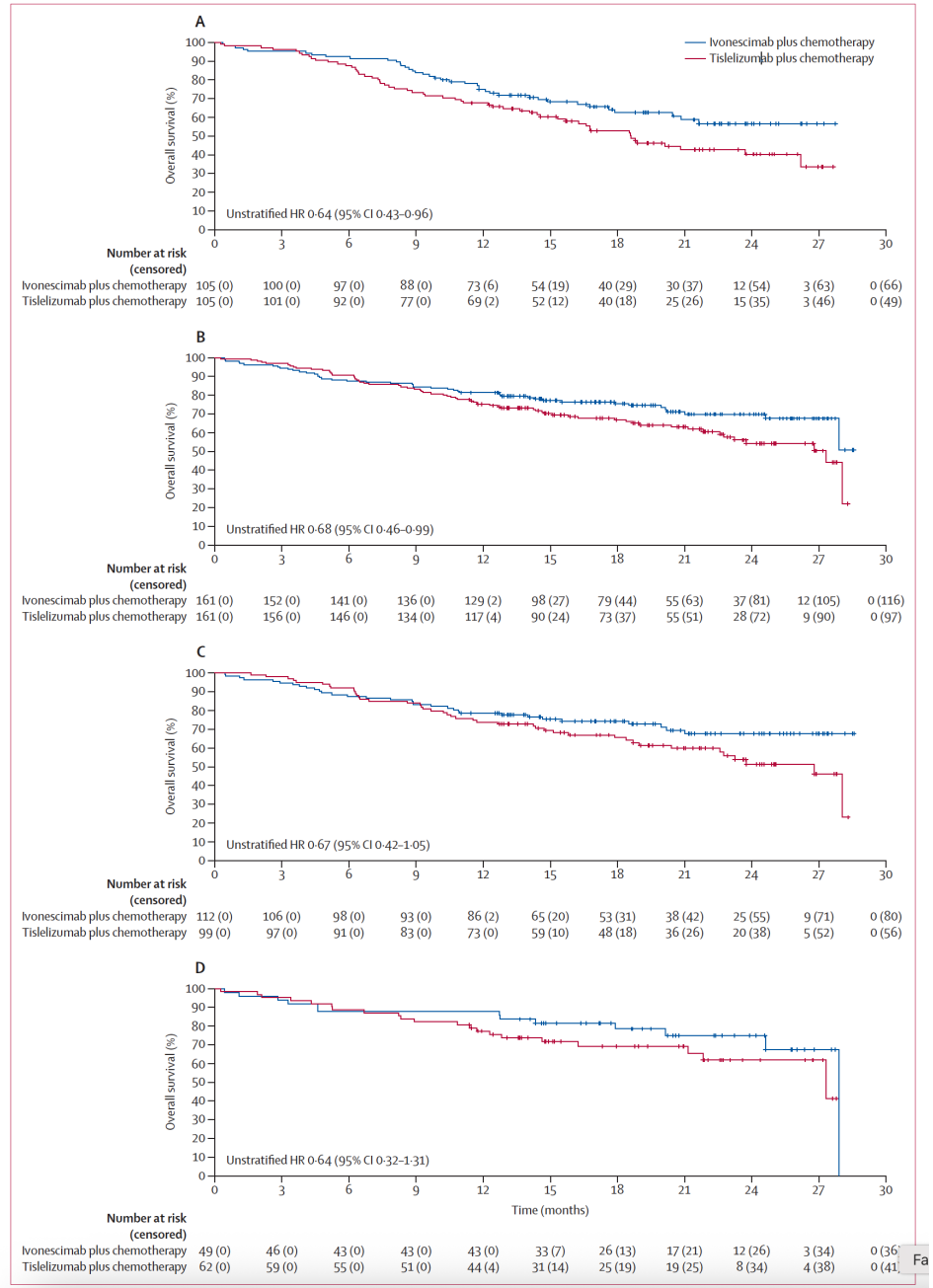


***Figure 3*: Kaplan–Meier estimates of overall survival in patients with PD-L1 TPS <1% (A); ≥1% (B); 1% to 49% (C); and ≥50% (D)**
HR=hazard ratio. PD-L1=programmed death-ligand 1. TPS=tumour proportion score.

	Ivonescimab plus chemotherapy (n=266)		Tislelizumab plus chemotherapy (n=265)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Treatment-related adverse events in ≥15% of patients*				
Alopecia	176 (66%)	0	163 (62%)	0
Anaemia	152 (57%)	19 (7%)	161 (61%)	13 (5%)
Neutrophil count decreased	125 (47%)	86 (32%)	118 (45%)	69 (26%)
White blood cell count decreased	101 (38%)	29 (11%)	98 (37%)	25 (9%)
Platelet count decreased	86 (32%)	8 (3%)	75 (28%)	8 (3%)
Hypoaesthesia	75 (28%)	0	69 (26%)	0
Decreased appetite	68 (26%)	6 (2%)	68 (26%)	2 (1%)
Alanine aminotransferase increased	60 (23%)	2 (1%)	61 (23%)	1 (<1%)
Pain in extremity	53 (20%)	3 (1%)	37 (14%)	1 (<1%)
Proteinuria	91 (34%)	12 (5%)	23 (9%)	0
Hypertriglyceridaemia	52 (20%)	5 (2%)	39 (15%)	6 (2%)
Hypoalbuminaemia	52 (20%)	0	31 (12%)	0
Aspartate aminotransferase increased	56 (21%)	3 (1%)	52 (20%)	5 (2%)
Nausea	43 (16%)	2 (1%)	53 (20%)	0
Hyperuricaemia	45 (17%)	1 (<1%)	23 (9%)	0
γ-glutamyl transferase increased	40 (15%)	7 (3%)	42 (16%)	6 (2%)
Hypothyroidism	50 (19%)	1 (<1%)	38 (14%)	0
Immune-related adverse event in ≥3% of patients†				
Blood urea increased	14 (5%)	0	12 (5%)	0
Alanine aminotransferase increased	12 (5%)	1 (<1%)	10 (4%)	1 (<1%)
Aspartate aminotransferase increased	12 (5%)	1 (<1%)	13 (5%)	4 (2%)
γ-glutamyltransferase increased	12 (5%)	2 (1%)	10 (4%)	2 (1%)
Blood bilirubin increased	9 (3%)	0	11 (4%)	1 (<1%)
Bile acids increased	8 (3%)	0	9 (3%)	0
Blood lactate dehydrogenase increased	6 (2%)	0	8 (3%)	0
α hydroxybutyrate dehydrogenase increased	5 (2%)	0	13 (5%)	0
Proteinuria	19 (7%)	2 (1%)	11 (4%)	0
Rash	13 (5%)	1 (<1%)	12 (5%)	2 (1%)
Hypothyroidism	17 (6%)	1 (<1%)	18 (7%)	0
Hyperthyroidism	5 (2%)	0	11 (4%)	0
Immune-mediated lung disease	11 (4%)	7 (3%)	10 (4%)	2 (1%)
Hyperglycaemia	7 (3%)	0	8 (3%)	0
Anaemia	11 (4%)	1 (<1%)	7 (3%)	1 (<1%)
Possible anti-VEGF-related adverse events				
Any	159 (60%)	33 (12%)	70 (26%)	8 (3%)
Proteinuria‡	113 (42%)	18 (7%)	34 (13%)	0
Haemorrhage‡	66 (25%)	7 (3%)	32 (12%)	2 (1%)
Hypertension‡	39 (15%)	10 (4%)	15 (6%)	5 (2%)
Arterial thromboembolism‡	4 (2%)	3 (1%)	0	0
Venous thromboembolism‡	2 (1%)	0	3 (1%)	1 (<1%)
Fistula	1 (<1%)	0	0	0

VEGF=vascular endothelial growth factor. *Treatment-related adverse events were defined as treatment-emergent adverse events with a causality assessment of related, probably related, or possibly related to any treatment drug (including ivonescimab, tislelizumab, paclitaxel, or carboplatin), and as well as those with a missing causality assessment. †Immune-related adverse events were assessed by investigators. ‡Grouped term.

Table 2: **Incidence of treatment-related adverse events, immune-related adverse events, and possible anti-VEGF-related adverse events**

Face

Implications of all the available evidence

As first-line treatment in patients with advanced squamous NSCLC, ivonescimab plus chemotherapy significantly improved overall survival compared with tislelizumab plus chemotherapy, with a manageable safety profile. This regimen could provide a novel treatment option for those patients. A global phase 3 study is underway to determine the generalisability of these findings.


NUTRI-SCORE
A B C D E

Ein **mehrgleisiges Kennzeichnungssystem für Lebensmittel** (*multipronged food labeling*) beschreibt eine politische Strategie, bei der verständliche **Nährwertlogos auf der Vorderseite** von Verpackungen mit weiteren gesetzlichen Schutzmaßnahmen kombiniert werden. Das Ziel dieses kombinierten Ansatzes ist es, eine gesündere Ernährungsumgebung zu schaffen und Übergewicht in der Bevölkerung – insbesondere bei Kindern – effektiv zu bekämpfen. Anstatt sich nur auf ein einzelnes Etikett zu verlassen, greifen bei diesem System mehrere regulatorische Maßnahmen wie Zahnräder ineinander.

Das weltweit bekannteste und wissenschaftlich am besten untersuchte Beispiel für diese Strategie ist das chilenische Gesetz zur Kennzeichnung und Werbung für Lebensmittel (*Food Labelling and Advertising Law*, FLAL).

Die wichtigsten Säulen des Ansatzes

Die Wirkung des mehrgleisigen Ansatzes basiert auf der Kombination verschiedener Maßnahmen:

•**Warnsymbole auf der Vorderseite (Front-of-Package Labels):** Gut sichtbare, schwarze, achteckige Stoppschild-Symbole weisen Verbraucher direkt beim Einkauf auf einen hohen Gehalt an Zucker, gesättigten Fettsäuren, Natrium (Salz) oder Kalorien hin.

•**Strikte Werbeverbote:** Lebensmittel, die diese Warnsymbole tragen müssen, dürfen nicht mehr im Fernsehen oder im Internet gezielt an Kinder vermarktet werden. Auch die Verwendung von Comicfiguren, Spielzeugbeilagen oder Maskottchen auf den Verpackungen ist verboten.

•**Verkaufsverbote an Schulen:** Produkte mit Warnsymbolen dürfen in Schulen weder verkauft noch kostenlos verteilt oder beworben werden. Schulmahlzeiten müssen stattdessen strengen Gesundheitsrichtlinien entsprechen.

Food labeling in Chile

The impact of Chile's multipronged food labelling and advertising law on early childhood excess weight: a cohort difference-in-differences study

Summary

Background The 2016 Chilean Food Labelling and Advertising Law (FLAL), featuring black octagonal front-of-package warning labels and marketing and school restrictions, was among the first sets of multiple healthy food policies globally. In spite of its relevance, no study has causally linked the FLAL implementation to health outcomes. We aimed to estimate the plausible causal effect of the implementation of phase 1 of the FLAL on the relevance of excess weight among young children.

Methods In this cohort difference-in-differences approach, we assessed the effect of phase 1 of the FLAL on children's BMI when initital thresholds for critical nutrients were subsequently increased and implemented. Our analysis used national administrative data from the Chilean National Board of School Aid and Scholarships covering more than 300 000 school children aged 4–6 years across public and publicly subsidised schools nationwide from 2012 to 2017. We primarily used the Nutritional Map (Mapa Nutricional), available beginning in 2012, complemented with the Vulnerability Survey (Encuesta de Vulnerabilidad), available beginning in 2019. We defined cohorts by the year students entered prekindergarten, and compared unexposed cohorts (2012 and 2013, control group) with cohorts exposed to phase 1 (2014 and 2015, treatment group) during prekindergarten, kindergarten, and first grade. The primary outcome was a binary indicator of excess weight (ie, overweight or obesity) analysed using logit models and reported as marginal effects. We conducted subgroup analyses by children's school type, school area, maternal education and age at childbirth, birthweight, and gender.

Findings The final analytical sample included 321 597 students (of cohorts 2012–15) covering the years 2012 to 2017 across prekindergarten, kindergarten, and first grade. Exposure to phase 1 of the FLAL led to significant reductions in the probability of a child having excess weight. Children exposed during both kindergarten and first grade (ie, 18 months of exposure) had the largest effects. Girls had a 2·85% lower probability of excess weight (95% CI –0·0407 to –0·0163), while boys had a 2·40% lower probability (–0·0358 to –0·0122). We also observed significant effects after 6 months of exposure (ie, first grade only): 1·91% lower probability (–0·0315 to –0·0068) for girls and 2·24% (–0·0345 to –0·0104) lower probability for boys.

Interpretation Phase 1 of Chile's comprehensive FLAL plausibly caused a measurable decrease in the prevalence of excess weight among young school children. The results provide crucial, evidence-based support for policy makers worldwide who are considering food environment policies as a scalable, impactful strategy to combat the childhood obesity epidemic.

Funding Bloomberg Philanthropies Grant.

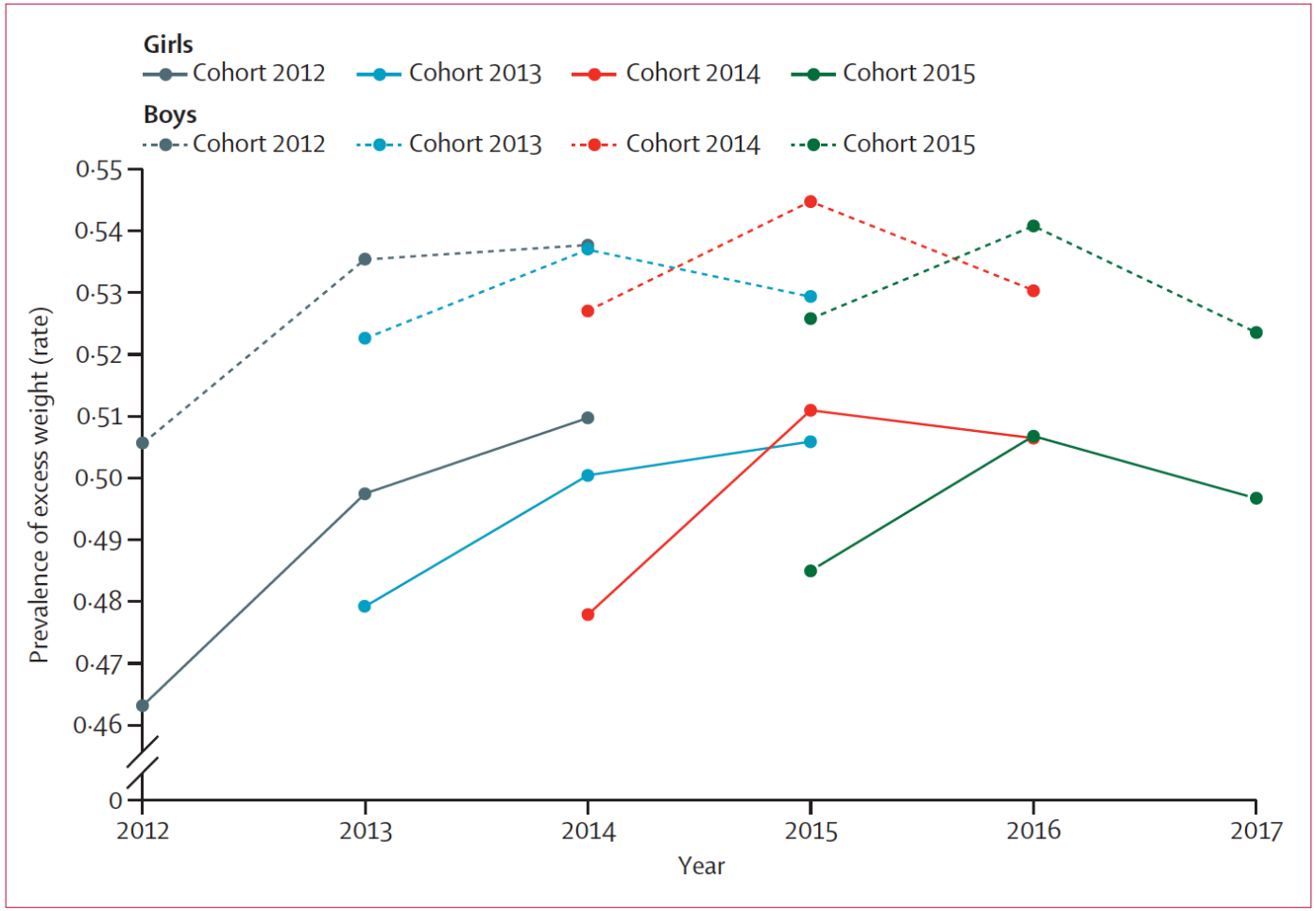


Figure 1: **Cohort-specific trends in the unconditional prevalence of childhood excess weight by school grade, year, and gender, children from public and publicly subsidised schools, 2012–17**

Each line represents a birth cohort of children followed over time from prekindergarten through to first grade between 2012 and 2017. The y-axis shows the proportion of children with excess weight (overweight or obesity) as defined by the age-adjusted BAZ (>1) and the x-axis shows the calendar year in which anthropometric measurements were taken. Full lines represent girls, while dashed lines represent boys. The first datapoint for each line indicates prekindergarten, the second represents kindergarten, and the third represents first grade. The Food Labelling and Advertising Law was implemented in 2016, affecting cohorts differently depending on their school grades at the time of implementation. Cohorts 2012 and 2013 were unexposed during early grades (control, grey and blue lines), while cohorts 2014 and 2015 were partially exposed (treatment, red and green lines). BAZ=BMI-for-age Z scores.

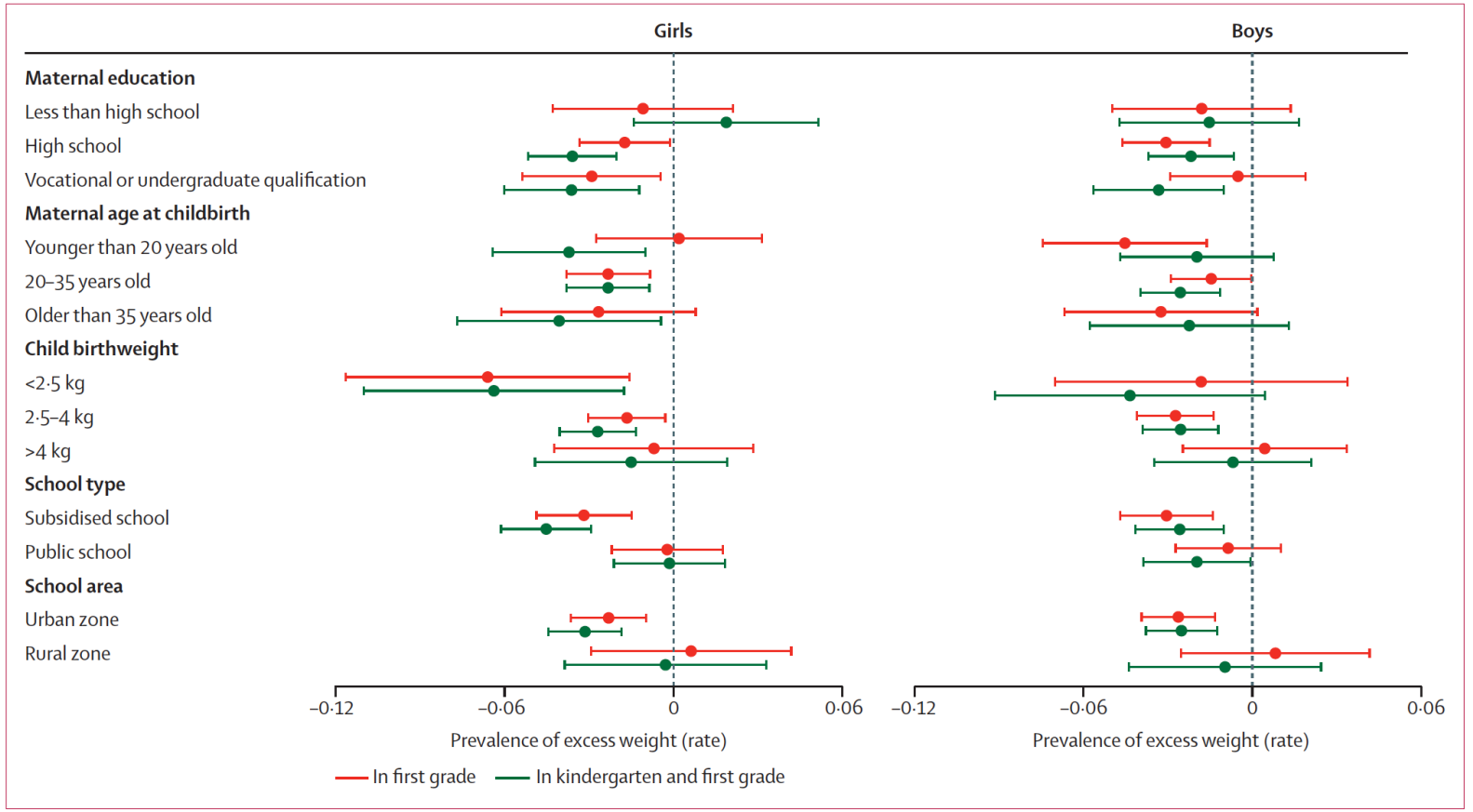


Figure 2: **ME (95% CI) of the FLAL on excess weight among girls and boys in public and publicly subsidised schools, 2012–17**

ME (95% CI) of the FLAL on excess weight (defined as BAZ >1) among girls and boys based on logit regressions. Results are reported separately for the 2014 (red) and 2015 (green) treatment cohorts (appendix p 10). Estimates are stratified by maternal education, maternal age at childbirth, child birthweight, school type, and school area. Effects represent slope changes in excess weight prevalence across school grades relative to the control cohorts. BAZ=BMI-for-age Z scores. FLAL=Food Labelling and Advertising Law. ME=marginal effects.

	Exposure to the FLAL in first grade			Exposure to the FLAL in kindergarten and first grade		
	Sample size, n	ME (95% CI)	Excess weight prevalence (rate) in pre-kindergarten (control and treated cohorts)	Sample size, n	ME (95% CI)	Excess weight prevalence (rate) in pre-kindergarten (control and treated cohorts)
Full sample	118 188	−0·0191* (−0·0315 to −0·0068)	0·474	121 982	−0·0285† (−0·0407 to −0·0163)	0·477
Maternal education						
Less than high school	17 374	−0·0108 (−0·0429 to 0·0212)	0·487	17 171	0·0188 (−0·0141 to 0·0516)	0·487
High school	71 606	−0·0173‡ (−0·0333 to −0·0012)	0·473	74 152	−0·0359† (−0·0516 to −0·0203)	0·476
More than high school	29 208	−0·0290‡ (−0·0536 to −0·0045)	0·471	30 659	−0·0362* (−0·0602 to −0·0121)	0·475
Maternal age at childbirth						
<20 years	21 337	0·0020 (−0·0275 to 0·0315)	0·468	23 816	−0·0371* (−0·0643 to −0·0099)	0·474
20 to 35 years	82 408	−0·0232* (−0·0380 to −0·0083)	0·474	84 198	−0·0232* (−0·0379 to −0·0085)	0·477
>35 years	14 443	−0·0266 (−0·0612 to 0·0080)	0·483	13 968	−0·0406‡ (−0·0768 to −0·0044)	0·485
Child birthweight						
<2·5 kg	9599	−0·0660‡ (−0·1164 to −0·0156)	0·410	10 753	−0·0638* (−0·1101 to −0·0175)	0·414
2·5 to 4 kg	99 091	−0·0165‡ (−0·0302 to −0·0029)	0·471	101 231	−0·0269† (−0·0404 to −0·0134)	0·474
>4 kg	9498	−0·0069 (−0·0423 to 0·0284)	0·575	9998	−0·0150 (−0·0492 to 0·0191)	0·581
School type						
Public	58 052	−0·0022 (−0·0219 to 0·0175)	0·479	59 132	−0·0014 (−0·0211 to 0·0183)	0·478
Subsidised	77 468	−0·0319† (−0·0487 to −0·0150)	0·471	80 371	−0·0452† (−0·0613 to −0·0292)	0·477
School location						
Urban	106 537	−0·0230† (−0·0364 to −0·0097)	0·473	110 198	−0·0314† (−0·0444 to −0·0184)	0·476
Rural	16 509	0·0063 (−0·0292 to 0·0419)	0·485	16 771	−0·0028 (−0·0386 to 0·0331)	0·484

ME (95% CI) from logit regressions assessing the impact of the FLAL on excess weight (defined as BAZ >1) among girls. ME are reported as the proportional change in the probability of excess weight, relative to the average prevalence observed in prekindergarten for the corresponding sample. The number of children in the school-type and school-location subgroups does not sum to the total in the full sample because some students switched schools over time and are thus included in both groups. Those exposed to the FLAL in the first grade had 6 months of exposure, while those exposed in kindergarten had 18 months. Standard errors are clustered at the individual (child) level. BAZ=BMI-for-age Z score. FLAL=Front-of-Package Labelling Law. ME=marginal effects. *p<0·01. †p<0·001. ‡p<0·05.

Table 1: **ME of exposure to Chile's FLAL on excess weight in girls, 2012–17**

	Exposure to the FLAL in first grade			Exposure to the FLAL in kindergarten and first grade		
	Sample size, n	ME (95% CI)	Excess weight prevalence (rate) in pre-kindergarten (control and treated cohorts)	Sample size, n	ME (95% CI)	Excess weight prevalence (rate) in pre-kindergarten (control and treated cohorts)
Full sample	107 393	−0·0224* (−0·0345 to −0·0104)	0·520	111 402	−0·0240* (−0·0358 to −0·0122)	0·520
Maternal education						
Less than high school	15 486	−0·0180 (−0·0497 to 0·0136)	0·529	15 308	−0·0153 (−0·0473 to 0·0166)	0·528
High school	65 181	−0·0307* (−0·0462 to −0·0152)	0·521	67 722	−0·0218† (−0·0370 to −0·0066)	0·519
More than high school	26 726	−0·0051 (−0·0292 to 0·0189)	0·513	28 372	−0·0333† (−0·0565 to −0·0102)	0·517
Maternal age at childbirth						
<20 years	19 382	−0·0453† (−0·0744 to −0·0162)	0·514	21 717	−0·0197 (−0·0469 to 0·0075)	0·511
20 to 35 years	75 075	−0·0146‡ (−0·0290 to −0·0003)	0·521	76 972	−0·0256* (−0·0397 to −0·0115)	0·523
>35 years	12 936	−0·0325 (−0·0668 to 0·0018)	0·520	12 713	−0·0224 (−0·0577 to 0·0130)	0·515
Child birthweight						
<2·5 kg	7835	−0·0182 (−0·0702 to 0·0339)	0·448	8819	−0·0435 (−0·0915 to 0·0045)	0·451
2·5 to 4 kg	86 412	−0·0273* (−0·0410 to −0·0137)	0·513	88 721	−0·0255* (−0·0390 to −0·0121)	0·512
> 4 kg	13 146	0·0044 (−0·0247 to 0·0335)	0·610	13 862	−0·0069 (−0·0349 to 0·0211)	0·609
School type						
Public	54 489	−0·0086 (−0·0273 to 0·0102)	0·526	55 677	−0·0197‡ (−0·0387 to −0·0007)	0·525
Subsidised	69 567	−0·0305* (−0·0470 to −0·0139)	0·516	73 005	−0·0258* (−0·0415 to −0·0102)	0·516
School location						
Urban	96 374	−0·0263* (−0·0394 to −0·0133)	0·517	100 328	−0·0252* (−0·0378 to −0·0125)	0·518
Rural	15 773	0·0082 (−0·0253 to 0·0417)	0·538	15 858	−0·0097 (−0·0438 to 0·0244)	0·533

ME (95% CI) from logit regressions assessing the impact of the FLAL on excess weight (defined as BAZ >1) among boys. ME are reported as the proportional change in the probability of excess weight, relative to the average prevalence observed in prekindergarten for the corresponding sample. The number of children in the school-type and school-location subgroups does not sum to the total in the full sample because some students switched schools over time and are thus included in both groups. Those exposed to the FLAL in the first grade has 6 months of exposure, while those exposed in kindergarten had 18 months. Standard errors are clustered at the individual (child) level. BAZ=BMI-for-age Z score. FLAL=Front-of-Package Labelling Law. ME=marginal effects. *p<0·001. †p<0·01. ‡p<0·05.

Table 2: **ME of exposure to Chile's FLAL on excess weight in boys, 2012–17**

Research in context

Evidence before this study

Although single national food environment policies, such as sugar-sweetened beverage taxes, have demonstrated effects on health outcomes, there are currently no published studies assessing the real-world health effects of multi-pronged food environment policies that integrate front-of-package warning labels, marketing restrictions, and school food environment regulations.

Added value of this study

This study offers the first plausible causal evidence at the national level that a comprehensive food environment policy influences children's excess weight. Using a national administrative dataset of more than 300 000 Chilean schoolchildren aged 4–6 years from 2012 to 2017 and a cohort difference-in-differences approach, we went beyond mere association to quantify the Food and Advertisement Law's (FLAL) direct, plausible causal impact. Our findings indicate that exposure to phase 1 of the Chilean FLAL during early school years resulted in a significant decrease in the likelihood of excess weight and in BMI. We also observed a strong protective effect for biologically vulnerable children (eg, those with low birthweight). Results for girls should be interpreted with caution regarding plausible causality.

Implications of all the available evidence

This research shows that a mutually reinforcing set of food environment policies, anchored by a front-of-package warning label, reduces the risk of excess weight among early school-age children. These findings provide crucial evidence-based support for policy makers worldwide who are considering mandatory nutritional warning labelling in particular, and food environment policies in general, as powerful, scalable strategies to address the childhood obesity epidemic.

Cardiometabolic Multiple Long-Term Conditions 1

Epidemiology of cardiometabolic multiple long-term conditions

Cardiometabolic multiple long-term conditions (MLTC), defined as the coexistence of two or more cardiometabolic diseases such as diabetes, cardiovascular disease, and chronic kidney disease, are increasingly prevalent and represent a growing challenge for health systems worldwide. Despite rising interest, progress in understanding cardiometabolic MLTC has been limited by substantial heterogeneity in definitions, measurements, and analytical approaches, restricting comparability across studies and limiting translation into clinical and public health practice. Reported prevalence estimates vary across populations, largely reflecting differences in study design and conditions included. The prevalence of cardiometabolic MLTC increases with age but is not confined to older populations, with these conditions often emerging in early adulthood, particularly among socioeconomically disadvantaged and minority ethnic populations, for whom these conditions also progress more rapidly. Longitudinal studies demonstrate disease accumulation and accelerating transitions following development of a cardiometabolic condition leading to premature mortality. These trajectories are shaped by interacting genetic, metabolic, behavioural, and psychosocial factors, while deprivation and structural inequities substantially amplify risk and earlier onset. Advancing research and improving care will require harmonised definitions, greater use of longitudinal data, and scalable analytical approaches that explicitly capture disease sequencing and transitions. To improve consistency and comparability, the definition of cardiometabolic MLTC should be standardised.

Smoking, Hypertension, Diabetes, Lipids, Obesity (+ aging for which there is no cure)

Key messages

Cardiometabolic MLTC represent a shift in global disease burden

The coexistence of multiple long-term conditions (MLTC) is a clinical reality across health systems. They are responsible for premature mortality, disability, and increasing health-care costs. Their development reflects the interaction of biological, behavioural, social, and environmental exposures operating through interconnected pathways.

Prognosis of cardiometabolic MLTC is driven by clustering

Disease progression occurs through shared pathophysiological pathways; each condition both increases the risk of other cardiometabolic conditions and is exacerbated by their presence.

Cardiometabolic MLTC emerge across the life course

Cardiometabolic MLTC are biologically and socially engrained early in life. MLTC can be thought of as the aggregate consequence of early-life biological programming, sustained cardiometabolic stress, and structural inequities.

Key determinants of poor outcomes include socioeconomic factors, ethnicity, and fragmented health-care systems

Socioeconomic factors and minority ethnic status are associated with earlier onset, faster progression, and earlier mortality. Fragmented, specialty-based care pathways and inappropriate polypharmacy prevent adequate management.

Health systems must transition from single-disease management to a life-course approach

Without standardised definitions and harmonised metrics, comparisons across nations are not possible and global actions cannot be implemented. Prevention must begin early with the development of person-centred models of care capable of addressing the complexity and mitigating the long-term progression of cardiometabolic MLTC.

Panel: Evolution of terminology of multimorbidity

- The term multimorbidity was first described by Brandlmeier in an urban German general practice in 1976.[3]
- In view of the confusion in terminologies between comorbidity and multimorbidity, a distinction was proposed in 1996 with the term comorbidity implying combined effects in reference to an index chronic condition (eg, stroke in a person with diabetes) and multimorbidity meaning co-occurrence of conditions without a single condition holding a priority over other co-occuring conditions.[4,5]
- The concept of multimorbidity as two or more chronic conditions was adopted by WHO in 2008 in recognition of its growing burden in an ageing society.[6]
- In 2018, the Academy of Medical Sciences published a landmark international policy report titled *Multimorbidity: a priority for global health research*. The report highlighted the rising burden of multiple long-term conditions and the lack of coherent evidence on its causes, prevention, and management.[7]
- Patients do not find multimorbidity an acceptable term to describe their condition and associate it with a negative image, giving the impression to patients that they are in poor health, their body is failing them, they may be dying soon, and there is nothing they can do about their condition. The UK National Institute for Health and Care Research Strategic Framework therefore emphasised their preferred term as multiple long-term conditions.[1]

	Constituent conditions	Key characteristics
Cardiometabolic cluster[24–26]	Hypertension, type 2 diabetes, and coronary artery disease	Most consistently identified cluster across populations; reflects strong metabolic–vascular interplay and shared risk factors
Diabetes–hypertension cluster[27,28]	Type 2 diabetes and hypertension (with or without chronic kidney disease)	Most dominant two-condition dyad; often early onset; associated with faster progression to complications
Atherosclerotic vascular cluster[13,19]	Myocardial infarction, stroke, peripheral arterial disease, and carotid disease	High prognostic burden; driven by inflammatory and vascular mechanisms; strongly associated with mortality
Metabolic–endocrine cluster[29–31]	Type 2 diabetes, hypertension, and liver disease	Highly prevalent; often precedes cardiovascular clustering; contributes to downstream disease transitions
Heart failure–cardiometabolic cluster[17,32]	Atrial fibrillation, hypertension, type 2 diabetes, and myocardial infarction	Recognised upstream drivers of incident heart failure; reflects cumulative cardiometabolic burden

Table 1: **Cardiometabolic conditions most strongly contributing to observed cardiometabolic multiple long-term condition clusters**

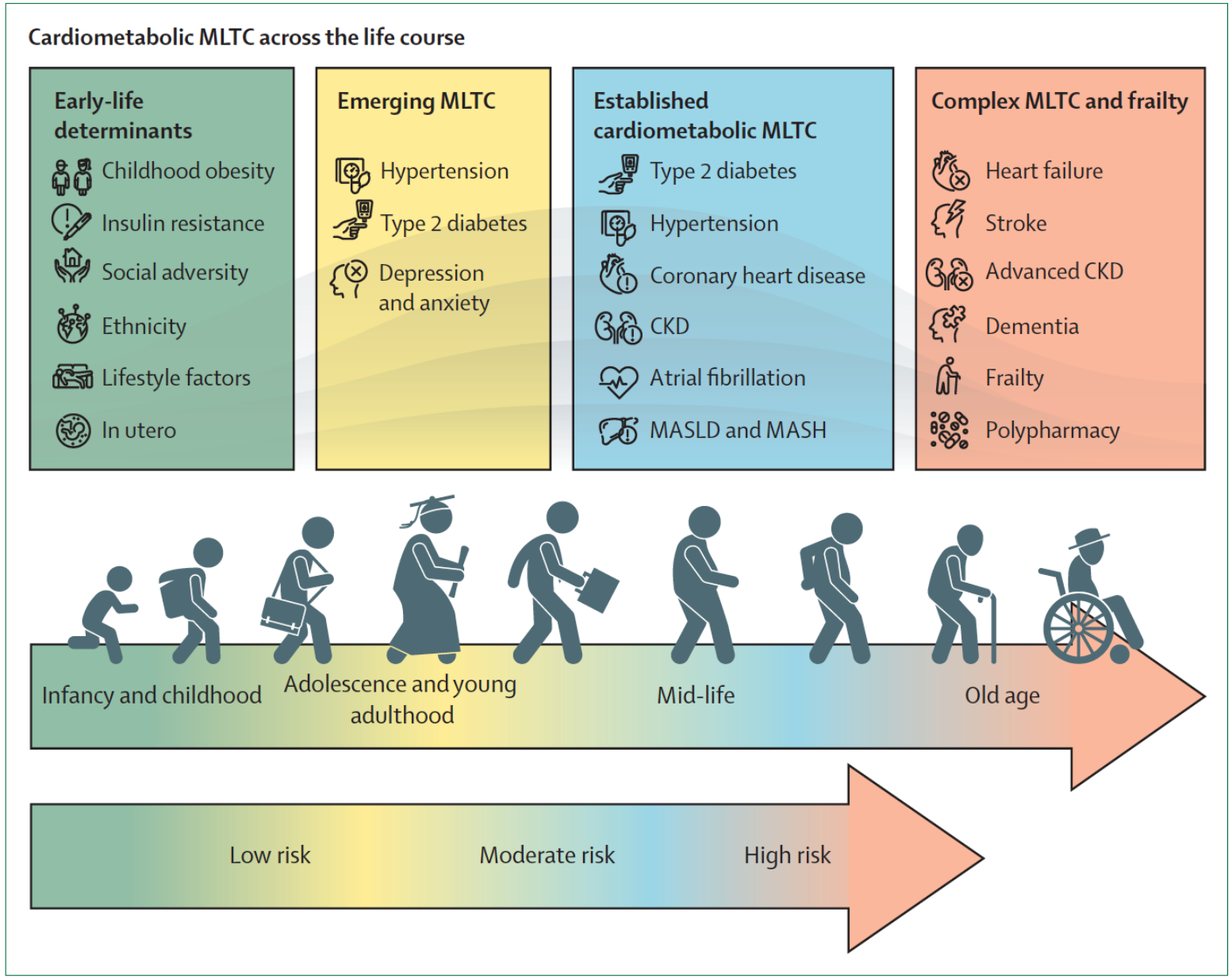


Figure 1: **MLTC across the life course**

MLTC=multiple long-term conditions. CKD=chronic kidney disease. MASLD=metabolic dysfunction-associated steatotic liver disease. MASH=metabolic dysfunction-associated steatohepatitis.

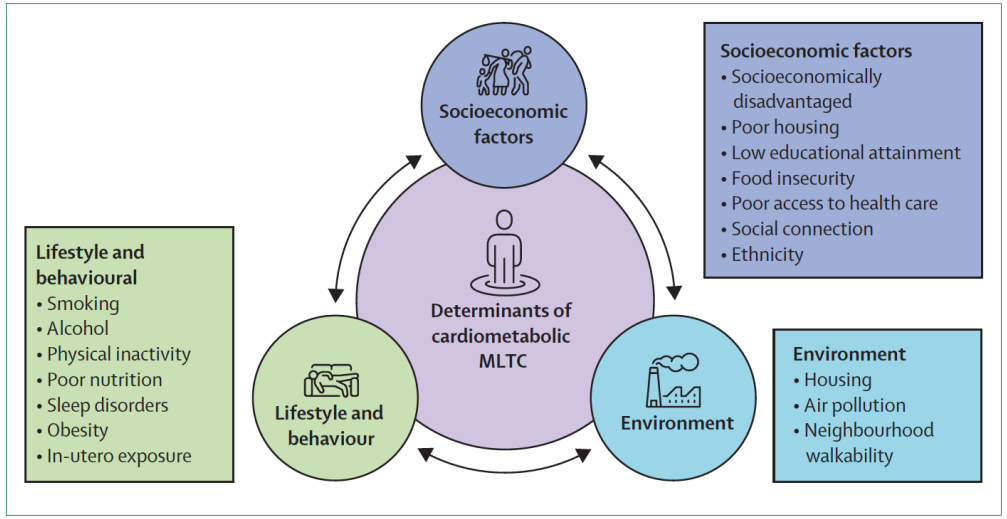


Figure 2: **Modifiable determinants of cardiometabolic MLTC**
MLTC=multiple long-term conditions.

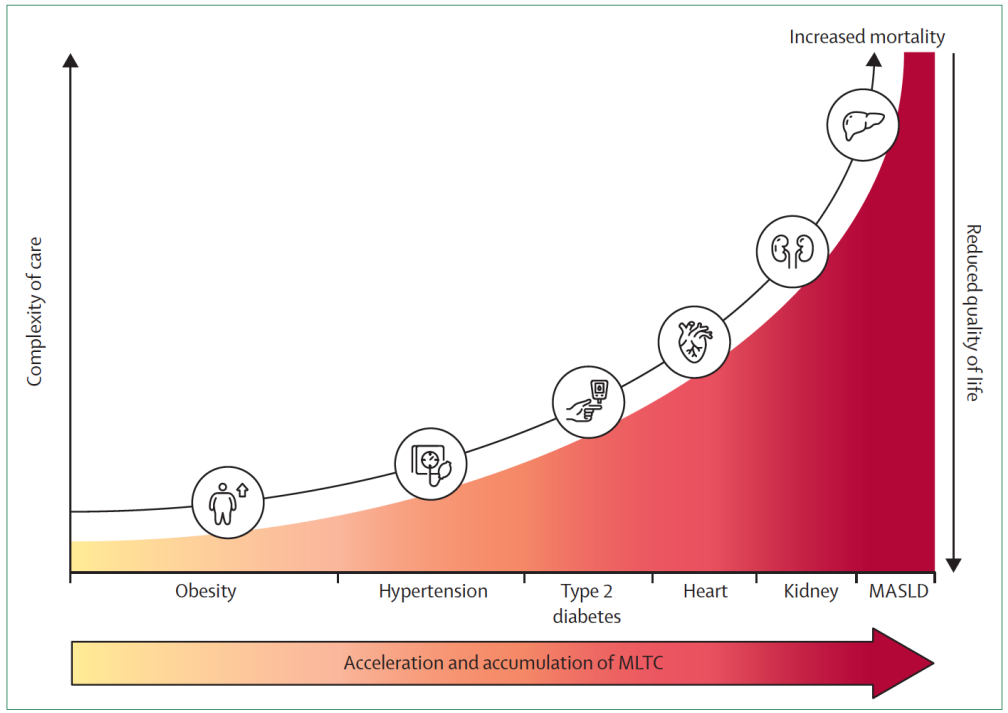


Figure 3: **Trajectories of cardiometabolic MLTC and effect on outcomes**
The sequencing of conditions and effect on outcomes is for illustration purposes only. MLTC=multiple long-term conditions. MASLD=metabolic dysfunction-associated steatotic liver disease.

	Specific research gaps	Rationale
Conceptualisation and measurement		
Definition and operationalisation	How can cardiometabolic MLTC (including constituent conditions) be defined and operationalised in ways that are clinically meaningful, comparable across settings, and sensitive to disease severity, activity, and duration?	Standardised yet clinically nuanced definitions are essential for cross-study comparability, accurate burden estimation, and translation into practice
Measurement validity and bias	To what extent do observed ethnic and socioeconomic differences reflect differential exposure to risk factors, differential disease detection, or survival differences?	Distinguishing true from biased aetiological variation is crucial for valid inference and equitable policy design
Life-course epidemiology and disease trajectories		
Age of onset and early-life determinants	At what ages do cardiometabolic MLTC trajectories most commonly begin, and which early-life exposures most strongly predict accelerated disease accumulation?	Identifying sensitive periods and early-life drivers supports primordial and primary prevention strategies
Trajectories in younger populations	What are the patterns, trajectories, and determinants of cardiometabolic MLTC in children, adolescents, and young adults?	Early-onset MLTC might follow distinct biological and social pathways with long-term implications for health systems
Sequence and order of accumulation	What are the most common sequences of cardiometabolic MLTC accumulation, and how do these vary by age, sex, ethnicity, and socioeconomic position?	Understanding temporal ordering informs mechanistic hypotheses and targeted intervention timing
High-risk combinations	Which combinations and temporal ordering of cardiometabolic conditions confer the greatest risk of adverse outcomes (eg, mortality, disability, and hospitalisation)?	Risk stratification depends not only on condition count but also on synergistic or high-risk clustering patterns
Social and structural determinants		
Structural drivers of inequality	How do structural determinants (eg, housing, employment, education, and health-care access) interact with biological risk to shape unequal MLTC trajectories?	Integrating structural and biological perspectives is necessary to explain and reduce health inequalities
Global and contextual variation	What is the burden and pattern of cardiometabolic MLTC in LMICs, and how do these trajectories interact with infectious diseases?	Evidence from LMICs remains scarce, and cardiometabolic–infectious multimorbidity might follow distinct epidemiological patterns
Data integration and methodological innovation		
Data linkage and multimodal integration	How can linked electronic health records, longitudinal cohort data, and multiomics platforms be integrated to better characterise MLTC trajectories?	Multimodal data integration can improve phenotyping, causal inference, and trajectory modelling
Advanced analytical approaches	How can emerging machine learning and data-driven clustering methods improve identification of heterogeneous MLTC trajectories and risk phenotypes?	Advanced analytics might uncover latent subgroups and non-linear patterns not detectable using conventional approaches

MLTC=multiple long-term conditions. LMICs=low-income and middle-income countries.

Table 2: **Research gaps**

Multiple, long-term conditions

Conclusion

Cardiometabolic MLTC are not an inevitable feature of ageing. They emerge across the life course, often begin with adverse trajectories established in early life and adolescence, and can progress quickly once conditions cluster. Their burden falls disproportionately on minority ethnic populations and those from socioeconomically disadvantaged areas, reflecting the combined effects of biological susceptibility and structural inequities that shape exposures, health-care access, and quality of care. As populations live longer and obesity remains highly prevalent, health systems will face increasing numbers of people living for decades with complex, treatment-intensive MLTC. The response must shift from single-disease paradigms to integrated, person-centred prevention and early risk factor control that also addresses behavioural, psychological, cognitive, and social determinants. To strengthen consistency, comparability, and action across studies and settings, cardiometabolic MLTC should be operationalised using a core set of conditions with transparent reporting of definitions and coding.

Cardiometabolic Multiple Long-Term Conditions 2

Biological and mechanistic pathways of cardiometabolic multiple long-term conditions

Cardiometabolic multiple long-term conditions (MLTC) arise from the complex interplay of biological, sociodemographic, environmental, and behavioural factors across the life course. Shared risk factors and mechanisms, including insulin resistance, adiposity, and chronic inflammation, underpin its development. Growing evidence also implicates that even low-level, long-term exposure to fine particulate matter, nitrogen dioxide, and related pollutants can accelerate the trajectory of cardiometabolic MLTC. Early-life exposures, including undernutrition and overnutrition, altered gut microbiome, and endocrine-disrupting chemicals, interact with social determinants of health to aggravate inflammatory and metabolic dysregulation. These mechanisms, together with genetic susceptibility, epigenetic modifications, and multiomics perturbations, shape disease progression, heterogeneity, and the clustering of cardiometabolic MLTC. Yet, fundamental gaps persist, whereby most mechanistic insights are derived from single-disease studies, leaving the temporal hierarchy, causal pathways, and population-level heterogeneity largely unresolved. Addressing these challenges will require life-course research, integrative systems approaches, and translational studies that link mechanistic insights to precision prevention and therapeutic strategies. By bridging discovery with actions, such efforts can enhance care for cardiometabolic MLTC and promote equitable health outcomes globally.

Key messages

- Cardiometabolic multiple long-term conditions (MLTC) are underpinned by shared, interconnected biological mechanisms. The central pathways driving organ dysfunctions include insulin resistance, ectopic fat deposition, chronic inflammation, and increased oxidative stress.
- Social determinants of health modulate systemic vulnerability and substantially influence the trajectory of cardiometabolic MLTC. Environmental factors, including pollution, accelerate disease progression.
- Nutritional transitions (undernutrition and overnutrition), gut microbiome dysbiosis, and endocrine-disrupting chemicals interact to worsen metabolic dysregulation. These early-life exposures imprint durable genetic and epigenetic effects, establishing a lifelong susceptibility to cardiometabolic MLTC.
- Leveraging genetic data through polygenic risk scores can improve population risk prediction, enable genomic risk stratification, and validate mechanistic targets for therapeutic development of cardiometabolic MLTC.
- High-throughput multiomics profiling serves as an observation window into shared biological mechanisms. Integrating these emerging biomarkers improves predictive performance for incident cardiometabolic MLTC beyond established clinical models.
- Addressing the growing burden of MLTC requires moving away from siloed, single-disease clinical frameworks. Future research and management strategies must embrace life-course cohort studies, diverse cross-ancestral data, and systems biology to drive precision prevention and treatment.

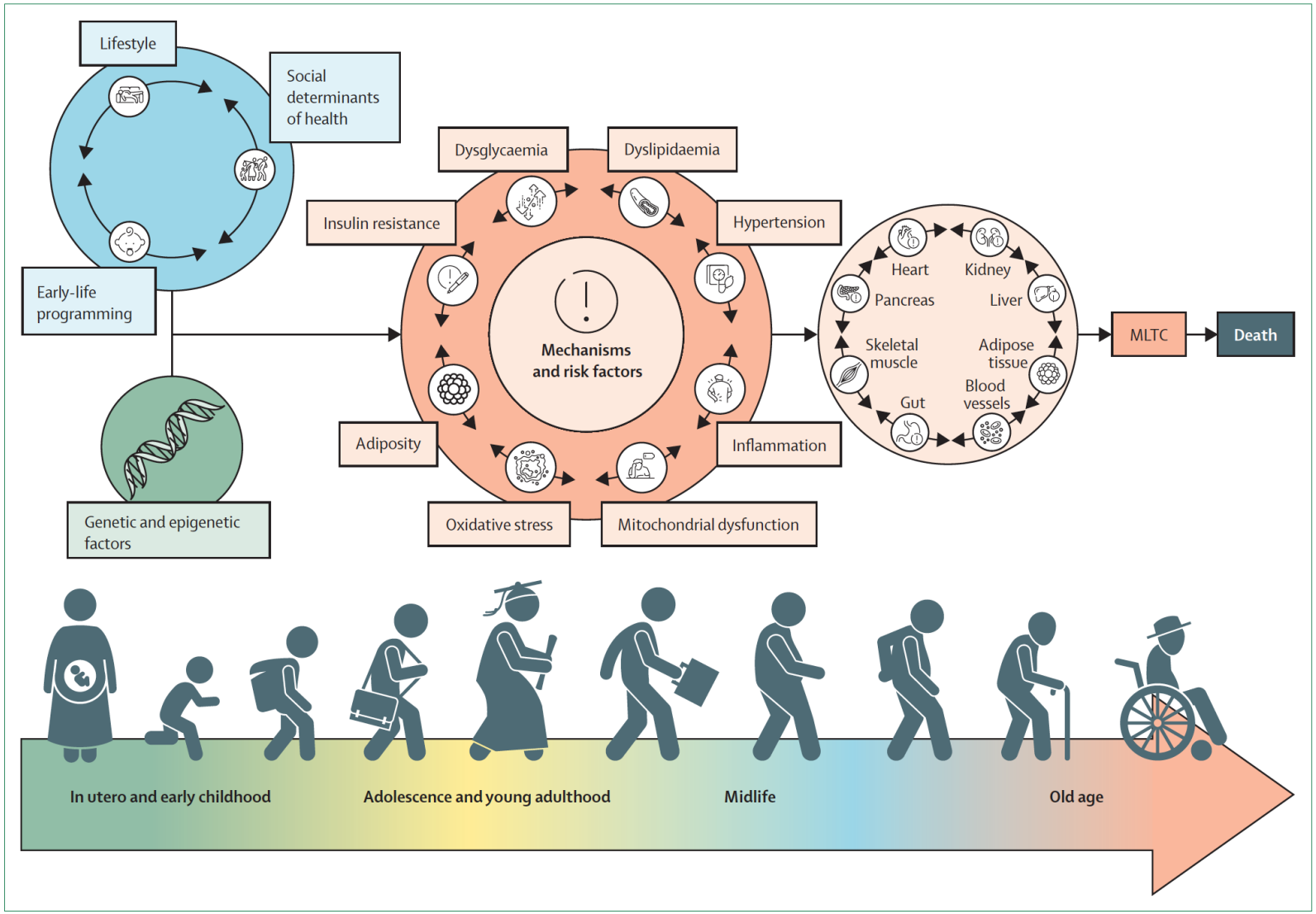


Figure 1: **An integrated model illustrating the common mechanisms of how social, behavioural, environmental, genetic, and epigenetic factors interact across the life course in the development and progression of cardiometabolic MLTC**
MLTC=multiple long-term conditions.

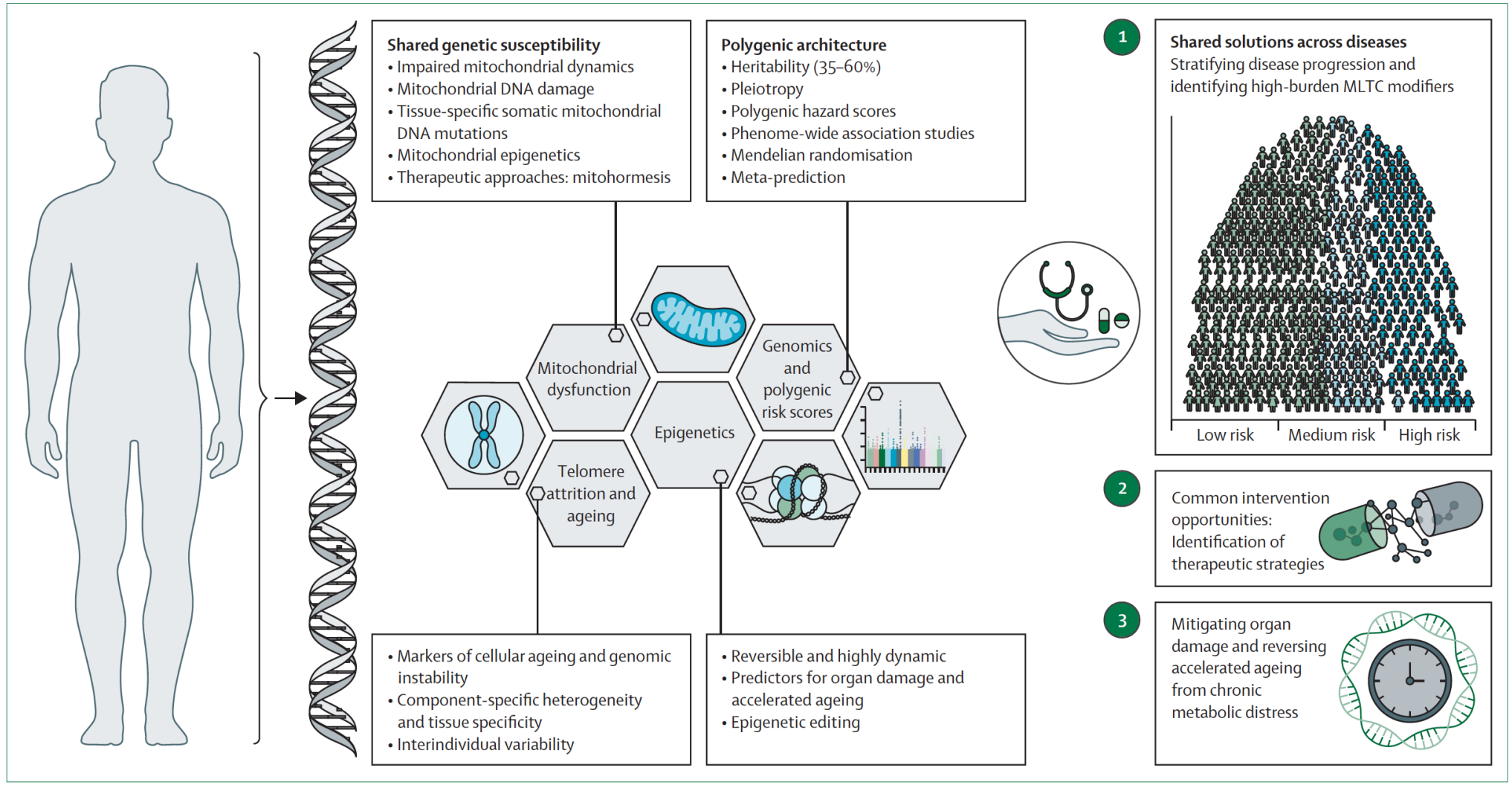


Figure 2: **Shared genetic and epigenetic drivers of cardiometabolic MLTC and opportunities for multidisease therapeutic strategies**

Elucidating shared molecular mechanisms enables a unified therapeutic approach across three primary domains: (1) shared solutions across diseases, focusing on stratifying disease trajectories and identifying high-burden MLTC modifiers; (2) common intervention opportunities, centred on the identification and development of broad-spectrum therapeutic strategies; and (3) organ protection, aiming to prevent downstream organ damage and reverse the accelerated ageing phenotypes induced by chronic metabolic distress. MLTC=multiple long-term conditions.

Panel: **Key evidence gaps and future research priorities in cardiometabolic MLTC**

Shared risk factors and mechanisms

- Identify shared causal molecular pathways for therapeutic targeting
- Delineate the neuroendocrine–immune axes that drive the development of cardiometabolic multiple long-term conditions (MLTC)
- Delineate the temporal stages in the evolution of cardiometabolic MLTC to identify critical windows for intervention

SDOH

- Standardise consensus-based criteria for the uniform definition of social determinants of health (SDOH) and objective measurements of cardiometabolic MLTC and disease severity
- Broaden the scope of SDOH by capturing socioeconomic, environmental, behavioural, and structural factors (eg, social support, housing quality, and neighbourhood safety) using standardised instruments
- Investigate the link between SDOH and cardiometabolic MLTC by conducting prospective real-world studies in diverse populations, including in marginalised groups and different health-care settings

Early-life exposures and programming

- Delineate the mechanisms by which early-life exposures alter the composition and functions of the gut microbiome
- Define the window-specific contribution of different developmental periods, from preconception, in utero, infancy, and adolescence to the final risk of cardiometabolic MLTC
- Analyse longitudinal trajectories for determining the crucial transition point at which cardiovascular and metabolic risk factors solidify into cardiometabolic MLTC

Genetic and epigenetic biomarkers

- Identify genetic modifiers within high-burden cardiometabolic MLTC, such as cardiovascular–kidney–liver–metabolic conditions
- Identify possible rare and structural variants and characterise their contributions to account for missing heritability
- Determine the relative influence of genetic, phenotypic, and environmental crosstalks on interindividual differences in MLTC progression
- Determine the cell-specific, persistent epigenetic changes (eg, DNA methylation and histone modifications in adipocytes or endothelial cells) that explain the effect of early-life exposures
- Measure and validate mitochondrial damage and dynamics markers (eg, cell-free mitochondrial DNA and key metabolites) in ethnically diverse cohorts

Emerging non-genetic biomarkers

- Integrate multiomics data for the discovery of novel, cross-disease biomarkers for improved risk stratification, prediction, and prognostication of cardiometabolic MLTC
- Validate multiomics signatures that can predict the transition from a single disease to cardiometabolic MLTC and the disease trajectories
- Delineate circulating molecular ageing markers that can predict and mediate inflammation-driven organ damage across various tissues

Conclusion

Cardiometabolic MLTC emerges from convergent perturbations across metabolic, inflammatory, and vascular pathways that collectively drive disease patterns and trajectories. By synthesising evidence from molecular pathways to multi-organ crosstalk, this Series paper delineates the mechanistic architecture underpinning systemic susceptibility and adverse health outcomes. These findings can identify novel opportunities for intervention and serve as a foundation for targeted prevention and management strategies that transcend single-disease frameworks (as outlined in the third paper in this Series).[6] The continued integration of multiomics, systems biology, and life-course approaches will further enhance personalised risk profiling and therapeutic discovery. Ultimately, these advancements will allow us to address cardiometabolic MLTC as a truly interconnected system.

Cardiometabolic Multiple Long-Term Conditions 3

Interventions for the prevention and management of cardiometabolic multiple long-term conditions

Multiple long-term conditions (MLTC or multimorbidity) are increasing in global prevalence and represent a growing burden for individuals and health-care systems. Grouping cardiometabolic MLTC can be justified because aetiological antecedents and risk factors are often shared, and similar therapeutic approaches can have positive effects on the prevention, treatment, and delayed progression of many of the constituent conditions. In this Series paper, we focus on interventions for the prevention and management of cardiometabolic MLTC, under the broad headings of population-level, individual-level, and system-level interventions. Population-level public health measures such as educational, fiscal, regulatory, and environmental policies, and population-level screening and early detection can result in improved risk factor identification and control, although evidence that they reduce incidence and progression of cardiometabolic MLTC is more scarce. At an individual level, lifestyle interventions and pharmacotherapeutics can reduce the incidence and progression of cardiometabolic MLTC and provide effective treatment. Together with pharmacotherapeutic strategies, approaches to improve medicines management could help to optimise clinical outcomes in those living with cardiometabolic MLTC. System-level solutions, including integrated models of care and care continuity, provide opportunities to better address the holistic needs of people living with cardiometabolic MLTC. Together, combinations of multilevel approaches are required.

Key messages

- Both public health interventions and population-based screening can improve risk factor control, the latter through increased risk factor identification, but evidence for reducing incidence and progression of cardiometabolic multiple long-term conditions (MLTC) through these approaches, and for reducing the associated morbidity and mortality burdens, remains limited.
- There is strong evidence for preventing cardiometabolic MLTC with combined multicomponent lifestyle interventions, primarily through reducing type 2 diabetes incidence. Evidence for associated reductions in cardiovascular events and mortality is less clear, although stronger for secondary prevention than for primary prevention.
- There is very strong evidence of benefit for newer drugs (eg, GLP-1 receptor agonists, GIP–GLP-1 receptor agonists, and SGLT2 inhibitors) that target multiple biological pathways implicated in the development and progression of cardiometabolic MLTC, with established beneficial effects on cardiovascular and renal events, as well as on mortality.
- Supportive medication management interventions can optimise cardiometabolic risk factor control through improved treatment concordance, with potential resulting benefits on clinical outcomes. Deprescribing can address treatment burden and quality of life, but the potential effect on cardiovascular events and mortality is unclear.
- A systems-based approach facilitating integrated care has been shown to improve risk factor control across settings, although the evidence of benefit for cardiometabolic MLTC management is more evolved for integration within primary care teams than within hospital environments. Successful integration across primary and secondary care settings is still in its early stages for the prevention and management of cardiometabolic MLTC.
- Digital delivery of interventions, some now with artificial intelligence enhancements, could enable more efficient integrated care for cardiometabolic MLTC prevention and management.
- International guidelines informing clinical practice of cardiometabolic MLTC need to move beyond single-disease frameworks.

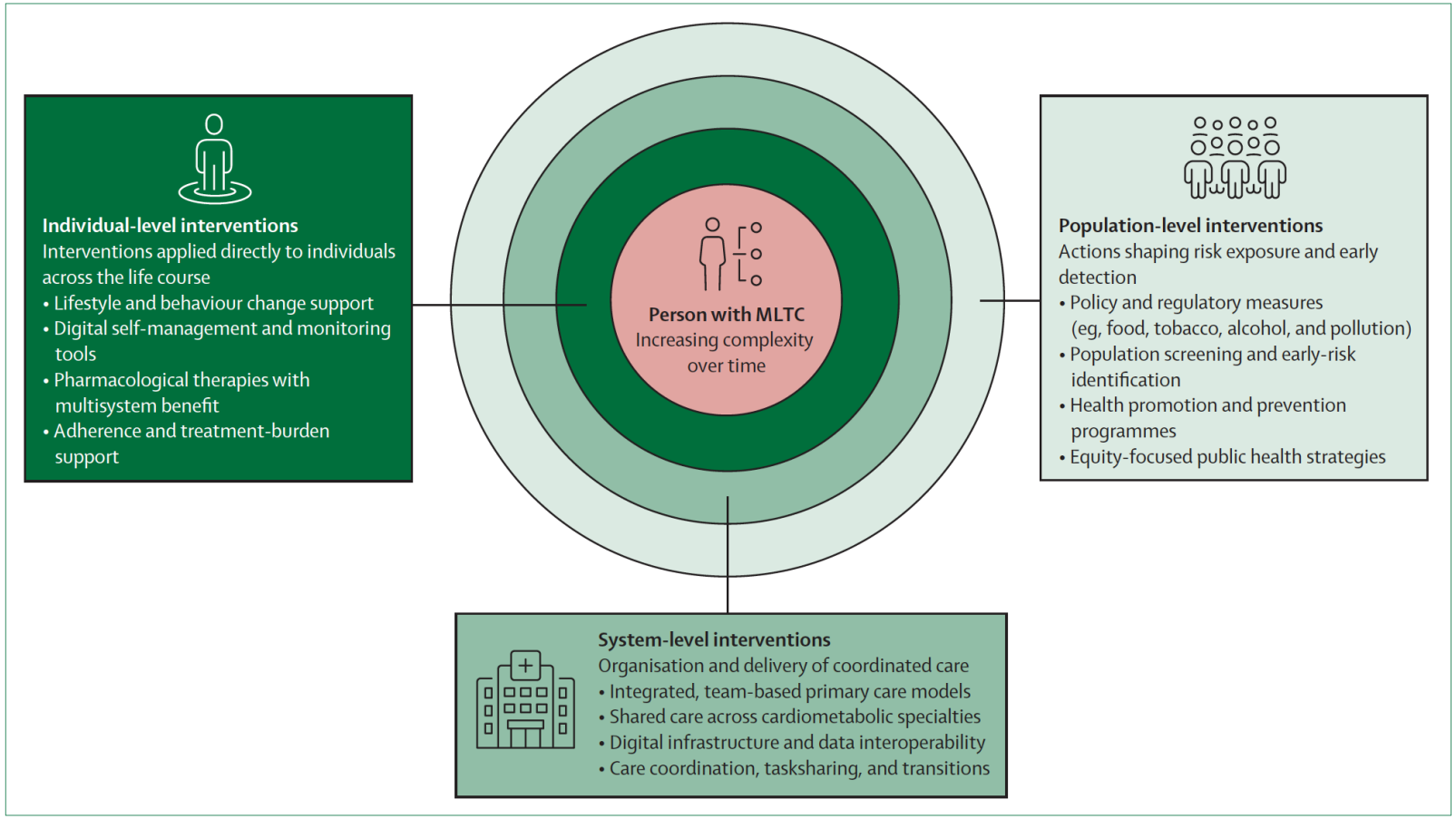


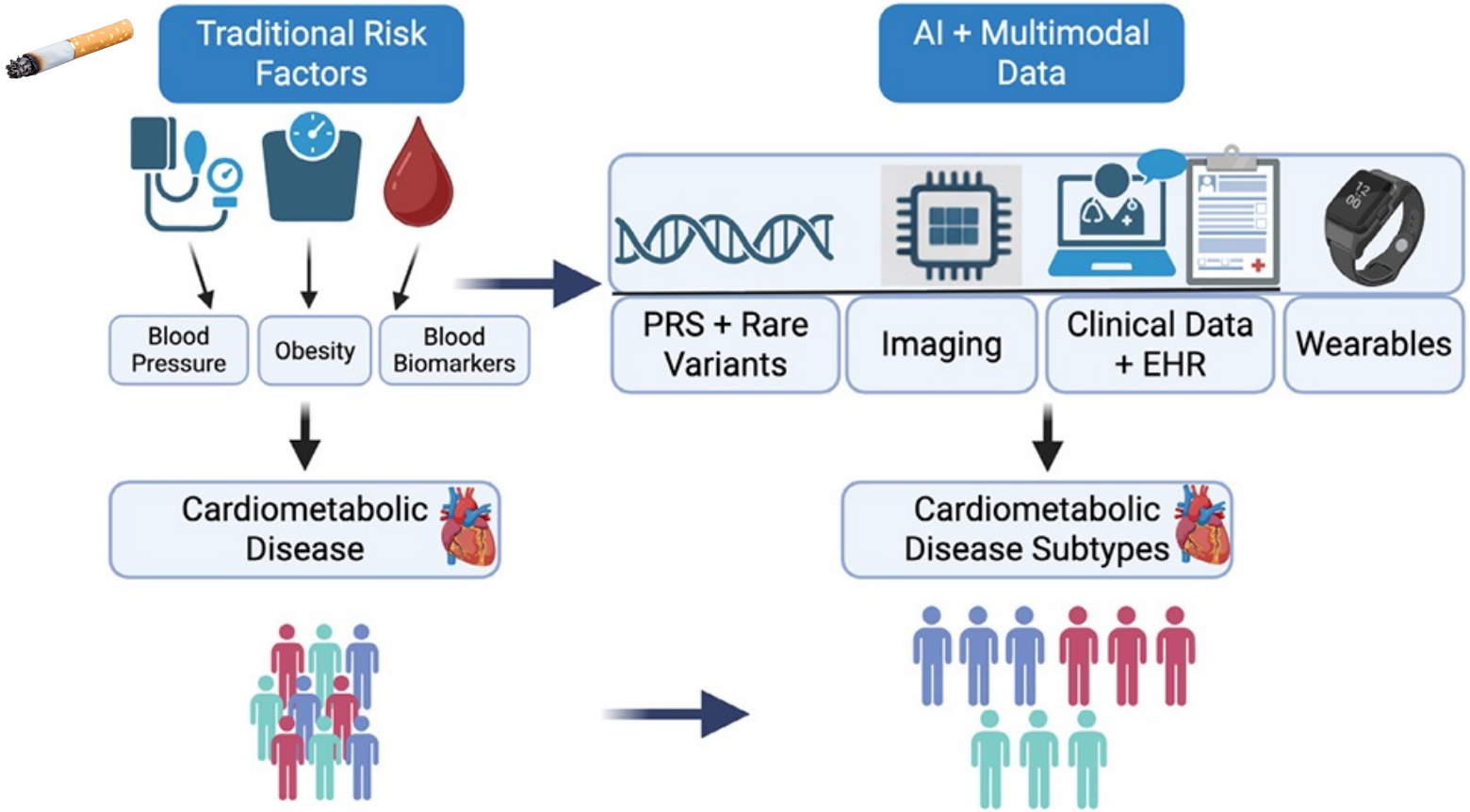
Figure: **Multifaceted approach to cardiometabolic MLTC**
MLTC=multiple long-term conditions.

	Evidence for risk factor control	Evidence for clinical outcomes	Evidence for multimorbidity-relevant outcomes (quality of life, function, and treatment burden)	Overall strength of evidence
Population-level interventions				
Public health policies (eg, tobacco control and fiscal food policies)	↑↑[18–22]	↑[15,21,24,25]	↔	↑
Population-based screening and early detection	↑↑[34,49,50]	↑[35,47,49]	↔	↑
Individual-level interventions				
Lifestyle interventions (eg, diet and physical activity)	↑↑↑[74,77,82,87,99–105,110,115,116]	↑↑[66–68,70,72,75,76,78,79,81,82,94,116]	↑↑[96,97,104]	↑↑
Pharmacological interventions with multisystem benefit (eg, SGLT2 inhibitors and GLP-1 receptor agonists)	↑↑↑[130,131,135,139,148,163,166]	↑↑↑[130–134,138,144–146,149–162]	↑↑[141,142,148]	↑↑↑
Polypharmacy and medication management	↑↑[172,181–184,190–192]	↑[190–192]	↑[188,193]	↑
System-level interventions				
Hospital-based multidisciplinary cardiometabolic clinics	↑↑[194]	↑[194]	↑[194]	↑
Integrated collaborative care (primary care-based)	↑↑[171,172,178,198,201]	↑[195,199]	↑↑[196,198]	↑↑
Digital decision support and system-level digital tools	↑[174,177,205,206]	↑[205]	↑[205]	↑

The number of arrows equals relative magnitude of beneficial impact. ↑=small magnitude. ↑↑=moderate magnitude. ↑↑↑=large magnitude. ↔=neutral or uncertain magnitude.

Table: **Evidence base for prevention and management interventions in cardiometabolic multiple long-term conditions**

Science Magazine last week



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

Panel 1: **Key research gaps**

Population-level interventions

- High-quality evaluations using real-world data, rather than modelling studies, are needed for assessing the effect of population-level interventions on the prevention and management of cardiometabolic multiple long-term conditions (MLTC).
- There is limited evidence on populations at high risk, such as those from socioeconomically deprived areas and minority ethnic communities.
- Most studies have been in older populations and further research is needed for younger populations who are facing a growing burden of MLTC.
- There is a scarcity of high-quality trials in low-income and middle-income countries.

Individual-level interventions

- Clarity is required as to what are the most meaningful primary endpoints for intervention trials in individuals with, or at risk of, cardiometabolic MLTC.
- There is insufficient high-quality evidence that in-person behavioural interventions in people with cardiometabolic MLTC produce sustained improvements in risk factor control and cardiometabolic outcomes.
- Evidence for digital and artificial intelligence-based delivery of lifestyle interventions to improve clinical outcomes and address health inequalities remains scarce.
- Evidence is needed to understand optimal timing and intensity of treatment with novel pharmacotherapies in different risk groups across the life course in cardiometabolic MLTC.
- Further evidence is required to understand the effect of rational polypharmacy and deprescribing on clinical outcomes in cardiometabolic MLTC across the life course.

System-level interventions

- Further research is required on pragmatic models of care for improving outcomes of people with established cardiometabolic MLTC.
- There is a lack of multimorbidity-specific outcomes, with most studies prioritising single behaviours or conditions rather than outcomes relevant to MLTC (eg, treatment burden, functional status, or integrated risk reduction).
- Future studies should include complex interventions integrating behavioural interventions, digital tools, care coordination, and health system infrastructure.
- Evidence for system-level digital interventions, including artificial intelligence and large language model-enabled decision-support systems, remains scarce.

Panel 2: **Practice and policy recommendations**

- Health policy should prioritise implementation of interventions with the strongest evidence for clinical benefit, in particular regulatory measures to support smoking cessation. For dietary policy interventions, evidence of benefit currently sits with reduced consumption and small improvements in BMI; besides modelling studies, there is weaker evidence for prevention or reduced progression of cardiometabolic multiple long-term conditions (MLTC).
- Population-health screening should be used to improve risk factor identification and subsequent risk factor control for cardiometabolic MLTC, despite limited evidence for long-term prevention or reduced progression of cardiometabolic MLTC.
- Multicomponent lifestyle interventions should be prioritised for both individual-level prevention and management of cardiometabolic MLTC, although the most compelling evidence is for type 2 diabetes prevention.
- Based on the strong evidence identified for prevention and management of cardiometabolic MLTC, newer pharmacotherapy with multisystem benefits (eg, GLP-1 receptor agonist-based drugs and SGLT2 inhibitors) should be prioritised within clinical guidelines.
- Structured medication reviews should be conducted in all patients with cardiometabolic MLTC at least annually, explicitly distinguishing optimisation and improved concordance from deprescribing.
- Cardiometabolic targets should be individualised based on patient priorities, frailty, and life expectancy.
- Clinicians should clarify longitudinal responsibility (ie, named clinician or team) to reduce care fragmentation.
- Digital tools should be used only when interoperable and workflow-aligned, avoiding siloed condition-specific pathways.

Conclusion

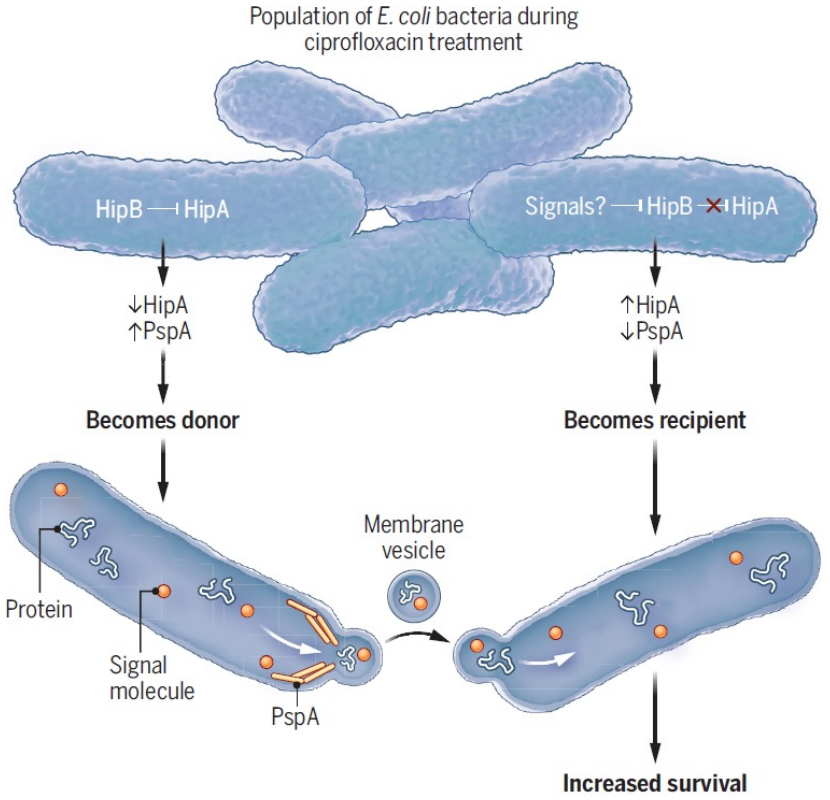
This Series on cardiometabolic MLTC has covered epidemiology, mechanisms and interventions. In this series paper, we have highlighted multilevel interventions, in which combinations might be required to address current challenges. Although this field is emerging, there are some practical recommendations aligned to the evidence presented (panel 2). These could help to identify opportunities and support care delivery to better address the holistic needs of people living with cardiometabolic MLTC.

Bacteria share proteins to survive antibiotics

Cell-to-cell cooperation through membrane vesicles enhances antibiotic persistence

Some bacteria that are harmful to humans escape elimination by antibiotics because they carry resistance genes. However, antibiotic-susceptible bacterial populations often harbor rare persister cells that survive antibiotic exposure without being resistant. Antibiotic persistence favors recurrent infections and resistance emergence and is a public health threat. Persister cells are thought to be metabolically dormant. Decreased activity of antibiotic targets would enable them to remain alive when antibiotics are present and to regrow after antibiotic removal. Wen *et al.* report that *Escherichia coli* persister cells do not simply enter a dormant state upon antibiotic treatment. Instead, genetically identical cells diverge into two physiological states. Some cells produce membrane vesicles that are loaded with specific proteins, which are taken up by other cells to enhance survival. Therefore, vesicle donors and recipients actively cooperate to benefit the entire bacterial population.

The formation of membrane vesicles in bacteria has mostly been attributed to damage to the envelope of the cells (the membranes and peptidoglycan wall around the cell). In the study by Wen *et al.*, membrane vesicle production was stimulated by low concentrations of ciprofloxacin—an antibiotic of the fluoroquinolone class that targets DNA gyrase, an enzyme involved in unwinding DNA. Notably, phage shock protein A (PspA) was enriched in membrane vesicles and was essential for their production (see the figure). How ciprofloxacin stimulates PspA synthesis is unclear. PspA has regulator and effector functions in the phage shock protein envelope stress-response system, which protects the bacterial envelope and supports survival during stress. PspA, which belongs to the endosomal sorting complexes required for transport III (ESCRTIII) superfamily, contributes to the formation of double-membrane vesicles and membrane remodeling in vitro. In eukaryotic organisms, ESCRT-III proteins promote membrane curvature, constriction, and fission and contribute to endosomal trafficking. However, the role of the PspA protein and other members of the phage shock protein response in membrane vesicle formation in bacteria in vivo remains to be elucidated.



HipA, serine/threonine-protein kinase toxin HipA; HipB, antitoxin HipB; PspA, phage shock protein A.

A strategy for antibiotic persistence

Low concentrations of the antibiotic ciprofloxacin promote the differentiation of two subpopulations of *Escherichia coli* bacteria within a population of cells with the same genes. The two subpopulations are characterized by differential expression of HipA, which is regulated by HipB. Cells with low HipA concentrations express PspA, which promotes the formation of membrane vesicles that carry proteins and signaling molecules. The recipient cells are characterized by high HipA and low PspA concentrations. Uptake of membrane vesicles increases the survival of recipient cells.

Dining chat: My wife and I are on GLP-1 drugs. Do restaurants care if we share an entree?

My wife and I are both on GLP-1 drugs that greatly reduce our appetites. We have found that sharing 1 appetizer and 1 entree is the perfect amount of food. We don't want to appear cheap, and if I announce to the waiter that my wife is on weight loss meds I will be eating alone. Do restaurants understand the trend that many people are on these drugs and eating less?

Yes, restaurants definitely understand that people are eating less, and some have gone so far as to add GLP-1 sections to their menus. (If chatters have seen GLP-1 menus around, please do let me know!) I've also noticed an increasing number of restaurants that are sure to have a simple, unsauced protein on the menu, along with the more garnished, richer dishes. Restaurants probably pay closer attention to changing habits than most any other businesses out there.

On the flip side, what's a restaurant to do, really? They profit from our consumption (literally!), and if they pare back too much, it could hurt their ability to turn a profit and create a strange dining experience for those who aren't on GLP-1s. The best we can hope for, I think, is what we've always hoped for at a great restaurant: Enough range and variety to please lots of different kinds of diners. And I wouldn't worry too much about explaining yourself to the restaurant. You're not the first people to come in for a light dinner, and you won't be the last. If you tip well and enjoy yourself, I expect all will be well.