

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

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

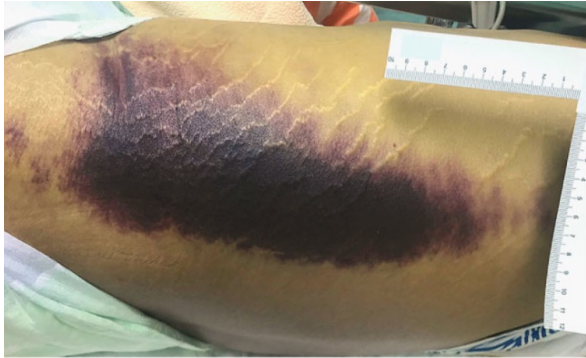
Usually every Wednesday 17:00 - 18:00



Klinische Forschung

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

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



(Grey-Turner's Sign)



The large ecchymosis on the flank is known as Grey Turner's sign and may indicate intraabdominal or retroperitoneal bleeding. Although this finding is classically associated with pancreatitis, it may occur in other conditions. The CT scan showed active extravasation of contrast material into the left psoas muscle and retroperitoneal space. A diagnosis of spontaneous retroperitoneal hemorrhage due to coagulopathy of liver disease was made.

A 46-year-old man with cirrhosis presented to the emergency department with a 1-week history of left flank pain. He reported no recent trauma, medical procedures, or use of anticoagulant or antiplatelet medications. His heart rate was 128 beats per minute, and his blood pressure was 64/37 mm Hg. Laboratory studies were notable for anemia, severe thrombocytopenia, and findings consistent with advanced liver disease. Physical examination and contrast-enhanced computed tomography of the abdomen are shown. What is the most likely diagnosis?

Acute hemorrhagic pancreatitis

Splenic rupture

☒ Spontaneous retroperitoneal hemorrhage

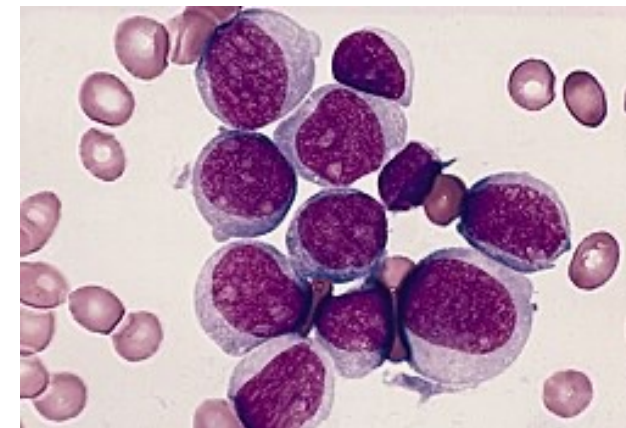
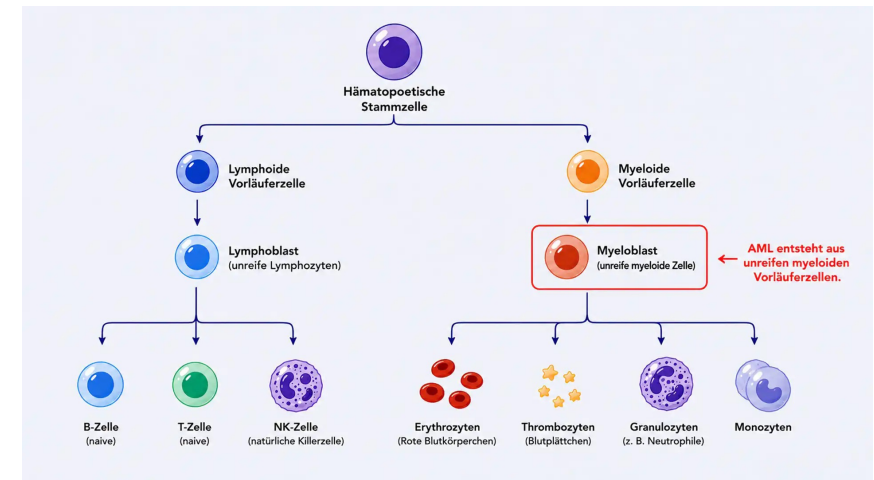
Rectus sheath hematoma

Ruptured abdominal aortic aneurysm

Die **Akute Myeloische Leukämie (AML)** ist eine aggressive, bösartige Erkrankung des blutbildenden Systems. Bei dieser Form von Blutkrebs vermehren sich unreife Knochenmarkszellen (sogenannte **Blasten**) unkontrolliert und verdrängen die gesunde Blutbildung. Eine AML entwickelt sich rasch und erfordert eine **sofortige medizinische Behandlung**, da sie unbehandelt innerhalb kurzer Zeit lebensbedrohlich ist.

Damit eine AML ausbricht, müssen in der Regel Mutationen aus zwei spezifischen Klassen in derselben Vorläuferzelle zusammenwirken:

- **Klasse-I-Mutationen (Proliferationsvorteil):** Diese Mutationen aktivieren Signalwege, die der Zelle befehlen, sich ununterbrochen zu teilen. Betroffen sind häufig Gene für Rezeptor-Tyrosinkinasen (z. B. *FLT3*, *KIT* oder *RAS*-Proteine). Sie versetzen die Zelle in einen Zustand der permanenten Vermehrung, entkoppelt von den Kontrollsignalen des Körpers.
- **Klasse-II-Mutationen (Differenzierungsblockade):** Diese Mutationen betreffen Transkriptionsfaktoren, die für die reguläre Ausreifung der Blutzellen verantwortlich sind (z. B. *RUNX1*, *Cebpa* oder Fusionsgene wie *PML-RARA* bei der Promyelozytenleukämie). Die Zellen bleiben auf einer unreifen Stufe – den sogenannten **Blasten** – stecken und erlangen nie ihre eigentliche Funktion (z. B. als funktionierende weiße Blutkörperchen)



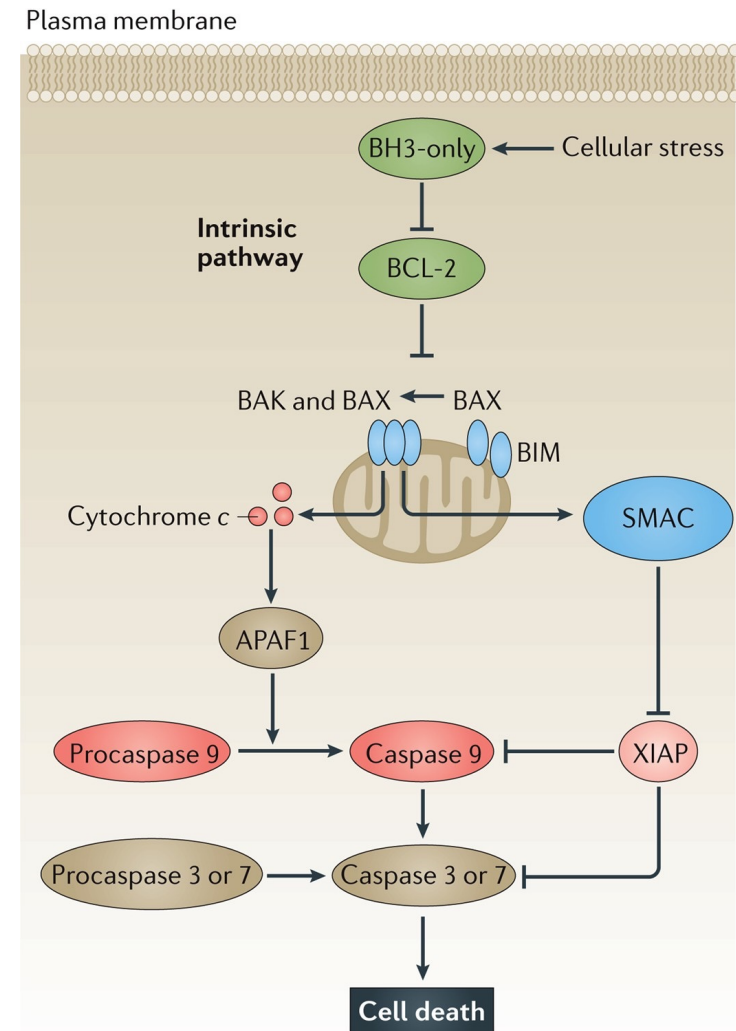
cytarabine and anthracyclines

Venetoclax (Handelsname *Venclyxto*) ist ein oral verabreichter BCL-2-Inhibitor, der zur zielgerichteten Behandlung bestimmter Formen von Blutkrebs wie der chronischen lymphatischen Leukämie (CLL) und der akuten myeloischen Leukämie (AML) eingesetzt wird.

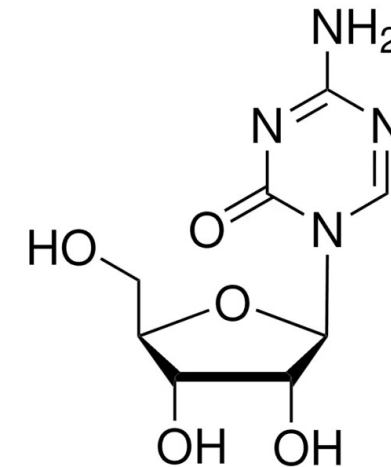
Bcl-2 (B-cell lymphoma 2) ist ein zentrales Regulatorprotein des programmierten Zelltods (**Apoptose**) und der Prototyp der gleichnamigen [Bcl-2-Proteinfamilie](#).

Biologische Funktion

- **Anti-apoptotische Wirkung:** Bcl-2 verhindert den Zelltod, indem es die äußere Mitochondrienmembran stabilisiert und die Freisetzung von pro-apoptotischen Faktoren wie Cytochrom c hemmt.
- **Gleichgewicht:** Das Überleben oder Absterben einer Zelle hängt von der Balance zwischen anti-apoptotischen (wie Bcl-2, Bcl-xL) und pro-apoptotischen Proteinen (wie Bax, Bak) ab

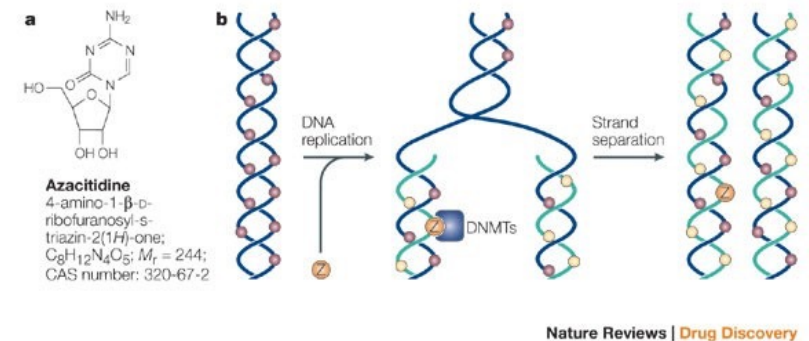


Azacitidin ist ein hypomethylierender Arzneistoff und Zytostatikum, das zur Behandlung von Blutkrebserkrankungen des Knochenmarks eingesetzt wird. Es funktioniert als chemisches Analogon des Nukleosids Cytidin und greift in die epigenetische Regulation der Zellen ein.



Wirkungsweise

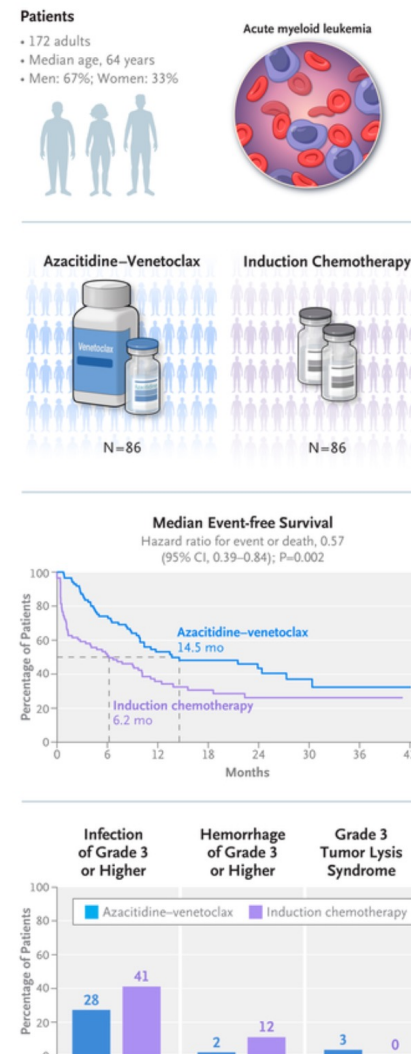
- **Epigenetik:** In niedrigen Dosen bewirkt der Stoff eine Hypomethylierung der DNA. Dadurch werden blockierte Gene, die für die normale Ausreifung von Blutzellen wichtig sind, wieder reaktiviert.
- **Zytotoxizität:** In höheren Dosen hemmt es direkt das Wachstum von sich schnell teilenden Krebszellen und führt zu deren Absterben im Knochenmark.



DNA-Methyltransferasen (DNMTs) sind Enzyme, die Methylgruppen auf die DNA übertragen, um als epigenetische Markierung die Aktivität von Genen zu steuern, ohne dabei die zugrundeliegende genetische Sequenz zu verändern.

Azacitidine–Venetoclax or Induction Chemotherapy for Acute Myeloid Leukemia

Induction chemotherapy has long been a key component of curative therapy for fit patients with acute myeloid leukemia (AML), despite its frequently severe side effects and substantial health care utilization. For patients who are ineligible for induction chemotherapy, hypomethylating therapy plus venetoclax is the standard treatment owing to its efficacy and side-effect profile. In this multicenter, phase 2 trial, we randomly assigned, in a 1:1 ratio, previously untreated adults with AML who were eligible for induction chemotherapy to receive either azacitidine plus venetoclax or induction chemotherapy. Patients with core binding factor fusions, mutations in the gene encoding FMS-like tyrosine kinase 3 (*FLT3*), or mutations in the gene encoding nucleophosmin-1 (*NPM1*; unless the patient was ≥ 60 years of age) were excluded. The primary end point was event-free survival.



For decades, the standard up-front treatment for functionally fit patients with acute myeloid leukemia (AML) has been intensive induction chemotherapy incorporating cytarabine and anthracyclines. Despite therapeutic advances in certain subsets of patients. Among patients 75 years or older or patients who were otherwise ineligible to receive induction chemotherapy, the VIALE-A trial established the superiority of combination treatment with azacitidine plus venetoclax, as compared with azacitidine monotherapy, with a median overall survival of 14.7 months and a composite complete remission in 66% of the patients in the azacitidine–venetoclax group.

Azacitidine–venetoclax therapy was associated with fewer and less-severe side effects than are usual with induction chemotherapy, with low early mortality. Combinations with a hypomethylating agent and venetoclax are now standard up-front therapies for patients who are ineligible for induction chemotherapy. Here, we report results from the PARADIGM trial, a randomized, phase 2 clinical trial designed to assess whether azacitidine–venetoclax would be superior to induction chemotherapy in patients with AML who were eligible to receive induction chemotherapy.

Methods

Trial Design, Randomization, Treatment, and Oversight

We conducted this investigator-initiated, open-label, multicenter, randomized, phase 2 clinical trial at nine academic centers in the United States.

Patients were randomly assigned in a 1:1 ratio to receive either azacitidine–venetoclax or induction chemotherapy. Patients in the azacitidine–venetoclax group received repeating 28-day cycles of azacitidine (75 mg per square meter of body-surface area, administered intravenously on days 1 through 7) and venetoclax (400 mg orally on days 1 through 28); adjustments to dose, cycle length, and duration of venetoclax therapy were allowed in accordance with the prescription label and as appropriate for cytopenias, other toxic effects, and concurrent use of CYP3A inhibitors. Bone marrow biopsies were performed at the end of each cycle (between day 21 and day 31) to assess for response (see below).

Patients

Eligible patients were at least 18 years of age with untreated AML, which had been pathologically confirmed and classified according to the World Health Organization 2016 criteria; each patient had to have been deemed by the investigator as being a candidate for induction chemotherapy.

End Points and Assessments

The primary end point was event-free survival.

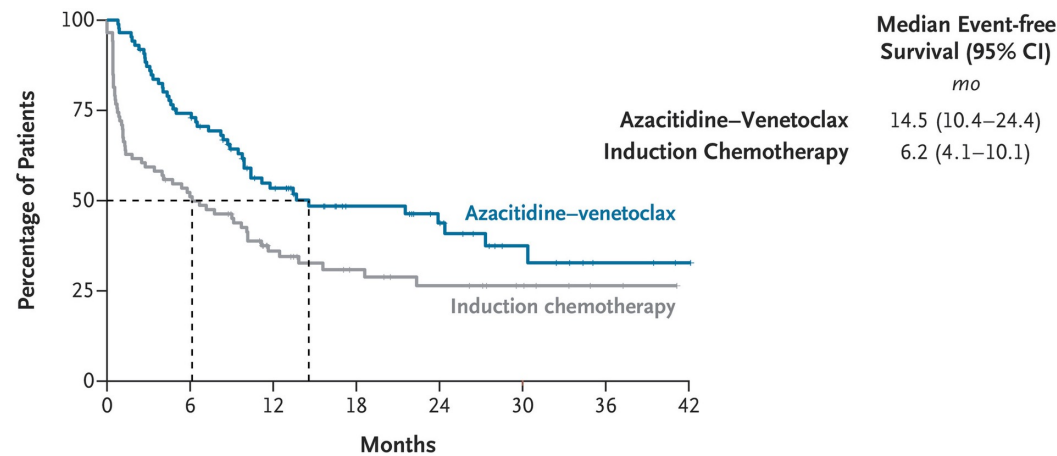
Baseline

Characteristic	Azacitidine– Venetoclax (N=86)	Induction Chemotherapy (N=86)	Total (N=172)
Age			
Median (range) — yr	65 (23–79)	64 (28–79)	64 (23–79)
Distribution — no. (%)			
≤64 yr	43 (50)	44 (51)	87 (51)
≥65 yr	43 (50)	42 (49)	85 (49)
Sex — no. (%)			
Male	55 (64)	60 (70)	115 (67)
Female	31 (36)	26 (30)	57 (33)
Race or ethnic group — no. (%)†			
White	65 (76)	69 (80)	134 (78)
Black	5 (6)	5 (6)	10 (6)
Hispanic	6 (7)	7 (8)	13 (8)
Asian	10 (12)	5 (6)	15 (9)
ECOG performance-status score — no. (%)‡			
0	30 (35)	38 (44)	68 (40)
1	49 (57)	44 (51)	93 (54)
2	7 (8)	3 (3)	10 (6)
Unknown	0	1 (1)	1 (1)
Secondary AML — no. (%)			
AML with myelodysplasia-related changes	50 (58)	46 (53)	96 (56)
Therapy-related AML	4 (5)	1 (1)	5 (3)
ELN 2022 risk status — no. (%)			
Favorable	13 (15)	9 (10)	22 (13)
Intermediate	15 (17)	11 (13)	26 (15)
Adverse	58 (67)	66 (77)	124 (72)
Mutations — no. (%)			
<i>NPM1</i>	11 (13)	5 (6)	16 (9)
<i>IDH1</i>	8 (9)	7 (8)	15 (9)
<i>IDH2</i>	19 (22)	9 (10)	28 (16)
<i>DNMT3A</i>	22 (26)	18 (21)	40 (23)
<i>TP53</i>	10 (12)	16 (19)	26 (15)
<i>RUNX1</i>	17 (20)	22 (26)	39 (23)
<i>CEBPA</i>	5 (6)	6 (7)	11 (6)
<i>KRAS</i>	6 (7)	5 (6)	11 (6)
<i>NRAS</i>	12 (14)	13 (15)	25 (15)

Adverse events

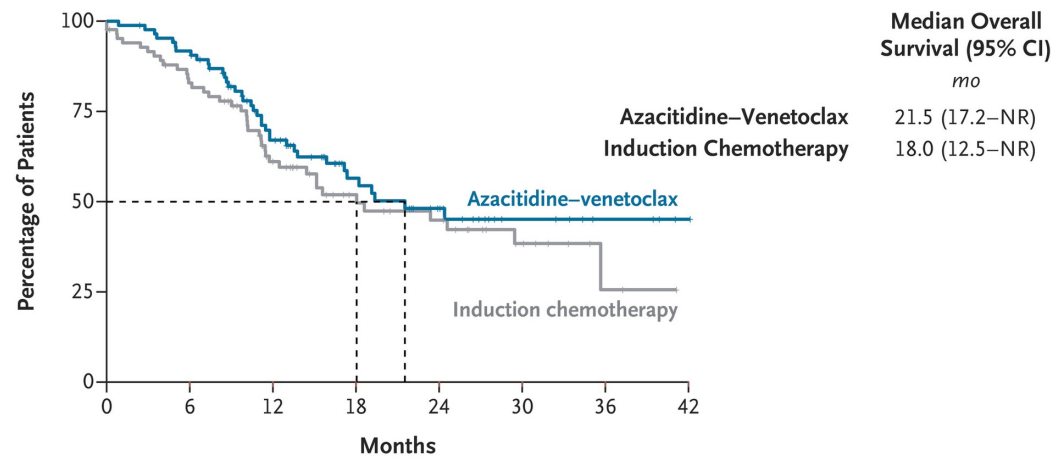
Event	Azacitidine–Venetoclax (N=86)				Induction Chemotherapy (N=82)			
	Grade 3	Grade 4	Grade 5	Grade ≥3	Grade 3	Grade 4	Grade 5	Grade ≥3
number of patients with event (percent)								
Grade ≥3 adverse events occurring in ≥10% of patients								
Febrile neutropenia	46 (53)	3 (3)	0	49 (57)	51 (62)	1 (1)	0	52 (63)
Platelet count decreased	8 (9)	38 (44)	0	46 (53)	3 (4)	47 (57)	0	50 (61)
Anemia	34 (40)	1 (1)	0	35 (41)	35 (43)	3 (4)	0	38 (46)
Neutrophil count decreased	1 (1)	48 (56)	0	49 (57)	1 (1)	39 (48)	0	40 (49)
White-cell count decreased	2 (2)	24 (28)	0	26 (30)	0	20 (24)	0	20 (24)
Lymphocyte count decreased	11 (13)	6 (7)	0	17 (20)	9 (11)	8 (10)	0	17 (21)
Lung infection	12 (14)	0	0	12 (14)	11 (13)	2 (2)	2 (2)	15 (18)
Sepsis	5 (6)	1 (1)	0	6 (7)	10 (12)	2 (2)	0	12 (15)
Anorexia	4 (5)	0	0	4 (5)	12 (15)	0	0	12 (15)
Hypoxemia	4 (5)	0	0	4 (5)	7 (9)	2 (2)	0	9 (11)
All grade ≥3 infectious adverse events								
Lung infection	12 (14)	0	0	12 (14)	11 (13)	2 (2)	2 (2)	15 (18)
Sepsis	5 (6)	1 (1)	0	6 (7)	10 (12)	2 (2)	0	12 (15)
Typhlitis or neutropenic enterocolitis	0	0	0	0	4 (5)	0	1 (1)	5 (6)
Catheter-related infection	2 (2)	0	0	2 (2)	5 (6)	0	0	5 (6)
Skin infection	2 (2)	0	0	2 (2)	5 (6)	0	0	5 (6)
Enterocolitis	0	0	0	0	5 (6)	0	0	5 (6)
Infection or infestation	1 (1)	0	0	1 (1)	4 (5)	0	0	4 (5)
Fungemia	0	0	0	0	3 (4)	0	0	3 (4)
Fever	0	0	0	0	2 (2)	0	0	2 (2)
Urinary tract infection	4 (5)	0	0	4 (5)	2 (2)	0	0	2 (2)
Bacteremia	0	0	0	0	1 (1)	0	0	1 (1)
Conjunctivitis	0	0	0	0	1 (1)	0	0	1 (1)
Pharyngitis	0	0	0	0	1 (1)	0	0	1 (1)
Wound infection	0	0	0	0	1 (1)	0	0	1 (1)
Anorectal infection	1 (1)	0	0	1 (1)	0	0	0	0
Lymph-gland infection	2 (2)	0	0	2 (2)	0	0	0	0
Sinusitis	1 (1)	0	0	1 (1)	0	0	0	0
Tooth infection	1 (1)	0	0	1 (1)	0	0	0	0
Upper respiratory tract infection	1 (1)	0	0	1 (1)	0	0	0	0
All grade ≥3 bleeding adverse events								
Hematoma	0	0	0	0	3 (4)	0	0	3 (4)
Lower GI hemorrhage	0	0	0	0	2 (2)	0	0	2 (2)
Epistaxis	1 (1)	0	0	1 (1)	2 (2)	0	0	2 (2)
Oral hemorrhage	0	0	0	0	1 (1)	0	0	1 (1)
Upper GI hemorrhage	1 (1)	0	0	1 (1)	1 (1)	0	0	1 (1)
Intracranial hemorrhage	0	0	0	0	1 (1)	0	0	1 (1)
Menorrhagia	1 (1)	0	0	1 (1)	0	0	0	0

A Event-free Survival



No. of Patients								
Azacitidine-venetoclax	86	62	38	23	17	8	3	1
Induction chemotherapy	86	43	24	15	11	7	2	0

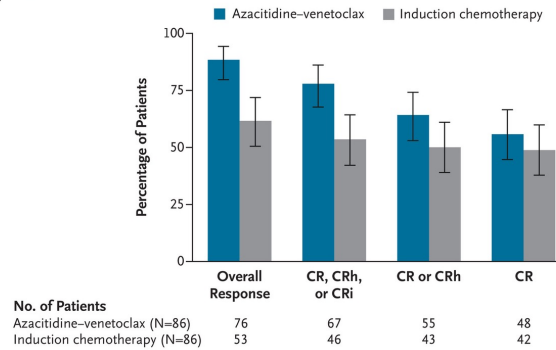
B Overall Survival



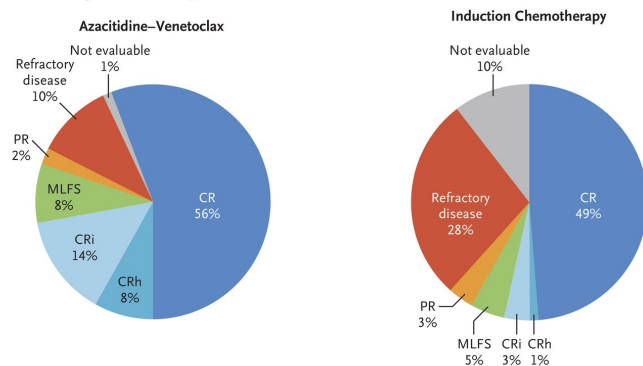
Event-free Survival and Overall Survival.

Shown are Kaplan–Meier curves for event-free survival (Panel A) and overall survival (Panel B) in the azacitidine–venetoclax and induction chemotherapy groups. Event-free survival was defined as the time from randomization to the first event of progressive disease, persistent disease prompting therapy change, relapse, hospice, or death, as determined by the investigator. Dashed lines indicate the median time to the first event, and tick marks indicate censored data. NR denotes not reached.

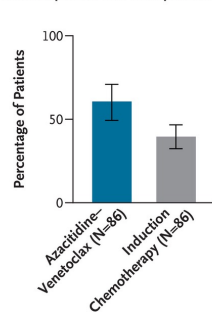
A Treatment Response



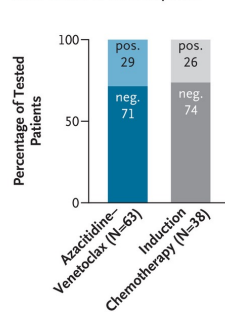
B Response According to Treatment Type



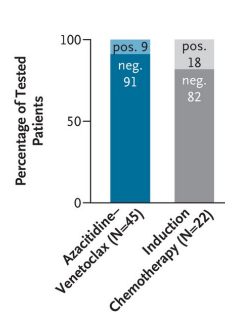
C Hematopoietic-Cell Transplantation



D MRD Status at Best Response



E MRD Status before HCT

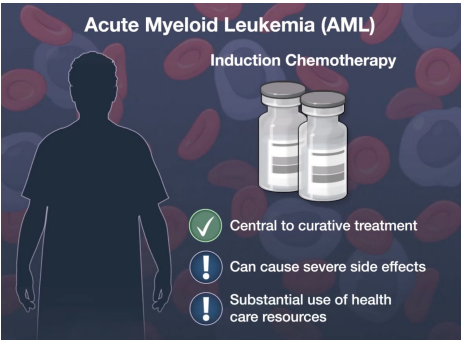


Treatment Response, Transition to HCT, and Measurable Residual Disease Status.

Shown are bar plots summarizing the overall percentages of patients with a response after treatment (Panel A), pie charts summarizing the best response to therapy in each treatment group (Panel B), and bar plots indicating successful transition of patients in first response to HCT (Panel C) in the azacitidine-venetoclax group (52 patients [60%]) and the induction chemotherapy group (34 patients [40%]). Overall response included complete remission (CR), complete remission with partial hematologic recovery (CRh), complete remission with incomplete hematologic recovery (CRi), partial remission (PR), and morphologic leukemia-free state (MLFS). Composite complete remission included CR, CRh, and CRi. The confidence intervals (I bars) in Panels A and C are not adjusted for multiplicity and may not be used in place of a hypothesis test. If no post-treatment bone marrow evaluation was available, then patients were considered not to have had a response and were included in the denominator for response assessment. Data on measurable residual disease (MRD) status (positive or negative) are provided on the basis of patients with available samples at the time of the best morphologic bone marrow response (CR, CRh, and CRi) (Panel D) and within 4 weeks before HCT among patients who underwent transplantation after trial treatment (Panel E).

Acute Myeloid Leukemia (AML)

Induction Chemotherapy



- ✓ Central to curative treatment
- ! Can cause severe side effects
- ! Substantial use of health care resources

Azacitidine-Venetoclax



(N=86)

Induction Chemotherapy



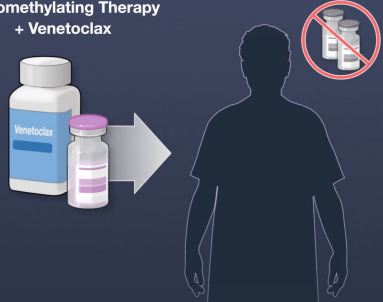
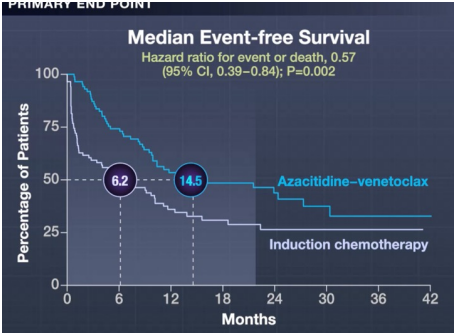
(N=86)

Azacitidine-Venetoclax



✓ Significantly longer event-free survival

Hypomethylating Therapy + Venetoclax

Azacitidine-Venetoclax

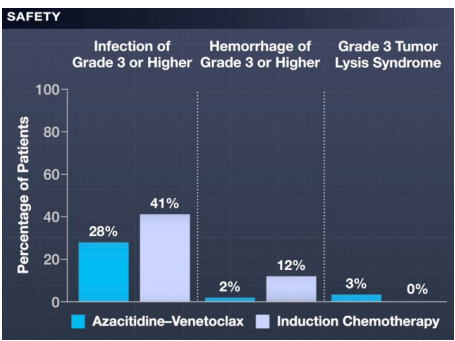


vs.

Induction Chemotherapy



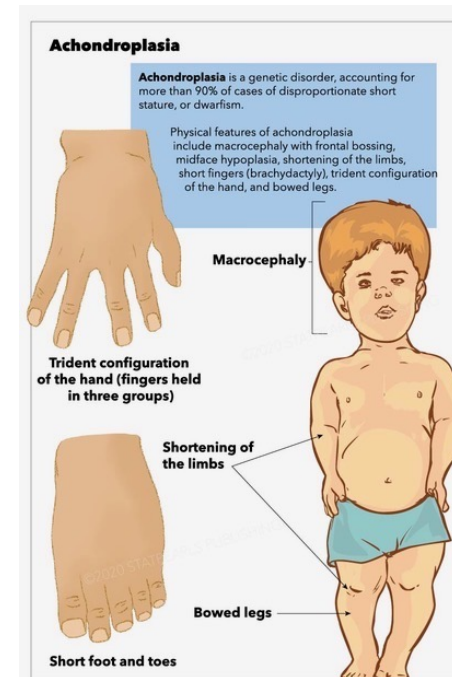
? Assessed superiority



Die **Achondroplasie** ist die häufigste Form des genetisch bedingten und disproportionierten Kleinwuchses und beruht auf einer angeborenen Störung der Knorpel- und Knochenbildung

Ursache und Genetik

- **FGFR3-Mutation:** Zu über 99 % wird die Erkrankung durch eine Punktmutation im *FGFR3*-Gen (Fibroblasten-Wachstumsfaktor-Rezeptor 3) verursacht.
- **Überaktivierung:** Der Rezeptor ist dauerhaft aktiv, was das Längenwachstum der langen Röhrenknochen in den Wachstumsfugen (enchondrale Ossifikation) hemmt.
- **Vererbung:** In etwa 80 % der Fälle entsteht die Mutation spontan (Neumutation) bei Eltern mit durchschnittlicher Körpergröße. Ansonsten wird sie autosomal-dominant vererbt

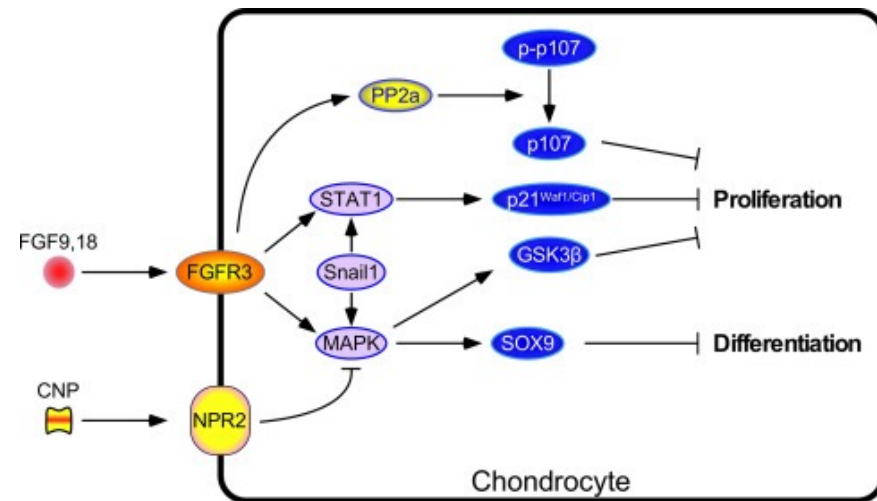


Bei der Achondroplasie ist primär das Längenwachstum der Röhrenknochen (wie Oberschenkel und Oberarm) gestört, während das Breitenwachstum und die Entwicklung flacher Knochen normal ablaufen. Ursache ist eine genetisch bedingte **Störung der endochondralen Ossifikation** (Knorpelverknöcherung), die durch eine Mutation im **FGFR3-Gen** hervorgerufen wird. Dieses Gen bremst im Normalfall das Knochenwachstum; durch die Mutation ist es jedoch dauerhaft überaktiv, wodurch der **unentbehrliche Knorpel in den Wachstumsfugen nicht richtig in Knochensubstanz umgewandelt wird**

FGFR3 mutations increase signaling through a combination of receptor stabilization, ligand-independent dimerization, and enhanced intrinsic kinase activity.

Mechanisms of Increased Signaling

- **Enhanced Dimerization:** Mutant receptors pair up and activate even without binding to a growth factor ligand.
- **Receptor Stabilization:** The mutant proteins remain on the cell surface longer, reducing normal receptor turnover and degradation.
- **Increased Kinase Activity:** The intrinsic tyrosine kinase portion of the receptor works at a higher baseline capacity.
- **Constant Activation:** For example, the common G380R change in achondroplasia locks the transmembrane domain into an active state.



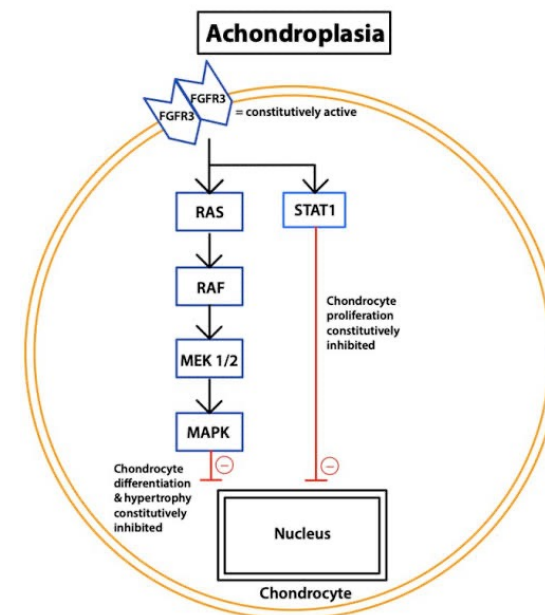
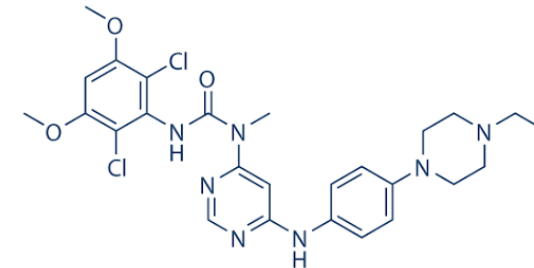
Hyperactivation of FGFR3 jams this delicate process by overstimulating two primary downstream intracellular pathways:

Affected Pathway	Molecular Action	Impact on Bone Development
STAT1 Pathway	Activates transcription factors that upregulate cell cycle inhibitors like <i>p21^{Waf1/Cip1}</i> .	Halts Chondrocyte Proliferation: It profoundly suppresses the cell division needed to generate new cartilage template tissue, narrowing the growth plate.
MAPK / ERK Pathway	Promotes an oncogene-like cellular senescence and disrupts downstream pathways like <i>Ihh</i> (Indian hedgehog).	Suppresses Maturation & Hypertrophy: It stops chondrocytes from expanding into large, structural hypertrophic cells. Without this expansion and the subsequent matrix remodeling, bone elongation drastically slows down.

Infigratinib ist ein **oral verabreichbarer Proteinkinaseinhibitor**, der gezielt die Aktivität von **Fibroblasten-Wachstumsfaktor-Rezeptoren (FGFR)** hemmt.

Anwendungsgebiete & Wirkungsweise

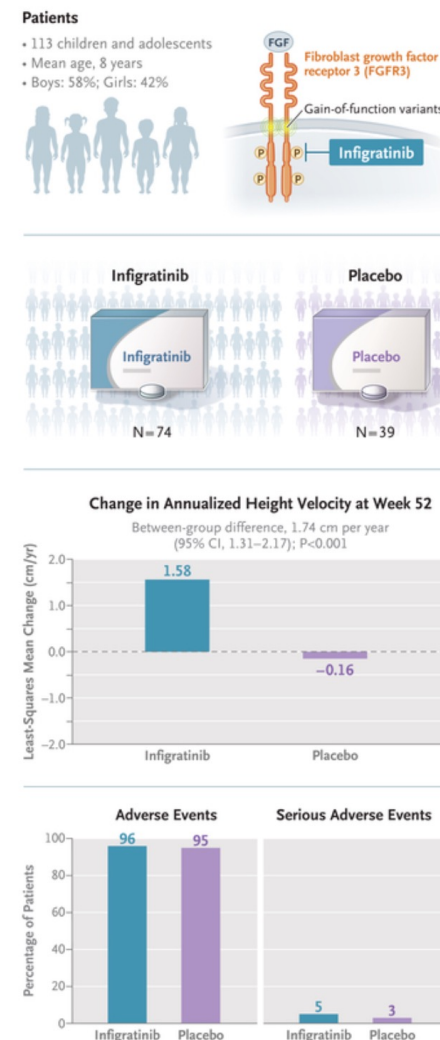
- **Gallengangskarzinom (Cholangiokarzinom):** Unter dem Handelsnamen *Truseltiq* wurde der Wirkstoff zur Behandlung von Erwachsenen mit lokal fortgeschrittenem oder metastasiertem Cholangiokarzinom mit FGFR2-Genfusionen oder -umlagerungen zugelassen, die nach einer vorherigen Chemotherapie fortgeschritten sind.
- **Achondroplasie:** Der Wirkstoff wird zudem in klinischen Studien (wie Phase-3-Studien) zur Behandlung von Kindern mit Achondroplasie (einer Form des Kleinwuchses) untersucht, um das Knochenwachstum und die Körperproportionen positiv zu beeinflussen.
- **Wirkmechanismus:** Durch die selektive Blockade von FGFR1–3 werden krankheitsrelevante Signalwege (wie MAPK) unterdrückt, die für das unkontrollierte Zellwachstum verantwortlich sind.



Phase 3 Trial of Oral Infigratinib in Children with Achondroplasia

Achondroplasia is a genetic skeletal condition caused by *FGFR3* pathogenic variants. Infigratinib, an oral FGFR1–3 tyrosine kinase inhibitor, down-regulates key pathways in the pathogenesis of achondroplasia.

In this phase 3, multicenter, double-blind, placebo-controlled trial, we randomly assigned children with achondroplasia (3 to 17 years of age) in a 2:1 ratio to receive infigratinib (at a dose of 0.25 mg per kilogram of body weight) or placebo once daily for 52 weeks. The primary end point was the change from baseline in the annualized height velocity in the infigratinib group as compared with the placebo group at week 52. Key secondary end points were the change from baseline in the height z score and in the upper-to-lower body segment ratio at week 52. The primary analysis evaluated the treatment effect at week 52 in the full analysis population, with missing data handled with a prespecified imputation approach.



Achondroplasia, a skeletal dysplasia that is characterized by disproportionate short stature, can lead to medical, functional, and psychosocial challenges. This condition is caused by pathogenic gain-of-function variants in the gene encoding fibroblast growth factor receptor 3 (*FGFR3*), which causes overactivity in downstream pathways, such as mitogen-activated protein kinase (MAPK) and signal transducer and activator of transcription 1 (STAT1). These changes result in impaired endochondral skeletal ossification through inhibition of chondrocyte proliferation and differentiation.

Infigratinib is an orally bioavailable FGFR1–3 selective tyrosine kinase inhibitor in development for achondroplasia. Infigratinib directly inhibits the phosphorylation of FGFR3 and attenuates key downstream signaling pathways, including MAPK and STAT1. In an open-label, dose-finding, phase 2 study (PROPEL 2), oral infigratinib (at a dose of 0.25 mg per kilogram of body weight) resulted in sustained increases in the annualized height velocity and height z score, along with a decrease in the upper-to-lower body segment ratio at 18 months. We conducted the present phase 3 trial (PROPEL 3) to further evaluate the efficacy and safety of infigratinib in children with achondroplasia.

Methods

Trial Design and Oversight

This phase 3, double-blind, randomized, placebo-controlled trial assessed the efficacy and safety of infigratinib in children with achondroplasia who had completed at least 26 weeks of participation in the observational PROPEL study.

Patients

Eligible children were 3 to 17 years of age at the time of screening and had a confirmed genetic diagnosis of achondroplasia.

Randomization and Treatment

Eligible patients were randomly assigned in a 2:1 ratio to receive either infigratinib or placebo for 52 weeks. Randomization was stratified according to a prespecified combination of age, sex, and pubertal stage as follows: an age of 3 or 4 years (in <20% of the patients); an age of 5 years or older and a Tanner stage of 1 (in ≥60% of the patients); and a Tanner stage of 2 or higher (in <20% of the patients [approximately 50% girls and 50% boys], including <5% with a Tanner stage of 4).

The patients received daily treatment with oral infigratinib (sprinkle capsules) at a dose of 0.25 mg per kilogram of body weight or placebo. Treatment could be paused and resumed at the same dose or decreased to a lower dose if a criterion for dose reduction or discontinuation was met.

End Points

The primary end point was the change from baseline in the annualized height velocity in the infigratinib group as compared with the placebo group at week 52.

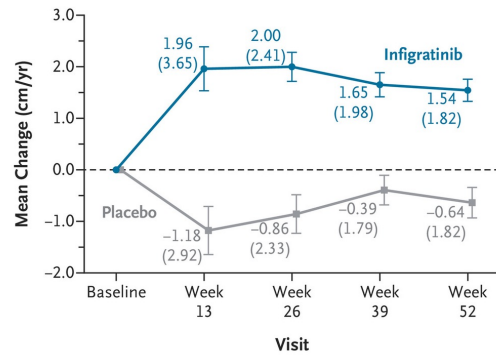
Subjects

Characteristic	Infigratinib (N = 74)	Placebo (N = 39)	All Patients (N = 113)
Age†			
Mean — yr	7.9±2.7	7.7±2.5	7.9±2.7
Median (range) — yr	7.3 (3.7–14.4)	7.2 (3.9–14.9)	7.3 (3.7–14.9)
Distribution — no. (%)			
3 to 7 yr	43 (58)	23 (59)	66 (58)
8 to 17 yr	31 (42)	16 (41)	47 (42)
Sex — no. (%)			
Male	42 (57)	23 (59)	65 (58)
Female	32 (43)	16 (41)	48 (42)
Race — no. (%)‡			
White	46 (62)	22 (56)	68 (60)
Asian	15 (20)	6 (15)	21 (19)
Black	3 (4)	2 (5)	5 (4)
Multiple	4 (5)	4 (10)	8 (7)
Tanner stage at baseline — no. (%)§			
1	61 (82)	33 (85)	94 (83)
2 to 4	13 (18)	6 (15)	19 (17)
2	12 (16)	5 (13)	17 (15)
3	1 (1)	0	1 (1)
4	0	1 (3)	1 (1)

Adverse events

Adverse Event	Infigratinib (N = 74)	Placebo (N = 39)	Risk Difference (95% CI)
	<i>number of patients (percent)</i>		<i>percentage points</i>
Pyrexia	16 (22)	10 (26)	−4 (−21 to 11)
Vomiting	14 (19)	9 (23)	−4 (−21 to 11)
Cough	13 (18)	9 (23)	−5 (−22 to 9)
Upper respiratory tract infection	13 (18)	7 (18)	0 (−17 to 13)
Headache	13 (18)	6 (15)	3 (−14 to 15)
Otitis media	11 (15)	6 (15)	0 (−16 to 12)
Nasopharyngitis	10 (14)	5 (13)	1 (−14 to 13)
Ear pain	8 (11)	2 (5)	6 (−7 to 16)
Dental caries	7 (9)	3 (8)	1 (−12 to 12)
Otitis externa	6 (8)	2 (5)	3 (−10 to 12)
Gastroenteritis			
Any	6 (8)	1 (3)	5 (−6 to 14)
Viral	5 (7)	1 (3)	4 (−7 to 13)
Arthralgia	5 (7)	3 (8)	−1 (−14 to 9)
Nasal congestion	5 (7)	3 (8)	−1 (−14 to 9)
Skin laceration	5 (7)	3 (8)	−1 (−14 to 9)
Tympanic membrane disorder	5 (7)	1 (3)	4 (−7 to 13)
Viral upper respiratory tract infection	5 (7)	0	7 (−3 to 15)
Abdominal pain			
Any	4 (5)	2 (5)	0 (−12 to 9)
Upper abdomen	4 (5)	3 (8)	−3 (−15 to 7)
Influenza	4 (5)	2 (5)	0 (−12 to 9)
Vitamin D deficiency	4 (5)	2 (5)	0 (−12 to 9)
Limb pain	4 (5)	1 (3)	2 (−8 to 11)
Rhinorrhea	4 (5)	1 (3)	2 (−8 to 11)

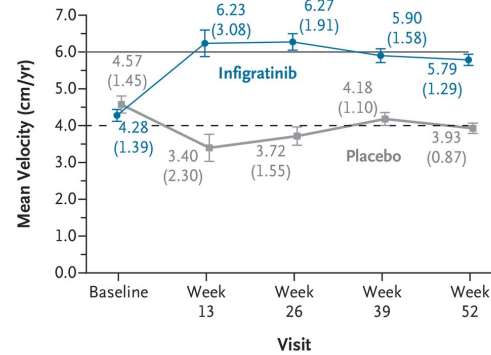
A Change in Annualized Height Velocity from Baseline



No. of Patients

Infigratinib	74	73	73	72	72
Placebo	39	39	39	39	38

B Annualized Height Velocity



No. of Patients

Infigratinib	74	73	73	72	72
Placebo	39	39	39	39	38

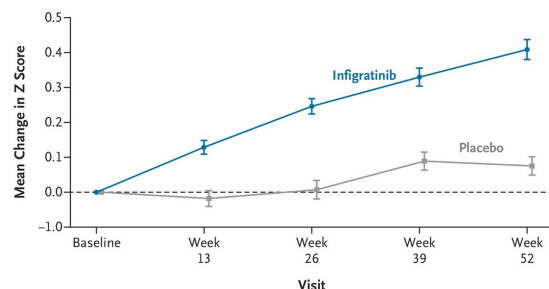
C Subgroup Analysis of Least-Squares Mean Change in Annualized Height Velocity from Baseline to Week 52

Subgroup	Infigratinib no. of patients (%)	Placebo no. of patients (%)	Difference in Least-Squares Mean (95% CI)	P Value
All patients	74 (100)	39 (100)	1.74 (1.31 to 2.17)	<0.001
Age				
3 to 7 yr	43 (58)	23 (59)	1.82 (1.24 to 2.39)	
8 to 17 yr	31 (42)	16 (41)	1.75 (1.10 to 2.40)	
Tanner stage				
1	61 (82)	33 (85)	1.81 (1.36 to 2.25)	
2 to 4	13 (18)	6 (15)	1.76 (0.26 to 3.26)	
Sex				
Male	42 (57)	23 (59)	1.79 (1.26 to 2.32)	
Female	32 (43)	16 (41)	1.71 (0.94 to 2.49)	
Height z score at baseline in relation to general pediatric reference data				
-6 or Less	10 (14)	8 (21)	1.11 (-0.11 to 2.34)	
Greater than -6 to -5	31 (42)	15 (38)	2.08 (1.37 to 2.79)	
Greater than -5	33 (45)	16 (41)	1.60 (0.87 to 2.33)	
Annualized height velocity at baseline				
≤3.5 cm/yr	23 (31)	7 (18)	1.99 (1.13 to 2.85)	
>3.5 to 4.5 cm/yr	21 (28)	11 (28)	1.56 (0.59 to 2.54)	
>4.5 cm/yr	30 (41)	21 (54)	2.07 (1.45 to 2.69)	

Annualized Height Velocity.

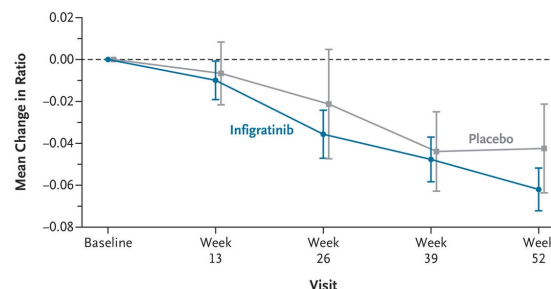
Shown is the mean change from baseline in the annualized height velocity in the infigratinib group and the placebo group (Panel A) and the overall mean annualized height velocity in each trial group (Panel B) at 52 weeks. Points represent the mean values at each visit, and I bars indicate the standard deviation. In Panel B, the reference annualized height velocity for children with achondroplasia and children with average stature are represented by the dashed horizontal line at 4.0 cm per year and the solid horizontal line at 6.0 cm per year, respectively.^{13,14} Also shown is the difference in the least-squares mean change from baseline to week 52 in the annualized height velocity, according to subgroup (Panel C). The height z score indicates the height of the patient as compared with a reference population; a negative number indicates that the height is below the mean of the reference population, and a positive number indicates that the height is above the mean of the population. The P value is reported only for the alpha-controlled end point of the difference in the least-squares mean change from baseline to week 52 in the annualized height velocity for infigratinib as compared with placebo in the overall trial population. For all subgroups, the widths of the 95% confidence intervals have not been adjusted for multiplicity, so the results should not be used for formal hypothesis testing. Additional results according to baseline strata are provided in Table S4.

A Change in Height z Score Relative to Achondroplasia Reference Data from Baseline



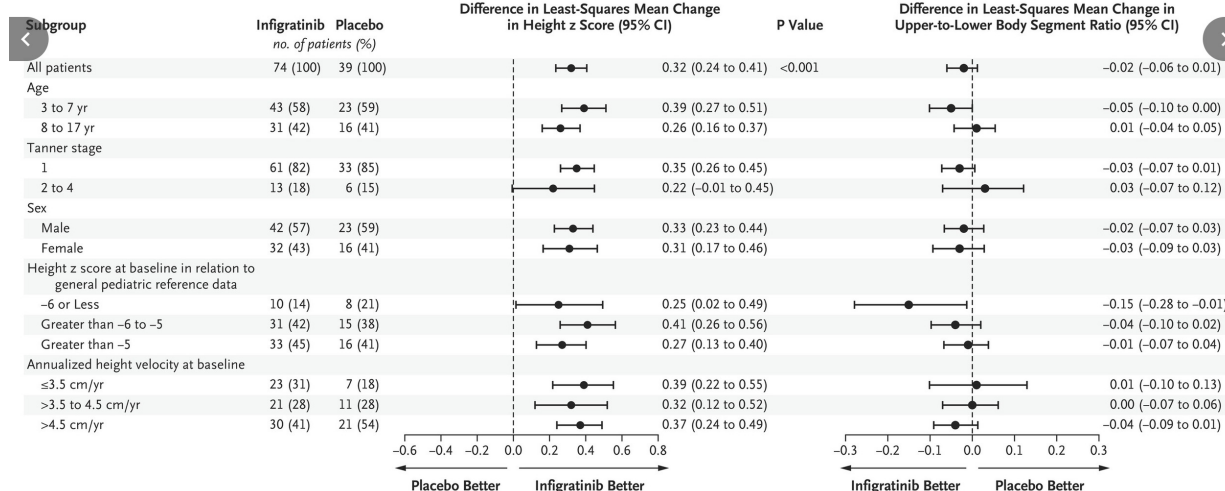
No. of Patients				
Infigratinib	74	73	73	72
Placebo	39	39	39	38

B Change in Upper-to-Lower Body Segment Ratio from Baseline



No. of Patients				
Infigratinib	74	73	73	72
Placebo	38	38	38	37

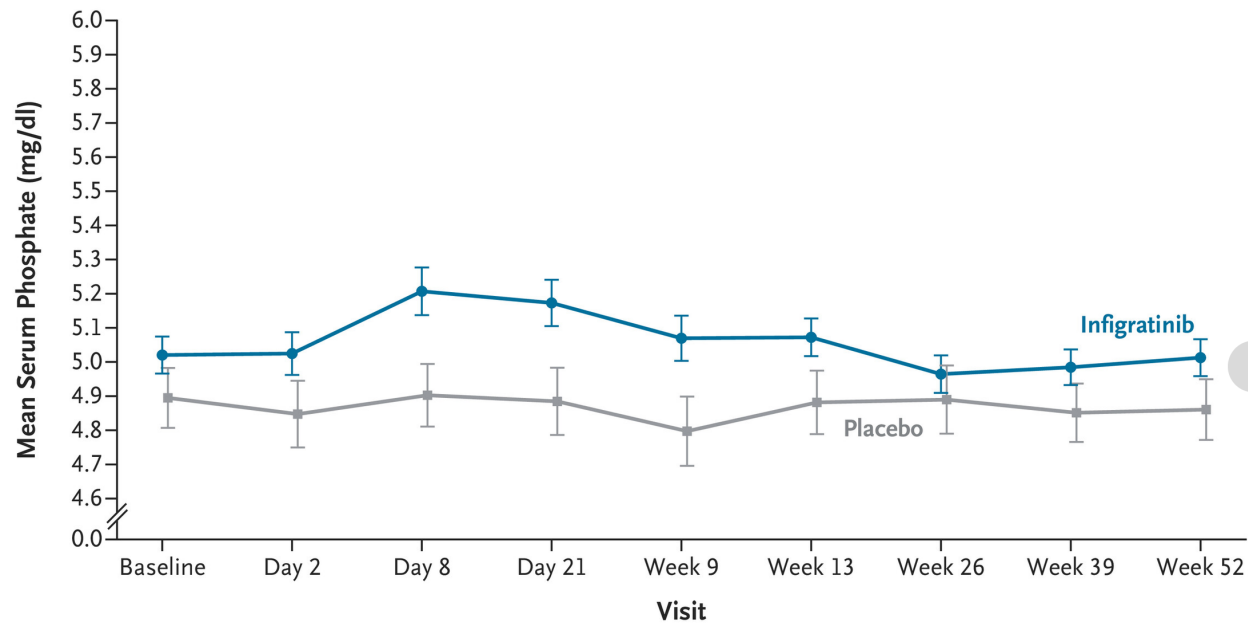
C Subgroup Analyses of Least-Squares Mean Changes in Height z Score Relative to Achondroplasia Reference Data and in the Upper-to-Lower Body Segment Ratio from Baseline to Week 52



Height z Score Relative to Achondroplasia Reference Data and Upper-to-Lower Body Segment Ratio.

Panel A shows the mean change from baseline in the height z score relative to achondroplasia reference data according to visit in the infigratinib group and the placebo group. Points represent mean values at each visit.

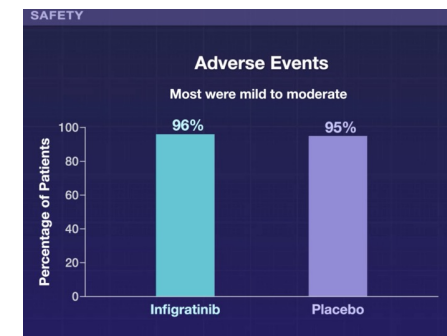
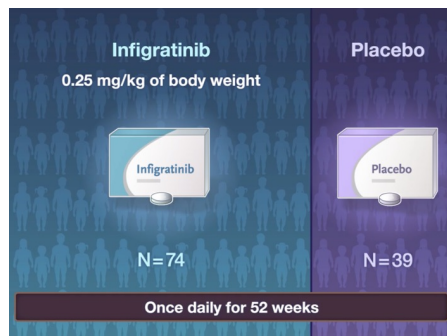
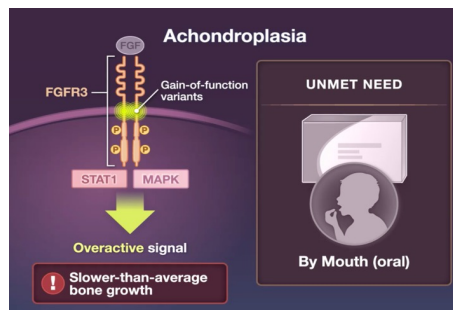
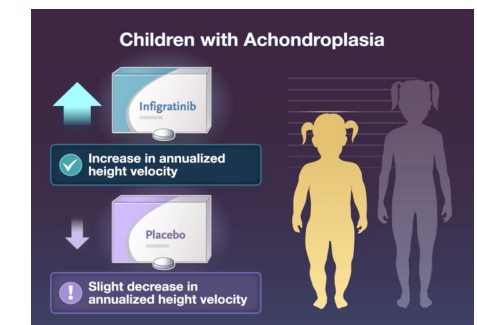
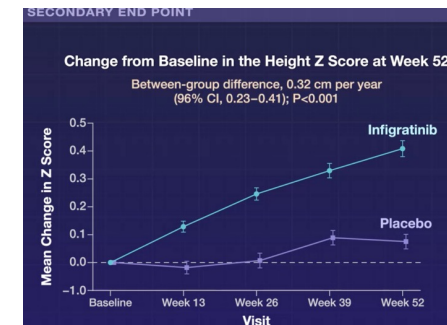
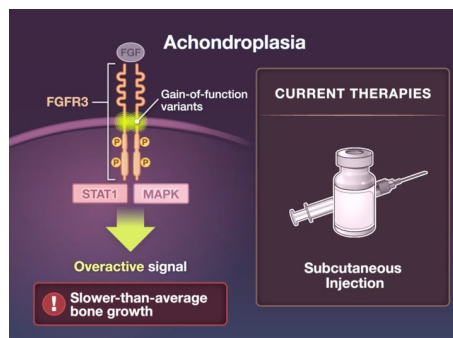
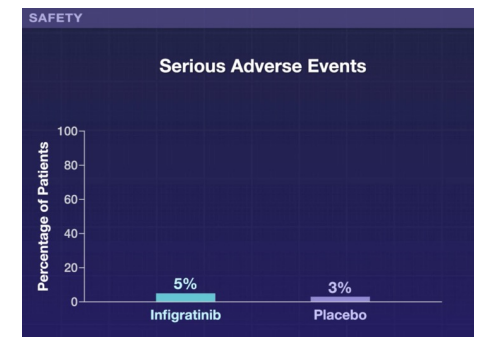
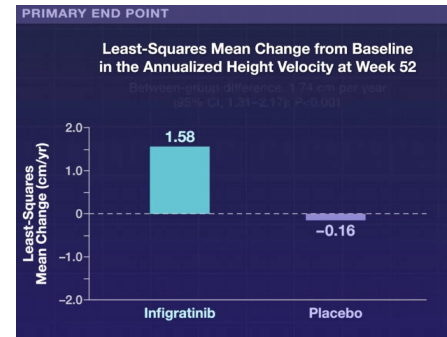
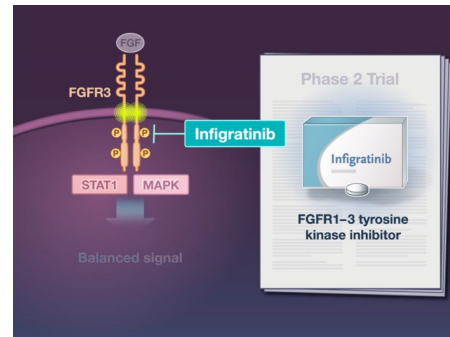
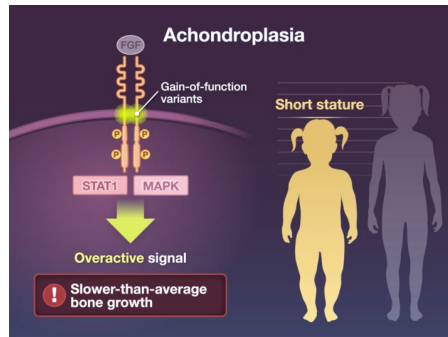
Panel B shows the mean change from baseline in the upper-to-lower body segment ratio according to visit in each trial group. In Panels A and B, the I bars indicate the standard deviation. Panel C shows the subgroup analyses of the least-squares mean change in the height z score relative to achondroplasia reference data and in the upper-to-lower body segment ratio from baseline to week 52. Additional results of subgroup analyses according to baseline strata are provided in Tables S5 and S6.



Action of FGF23 is inhibited to some degree.

Mean Serum Phosphate Level.

Points represent mean values at each visit, and I bars indicate the standard deviation. Hyperphosphatemia was defined as a persistent serum phosphate level of more than 6.0 mg per deciliter in children aged 3 to 12 years, more than 5.4 mg per deciliter in children aged 13 to 15 years, and more than 5.0 mg per deciliter in children aged 16 years or older. Phosphate levels were considered to be elevated if the test result had no other reasonable explanation and was confirmed within 14 days by repeat testing.



Infigratinib increases blood phosphate levels (hyperphosphatemia) because it blocks fibroblast growth factor receptor 1 (FGFR1), which disrupts the normal signaling of FGF23 that controls phosphate balance.

Isotonische Kochsalzlösung (NaCl 0,9 %)

- **Zusammensetzung:** Enthält ausschließlich Natrium (154 mmol/l) und Chlorid (154 mmol/l).
- **Nachteile:** Große Mengen führen oft zu Hyperchlorämie (zu viel Chlorid im Blut), hyperchlorämischer metabolischer Azidose (Übersäuerung) und Nierenschäden.
- **Ausnahmen/Vorteile:** Kann bei Patienten mit erhöhtem Hirndruck (Schädel-Hirn-Trauma) sinnvoll sein, da der höhere Natriumgehalt das Gehirn vor zusätzlicher Wassereinlagerung schützt.

Balancierte Vollelektrolytlösungen (BVE)

- **Zusammensetzung:** Ahmen das Blutplasma nach und enthalten neben Natrium und Chlorid auch Kalium, Calcium, Magnesium sowie Puffer wie Laktat oder Acetat.
- **Vorteile:** Zeigen ein günstigeres Nebenwirkungsprofil, belasten die Nieren weniger und verhindern eine überschießende Übersäuerung des Blutes bei großvolumiger Infusionstherapie.
- **Einsatzbereich:** Gilt in der modernen Notfall- und Intensivmedizin zunehmend als Standardersatz für die reine Kochsalzlösung.

Möchten Sie wissen, **welche Infusionstherapie bei bestimmten Krankheitsbildern** (wie Sepsis oder Operationen) empfohlen wird?



0,9&%

154 mmol/L Na

154 mmol/L Cl

Na and Cl 20 mmol/L higher than plasma; could lead to expansion acidosis



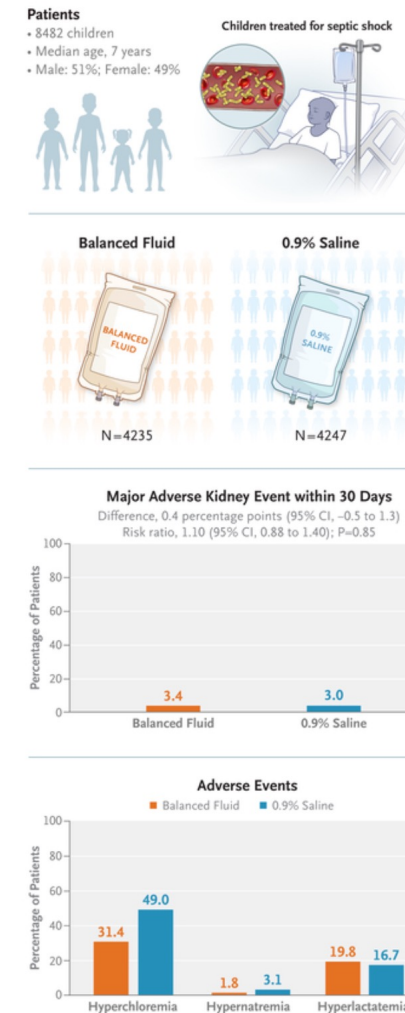
Sterofundin usw

Natrium (Na ⁺)	145,0
Chlorid (Cl ⁻)	127,0
Kalium (K ⁺)	4,0
Calcium (Ca ²⁺)	2,5
Acetat	24,0
Magnesium (Mg ²⁺)	1,0

Acetate metabolized to CO₂, water, and bicarbonate

Balanced Fluid or 0.9% Saline in Children Treated for Septic Shock

Whether treatment with balanced crystalloid fluid leads to better outcomes than 0.9% saline in children treated for septic shock is debated. In this pragmatic clinical trial conducted at 47 emergency departments in five countries, patients (2 months to <18 years of age) with suspected septic shock and abnormal perfusion were randomly assigned to receive fluid resuscitation with either balanced fluid or 0.9% saline for up to 48 hours. The primary outcome was a major adverse kidney event (a composite of death, new renal-replacement therapy, or persistent kidney dysfunction) at 30 days after enrollment or hospital discharge, whichever occurred first.



Crystalloid fluid is commonly used to resuscitate children with septic shock. Options for crystalloids include 0.9% sodium chloride (saline) or balanced fluid, such as lactated Ringer's solution or Plasma-Lyte. Despite its widespread use, 0.9% saline contains a supraphysiologic concentration of chloride that is associated with hyperchloremia, metabolic acidosis, and decreased renal blood flow. In contrast, balanced fluid has an electrolyte composition that more closely resembles that of human plasma and has been shown to be associated with lower frequencies of acute kidney injury, receipt of renal-replacement therapy, and death than 0.9% saline in some studies involving adults and in some involving children. However, other studies have shown that balanced fluid does not provide any benefit or is associated with harm. Consequently, the Surviving Sepsis Campaign issued a conditional recommendation for treatment with balanced fluids over 0.9% saline in children with septic shock.

To determine whether resuscitation with balanced fluid would result in a lower frequency of major adverse kidney events within 30 days than resuscitation with 0.9% saline in children treated for septic shock, we conducted the Pragmatic Pediatric Trial of Balanced versus Normal Saline Fluid in Sepsis.

Methods

Trial Design and Oversight

We conducted a multicenter, pragmatic, open-label, interventional trial in which children with suspected septic shock treated in an emergency department between August 25, 2020, and October 31, 2025, were randomly assigned to receive either balanced crystalloid fluid or 0.9% saline for resuscitation and maintenance hydration.

Trial Patients

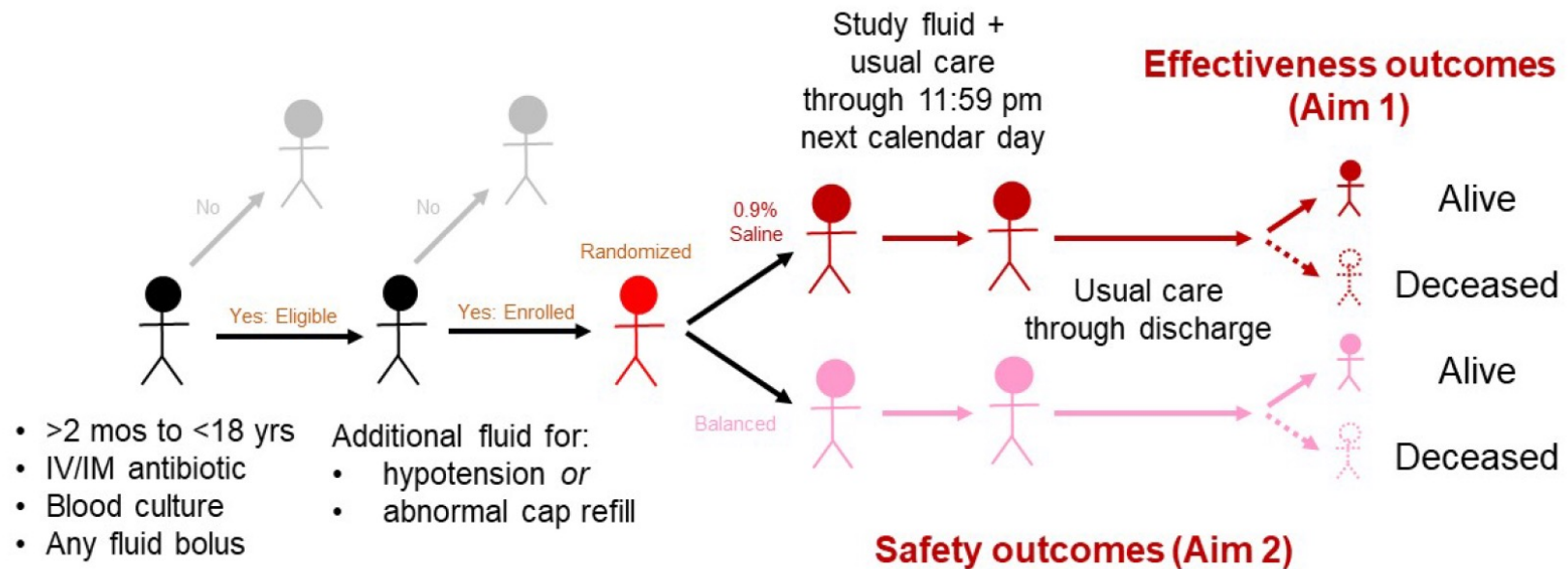
Children (2 months to <18 years of age) with **suspected septic shock** who were being treated with fluid resuscitation for abnormal perfusion in an emergency department were eligible for enrollment if the total volume of crystalloid fluid administered before enrollment was confirmed as 40 ml per kilogram of body weight or less. All the clinicians in the participating emergency departments screened patients during routine care, but only those trained regarding trial procedures could enroll patients.

Intervention

We compared treatment with a predominantly balanced fluid and treatment with 0.9% saline, acknowledging that routine care often includes multiple fluid types. Balanced fluids could be lactated Ringer's solution, Plasma-Lyte, or Hartmann's solution, depending on availability or clinician preference.

Outcomes

The primary outcome was a **major adverse kidney event** — defined as a composite of death from any cause, initiation of renal-replacement therapy, or persistent kidney dysfunction — within 30 days after trial enrollment or hospital discharge, whichever occurred first.



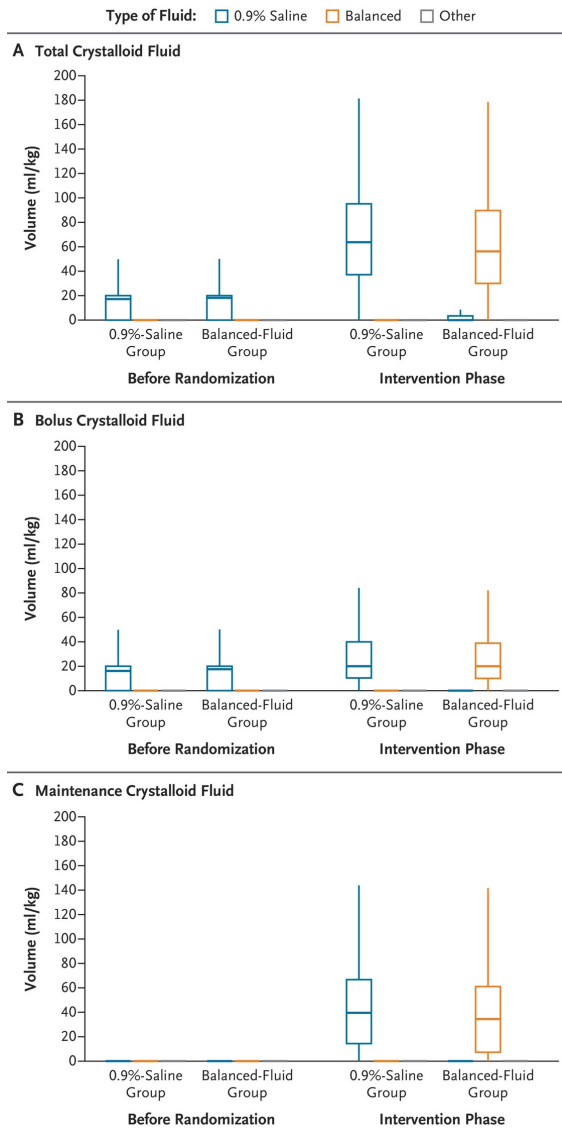
The figure illustrates the overall design and flow of participants through the study. Patients who were between 2 months and 18 years-old and treated for suspected septic shock, as indicated by clinical decision to collect a blood culture and administers a parenteral antibiotic dose, were eligible and enrolled if fluid bolus therapy was administered for abnormal perfusion (defined by either clinician judgement that hypotension or abnormal capillary refill (either “flash” or “prolonged”) capillary refill were present).

Patients at Baseline.

Characteristic	Balanced Fluid (N = 4235)	0.9% Saline (N = 4247)
Median age (IQR) — yr†	6.8 (2.8–12.8)	6.8 (2.8–12.8)
Male sex — no./total no. (%)	2166/4232 (51.2)	2136/4242 (50.4)
Coexisting conditions — no./total no. (%)		
Hematogenous or solid-tumor cancer	603/4224 (14.3)	613/4236 (14.5)
Bone marrow or solid-organ transplant	165/4224 (3.9)	158/4236 (3.7)
Cardiomyopathy or heart failure	43/4224 (1.0)	47/4236 (1.1)
Pulmonary hypertension	28/4224 (0.7)	30/4236 (0.7)
Kidney disease	193/4224 (4.6)	175/4236 (4.1)
Neurologic dysfunction causing severe developmental delay	1182/4224 (28.0)	1182/4236 (27.9)
Sickle cell disease	61/4224 (1.4)	59/4236 (1.4)
Chronic ventilator dependence	247/4224 (5.8)	219/4236 (5.2)
Indwelling central catheter	745/4224 (17.6)	742/4236 (17.5)
Median time from emergency department arrival to first antibiotic administration (IQR) — min‡	94 (50–183)	90 (48–183)
Median time from emergency department arrival to trial enrollment (IQR) — min§	103 (50–191)	101 (49–188)
Median volume of crystalloid fluid received before enrollment (IQR) — ml/kg		
0.9% Saline	18 (0–20)	17 (0–20)
Balanced fluid	0 (0–0)	0 (0–0)
Median initial blood lactate level (IQR) — mmol/liter¶	1.9 (1.3–3.0)	1.9 (1.3–3.0)
Median baseline serum creatinine level (IQR) — mg/dl	0.30 (0.25–0.50)	0.30 (0.25–0.47)
Acute kidney injury stage at enrollment — no. (%)**		
Stage 1	560 (13.2)	612 (14.4)
Stage 2	201 (4.7)	214 (5.0)
Stage 3	204 (4.8)	228 (5.4)

Primary, Secondary, and Safety Outcomes.

Outcome®	Balanced Fluid	0.9% Saline	Risk Difference (95% CI)†	Effect Measure (95% CI)‡	P Value§
Primary outcome					
Major adverse kidney event within 30 days — no./total no. (%)¶	137/4073 (3.4)	124/4068 (3.0)	0.004 (–0.005 to 0.013)	1.10 (0.88 to 1.40)	0.85
Secondary effectiveness outcomes					
Death within 30 days — no./total no. (%)	41/4214 (1.0)	39/4226 (0.9)	0.001 (–0.004 to 0.005)	1.07 (0.70 to 1.64)	
New renal-replacement therapy — no./total no. (%)	26/4214 (0.6)	31/4226 (0.7)	–0.001 (–0.005 to 0.002)	0.84 (0.50 to 1.42)	
Persistent kidney dysfunction at hospital discharge — no./total no. (%)	93/4085 (2.3)	78/4079 (1.9)	0.004 (–0.004 to 0.012)	1.15 (0.88 to 1.49)	
Death before hospital discharge — no. /total no. (%)	48/4216 (1.1)	47/4230 (1.1)	0.001 (–0.005 to 0.005)	1.02 (0.69 to 1.51)	
Death within 90 days — no./total no. (%)	90/3857 (2.3)	83/3867 (2.1)	0.002 (–0.005 to 0.008)	1.07 (0.80 to 1.42)	
Median length of hospital stay (IQR) — days**	5.0 (3.0 to 9.0)	5.0 (3.0 to 9.0)		0 (0 to 0)	
Median no. of hospital-free days during 28 days (IQR)††	23 (19 to 25)	23 (19 to 25)		0 (0 to 0)	
Safety outcomes — no./total no. (%)‡‡					
Thrombosis	55/4216 (1.3)	55/4230 (1.3)	0 (–0.005 to 0.005)	1.00 (0.69 to 1.45)	0.91
Cerebral edema	18/4216 (0.4)	17/4230 (0.4)	0.001 (–0.003 to 0.003)	1.09 (0.55 to 2.13)	0.57
Sodium >155 mmol/liter	52/2830 (1.8)	89/2882 (3.1)	–0.013 (–0.021 to –0.004)§§	0.60 (0.43 to 0.84)§§	0.003
Sodium <128 mmol/liter	2/2830 (0.1)	0/2882 (0)	—	—	—
Chloride >110 mmol/liter	868/2765 (31.4)	1383/2823 (49.0)	–0.176 (–0.201 to –0.151)§§	0.64 (0.60 to 0.69)§§	<0.001
Potassium >6 mmol/liter	63/2798 (2.3)	74/2853 (2.6)	–0.003 (–0.011 to 0.005)§§	0.87 (0.62 to 1.20)§§	0.39
Total calcium level >12 mg/dl or ionized calcium level >1.35 mmol/liter	127/926 (13.7)	140/1005 (13.9)	–0.002 (–0.033 to 0.029)§§	0.95 (0.76 to 1.18)§§	0.62
Lactate level >4 mmol/liter	260/1314 (19.8)	228/1363 (16.7)	0.031 (0.001 to 0.060)§§	1.18 (1.01 to 1.39)§§	0.04

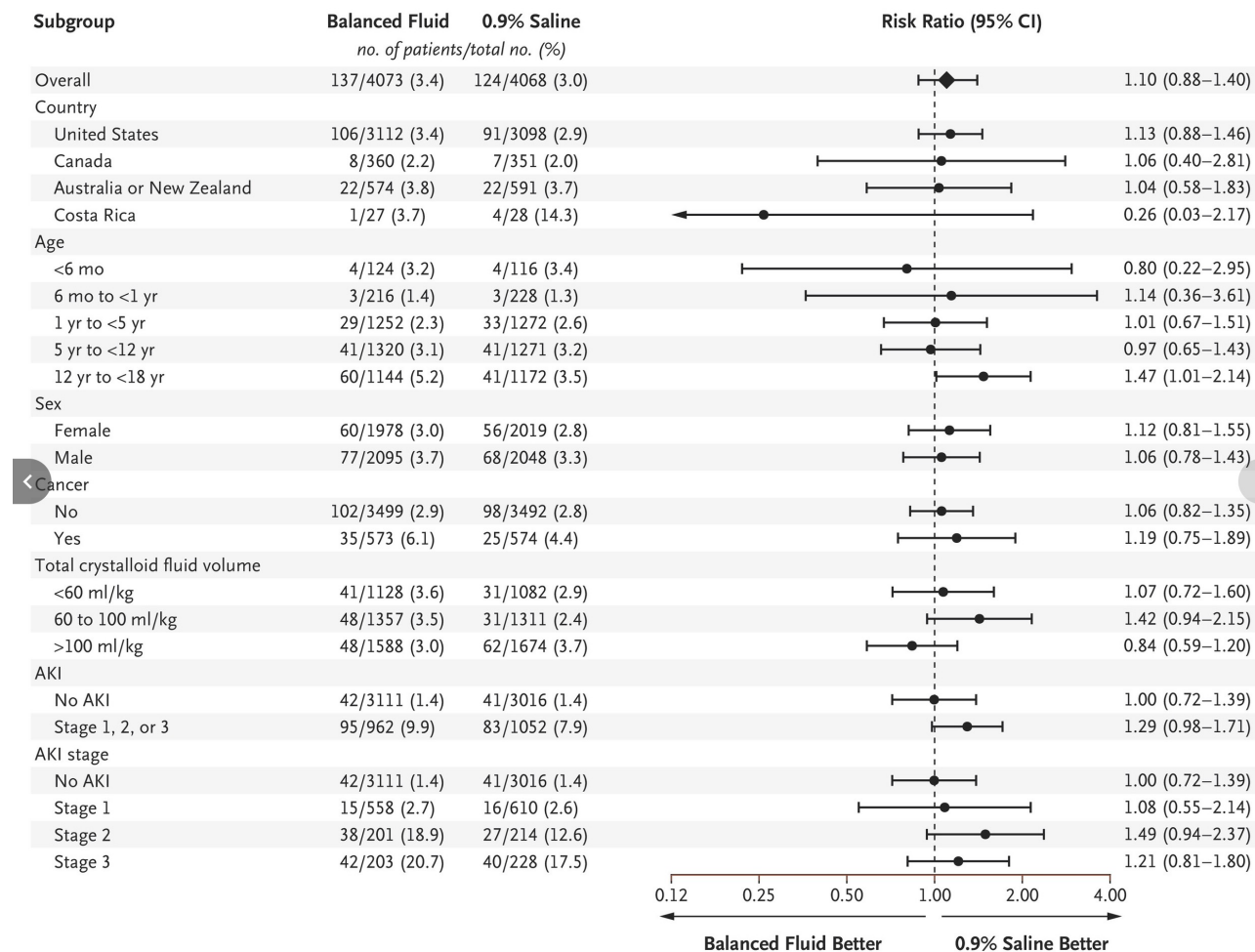


Type and Volume of Fluid Administration.

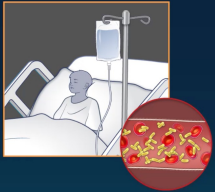
Shown are box plots of the total volume of crystalloid fluid (Panel A), the volume of bolus crystalloid fluid (Panel B), and the volume of maintenance crystalloid fluid (Panel C) administered to patients from presentation at the emergency department until 11:59 p.m. on the calendar day after the day of randomization, with stratification according to assigned treatment group (balanced fluid or 0.9% saline). Maintenance fluids were defined as the base fluid administered regardless of additives (e.g., dextrose or potassium). In the box plots, the horizontal line within the box indicates the median; the bottom and the top of the boxes indicate the 25th and 75th percentiles, respectively; and the whiskers indicate the lowest and highest values within 1.5 times the interquartile range (outliers beyond these thresholds are not shown).

Subgroup Analyses of the Primary Outcome.

Shown are the subgroup analyses of the percentage of patients in the balanced-fluid group and in the 0.9%-saline group who met the criteria for a major adverse kidney event (defined as a composite of death from any cause, new renal-replacement therapy, or persistent kidney dysfunction) within 30 days after enrollment or hospital discharge, whichever occurred first. Cancer was considered to be present if the patient was being treated or monitored for a blood or solid-tissue cancer before trial enrollment or started treatment during the trial-related hospitalization; previous cancer diagnoses that were considered to be cured or resolved were not included. Total crystalloid fluid volume refers to the total volume of crystalloid fluid administered either as a bolus or as maintenance hydration during the combined prandomization and intervention phases. Acute kidney injury (AKI) stage was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) creatinine criteria (see the [Supplementary Appendix](#)).



Children Treated for Septic Shock



- Resuscitation
- Maintenance hydration

CRYSTALLOID FLUID

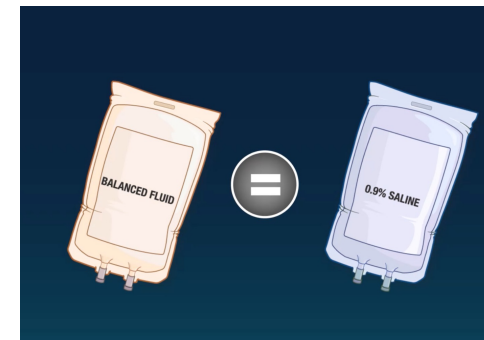
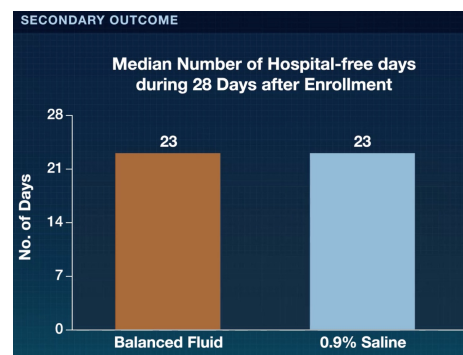
BALANCED FLUID

N=4235

0.9% SALINE

N=4247

For up to 48 hours



Isotonic Crystalloid



VS.



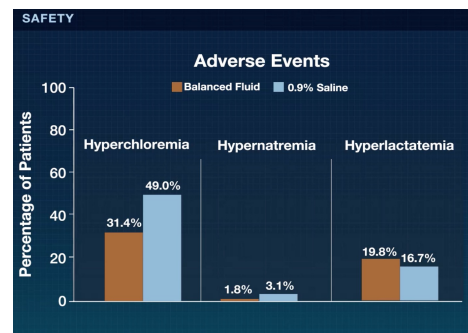
? Better outcomes

PRIMARY OUTCOME

Major Adverse Kidney Event

A composite of...

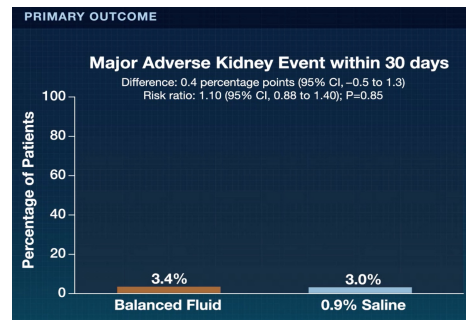
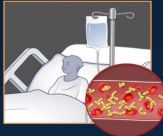
- Death
- New kidney-replacement therapy
- Persistent kidney dysfunction



PRoMPT BOLUS Trial

- International
- Pragmatic
- Open-label
- Randomized
- Interventional

- 8482 Children and adolescents
- 2 Months to <18 years old
- With suspected septic shock
- Treated with fluid resuscitation for abnormal perfusion

Among children treated for septic shock

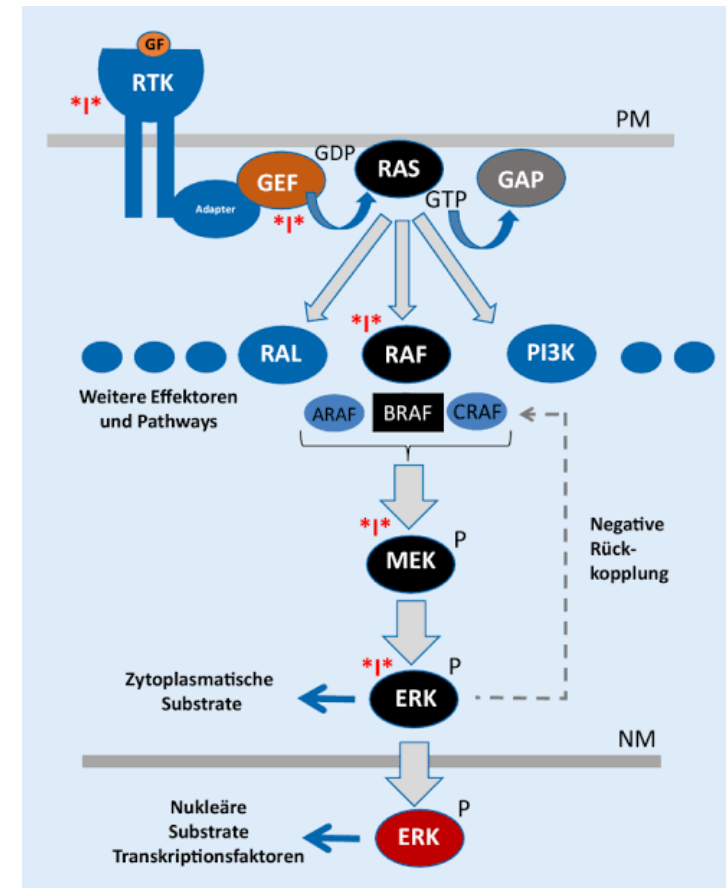
The Incidence of...

- Death
- New kidney-replacement therapy
- Persistent kidney dysfunction

RAS-Mutationen sind genetische Veränderungen in der KRAS-, NRAS- oder HRAS-Genfamilie, die als molekulare Schalter das Zellwachstum unkontrolliert anregen und zu den häufigsten Treibern bei Krebserkrankungen zählen.

Was sind RAS-Mutationen?

- **Funktion:** Das RAS-Protein reguliert als kleines G-Protein normalerweise die Signalübertragung für Zellwachstum und -teilung.
- **Defekt:** Durch die Mutation verbleibt das Protein in einem permanent aktiven (GTP-gebundenen) Zustand, wodurch Zellen unaufhörlich wachsen.
- **Häufigkeit:** Sie treten in ca. 30 % aller menschlichen Tumoren auf – besonders oft bei Bauchspeicheldrüsenkrebs (bis zu 90–95 %), Darmkrebs (ca. 40 %) und Lungenkrebs (ca. 25 %).



Daraxonrasib for Previously Treated RAS-Mutant Non–Small-Cell Lung Cancer

RAS mutations, as a group, are the most common oncogenic drivers of non–small-cell lung cancer (NSCLC), and they occur in approximately 30% of patients. Whether daraxonrasib (RMC-6236) — an oral RAS(ON) multiselective, tri-complex inhibitor of guanosine triphosphate-bound mutant and wild-type RAS protein isoforms — is safe and effective in patients with *RAS*-mutant NSCLC is unknown.

In this phase 1–2, multicenter, dose-escalation and dose-expansion study of daraxonrasib, we enrolled patients with previously treated advanced *RAS*-mutant NSCLC and administered daraxonrasib in doses of 10 to 400 mg orally once daily in 21-day cycles. The primary end point was safety. Secondary end points included investigator-assessed objective response (complete or partial response) and the duration of response, with response assessed according to Response Evaluation Criteria in Solid Tumors, version 1.1.

Conclusions

Among patients with previously treated metastatic *RAS*-mutant NSCLC receiving daraxonrasib at a dose of 300 mg or less daily, 54% had adverse events of grade 3 or higher, and antitumor activity was reported in more than 30%.

Methods

Study Design and Patients

RMC-6236-001 is a phase 1–2, multicenter, open-label, two-part (dose escalation and dose expansion) study of daraxonrasib involving patients with advanced solid tumors harboring *RAS* mutations; the study design has been described previously.

Treatment

Patients with *RAS*-mutant solid tumors received 10 to 400 mg of daraxonrasib, administered orally once daily in 21-day cycles; the maximum tolerated dose and recommended phase 2 dose were identified with the use of a Bayesian optimal interval design, as described previously. The maximum tolerated dose was not reached, but frequent dose modifications at 400 mg prevented sustained treatment at this level. Expansion cohorts of patients with *KRAS* G12–mutant NSCLC were enrolled and received daraxonrasib at doses of 120 mg, 200 mg, or 300 mg, and additional patients with NSCLC harboring mutations other than *RAS* G12 were enrolled in separate cohorts and received daraxonrasib at doses of 200 mg and 300 mg. Treatment continued until the occurrence of unacceptable toxic effects, withdrawal of consent, or study discontinuation, whichever occurred first; patients who met the protocol-specified criteria for clinical benefit could continue treatment beyond disease progression.

End Points and Assessments

The primary end point was the safety and side-effect profile of daraxonrasib. Adverse events that emerged during treatment and those that were related to treatment were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events.

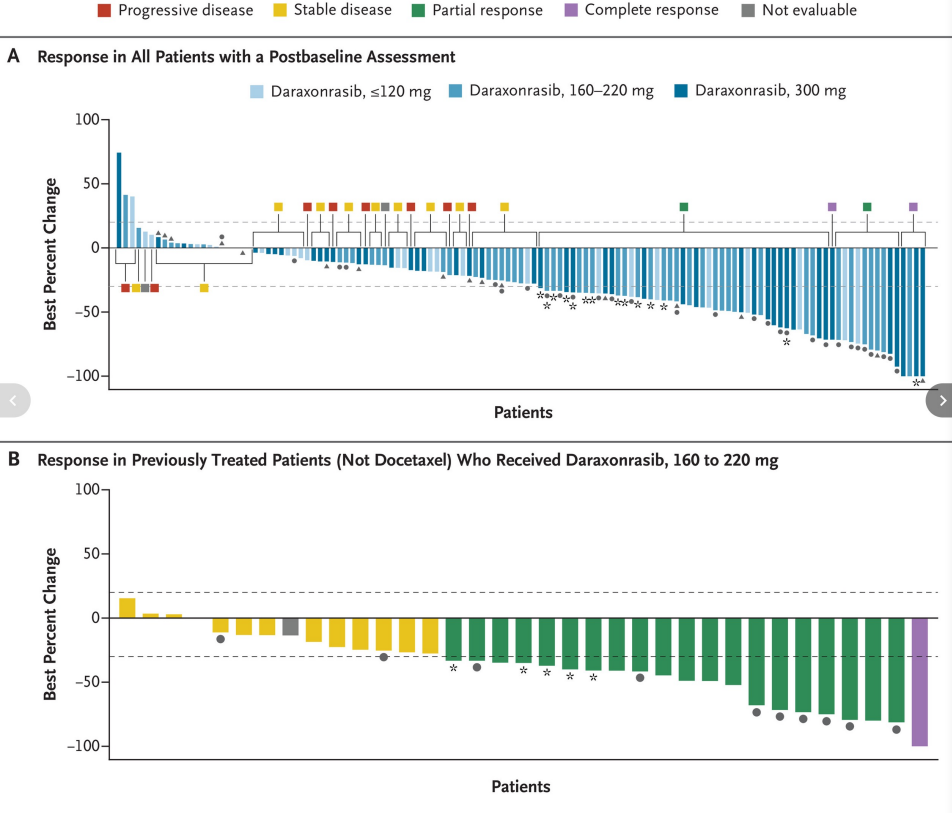
Characteristic	Patients (N = 136)
Median age (range) — yr	66 (31–89)
Male sex — no. (%)	52 (38)
Race — no. (%)†	
White	102 (75)
Black	8 (6)
Other	26 (19)
ECOG performance-status score of 1 — no. (%)‡	107 (79)
RAS mutations — no. (%)	
RAS G12V	50 (37)
RAS G12D	41 (30)
Other RAS G12, excluding G12D and G12V§	26 (19)
Non-RAS G12¶	19 (14)
Key co-mutations — no./total no. (%)	
TP53	69/130 (53)
STK11	26/130 (20)
KEAP1	13/130 (10)
Median lines of previous therapy for metastatic disease (range) — no.	2 (0–7)
Type of previous systemic anticancer therapy — no. (%)	
Anti-PD-1 or anti-PD-L1 therapy	134 (99)
Platinum-based chemotherapy	135 (99)
Docetaxel	27 (20)
Smoking history — no. (%)	
Never smoked	34 (25)
Former smoker	96 (71)
Current smoker	6 (4)
Brain metastases — no. (%)	40 (29)
Stage IV disease at diagnosis — no. (%)	77 (57)
Disease stage at study enrollment — no. (%)	
III	5 (4)
IV	131 (96)

Safety in Patients with *RAS*-Mutant NSCLC.

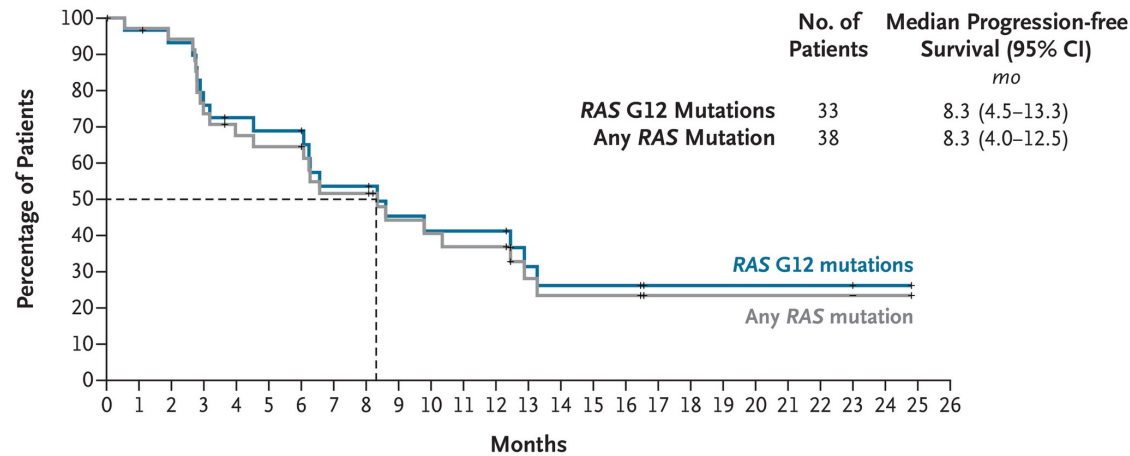
Event	All Patients (N = 136)		Daraxonrasib, ≤120 mg (N = 26)		Daraxonrasib, 160–220 mg (N = 59)		Daraxonrasib, 300 mg (N = 51)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
≥1 Adverse event	135 (99)	73 (54)	25 (96)	10 (38)†	59 (100)	30 (51)‡	51 (100)	33 (65)§
≥1 Treatment-related adverse event	134 (99)	41 (30)	25 (96)	3 (12)¶	59 (100)	15 (25)¶	50 (98)	23 (45)
Serious adverse event								
Any	55 (40)	46 (34)	6 (23)	4 (15)	26 (44)	23 (39)	23 (45)	19 (37)
Treatment-related	11 (8)	11 (8)	0	0	4 (7)	4 (7)	7 (14)	7 (14)
Adverse event leading to dose modification								
Any	98 (72)	NA	14 (54)	NA	42 (71)	NA	42 (82)	NA
Treatment-related	73 (54)	33 (24)	7 (27)	1 (4)	28 (47)	11 (19)	38 (75)	21 (41)
Leading to dose interruption								
Any	95 (70)	NA	13 (50)	NA	40 (68)	NA	42 (82)	NA
Treatment-related	69 (51)	32 (24)	6 (23)	1 (4)	25 (42)	11 (19)	38 (75)	20 (39)
Leading to dose reduction								
Any	48 (35)	NA	3 (12)	NA	18 (31)	NA	27 (53)	NA
Treatment-related	46 (34)	15 (11)	2 (8)	1 (4)	17 (29)	3 (5)	27 (53)	11 (22)
Adverse event leading to discontinuation								
Any	15 (11)	NA	1 (4)	NA	6 (10)	NA	8 (16)	NA
Treatment-related	6 (4)	1 (1)	1 (4)	0	1 (2)	0	4 (8)	1 (2)
Adverse events in ≥20% of patients								
Rash**	122 (90)	11 (8)	21 (81)	2 (8)	54 (92)	5 (8)	47 (92)	4 (8)
Diarrhea	99 (73)	12 (9)	16 (62)	0	40 (68)	2 (3)	43 (84)	10 (20)
Nausea	84 (62)	1 (1)	13 (50)	0	35 (59)	1 (2)	36 (71)	0
Vomiting	74 (54)	6 (4)	11 (42)	0	29 (49)	5 (8)	34 (67)	1 (2)
Mucositis or stomatitis††	55 (40)	4 (3)	6 (23)	0	25 (42)	0	24 (47)	4 (8)
Paronychia	37 (27)	0	7 (27)	0	14 (24)	0	16 (31)	0
Fatigue	34 (25)	0	3 (12)	0	15 (25)	0	16 (31)	0
Decreased appetite	33 (24)	0	2 (8)	0	15 (25)	0	16 (31)	0
Anemia	30 (22)	7 (5)	4 (15)	1 (4)	14 (24)	1 (2)	12 (24)	5 (10)
Aspartate aminotransferase increased	29 (21)	5 (4)	5 (19)	1 (4)	16 (27)	1 (2)	8 (16)	3 (6)
Dyspnea	29 (21)	3 (2)	4 (15)	1 (4)	12 (20)	1 (2)	13 (25)	1 (2)
Hypoalbuminemia	28 (21)	2 (1)	3 (12)	1 (4)	12 (20)	0	13 (25)	1 (2)

Investigator-Assessed Confirmed Best Response with Daraxonrasib at Doses of 160–220 mg.

Outcome	Any <i>RAS</i> -Mutant NSCLC (N = 38)	<i>RAS</i> G12-Mutant NSCLC (N = 33)
Median duration of follow-up (IQR) — mo	18.3 (14.4–24.5)	20.4 (16.5–24.7)
Objective response		
No. of patients	16	14
% (95% CI)	42 (26–59)	42 (25–61)
Confirmed best overall response — no. (%) [†]		
Complete response	1 (3)	1 (3)
Partial response	15 (39)	13 (39)
Stable disease	18 (47)	15 (45)
Progressive disease	0	0
Not evaluable [‡]	4 (11)	4 (12)
Disease control [§]		
No. of patients	34	29
% (95% CI)	89 (75–97)	88 (72–97)
Median duration of response (95% CI) — mo	11.5 (4.6 to NE)	NE (4.6 to NE)
Kaplan–Meier estimate of patients with a response at 18 months — % (95% CI)	48 (19–72)	51 (21–75)



A Progression-free Survival



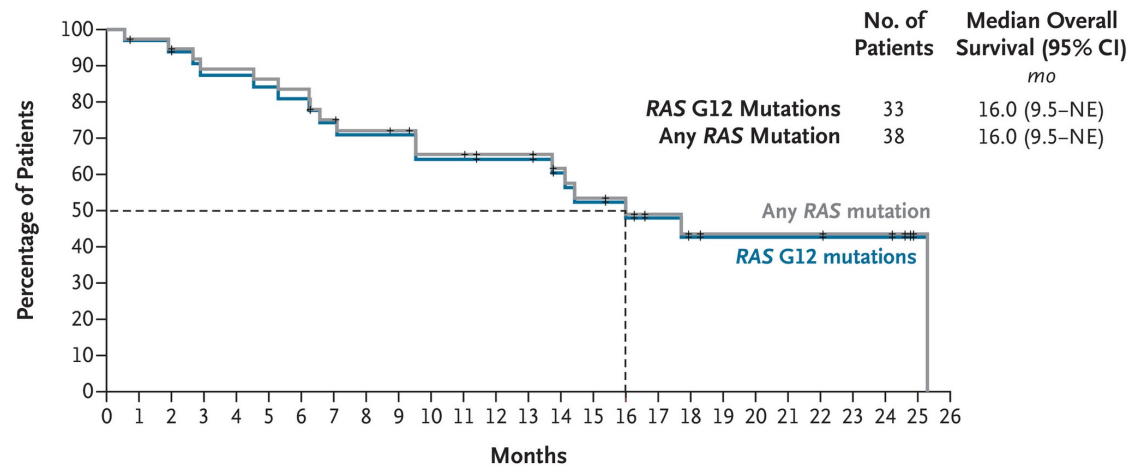
No. at Risk

<i>RAS</i> G12 mutations	33	29	27	22	20	19	19	14	14	11	10	10	10	6	5	5	5	2	2	2	2	2	2	1	1	0
Any <i>RAS</i> mutation	38	34	32	25	22	21	21	16	16	12	11	10	10	6	5	5	5	2	2	2	2	2	2	1	1	0

Progression-free and Overall Survival.

Panel A shows progression-free survival and Panel B shows overall survival in patients with *RAS*-mutant and *RAS* G12-mutant NSCLC who had received previous first- or second-line platinum-based chemotherapy and anti-programmed cell death 1 or anti-programmed cell death ligand 1 therapy but not docetaxel and received 160 to 220 mg of daraxonrasib.

B Overall Survival



Discussion

Among patients with *RAS*-mutant NSCLC who had disease progression after platinum-based chemotherapy and anti-PD-1 or anti-PD-L1 therapy, daraxonrasib was associated with adverse events of grade 3 or higher, regardless of attribution, in 54% and treatment-related adverse events of grade 3 or higher in 30%, along with a response in more than 30% of patients. The results are notable in a treatment landscape characterized by limited options with modest clinical benefit and substantial toxic effects. These findings highlight the therapeutic potential of RAS(ON) multiselective inhibition.

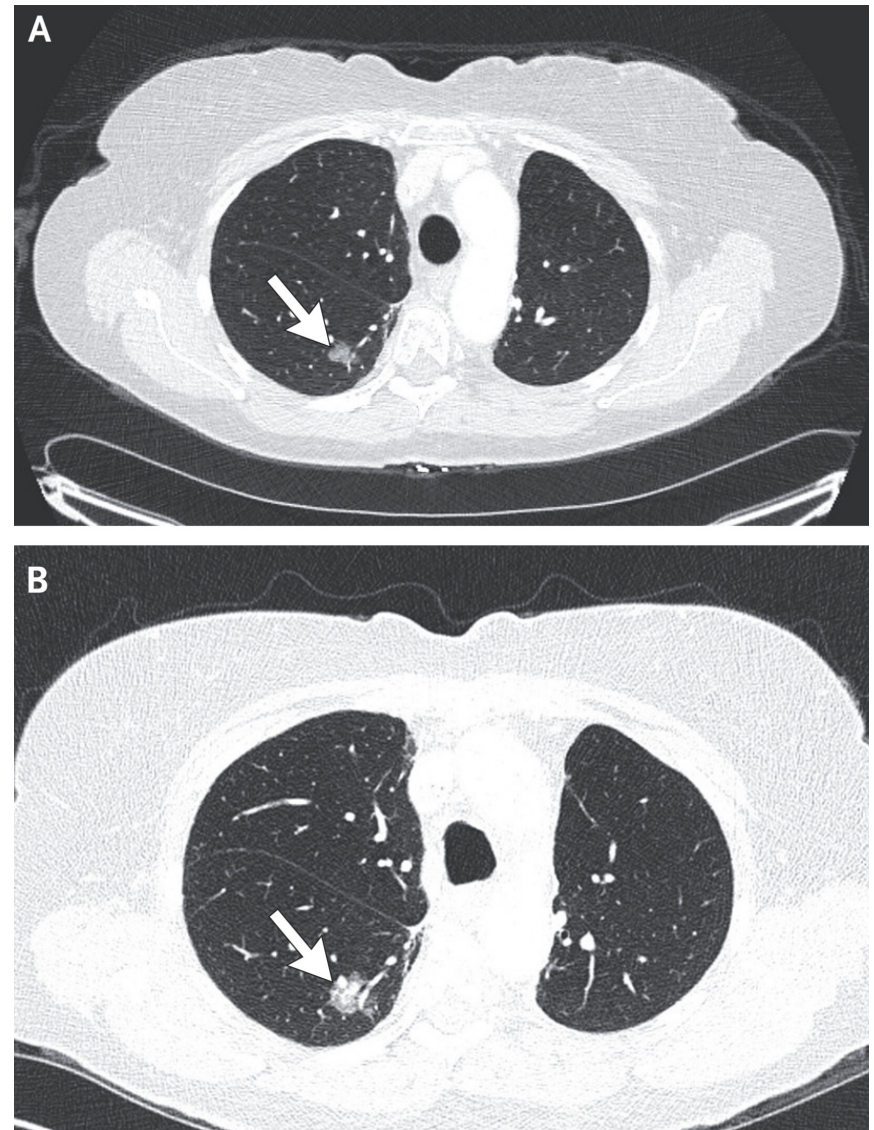
These data support the ongoing phase 3, randomized RASolve 301 trial of second-line daraxonrasib as compared with docetaxel in patients with *RAS*-mutant NSCLC (ClinicalTrials.gov).

Pulmonary Nodules

Summary

Pulmonary nodules are classified as solid or subsolid, with subsolid nodules further classified as part-solid or pure ground-glass. Management strategies differ according to the type of nodule. A comparison of current and previous imaging studies, when available, is essential to assess the risk of the nodule being malignant. Solid nodules that have been stable for 2 years are considered to be benign, whereas subsolid nodules require a longer period of stability to be considered benign. Prediction models to stratify the risk of the nodule being malignant can be used to guide the management of **solid nodules**. Computed tomographic (CT) surveillance is indicated for low-risk nodules; positron-emission tomography–CT, biopsy, or both for intermediate-risk nodules; and surgical resection for selected high-risk nodules. **Subsolid nodules** are often slower growing than solid nodules but are associated with a higher risk of being malignant, especially if a solid component develops or progressively enlarges. Biopsy methods include transthoracic needle biopsy and navigational bronchoscopy. Optimal overall management balances timely diagnosis in persons who have cancer with the avoidance of unnecessary invasive procedures in persons who have benign disease.

A 67-year-old man underwent computed tomography (CT) of the chest to investigate breathlessness and a persistent cough. He had a smoking history of **28 pack-years**, having quit at 45 years of age, had no history of cancer, and did not live in an area where fungal infection is endemic. He was otherwise fit with no clinically significant cardiac or respiratory disease, was able to walk 2 miles without stopping, and played golf regularly. A pure ground-glass nodule with a maximum axial diameter of **19 mm** was discovered in the periphery of the apical segment of the lower lobe of the right lung ([Figure 1A](#)). After clinical review, CT surveillance was planned, with repeat scans at 6 and 12 months. The CT scan at 6 months showed no change, whereas the scan at 12 months showed that the nodule had increased to **21 mm** in axial diameter and had developed a solid component within the preexisting pure ground-glass lesion, thereby becoming a part-solid nodule ([Figure 1B](#)). **How would you manage this patient's pulmonary nodule?**



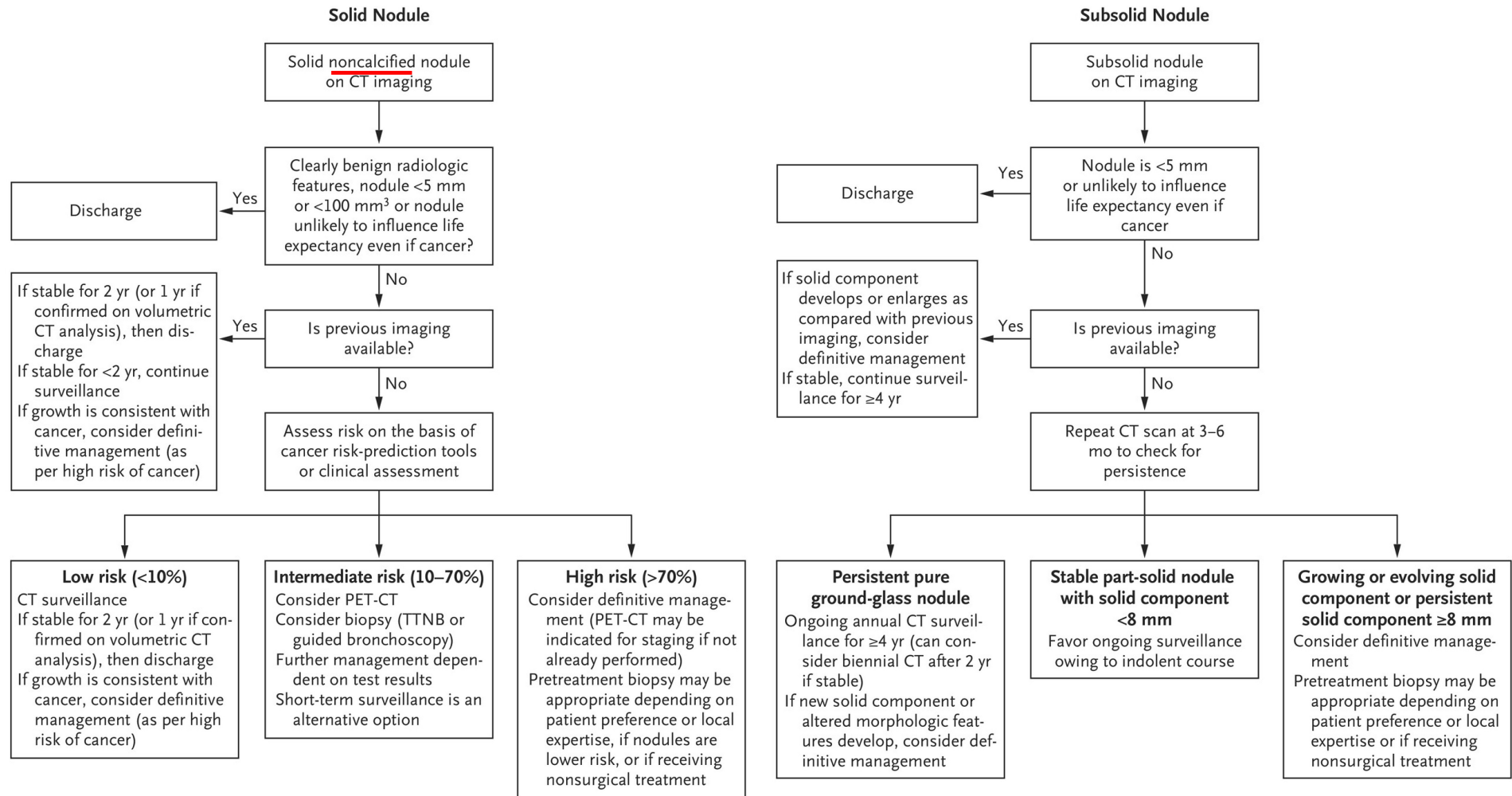
Pulmonary Nodules

- Nodules can be categorized on the basis of morphologic features as solid or subsolid, with management recommendations differing substantially between nodule types.
- Solid nodules that have been stable for 2 years are considered to be benign; subsolid nodules require a longer period of stability (≥ 4 years) before they can be considered benign.
- Prediction models have been developed to estimate the likelihood that a pulmonary nodule is malignant; these models are used predominantly for solid nodules.
- Computed tomographic (CT) surveillance is appropriate for low-risk nodules and positron-emission tomography–CT, biopsy, or both for intermediate-risk nodules. In select high-risk nodules, surgery may be considered without preoperative biopsy.
- Methods of obtaining biopsy samples of pulmonary nodules include transthoracic needle biopsy or navigational bronchoscopy; the procedures have an equivalent diagnostic accuracy, but the incidence of complications is lower with bronchoscopy.

Variable	Mayo Clinic Model ²¹	Veterans Affairs Model ¹⁶	Brock University Model ¹⁸	Herder Model ¹⁷	BIMC Model ²⁰	Cleveland Clinic Model ¹⁹
Development population	629 patients with nodules detected on chest radiography	375 patients with nodules detected on chest radiography	1871 participants with nodules detected on low-dose CT screening scans	106 patients with nodules detected on CT of the chest and referred for PET-CT	343 patients with nodules detected on CT of the chest	301 patients with nodules referred being considered for biopsy
Type of nodule	Solid	Solid	Solid, part-solid, or pure ground-glass	Solid	Solid	Solid, part-solid, or pure ground-glass
Prevalence of cancer in development population — %	23	54	5.5	57	58	66
Factor	Age Cigarette smoker Diameter Previous extrathoracic cancer Spiculation Upper-lobe location	Age Diameter Smoking history Time since quitting smoking	Age Diameter Emphysema Family history of lung cancer Nodule type Sex Spiculation Nodule count per scan Upper-lobe location	Age Cigarette smoker Diameter FDG avidity Previous extrathoracic cancer Spiculation Upper-lobe location	Age Diameter Edges Enhancement on contrast-enhanced CT FDG avidity Lobe Minimum Hounsfield units Previous cancer Smoking history Volume-doubling time	Age Emphysema FDG avidity Irregular or spiculated Previous extrathoracic cancer Smoking history Upper-lobe location
Model performance†	0.83 (model development), 0.73–0.90 (external validation) ^{22,23}	0.79 (model development), 0.74 (external validation) ²³	0.94 (model development), 0.97 (internal validation), 0.80–0.91 (external validation) ^{23–25}	0.92 (model development), 0.81–0.92 (external validation) ^{23,26}	0.89 (model development), 0.82 (external validation) ²⁶	0.79 (model development), 0.67 (internal validation)

Guidelines for the Management of Pulmonary Nodules.

Nodule Type	Lung-RADS ^{23,†}	European Society of Thoracic Imaging ⁴³	Fleischner Society ¹²	American College of Chest Physicians ³⁶	British Thoracic Society ³⁹
	Detected during Screening	Detected during Screening	Detected Incidentally	Detected Incidentally	Detected during Screening or Incidentally
Solid nodules	<6 mm at baseline or <4 mm if new: low-dose CT at 12 mo 6 to <8 mm at baseline or 4 to <6 mm if new: low-dose CT at 6 mo 8 to <15 mm at baseline, <8 mm if growing, or 6 to <8 mm if new: PET-CT (if ≥8 mm) or low-dose CT at 3 mo ≥15 mm at baseline or ≥8 mm if new or growing: refer for further evaluation	<100 mm³: low-dose CT at 12 mo with further workup if volume-doubling time is <500 days 100 to <250 mm³: low-dose CT at 6 mo with further workup if volume-doubling time is <400 days 250 to <500 mm³: low-dose CT at 3 mo with further workup if volume-doubling time is <250 days ≥500 mm³: further workup ≥30 mm³ and new: low-dose CT at 3 mo with further workup if volume increases by >15% or diameter increases by >1.5 mm	<6 mm or <100 mm³: no routine follow-up unless risk is high, in which case consider optional CT at 12 mo 6–8 mm or 100–250 mm³: CT at 6–12 mo if single nodule or at 3–6 mo if multiple nodules >8 mm or >250 mm³: CT at 3 mo or PET-CT or sampling if single nodule; CT at 3–6 mo if multiple nodules	≤4 mm and no risk factors: discharge >4–6 mm: repeat CT at 12 mo if low risk or at 6–12 mo if high risk >6–8 mm: repeat CT at 6–12 mo if low risk or at 3–6 mo if high risk >8 mm: assess pretest cancer risk <5% risk: repeat CT in 3–6 mo 5–65% risk: suggest PET-CT with or without nonsurgical biopsy >65% risk: suggest surgical diagnosis (thoracoscopic wedge resection)	<80 mm³: no further surveillance 80 to <300 mm³: CT surveillance at 3 mo ≥300 mm³: calculate cancer risk with or without PET-CT <10% risk: CT surveillance at 3 mo 10–70% risk: consider image-guided biopsy (or surveillance or excision biopsy) >70% risk: consider definitive management with or without nonsurgical biopsy After CT surveillance, assess growth on the basis of volume-doubling time ≤400 days: definitive management >400 to ≤600 days: biopsy or surveillance >600 days: surveillance or discharge
Part-solid nodules	<6 mm total mean diameter at baseline: low-dose CT at 12 mo ≥6 mm total mean diameter with solid component of <6 mm total mean diameter at baseline or <6 mm total mean diameter if new: low-dose CT at 6 mo ≥6 mm total mean diameter with solid component of 6 to <8 mm at baseline or solid component of <4 mm if new or growing: low-dose CT at 3 mo Solid component of ≥8 mm at baseline or solid component of ≥4 mm if new or growing: refer for further evaluation	≥500 mm³ solid component: low-dose CT after 1 mo with further workup if stable or growing Other sizes: management is equivalent to that for solid nodules (size thresholds apply to the solid component)	<6 mm single nodule: no routine follow-up ≥6 mm single nodule or multiple nodules of any size: CT at 3–6 mo to confirm persistence If unchanged and solid component of <6 mm: annual CT for 5 yr If persistent with suspicious morphologic features, growing solid component, or solid component of >8 mm: consider PET-CT, biopsy, or resection	≤8 mm total diameter: CT surveillance at 3 and 12 mo; if growth or further development of solid component, suggest further evaluation, consideration of resection, or both >8 mm total diameter: repeat CT at 3 mo followed by further evaluation with PET-CT, nonsurgical biopsy, surgical resection, alone or in combination, for persistent nodules	Repeat CT at 3 mo to confirm persistence If growth or altered morphologic features: favor resection or nonsurgical treatment If stable: assess cancer risk on the basis of morphologic features or Brock model Low risk (<10%): CT surveillance at 1, 2, and 4 yr Higher risk (≥10%): discuss options of surveillance, nonsurgical biopsy, or definitive management with patient
Pure ground-glass nodules; also known as nonsolid nodules	<30 mm at baseline or if new or growing: low-dose CT at 12 mo ≥30 mm if stable or slow-growing: low-dose CT at 12 mo ≥30 mm at baseline or if new: low-dose CT at 6 mo	<30 mm: low-dose CT at 12 mo with further workup if volume-doubling time is <500 days or diameter increases by >5 mm	<6 mm single nodule: no routine follow-up ≥6 mm single nodule or multiple nodules of any size: CT at 6–12 mo to confirm persistence If persistent and unchanged: continue CT surveillance every 2 yr through year 5 If solid component or growth develops: consider resection	≤5 mm: no further evaluation >5 mm: annual CT surveillance for ≥3 yr	Management is equivalent to that for part-solid nodules



Conclusions and Recommendations

For the patient described in the vignette, the repeat CT of the chest shows that the nodule increased from 19 mm to 21 mm in axial diameter and developed a solid component within the preexisting pure ground-glass lesion, thereby becoming a part-solid nodule. We would consider the nodule to have a high risk (>95%) of being an invasive adenocarcinoma and would discuss the options of percutaneous biopsy or diagnostic resection with the patient.

If the patient opted for a preoperative biopsy that confirmed a diagnosis of lung cancer or for diagnostic resection without a preoperative biopsy, we would recommend PET-CT for staging, followed by a robotic-assisted segmentectomy. If the preoperative biopsy was nonspecific or nondiagnostic, we would discuss with the patient the options of diagnostic surgery or repeat biopsy. Ongoing CT surveillance would be another option if the patient preferred, although we would emphasize the high risk of the nodule being malignant in this situation, given the change in radiologic findings. Postoperative management would depend on the pathological stage, with CT surveillance for 5 years for early-stage lung cancer (stage IA) and CT surveillance plus optional adjuvant oncologic treatment for more advanced stages, depending on the pathological and molecular subtypes of the cancer.

IMAGES IN CLINICAL MEDICINE

Scrofuloderma



A 72-year-old man presented to the emergency department with a 2-month history of an enlarging, painful lump on his neck. On physical examination, there was a fixed, erythematous, 5-cm mass in the anterior triangle of the neck on the right side (Panel A). Computed tomography (CT) of the neck showed a large necrotic right cervical mass with no identifiable primary tumor. Testing for human immunodeficiency virus was negative, as was an interferon-gamma release assay. The neck mass subsequently enlarged (Panel B, 3 days after presentation). Cytologic analysis of a fine-needle aspiration specimen (obtained 12 days after admission) was consistent with suppurative lymphadenopathy; mycobacterial cultures were negative. The mass subsequently ulcerated and released purulence (Panel C, 17 days after presentation), and a fistulous tract developed (Panel D, 32 days after presentation). A repeat mycobacterial culture of the purulent discharge grew *Mycobacterium tuberculosis* complex; species-level identification was not performed. A diagnosis of scrofuloderma was made. Scrofuloderma is a form of cutaneous tuberculosis that results from contiguous spread of infection from a deep structure — most commonly a cervical lymph node — into the overlying skin. Antituberculous therapy and wound care were initiated. Evaluation for concurrent pulmonary tuberculosis included chest CT, which showed bilateral pulmonary micronodules that remained stable on follow-up imaging, and bronchoscopy with bronchial sampling. The results of smear microscopy for acid-fast bacilli, nucleic acid amplification testing for *M. tuberculosis* complex, and mycobacterial cultures (Lowenstein-Jensen and Mycobacterial Growth Indicator Tube) were all negative. Six months after the initiation of treatment, the fistula had healed (Panel E).

Lydia Rabinowitsch Kempner

IMAGES IN CLINICAL MEDICINE

Acro-Osteolysis

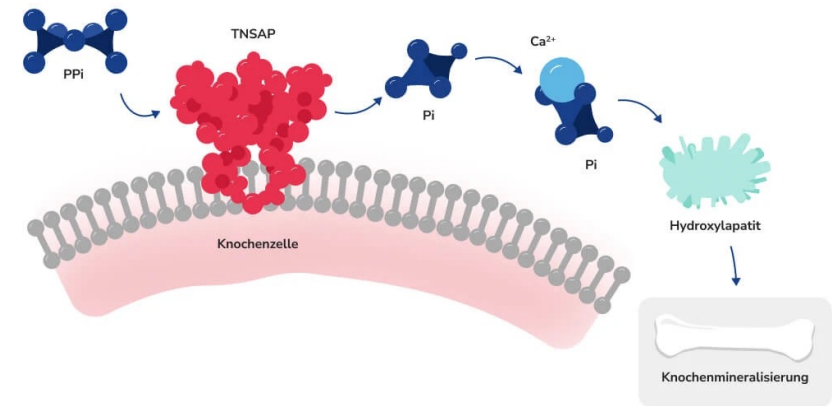


A 46-year-old man with chronic kidney disease presented to the internal medicine clinic with a 2-year history of painless shortening and rounding of the fingertips. Ten years earlier, he had received a diagnosis of chronic kidney disease due to obstructive nephropathy from nephrolithiasis. Since then, he had been intermittently lost to follow-up. On physical examination, all the fingertips were short, broad, and bulbous, with a pseudoclubbing appearance (Panel A). The toes had similar but less severe changes. Radiographs of the hands showed resorption of the terminal tufts of all the distal phalanges (Panel B). The patient was also found to have osteopenia, vascular calcification, chondrocalcinosis of the wrists, and osteolytic lesions in the distal ends of several metacarpals that were consistent with osteitis fibrosa cystica. Bone resorption of the distal phalanges of the hands or feet — known as acro-osteolysis — is associated with several conditions, including systemic sclerosis, Raynaud's phenomenon, exposure to vinyl chloride, and thermal injury. In this case, renal osteodystrophy and tertiary hyperparathyroidism in the context of end-stage kidney disease were identified as the etiologic factors. Owing to persistent hypercalcemia despite hemodialysis and medical management of hyperparathyroidism, total parathyroidectomy with autotransplantation was performed 3 months after presentation. At a postoperative follow-up visit 6 months after surgery, the patient's calcium and parathyroid hormone levels had normalized but the fingertips remained unchanged.

Die Alkalische Phosphatase (AP oder ALP) ist eine Gruppe von Enzymen, deren Hauptaufgabe darin besteht, Phosphatgruppen von verschiedenen Molekülen abzuspalten. Sie ist in einem leicht basischen (alkalischen) Milieu am aktivsten.

Die wichtigsten Funktionen im Körper

- **Knochenmineralisierung:** Die im Knochen gebildete AP fördert den Einbau von Calcium und Phosphat, was für den Aufbau und Erhalt gesunder Knochen und Zähne essenziell ist.
- **Stoffwechselsteuerung:** Das Enzym spaltet Phosphatgruppen ab und steuert dadurch zahlreiche biochemische Prozesse im Gewebe.
- **Leber- und Gallenfunktion:** In der Leber und den Gallengängen hilft die AP bei Stoffwechsel- und Transportprozessen.



Die alkalische Phosphatase (AP) ist ein Enzym, das in verschiedenen Geweben wie Knochen, Leber und Muskeln vorkommt. Besonders wichtig ist die vom *ALPL*-Gen kodierte gewebeunspezifische alkalische Phosphatase (TNSAP) für die Knochenmineralisierung.

Sie dephosphoryliert Substrate wie anorganisches Pyrophosphat (PPi), das im Prozess der Knochenmineralisierung essenziell ist, und Pyridoxalphosphat (PLP), das für die Synthese von Neurotransmittern wie Gamma-Aminobuttersäure (GABA) benötigt wird.

Break a Leg

A 46-year-old woman presented to her primary care physician with a 3-week history of **right forefoot pain**. The pain had **begun spontaneously**, worsened with weight bearing, and was not preceded by trauma. She reported no joint pain, fever, or other systemic symptoms. Her medical history included hypertension, which was being treated with losartan, and a cesarean section 25 years earlier. She said that she did not participate in high-impact exercise and that she worked as an office manager. On physical examination, the foot had no wounds, deformities, swelling, or erythema. Palpation over the fourth metatarsal and axial loading of the fourth toe reproduced the pain; mediolateral metatarsal compression did not. The ankle, foot, and toes had full, painless range of motion. Her gait was normal. Neurologic function, arterial pulses, and capillary refill were intact.

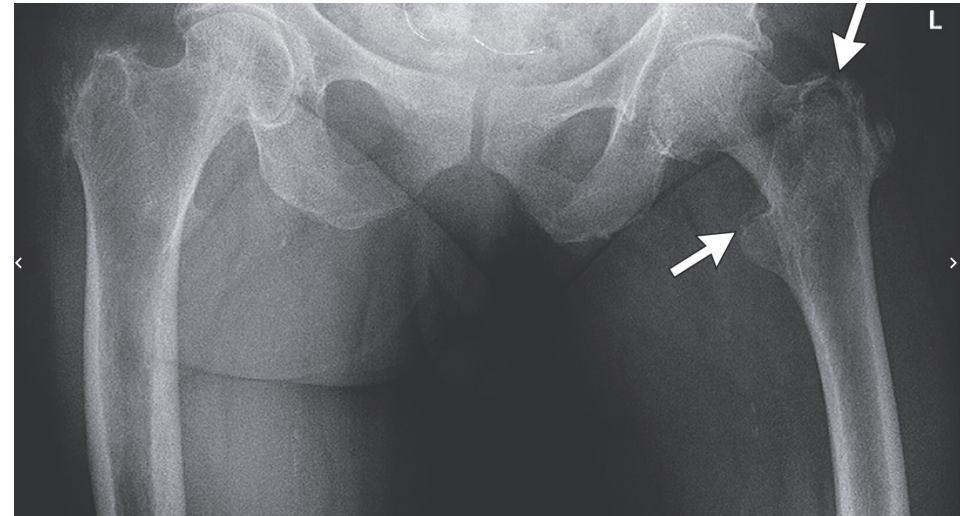
A plain radiograph of the right foot showed a fracture of the fourth metatarsal ([Figure 1](#)). The patient was referred to the emergency department and evaluated by an orthopedic surgeon. A short course of nonsteroidal antiinflammatory medication was prescribed, and supportive footwear, with weight bearing as tolerated, was recommended. A follow-up radiograph obtained 12 weeks later showed healing of the fracture. Dual-energy x-ray absorptiometry (DXA) showed a bone mineral density (BMD) of 1.086 g per square centimeter at the lumbar spine (T score, 0.4; z score, 0.9) and 0.785 g per square centimeter at the left total hip (T score, -1.3; z score, -0.9). Vertebral-fracture assessment showed no fractures. The patient was referred to a fracture liaison service.



At the fracture liaison service, the patient was evaluated by an endocrinologist. The patient reported no previous fractures or falls, was premenopausal, and said that she did not use medications or have medical conditions associated with bone loss. Her daily calcium intake was 1200 mg. She had stopped smoking 9 years earlier after a 25-pack-year history and did not drink alcohol. Her family history was unremarkable, without fractures or osteoporosis among first-degree relatives. Her height was 152 cm (unchanged from her maximum recorded adult height), and her body weight was 87 kg (body-mass index [BMI, the weight in kilograms divided by the square of the height in meters], 37.7).

Physical examination showed no facial plethora, dorsocervical fat pad, muscle wasting, bruising, or urticaria pigmentosa. Laboratory testing showed a serum creatinine level of 0.8 mg per deciliter (71 μ mol per liter; reference range, 0.5 to 1.0 mg per deciliter [44 to 88 μ mol per liter]), a calcium level of 9.2 mg per deciliter (2.30 mmol per liter; reference range, 8.4 to 10.2 mg per deciliter [2.10 to 2.55 mmol per liter]), an albumin level of 4.1 g per deciliter (reference range, 3.5 to 5.2), and a 25-hydroxyvitamin D level of 40 ng per milliliter (reference range, 20 to 60). The thyrotropin level and a complete blood count were normal. Oral ibandronate (at a monthly dose of 150 mg) was initiated, with a planned 5-year course and follow-up DXA. (No phosphate or alkaline phosphatase reported)

Four years after starting ibandronate, the patient presented to the emergency department after a fall from standing height, reporting pain in the left leg and an inability to stand. Physical examination revealed a shortened, externally rotated leg. Plain radiography revealed a pertrochanteric femoral fracture ([Figure 2](#)). The patient was reassessed by an endocrinologist. DXA, performed 2 months after the fracture, showed a decline in BMD, with a BMD of 0.824 g per square centimeter at the lumbar spine (T score, -2.0; z score, -1.1) and of 0.547 g per square centimeter at the right total hip (T score, -3.2; z score, -2.7). The patient reported adherence to ibandronate therapy and ongoing menses.



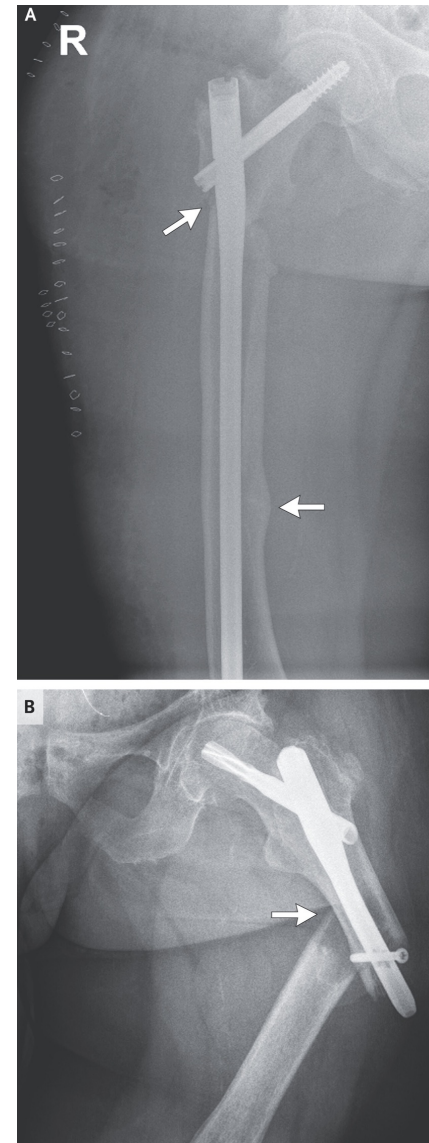
She was questioned about any new medical conditions and changes in her medications since her previous evaluation and reported having undergone laparoscopic gastric bypass surgery 3 years earlier (1 year after her initial evaluation by the fracture liaison service). She had subsequently lost 20 kg, with weight stabilization at 67 kg (BMI, 29) 2 years after the **bariatric surgery**. Since the surgery, she had been taking multivitamin supplementation, as well as pantoprazole for gastroesophageal reflux.

Repeat laboratory testing showed stable kidney function and normal levels of calcium, albumin, and 25-hydroxyvitamin D; a complete blood count was also normal. **The alkaline phosphatase level was 27 U per liter (reference range, 47 to 98),** and the 24-hour urinary calcium excretion was 2.3 mmol (reference range, 2.5 to 7.5). Levels of phosphate, γ -glutamyltransferase, sodium, potassium, magnesium, iron indexes, vitamin B₁₂, folate, zinc, parathyroid hormone, thyrotropin, and glycated hemoglobin and the lipid profile, erythrocyte sedimentation rate, protein electrophoresis, and celiac serologic tests were normal. Previous health care providers were contacted, but no historical values for alkaline phosphatase were available. **The low alkaline phosphatase level was attributed to bisphosphonate therapy,** and the fracture and decline in BMD were ascribed to bariatric surgery and pantoprazole use. Hypercortisolism was not evaluated. Oral ibandronate was replaced with annual intravenous administration of zoledronic acid (5 mg), and repeat DXA was planned in 2 years.

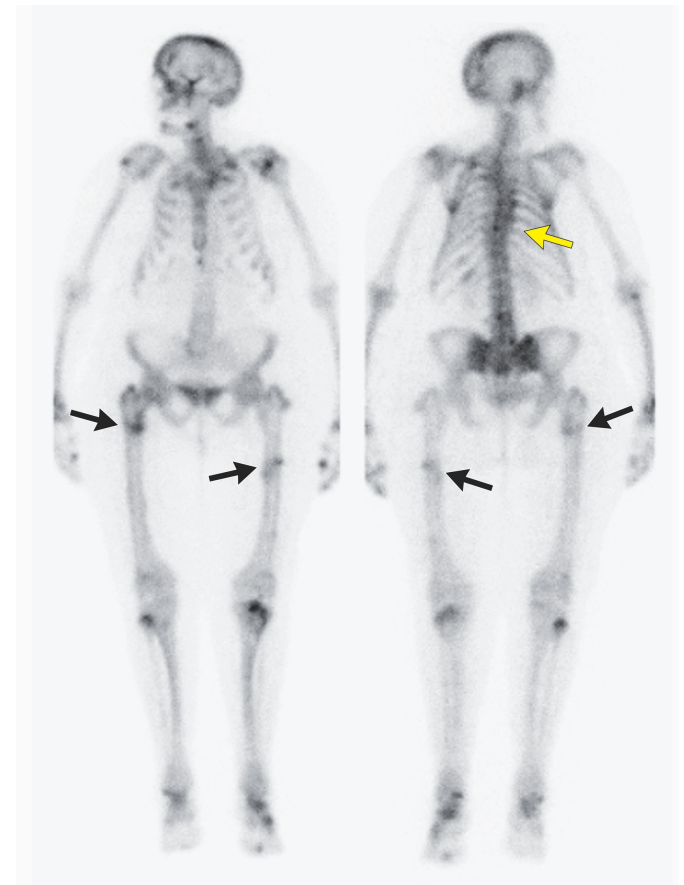
One year after initiating therapy with zoledronic acid, the patient presented to an orthopedic surgeon with right groin pain that had developed insidiously over a 2-month period. She reported no trauma or recent physical activity. Physical examination revealed tenderness over the greater trochanter and pain with axial loading of the femur. Neurologic examination was normal. Exhalation against a closed airway did not elicit groin swelling.

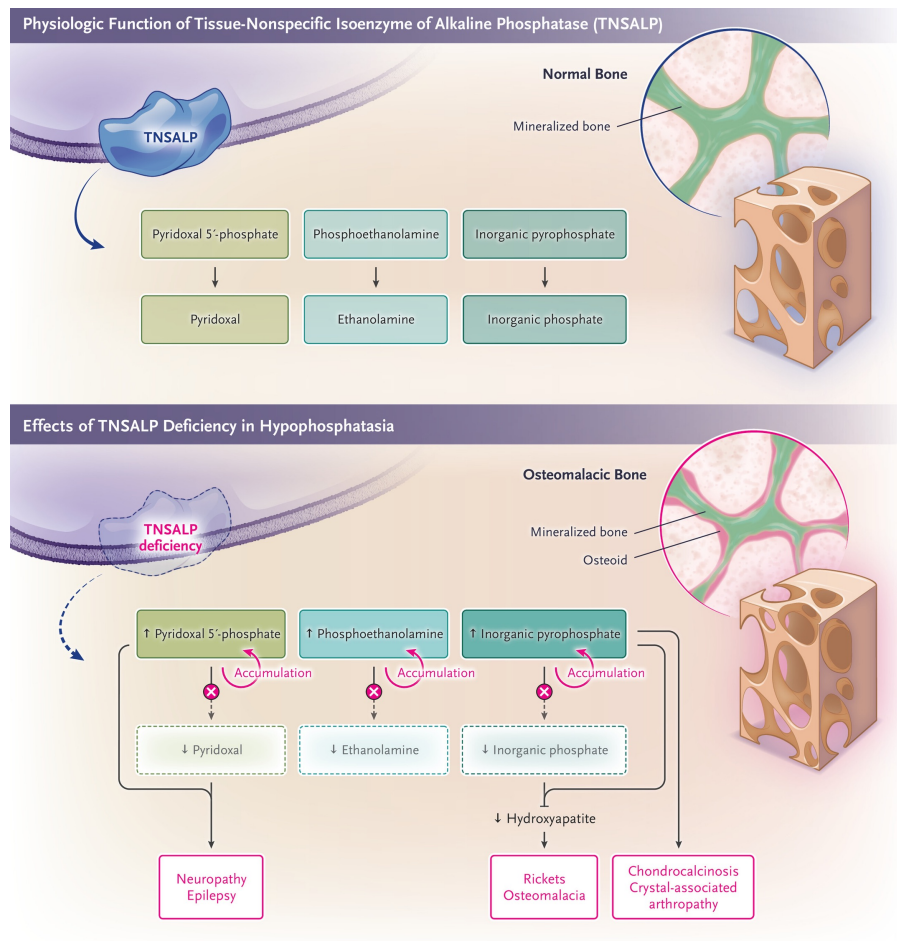
A plain radiograph of the right proximal femur and hip showed no abnormalities. MRI was scheduled. One week before the planned MRI, the patient felt a “crack” in her right leg, followed by a fall and severe pain, and was transported to the emergency department. Radiography revealed transverse and impending mid-diaphyseal femoral fractures. She underwent uneventful fixation with a long intramedullary nail ([Figure 3A](#)).

Four months after placement of the long intramedullary nail in the right femur, the patient sustained a periprosthetic fracture in the left femur after a fall from standing height ([Figure 3B](#)). The previously implanted proximal femoral nail was replaced with a long intramedullary nail, and she was referred to our metabolic bone disease center.



History taking revealed frequent dental caries without premature tooth loss, delayed ambulation until 2 years of age, and an adult height that was 20 cm shorter than that of her sister. The patient reported no history of chronic pain. Physical examination showed scoliosis without blue sclerae. Bone scintigraphy revealed diffuse skeletal uptake with reduced renal activity and **focal uptake at recent fracture sites** (Figure 4). Laboratory testing showed **a vitamin B₆ level of 80 ng per milliliter (480 nmol per liter; reference range, 6 to 18 ng per milliliter [35 to 110 nmol per liter])**, measured 1 week after temporary discontinuation of the multivitamin, and a **urinary phosphoethanolamine level of 76 mmol per mole of creatinine (reference value, <8)**. Sequencing of the gene *ALPL* identified a pathogenic variant, NM_000478.4(*ALPL*):c.526G→A (p.Ala176Thr), and a likely pathogenic variant, NM_000478.6(*ALPL*):c.379A→G (p.Thr127Ala) — findings that confirmed the diagnosis of **hypophosphatasia**, probably of childhood onset.





This case underscores the importance of measuring alkaline phosphatase. Low values may indicate hypophosphatasia — a disease in which antiresorptive therapy is contraindicated.

Physiologic Function of Tissue-Nonspecific Isoenzyme of Alkaline Phosphatase.

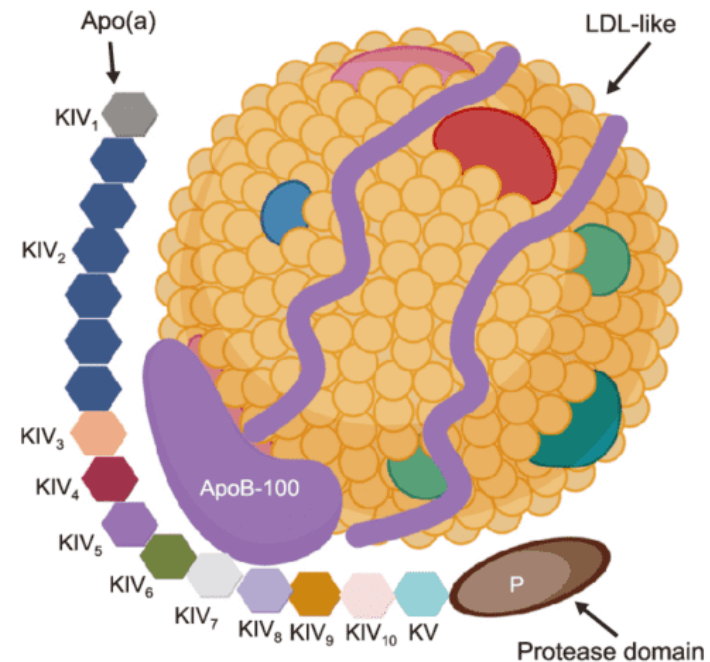
Alkaline phosphatase comprises four membrane-bound isoenzymes, three of which are tissue-specific and one of which — **tissue-nonspecific isoenzyme of alkaline phosphatase (TNSALP), encoded by *ALPL*** — is broadly expressed, predominantly in bone, the liver, the kidneys, and teeth. TNSALP hydrolyzes pyridoxal 5'-phosphate to pyridoxal, phosphoethanolamine to ethanolamine, and inorganic pyrophosphate to inorganic phosphate. In persons with hypophosphatasia, a hereditary form of rickets or osteomalacia caused by TNSALP deficiency, pyridoxal 5'-phosphate, phosphoethanolamine, and inorganic pyrophosphate accumulate. Excess inorganic pyrophosphate, together with locally reduced inorganic phosphate, inhibits hydroxyapatite formation and impairs skeletal and dental mineralization. Bisphosphonates (structural analogues of inorganic pyrophosphate) may further exacerbate this imbalance by impairing mineralization, suppressing bone turnover, and binding zinc and magnesium, which serve as TNSALP cofactors. Denosumab also suppresses bone turnover. Consequently, therapy with bisphosphonates (in particular) or denosumab is contraindicated in hypophosphatasia. Accumulation of inorganic pyrophosphate also promotes calcium pyrophosphate and calcium phosphate crystal deposition in articular and periarticular tissues, contributing to chondrocalcinosis and crystal-associated arthropathy. Accumulation of phosphoethanolamine has not been associated with specific clinical manifestations. In contrast, an elevated pyridoxal 5'-phosphate level, together with intracellular pyridoxal deficiency, may impair neurologic function and contribute to neuropathic pain and, in perinatal and infantile hypophosphatasia, to epilepsy. On the right, sections of normal and osteomalacic bone are shown. Osteomalacic bone is characterized by prominent osteoid, the unmineralized organic matrix of bone.

THE LANCET

Ein erhöhter Lipoprotein(a)-Wert (kurz **Lp(a)**) ist ein genetisch festgelegter Risikofaktor für Herz-Kreislauf-Erkrankungen wie Herzinfarkt, Schlaganfall oder Aortenklappenstenose.

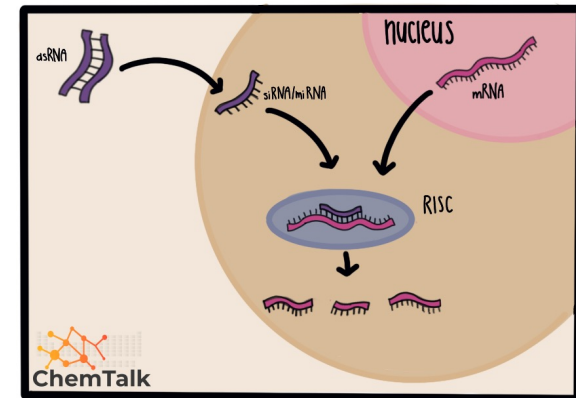
Was ist Lipoprotein(a)?

- Lp(a) ist ein spezielles Transportpartikel für Fette im Blut, das dem LDL-Cholesterin ähnelt.
- Es besitzt zusätzlich das Eiweiß **Apolipoprotein(a)**, welches Gefäßverkalkung (Arteriosklerose) und Entzündungen fördert sowie die Auflösung von Blutgerinnseln behindern kann.
- Der Wert wird zu rund 90 % **vererbt** und bleibt im Leben meist konstant. Etwa jeder Fünfte hat erhöhte Werte.



LDL attaches to LDL-R via
APO-B 100 and APOE

Small interfering RNAs (siRNAs), auch bekannt als kurze interferierende RNAs, sind eine Klasse von doppelsträngigen, nicht-codierenden RNA-Molekülen, die typischerweise eine Länge von 20 bis 25 Basenpaaren aufweisen. Sie spielen eine zentrale Rolle im Mechanismus der **RNA-Interferenz (RNAi)**, indem sie die Expression spezifischer Gene nach der Transkription gezielt abschalten (Post-transkriptionelles Gen-Silencing).



Der Prozess, durch den siRNAs die Genexpression hemmen, läuft in der Zelle in mehreren präzisen Schritten ab:

1. **Entstehung:** Lange doppelsträngige RNA (dsRNA), die entweder aus der Zelle selbst stammt, von Viren eingeschleust oder künstlich eingebracht wurde, wird durch das Enzym **Dicer** in kurze siRNA-Fragmente geschnitten.
2. **RISC-Bildung:** Die kurzen siRNA-Fragmente binden im Zytoplasma an Proteine (unter anderem aus der Argonaute-Familie), um den **RNA-induced silencing complex (RISC)** zu bilden.
3. **Auftrennung:** Der Doppelstrang der siRNA wird aufgetrennt. Der sogenannte *Passenger-Strang* wird abgebaut, während der komplementäre *Guide-Strang* im Komplex verbleibt.
4. **Ziel-Erkennung und Abbau:** Der Guide-Strang führt den RISC-Komplex mit perfekter Sequenzkomplementarität zu einer passenden **Boten-RNA (mRNA)**. Das Enzym Argonaute zerschneidet diese mRNA, was deren Abbau einleitet. Ohne die intakte mRNA kann das entsprechende Protein nicht mehr synthetisiert werden – das Gen ist "stillgelegt".

Die wichtigsten Fakten zu Kylo-11:

- **Wirkmechanismus:** Der Wirkstoff blockiert über RNA-Interferenz gezielt die Produktion von Apolipoprotein(a) in den Leberzellen. Dadurch kann der Körper kaum noch neues Lp(a) herstellen.
- **Enorme Senkung:** Daten aus der klinischen Phase-I-Studie (veröffentlicht im renommierten Fachmagazin *The Lancet* Ende August 2026) zeigten, dass eine einzige Injektion bei höheren Dosen die Lp(a)-Konzentration im Blut um **bis zu 97 %** reduzieren kann.
- **Mögliche Jahresspritze:** Das Besondere an Kylo-11 ist seine ungewöhnlich lange Verweildauer und Wirkung im Körper aufgrund einer speziellen molekularen Struktur (nicht-kanonische siRNA-Struktur mit vier GalNAc-Verbindungen). Die Wirkung hielt in Studien über 48 Wochen (fast ein ganzes Jahr) an. Forscher hoffen daher, dass künftig **eine einzige Injektion pro Jahr** ausreichen könnte.
- **Aktueller Status:** Das Medikament befindet sich derzeit in der klinischen **Phase-II-Studie**, in der die Wirksamkeit und Sicherheit an einer größeren Patientengruppe mit atherosklerotischen Herz-Kreislauf-Erkrankungen (ASCVD) in den USA und China untersucht wird.

Das Konstrukt bindet im Körper auf zwei verschiedenen Ebenen an spezifische Zielstrukturen:

1. **Auf Zellebene (Leber-Targeting):** Die angehängten GalNAc-Zuckerstrukturen binden gezielt an den **Asialoglycoprotein-Rezeptor (ASGPR)** auf der Oberfläche von **Leberzellen (Hepatozyten)**. Dies führt dazu, dass der Wirkstoff per Endozytose selektiv in die Leber aufgenommen wird, wo Lipoprotein(a) produziert wird.
2. **Auf genetischer Ebene (Wirkmechanismus):** Im Inneren der Leberzelle bindet die siRNA spezifisch an die **LPA-mRNA** (die Boten-RNA des LPA-Gens).

Safety and lipoprotein(a)-lowering effects of Kylo-11, a non-canonical, long-duration small interfering RNA targeting lipoprotein(a): a first-in-human, randomised, double-blind, placebo-controlled, phase 1 trial

Kylo siRNA
knocks
down
Lp(a)

Summary

Background Elevated lipoprotein(a) concentrations are associated with the development of atherosclerotic cardiovascular disease. The aim of this study was to evaluate the safety and lipoprotein(a)-lowering effects of Kylo-11, a very long-acting small interfering RNA that targets lipoprotein(a).

Methods This randomised, double-blind, placebo-controlled, phase 1 trial was performed in a single hospital-based site in China in adults aged 18–55 years with elevated lipoprotein(a) concentrations who were otherwise healthy. Participants were randomly assigned to receive a single, subcutaneous dose of Kylo-11 or placebo (8:2) across seven dosing cohorts. Kylo-11 recipients could enter conditional extension follow-up up to day 337, whereas placebo recipients were followed up to day 169. Participants with lipoprotein(a) concentrations of 75–200 nmol/L were enrolled into cohorts 1–6 (ie, doses of 9, 30, 75, 225, 450, and 600 mg). Participants with lipoprotein(a) concentrations of more than 200 nmol/L were enrolled into cohort 7 (225 mg). The randomisation schedule was generated by an unmasked statistician with no involvement in study conduct, efficacy or safety analyses, or blinded data analysis, and assigned to treatment groups by an interactive web response system. Participants, investigators, and study personnel were masked to cohort assignment. The primary endpoint was the incidence of investigator-assessed adverse events within 24 weeks. All randomly assigned participants who received a dose of investigational product were included in the safety analysis set. All randomly assigned participants who received a dose of Kylo-11 and had at least one pharmacodynamic datapoint were included in the pharmacodynamic analysis set. Missing data were not imputed. The trial was registered on ClinicalTrials.gov (NCT06363851) and is now complete.

Findings Between May 30, 2024, and Dec 30, 2024, 71 participants were randomly assigned to the Kylo-11 cohorts (n=57) or the placebo cohort (n=14) and 70 participants received a dose. The median age of participants was 27·5 years (IQR 22·0–32·0), and 46 (65%) participants were male and 25 (35%) were female. Participants were followed up for a median of 337 days (IQR 334–337). 37 (53%) of 70 participants had adverse events up to 24 weeks, the majority of which were grade 1–2 and deemed unrelated to the study drug by the investigators. There were no injection-site reactions, no serious adverse events, no drug-related adverse events, and no deaths. Two grade 3 or higher events (ie, transient hypertriglyceridaemia at day 168 and elevated creatine phosphokinase at day 168) in the 225 mg cohort were adjudicated as unrelated to the study drug; one grade 3 or higher event (transient hypertriglyceridaemia) occurred in the placebo group at day 84. The prespecified pharmacodynamic secondary endpoints of median percent and absolute reductions in serum lipoprotein(a) over time at the final follow-up timepoint of 48 weeks for the Kylo-11 groups ranged from –53% (IQR –71 to –41) and –71 nmol/L (–79 to –60) in the 9 mg cohort to –97% (–98 to –97) and –129 nmol/L (–153 to –99) in the 600 mg cohort. In cohort 7 (225 mg; baseline lipoprotein(a) >200 nmol/L), the median reductions were –96% (–98 to –91) and –208 nmol/L (–222 to –198).

Interpretation A single dose of Kylo-11 was well tolerated, and at doses of 225 mg or higher, durably reduced serum lipoprotein(a) concentrations up to 48 weeks.

Funding Kylonova Biopharma.

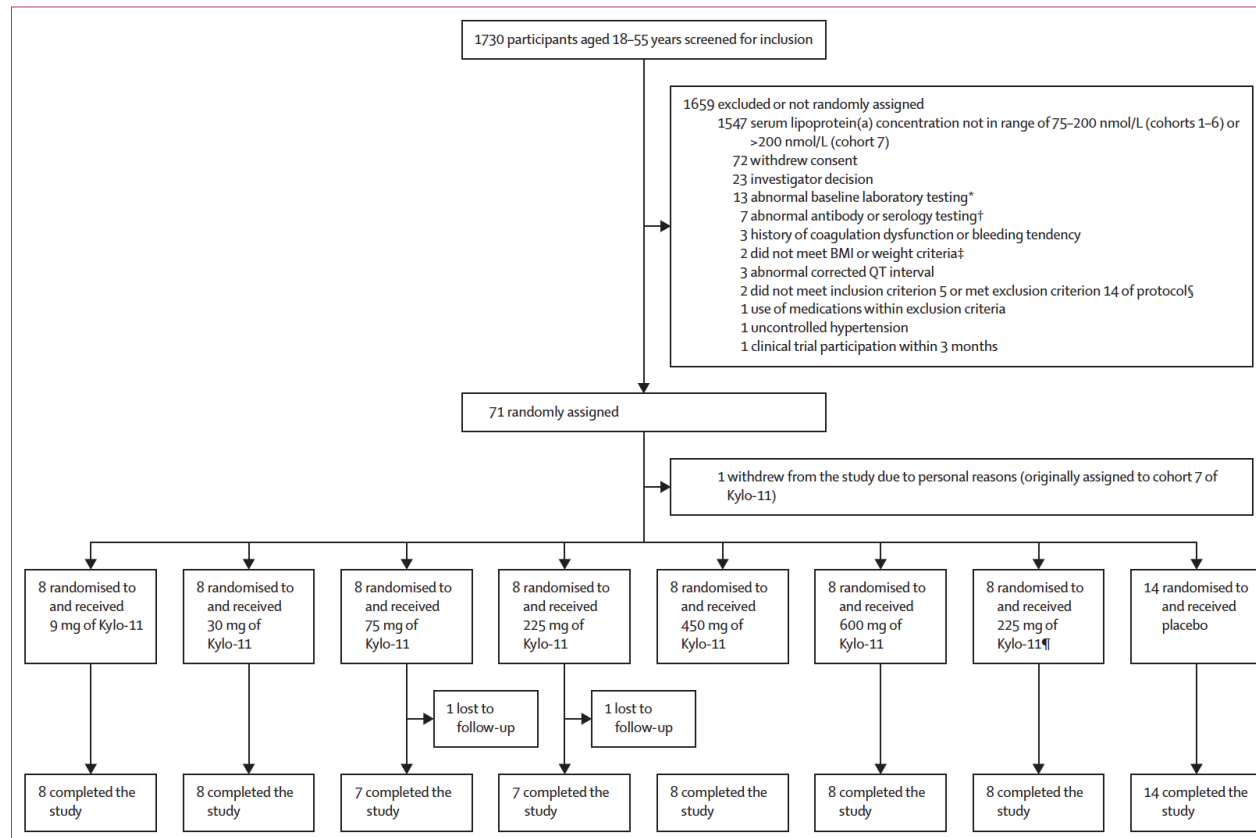


Figure 1: CONSORT diagram

Reasons for exclusion or screening failure were not mutually exclusive. *Participants with any of the following laboratory abnormalities: international normalised ratio $>1.5 \times$ upper limit of normal; cardiac troponin I concentration above the upper limit of normal; estimated glomerular filtration rate <90 mL/min per 1.73 m² (calculated according to the Chronic Kidney Disease Epidemiology Collaboration formula) or serum creatinine concentration above the upper limit of normal, considered clinically significant by the investigator; aspartate aminotransferase $>1.5 \times$ upper limit of normal; alanine aminotransferase $>1.5 \times$ upper limit of normal; creatine kinase $>2.5 \times$ upper limit of normal. †Positive result for any of the following: hepatitis B surface antigen, hepatitis C virus antibody, HIV antibody, or treponema pallidum-specific antibody. ‡BMI within 19.0–30.0 kg/m² (inclusive); weight ≥ 50 kg for male participants and ≥ 45 kg for female participants. §Inclusion criterion 5: female participants (except those who have undergone surgical sterilisation, hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) must be negative for blood pregnancy test at screening and before the dosing; women of childbearing potential must agree not to attempt pregnancy, not to donate eggs, and must use an effective contraceptive method throughout the study period. Exclusion criterion 14: pregnant or lactating women, or female participants who have had unprotected sexual intercourse within 14 days before screening. ¶Cohort 7 (dose 225 mg) enrolled participants with baseline lipoprotein(a) concentrations >200 nmol/L.

	Cohort 1, 9 mg Kylo-11 (n=8)	Cohort 2, 30 mg Kylo-11 (n=8)	Cohort 3, 75 mg Kylo-11 (n=8)	Cohort 4,* 225 mg Kylo-11 (n=8)	Cohort 5, 450 mg Kylo-11 (n=8)	Cohort 6, 600 mg Kylo-11 (n=8)	Cohort 7,* 225 mg Kylo-11 (n=8)	Placebo (n=14)
Age, years	33.0 (27.5–39.5)	27.5 (24.0–32.0)	22.0 (19.5–27.0)	28.0 (23.0–36.5)	30.0 (25.0–31.0)	28.0 (23.0–33.5)	27.5 (21.0–35.5)	27.0 (22.0–32.0)
Sex								
Male	3 (38%)	4 (50%)	6 (75%)	4 (50%)	6 (75%)	6 (75%)	6 (75%)	10 (71%)
Female	5 (62%)	4 (50%)	2 (25%)	4 (50%)	2 (25%)	2 (25%)	2 (25%)	4 (29%)
BMI, kg/m ²	25.5 (23.9–25.9)	24.7 (21.8–25.4)	23.9 (21.4–25.8)	21.7 (20.3–24.4)	25.1 (23.9–27.5)	24.4 (20.6–26.4)	24.5 (23.2–26.1)	24.5 (21.5–26.2)
Chinese ethnicity	8 (100%)	8 (100%)	8 (100%)	8 (100%)	8 (100%)	8 (100%)	8 (100%)	14 (100%)
Family history of atherosclerotic cardiovascular disease	0	0	0	0	0	0	0	1 (7%)
History of tobacco use	0	0	1 (13%)	0	0	1 (13%)	0	1 (7%)
Cholesterol, mmol/L								
Total cholesterol	4.46 (0.61)	4.59 (0.97)	4.36 (0.97)	4.56 (1.08)	4.70 (0.70)	4.13 (0.77)	4.70 (0.39)	4.64 (0.83)
HDL cholesterol	1.25 (0.25)	1.21 (0.42)	1.21 (0.26)	1.27 (0.18)	1.16 (0.11)	1.39 (0.37)	1.21 (0.19)	1.23 (0.27)
LDL cholesterol	2.70 (0.56)	2.74 (0.80)	2.69 (0.81)	2.66 (0.90)	3.22 (0.53)	2.45 (0.50)	3.06 (0.38)	3.01 (0.79)
Non-HDL cholesterol	3.21 (0.83)	3.38 (0.97)	3.15 (0.91)	3.29 (1.18)	3.54 (0.65)	2.73 (0.51)	3.49 (0.46)	3.41 (0.83)
Very-LDL cholesterol	0.71 (0.29)	0.81 (0.40)	0.73 (0.29)	0.78 (0.66)	0.53 (0.14)	0.69 (0.40)	0.70 (0.34)	0.70 (0.28)
Triglycerides, mmol/L	1.56 (1.0–2.1)	1.91 (0.9–2.4)	1.35 (1.2–2.0)	1.20 (0.9–1.8)	1.17 (0.9–1.4)	1.23 (1.0–1.7)	1.33 (1.0–1.8)	1.37 (1.2–1.9)
Lipoprotein(a), nmol/L	134.5 (99.9–168.0)	122.7 (76.3–143.6)	103.7 (72.5–129.5)	118.7 (100.8–154.4)	123.8 (111.8–163.1)	134.4 (100.9–155.7)	217.7 (211.2–229.7)	123.3 (104.3–157.3)
Apolipoprotein A1, g/L	1.34 (0.16)	1.24 (0.24)	1.30 (0.20)	1.39 (0.17)	1.25 (0.10)	1.41 (0.40)	1.31 (0.13)	1.28 (0.15)
Apolipoprotein B, g/L	0.89 (0.20)	0.87 (0.27)	0.87 (0.23)	0.86 (0.28)	0.91 (0.15)	0.77 (0.10)	0.92 (0.12)	0.92 (0.21)

Data are n (%), mean (SD), or median (IQR). To convert cholesterol values to mg/dL, multiply by 38.67. To convert triglyceride values to mg/dL, multiply by 88.57. *Those in cohort 4 receiving a Kylo-11 dose of 225 mg were enrolled with a baseline lipoprotein(a) concentration of 75–200 nmol/L, whereas those in cohort 7 were enrolled with a baseline lipoprotein(a) concentration greater than 200 nmol/L.

	Cohort 1, 9 mg Kylo-11 (n=8)	Cohort 2, 30 mg Kylo-11 (n=8)	Cohort 3, 75 mg Kylo-11 (n=8)	Cohort 4, 225 mg Kylo-11 (n=8)	Cohort 5, 450 mg Kylo-11 (n=8)	Cohort 6, 600 mg Kylo-11 (n=8)	Cohort 7,* 225 mg Kylo-11 (n=8)	Placebo (n=14)
Serious adverse events	0	0	0	0	0	0	0	0
Any treatment-emergent adverse event	4 (50%)	5 (63%)	4 (50%)	7 (88%)	6 (75%)	2 (25%)	2 (25%)	7 (50%)
Grade 1†	4 (50%)	5 (63%)	4 (50%)	5 (63%)	5 (63%)	2 (25%)	1 (13%)	7 (50%)
Grade 2‡	0	3 (38%)	1 (13%)	4 (50%)	2 (25%)	1 (13%)	2 (25%)	3 (21%)
Grade ≥3‡	0	0	0	2 (25%)	0	0	0	1 (7%)
Injection-site reactions	0	0	0	0	0	0	0	0
Treatment-emergent adverse events related to study drug	0	0	0	0	0	0	0	0
Treatment-emergent adverse events resulting in dose interruption or discontinuation	0	0	0	0	0	0	0	0
Treatment-emergent adverse events resulting in withdrawal from study	0	0	0	0	0	0	0	0
Treatment-emergent adverse events resulting in death	0	0	0	0	0	0	0	0
Most common treatment-emergent adverse events								
Increased alanine aminotransferase	0	3 (38%)	0	0	1 (13%)	0	0	1 (7%)
Increased alanine aminotransferase greater than 3 times the upper limit of normal§	0	0	0	0	0	1 (13%)	0	0
Increased alanine aminotransferase and bilirubin¶	0	1 (13%)	0	0	0	0	0	0
Increased white blood cell count	0	1 (13%)	0	1 (13%)	1 (13%)	1 (13%)	0	1 (7%)
Increased uric acid	3 (38%)	0	0	0	0	0	0	1 (7%)
Increased bilirubin	0	1 (13%)	0	1 (13%)	0	1 (13%)	1 (13%)	0
Increased triglycerides	0	0	1 (13%)	1 (13%)	0	0	0	3 (21%)
Increased creatine phosphokinase	0	0	0	1 (13%)	1 (13%)	0	0	0
Abnormal T-wave on electrocardiogram	0	0	1 (13%)	0	1 (13%)	0	0	0

* Cohort 7 were enrolled with a baseline lipoprotein(a) concentration greater than 200 nmol/L. All other cohorts were enrolled with baseline lipoprotein(a) concentration of 75–200 nmol/L. †Severity was assessed according to the Common Terminology Criteria for Adverse Events version 5.0.³² Increases in laboratory values were investigator-reported according to local standards and subsequently graded according to Common Terminology Criteria for Adverse Events version 5.0. The rows indicate the number of participants with at least one event of that grade. ‡Two grade ≥3 events (transient hypertriglyceridaemia at day 168, elevated creatine phosphokinase at day 168) occurred in the 225 mg cohort; one grade 3 event (transient hypertriglyceridaemia) occurred in the placebo group at day 84. These events were not related to Kylo-11 or placebo as judged by the investigator. The events of increased triglycerides were judged as being related to a high-fat diet. The event of increased creatine phosphokinase was judged as being related to strenuous exercise. §One participant in the 600 mg dosing group had alanine transaminase elevation greater than 3 times the upper limit of normal, which was observed at day 141, and subsequently decreased to less than 3 times the upper limit of normal by day 149. ¶One participant in the 30 mg Kylo-11 dosing group had elevations in both alanine aminotransferase (on day 15, less than 3 times the upper limit of normal) and total bilirubin (on day 85, less than twice the upper limit of normal). These adverse events of alanine aminotransferase and total bilirubin elevations were separated by approximately 2 months, occurring within the 24 weeks of dosing.

Table 2: Investigator-determined adverse events within 24 weeks of Kylo-11 dosing (primary endpoint)

	Cohort 1, 9 mg Kylo-11 (n=8)	Cohort 2, 30 mg Kylo-11 (n=8)	Cohort 3, 75 mg Kylo-11 (n=8)	Cohort 4, 225 mg Kylo-11 (n=8)	Cohort 5, 450 mg Kylo-11 (n=8)	Cohort 6, 600 mg Kylo-11 (n=8)	Cohort 7,* 225 mg Kylo-11 (n=8)	Placebo (n=14)
Median baseline (IQR); n, nmol/L	134.5 (99.9 to 168.0); 8	122.7 (76.3 to 143.6); 8	103.7 (72.5 to 129.5); 8	118.7 (100.8 to 154.4); 8	123.8 (111.8 to 163.1); 8	134.4 (100.9 to 155.7); 8	217.7 (211.2 to 229.7); 8	123.3 (104.3 to 157.3); 14
Median end of study (IQR); n, nmol/L	55.2 (36.2 to 96.6); 8	27.2 (11.4 to 43.9); 8	12.8 (3.3 to 24.4); 7	7.8 (2.8 to 10.7); 7	5.7 (1.6 to 7.6); 8	3.2 (2.4 to 5.2); 8	10.5 (3.7 to 18.1); 8	129.9 (116.1 to 176.4); 14
Median absolute change from baseline (IQR); n, nmol/L	-70.9 (-78.9 to -59.8); 8	-84.2 (-101.6 to -67.1); 8	-103.0 (-117.6 to -72.1); 7	-108.6 (-136.9 to -77.7); 7	-120.9 (-155.6 to -110.3); 8	-129.1 (-153.1 to -98.8); 8	-207.7 (-222.4 to -197.6); 8	9.9 (3.5 to 14.9); 14
Median percent change from baseline (IQR); n	-53.2% (-71.4 to -40.7); 8	-77.6% (-87.0 to -68.6); 8	-89.3% (-95.6 to -86.3); 7	-94.6% (-97.5 to -88.0); 7	-96.3% (-98.7 to -95.3); 8	-97.0% (-98.3 to -96.7); 8	-95.6% (-98.2 to -91.3); 8	6.6% (2.8 to 13.7); 14
Number of participants with lipoprotein(a) below lower limit of quantitation	0	0	0	0	2	1	0	0

Observed day 337 values were used to calculate the absolute and percent change from baseline for all the active Kylo-11 dose groups. Day 169 was used to calculate the absolute and percent change from baseline in the placebo group. No missing data were imputed. *Cohort 7 enrolled participants with baseline lipoprotein(a) concentration of >200 nmol/L.

Table 3: Serum lipoprotein(a) concentrations from baseline to end of study (48 weeks for Kylo-11 and 24 weeks for placebo) by dose group (prespecified secondary pharmacodynamic endpoint)

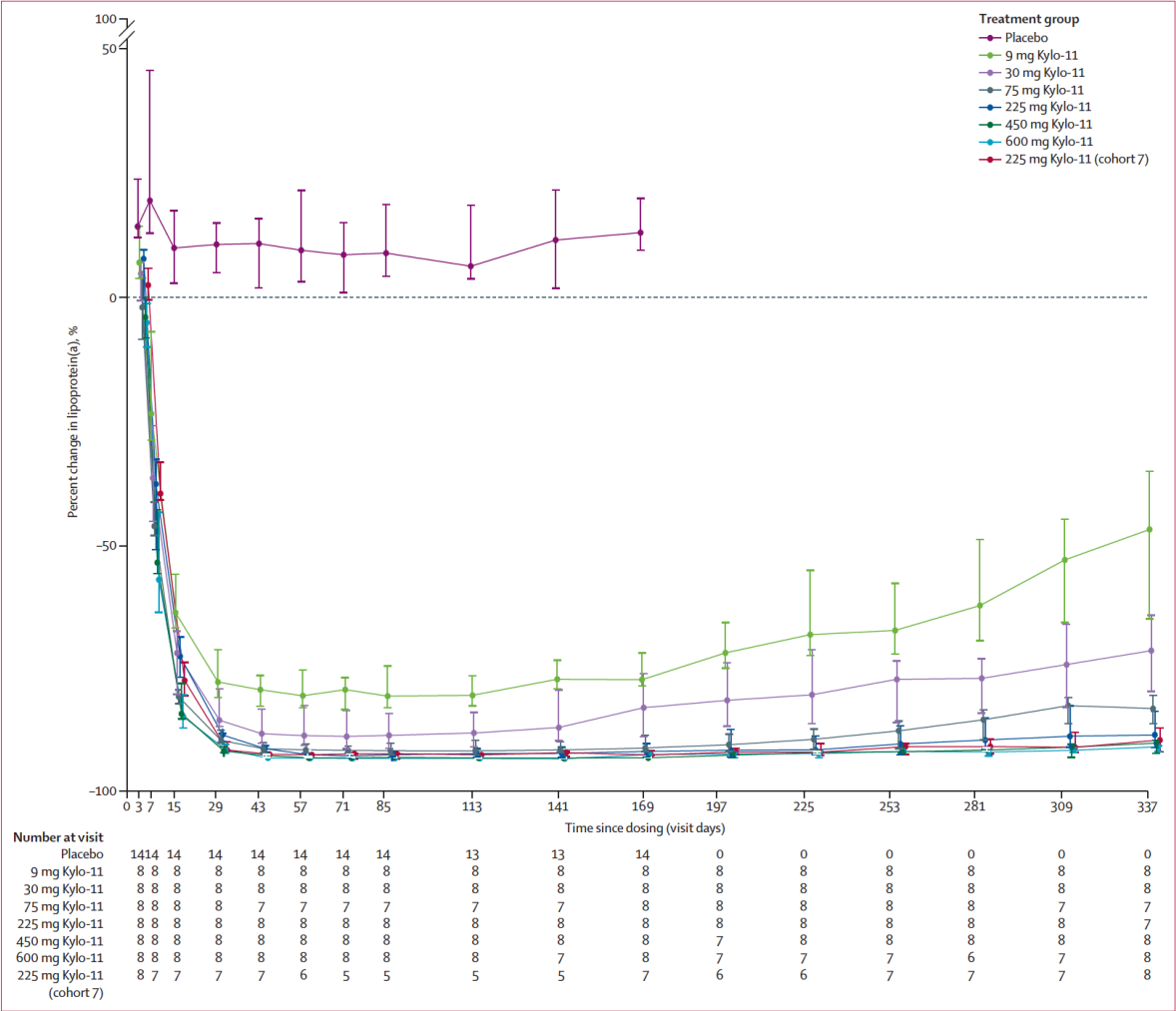


Figure 2: Median percent change in serum lipoprotein(a) concentrations over time from baseline to day 337 (48 weeks) in each Kylo-11 dosing group and placebo
Cohorts 1-6 enrolled participants with baseline lipoprotein(a) concentrations of 75-200 nmol/L, and cohort 7 (dose 225 mg) enrolled participants with baseline lipoprotein(a) concentration >200 nmol/L. The error bars show the IQR.

Research in context

Evidence before this study

On July 28, 2026, we searched PubMed for all articles published from database inception to July 28, 2026, with the search terms: ("lipoprotein(a)" OR "lipoprotein a" OR "Lp(a)" OR "apolipoprotein(a)" OR "apo(a)" OR "LPA") AND ("small interfering RNA" OR "siRNA" OR "RNA interference" OR "RNAi" OR "antisense oligonucleotide*" OR "antisense" OR "ASO") OR ("pelacarsen" OR "TQJ230" OR "AKCEA-APO(a)-LRx" OR "IONIS-APO(a)-LRx" OR "IONIS-APO(a)Rx" OR "olpasiran" OR "AMG890" OR "lepodisiran" OR "LY3819469" OR "zerlasiran" OR "SLN360") AND ("randomi*" OR "RCT" OR "trial" OR "placebo" OR "phase"). We included clinical trials or meta-analyses and restricted the search to studies published in English and those done in humans. 48 studies resulted from the search. The available evidence shows that the RNA interference therapies that have been studied in clinical trials for lipoprotein(a) reduction include pelacarsen (an antisense oligonucleotide), and lepodisiran, olpasiran, and zerlasiran (small interfering RNA therapies). Of these, pelacarsen, lepodisiran, and olpasiran are in ongoing phase 3 outcome studies. Although approximately one-fifth of the global population is estimated to have elevated lipoprotein(a) concentrations, an independent therapy for lipoprotein(a) lowering has not yet been approved by regulatory authorities.

Added value of this study

This study showed that a single subcutaneous dose of Kylo-11 ranging from 9 mg to 600 mg was well tolerated in otherwise healthy adults. Among participants with available data during extension follow-up, reductions in serum lipoprotein(a) concentrations persisted up to day 337 (48 weeks), with numerically greater reductions at doses of 225 mg or higher than at lower doses. There were no injection-site reactions, serious adverse events, or deaths in any treatment group. To our knowledge, this is the first in-human study reporting the safety, tolerability, and durable lipoprotein(a)-lowering effects of Kylo-11, a non-canonical small interfering RNA therapy, and it provides initial evidence of its safety, tolerability, and durable lipoprotein(a)-lowering effects.

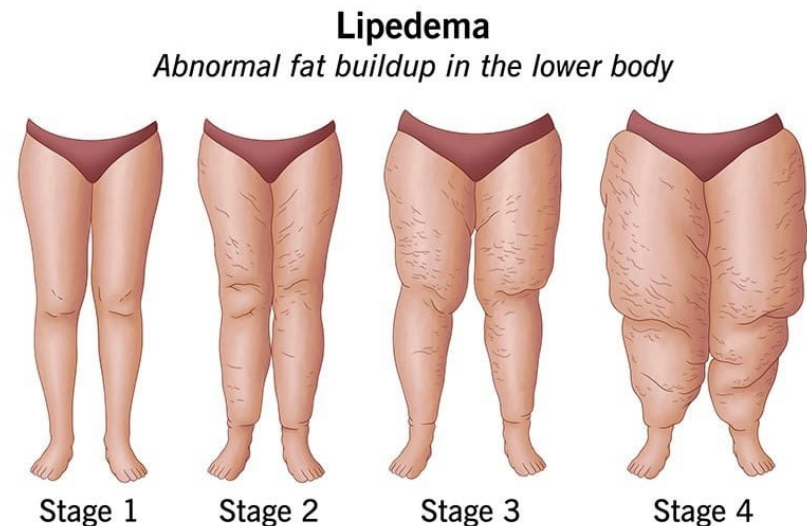
Implications of all the available evidence

Elevated serum lipoprotein(a) is a causal risk factor for atherosclerotic cardiovascular disease and aortic stenosis. No treatment has yet been shown in a dedicated cardiovascular outcomes trial to reduce atherosclerotic cardiovascular events by specifically lowering lipoprotein(a). This study supports future phase 2 and phase 3 trials to evaluate the safety, efficacy, and appropriate dosing interval of Kylo-11.

Ein Lipödem ist eine chronische Fettverteilungsstörung, die fast ausschließlich Frauen betrifft und zu symmetrischen Schwellungen sowie Schmerzen an den Beinen und oft auch an den Armen führt.

Symptome und Merkmale

- **Symmetrische Fettvermehrung:** Betroffen sind vor allem Hüften, Gesäß, Oberschenkel, Unterschenkel oder Arme, während Hände und Füße ausgespart bleiben.
- **Schmerzen und Druckempfindlichkeit:** Die betroffenen Bereiche schmerzen bei Druck, zudem spüren Betroffene oft ein Spannungs- oder Schweregefühl, das sich im Tagesverlauf verschlimmert.
- **Blaue Flecken:** Es besteht eine starke Neigung zu Blutergüssen nach leichten Berührungen.
- **Kein Ansprechen auf Diäten:** Das krankhafte Fettgewebe lässt sich durch übliche Abnehmversuche oder Sport nicht einfach reduzieren.



Liposuction versus conservative therapy for patients with lipoedema in Germany: a multicentre, randomised controlled clinical trial

Summary

Background Lipoedema is a painful, chronic disease of the subcutaneous adipose tissue, predominantly affecting women. Conservative complex decongestive therapy is the standard of care but offers limited symptom relief. Liposuction appears to be a promising approach but lacks evidence of effectiveness and safety. The aim of this trial was to show superiority of liposuction compared with conservative therapy regarding relevant pain reduction with reasonable safety.

Methods In this multicentre, randomised controlled trial at 11 German centres, eligible women with stage I, II, or III lipoedema and leg pain of at least 4 points on a 0–10 numeric rating scale received conservative therapy for up to 7 months and then were randomly assigned to liposuction or conservative therapy (2:1) stratified by lipoedema stage and study site. For all visits involving an assessment, patches were applied to the legs of all patients, and patients were instructed not to reveal the treatment they had received, in order to mask the assessor. The primary endpoint was reduction of patient-reported leg pain by at least 2 points after 12 months, and missing assessment was considered non-successful. The primary outcome was analysed in the intention-to-treat population which included all randomly assigned patients, and safety analysis included all enrolled patients. A long-term follow-up of 36 months is ongoing. This study is registered at ClinicalTrials.gov, NCT04272827.

Findings Of 1973 patients screened between Jan 19, 2021, and June 7, 2022, 453 were enrolled, and 410 were randomly assigned to the liposuction group (n=278) or to the conservative therapy group (n=132). All 410 patients were included in the intention-to-treat analysis (mean age 42.9 [SD 10.6]; ethnicity data were not collected). After 12 months, 190 (68%) of 278 randomly assigned patients undergoing liposuction achieved the primary endpoint of pain reduction versus ten (8%) of 132 randomly assigned to conservative therapy (odds ratio 26.2 [95% CI 13.1–52.5]; $p<0.0001$). Adverse events occurred in 124 (47%) of 265 patients undergoing liposuction, and 20 (8%) of 265 were rated as serious. In the conservative therapy group, 30 (21%) of 145 patients reported adverse events, and five (3%) 145 were rated as serious. Secondary endpoints regarding quality of life showed greater improvement in the liposuction group.

Interpretation Liposuction was superior to conservative therapy in reducing leg pain and improving quality of life in patients with lipoedema, but was associated with a higher rate of serious adverse events. Liposuction has the potential to be a promising treatment option for patients with lipoedema.

Funding The Federal Joint Committee, Germany.

Lipoedema
improved by
liposuction.

Now approved by
3rd-party payers.

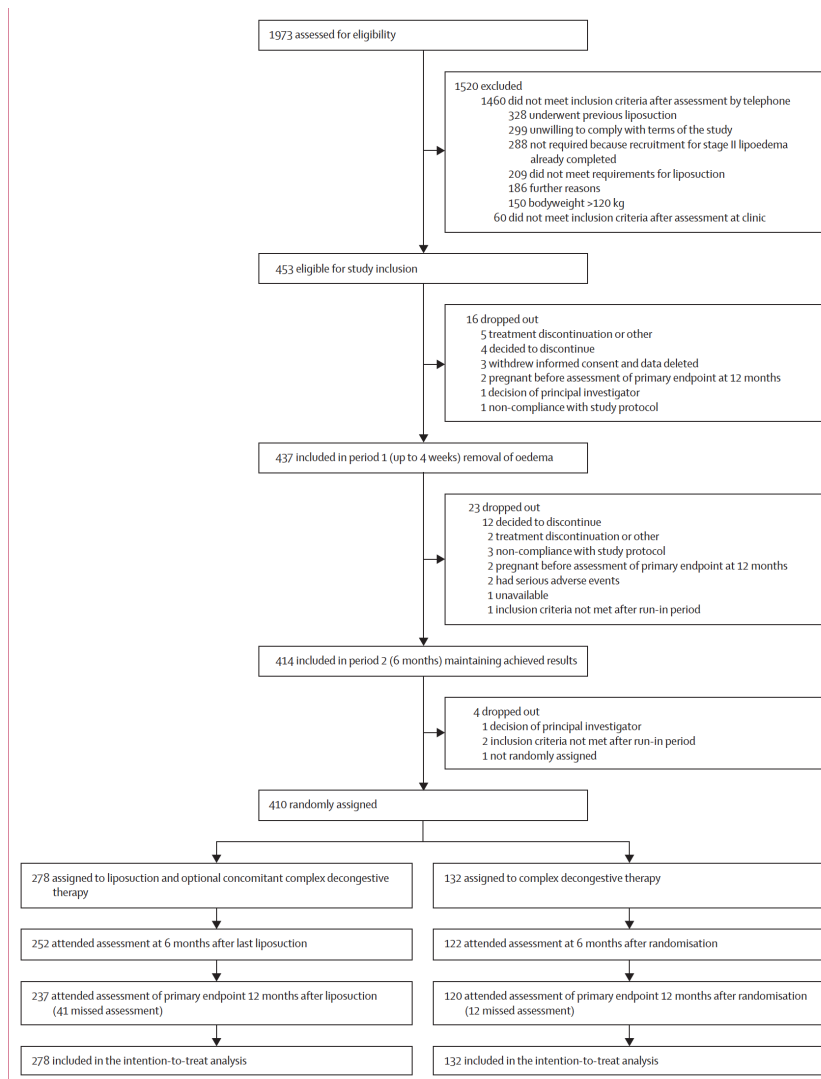
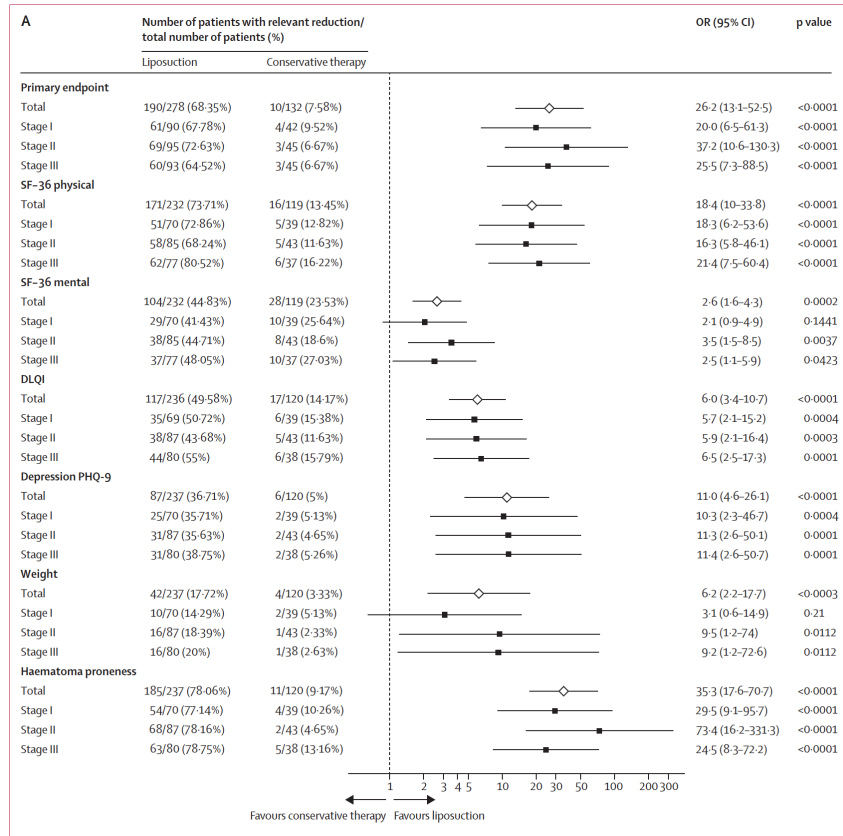


Figure 1: Trial profile
After the 12-month visit, the conservative therapy group was offered liposuction. Both groups will be followed up until 36 months. The final analysis will be performed after the study is completed.

	Liposuction (n=278)	Conservative therapy (n=132)
Demographics		
Age, years*	43 (10.5)	43 (10.8)
Height, cm	167.0 (5.9)	166.6 (6.5)
Bodyweight, kg	89.5 (17.1)	91.2 (16.7)
Body fat (%)	43.7 (9.6)	45.0 (8.4)
BMI (kg/m ²)	32.1 (6.1)	32.9 (5.9)
Waist circumference, cm	95.6 (13.5)	96.6 (11.7)
Hip circumference, cm	115.8 (13.4)	117.2 (11.8)
Waist-to-hip ratio	0.83 (0.08)	0.83 (0.07)
Waist-to-height ratio	0.57 (0.08)	0.58 (0.07)
Lipodema stage		
Stage I	90 (32%)	42 (32%)
Stage II	95 (34%)	45 (34%)
Stage III	93 (34%)	45 (34%)
Patient-reported outcomes and other outcomes		
Average leg pain intensity	6.2 (1.6)	6.3 (1.6)
PHQ-9 depression	8.9 (5.4)	8.3 (5.0)
SF-36 mental health component	40.7 (14.0)	42.6 (14.1)
SF-36 physical health component	37.4 (8.8)	37.7 (9.0)
DLQI	9.2 (7.7)	9.1 (7.4)
WHOQOL-BREF, G1 rating quality of life	56.1 (20.2)	60 (20.2)
WHOQOL-BREF, G4 content with quality of life	36 (20.7)	40.5 (22.8)
WHOQOL-BREF, D1 physical health	52.6 (17.9)	55.4 (19.2)
WHOQOL-BREF, D2 mental health	54.9 (18.3)	57.4 (18.3)
WHOQOL-BREF, D3 social relationships	67 (18.4)	67.6 (20.4)
WHOQOL-BREF, D4 environment	71.5 (14.1)	74 (15.7)
General impairment (legs)	7.4 (1.7)	7.5 (1.4)
Haematoma proneness (legs)	8.2 (2.2)	8.5 (2.0)
Movement restrictions (Lower Extremity Functional Scale, sum)	48.6 (17.3)	48.5 (17.3)
Number of oedemas	0.5 (1.5)	0.5 (1.3)

Data are n (%), median (IQR), or mean (SD), collected at randomisation. Body measurements were missing in less than 2% of cases. Lipodema stage I is defined as soft, homogeneous increase of subcutaneous adipose tissue, stage II as increased volume with nodular subcutaneous adipose tissue and uneven skin surface, and stage III is characterised by large nodules, tender, hanging flaps of adipose tissue and skin, especially on the thighs and knees.¹ PHQ=Patient Health Questionnaire. SF-36=36-Item Short Form Health Survey. DLQI=Dermatology Life Quality Index. WHOQOL-BREF=World Health Organization Quality of Life–Brief Version. * Age on day of consent.

Table 1: Patient characteristics in the intention-to-treat population



(Figure 2 continues on next page)

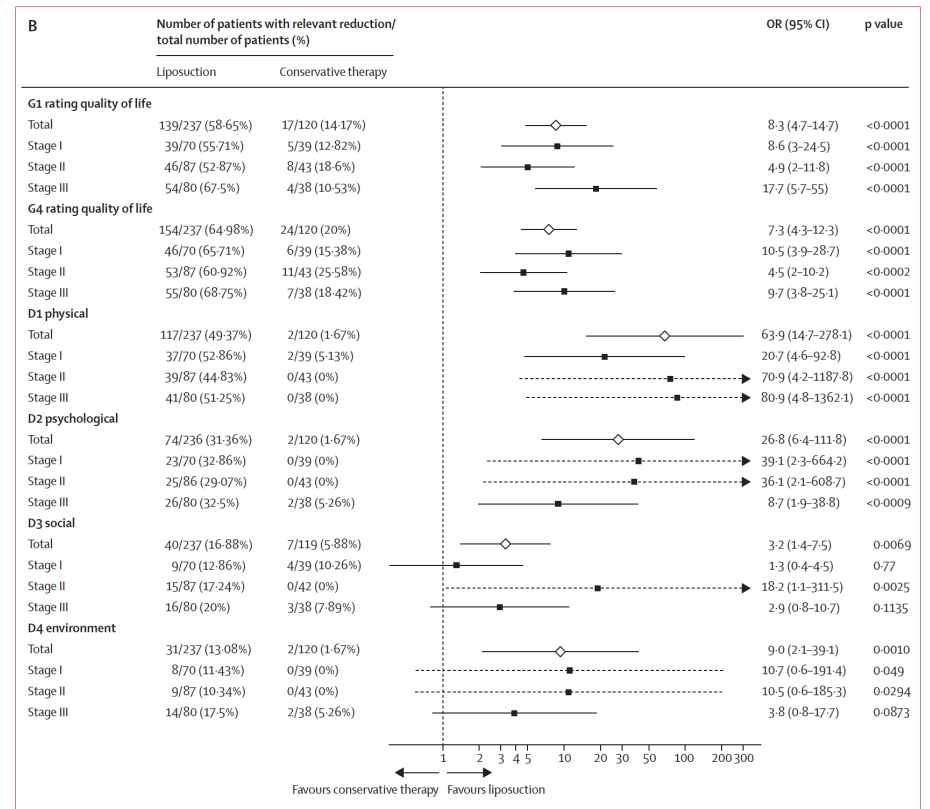


Figure 2: Forest plot of primary and secondary endpoints

(A) Results of the primary endpoint: relevant improvement of pain 12 months after start of conservative therapy or last liposuction, and relevant improvement of further secondary endpoints. A missing primary endpoint was considered non-successful (liposuction: 41 of 278; conservative therapy: 12 of 132). (B) Results of the secondary endpoints: WHO-BREF domains and selected items. Odds ratios and corresponding confidence intervals with dashed lines were computed using the Haldane-Anscombe correction, whereby 0.5 was added to each cell in contingency tables containing empty cells. Visual display of upper limits of confidence intervals was cut off at 300. OR=odds ratio. PHQ=Patient Health Questionnaire. SF-36=36-Item Short Form Health Survey. DLQI=Dermatology Life Quality Index. WHOQOL-BREF=World Health Organization Quality of Life-Brief Version.

	Stage I	Stage II	Stage III	All stages
Liposuction technique details				
Liposuction performed	85/90 (94%)	92/95 (97%)	88/93 (95%)	265/278 (95%)
Power-assisted technique	75/85 (88%)	72/92 (78%)	69/88 (78%)	216/265 (82%)
Water-jet assisted technique	10/85 (12%)	20/92 (22%)	19/88 (22%)	49/265 (18%)
Liposuctions per patient				
1	2/85 (2%)	0/92 (0%)	0/88 (0%)	2/265 (1%)
2	18/85 (21%)	11/92 (12%)	1/88 (1%)	30/265 (11%)
3	15/85 (18%)	30/92 (33%)	11/88 (13%)	56/265 (21%)
4	50/85 (59%)	51/92 (55%)	76/88 (86%)	177/265 (67%)
Aspirate volume, L				
First liposuction	4.29 (1.87); n=85	5.17 (2.14); n=90	5.18 (2.03); n=87*	4.89 (2.05); n=262
Second liposuction	3.98 (1.66); n=83	4.76 (1.89); n=90	4.77 (1.66); n=88	4.51 (1.78); n=261
Third liposuction	2.87 (0.98); n=65	3.33 (1.32); n=79	4.72 (3.72); n=87	3.72 (1.61); n=231
Fourth liposuction	2.69 (0.80); n=50	3.21 (1.14); n=51	4.01 (1.11); n=76	3.41 (1.18); n=177
Median duration, days				
Randomisation to first liposuction	23 (15–27)	20 (9–25)	22 (15–27)	22 (13–27)
First to last liposuction	106 (75–125)	105 (84–122)	126 (112–139)	112 (91–129)
Data are n/N (%), median (IQR), or mean (SD) with n. Of 278 patients randomly assigned to the liposuction group, 265 had at least one liposuction. 13 patients discontinued after randomisation and before first liposuction. * The aspirate volume in the first liposuction was missing in one patient.				
Table 2: Details of liposuction				

	Descriptive analysis			Estimates from mixed model for repeated measures*		
	At randomisation	After 12 months	Change from randomisation	After 12 months	Change from randomisation	p value
All stages						
Conservative therapy	6.3 (1.6); 132	6.6 (1.5); 120	0.30 (1.33); 120	6.38 (5.98 to 6.77)	0.41 (−0.02 to 0.81)	..
Liposuction	6.2 (1.6); 275	2.6 (2.5); 237	−3.74 (2.43); 237	2.34 (2.05 to 2.63)	−3.63 (−3.92 to −3.33)	..
Difference between treatments	..	..	..	−4.04 (−4.49 to 3.59)	−4.04 (−4.49 to 3.59)	<0.0001
Stage I						
Conservative therapy	6.0 (1.5); 42	6.3 (1.6); 39	0.23 (1.22); 39	5.99 (5.21 to 6.77)	0.48 (−0.30 to 1.26)	..
Liposuction	5.5 (1.5); 90	1.8 (2.1); 70	−3.87 (2.24); 70	1.85 (1.22 to 2.48)	−3.76 (−4.39 to −3.12)	..
Difference between treatments	..	..	..	−4.24 (−4.99 to −3.49)	−4.24 (−4.99 to −3.49)	<0.0001
Stage II						
Conservative therapy	6.3 (1.3); 45	6.7 (1.5); 43	0.49 (1.37) 43	6.22 (5.58 to 6.86)	−0.16 (−0.48 to 0.80)	..
Liposuction	6.4 (1.5); 95	2.7 (2.5); 87	−3.69 (2.42) 87	2.37 (1.91 to 2.82)	−3.68 (−4.14 to −3.23)	..
Difference between treatments	..	..	..	−3.85 (−4.58 to −3.12)	−3.85 (−4.58 to −3.12)	<0.0001
Stage III						
Conservative therapy	6.8 (1.9); 45	6.8 (1.5); 38	0.16 (1.39) 38	6.90 (6.09 to 7.71)	0.57 (−0.24 to 1.38)	..
Liposuction	6.8 (1.6); 90	3.1 (2.7); 80	−3.67 (2.62) 80	2.92 (2.30 to 3.53)	−3.41 (−4.02 to −2.79)	..
Difference between treatments	..	..	..	3.98 (−4.87 to −3.09)	3.98 (−4.87 to −3.09)	<0.0001

Data present the average leg pain intensity in the past 4 weeks assessed at randomisation and after 12 months. Descriptive results are given as mean (SD); n. Estimated marginal means were derived from mixed models for repeated measures and are presented along with 95% CIs. The difference between treatments was calculated as liposuction minus conservative therapy. *Covariates appearing in the models are evaluated at the following values. All stages: pain intensity at randomisation=5.96, age=42; interaction term: treatment group × visit: F=0.99, df= 356.29; stage I: pain intensity at randomisation=5.48, age=39; interaction term: treatment group × visit: F=0.09, df=107.76; stage II: pain intensity at randomisation=6.05, age=44; interaction term: treatment group × visit: F=2.63, df=128.11; stage III: pain intensity at randomisation=6.32, age=44; interaction term: treatment group × visit: F=0.10, df=115.61.

Table 3: Leg pain intensity in the intention-to-treat population

	Liposuction (n=265)	Conservative therapy (n=145)	Risk difference (95% CI; liposuction–conservative therapy)
Adverse events			
Patients without any adverse events	141 (53.2%; 47.2 to 59.1)	117 (80.7%; 73.5 to 86.3)	−27.5 (−36.0 to −17.8)
Patients with at least one adverse event	124 (46.8%; 40.7 to 53.0)	30 (20.7%; 14.4 to 28.2)	26.1 (16.3 to 34.8)
Severity			
Patients with at least one severe adverse event	11 (4.2%; 2.1 to 7.3)	6 (4.1%; 1.5 to 8.8)	0 (−5.4 to 4.2)
Patients with at least one moderate adverse event	54 (20.4%; 15.7 to 25.7)	15 (10.3%; 5.9 to 16.5)	10 (2.1 to 16.9)
Patients with at least one mild adverse event	59 (22.3%; 17.4 to 27.8)	9 (6.2%; 2.9 to 11.5)	16.1 (8.7 to 22.5)
Serious adverse events			
Patients with at least one serious adverse event	20 (7.5%; 4.7 to 11.4)	5 (3.4%; 1.1 to 7.9)	4.1 (−1.5 to 8.7)
Patients with at least one serious prespecified adverse event	11 (4.2%; 2.1 to 7.3)	0 (0%; 0 to 2.5)	4.2 (0.4 to 7.5)
By prespecified category			
Erysipelas	4 (1.5%; 0.4 to 3.8)	0 (0%; 0 to 2.5)	1.5 (−1.9 to 4.1)
Post-surgical decrease in haemoglobin	4 (1.5%; 0.4 to 3.8)	0 (0%; 0 to 2.5)	1.5 (−1.9 to 4.1)
Surgical site abscess	3 (1.1%; 0.2 to 3.3)	0 (0%; 0 to 2.5)	1.1 (−2.2 to 3.5)
Post-surgical pain	1 (0.4%; 0 to 2.1)	0 (0%; 0 to 2.5)	0.4 (−2.9 to 2.4)
Patients with at least one prespecified adverse event			
Post-surgical decrease in haemoglobin	15 (5.7%; 3.2 to 9.2)	..	..
Surgical site abscess*	5 (1.9%; 0.6 to 4.3)	..	..
Erysipelas	15 (5.7%; 3.2 to 9.2)	0 (0%; 0 to 2.5)	5.7 (1.7 to 9.4)
Seroma	10 (3.8%; 1.8 to 6.8)	0 (0%; 0 to 2.5)	3.8 (0.1 to 7.0)
Venous thrombosis	3 (1.1%; 0.2 to 3.3)	0 (0%; 0 to 2.5)	1.1 (−2.2 to 3.5)
Perioperative or postoperative pain	2 (0.8%; 0.1 to 2.7)	0 (0%; 0 to 2.5)	0.8 (−2.3 to 3.0)
Pulmonary embolism	1 (0.4%; 0 to 2.1)	1 (0.7%; 0 to 3.8)	−0.3 (−4.0 to 1.8)
By system organ class			
Blood and lymphatic system disorders	3 (1.1%; 0.2 to 3.3)	0 (0%; 0 to 2.5)	1.1 (−2.2 to 3.5)
Ear and labyrinth disorders	1 (0.4%; 0 to 2.1)	0 (0%; 0 to 2.5)	0.4 (−2.9 to 2.4)
Gastrointestinal disorders	3 (1.1%; 0.2 to 3.3)	0 (0%; 0 to 2.5)	1.1 (−2.2 to 3.5)
General disorders and administration site conditions	2 (0.8%; 0.1 to 2.7)	0 (0%; 0 to 2.5)	0.8 (−2.5 to 3.0)
Infections and infestations	4 (1.5%; 0.4 to 3.8)	0 (0%; 0 to 2.5)	1.5 (−1.9 to 4.1)
Injuries, poisoning, and procedural complications	2 (0.8%; 0.1 to 2.7)	0 (0%; 0 to 2.5)	0.8 (−2.5 to 3.0)
Musculoskeletal and connective tissue disorders	0 (0%; 0 to 1.4)	1 (0.7%; 0 to 3.8)	−0.7 (−4.4 to 1.2)
Neoplasms benign, malignant and unspecified	2 (0.8%; 0.1 to 2.7)	0 (0%; 0 to 2.5)	0.8 (−2.5 to 3.0)
Nervous system disorders	1 (0.4%; 0 to 2.1)	1 (0.7%; 0 to 3.8)	−0.3 (−4.0 to 1.8)
Reproductive system and breast disorders	1 (0.4%; 0 to 2.1)	2 (1.4%; 0.2 to 4.9)	−1.0 (−5.0 to 1.3)
Respiratory, thoracic and mediastinal disorders	1 (0.4%; 0 to 2.1)	0 (0%; 0 to 2.5)	0.4 (−2.9 to 2.4)
Skin and subcutaneous tissue disorders	1 (0.4%; 0 to 2.1)	0 (0%; 0 to 2.5)	0.4 (−2.9 to 2.4)
Surgical and medical procedures	0 (0%; 0 to 1.4)	1 (0.7%; 0 to 3.8)	−0.7 (−4.4 to 1.2)
Vascular disorders	0 (0%; 0 to 1.4)	1 (0.7%; 0 to 3.8)	−0.7 (−4.4 to 1.2)
Causal relation to liposuction			
Possibly related	45 (17%; 12.7 to 22.1)	..	..
Not related	79 (29.8%; 24.4 to 35.7)	..	..
Causal relation to conservative therapy			
Possibly related†	2 (0.8%; 0.1 to 2.7)	0 (0%; 0 to 2.5)	0.8 (−2.5 to 3.0)
Not related	122 (46%; 39.9 to 52.2)	30 (20.7%; 14.4 to 28.2)	25.3 (15.5 to 34.0)
Data are given as n (%; 95% CI) and indicate the frequency of patients with at least one event in the period from randomisation (conservative group) or from first liposuction (liposuction group), respectively, to the 12-month visit. The severity of adverse events is assessed by evaluating each patient based on the event with the highest intensity. Patients were counted once per prespecified category. 13 patients who were randomly assigned to the liposuction group and discontinued before the first liposuction were evaluated in the conservative therapy group. In only two cases did a serious adverse event result in study discontinuation; in one instance (liposuction group), a serious infection developed after the first surgery, which precluded further treatment in the surgical group. The other case (control group) involved a diagnosis of multiple sclerosis that led to discontinuation. No serious adverse event resulted in death. Of the serious adverse events which occurred after the first liposuction, two were reported as condition improving, all others as resolved without sequelae. *One patient with both a surgical site abscess and erysipelas after the first liposuction terminated study participation prematurely (serious adverse event, Ipoedema stage I). †Two patients had a seroma (non-serious, mild intensity) that occurred after the second liposuction; both events were reported as causally related to liposuction and to conservative therapy.			
Table 4: Adverse events in the safety population			

Research in context

Evidence before this study

The current standard of care for patients with lipoedema is conservative complex decongestive therapy, comprising compression, manual lymphatic drainage, physical activity, and skin care. Conservative therapy has been shown to reduce oedema but has limited effects on pain, the key symptom of lipoedema, and cannot stop disease progression. Liposuction has emerged as a treatment option, especially in refractory disease. To identify studies comparing efficacy and safety of liposuction and conservative therapy for lipoedema we searched PubMed, Embase, and the Cochrane Library for articles published up to Dec 1, 2025, using the search terms "lipoedema" AND "liposuction" AND ("decongestive therapy" OR "physiotherapy" OR "compression") without language restrictions. Only small, uncontrolled case series and retrospective cohort studies were found, that suggested liposuction might improve pain, haematoma proneness, and impairment in quality of life in patients with lipoedema. High-quality evidence from large randomised controlled trials evaluating efficacy and safety of liposuction for lipoedema was scarce.

Added value of this study

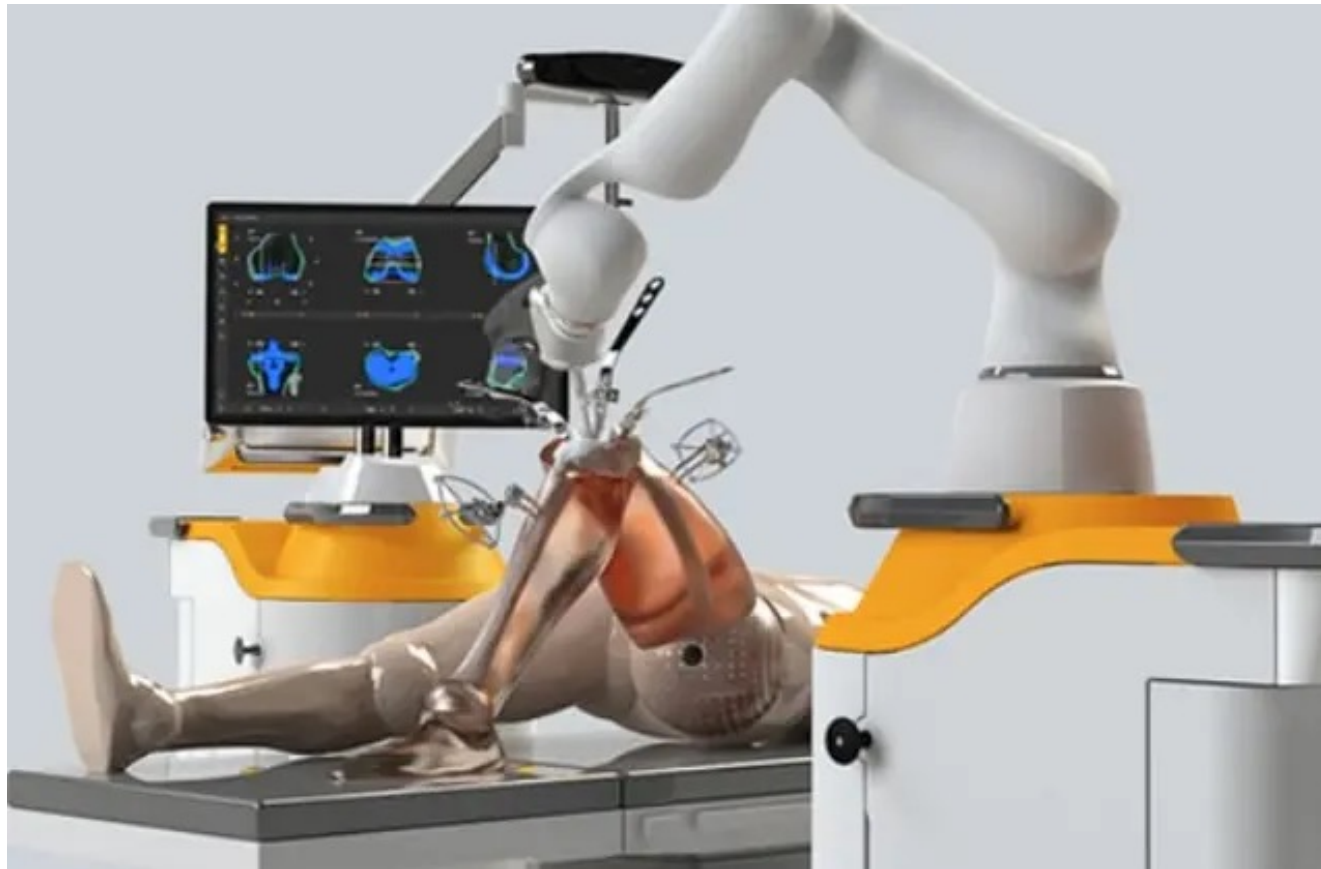
The LIPLEG trial is the first multicentre, randomised controlled trial comparing liposuction with conservative therapy in patients with lipoedema. Liposuction showed superiority over conservative therapy for the primary endpoint, the relevant reduction in patient-reported leg pain by at least 2 points on a numerical rating scale 12 months after completion of treatment. The findings were consistent across all lipoedema

stages. Liposuction resulted in significant improvements in quality of life, physical health, and haematoma proneness, while these did not change much with conservative therapy alone. In this study, most patients in the liposuction group received concomitant conservative therapy, underscoring that reduction in pain and functional improvements were primarily attributed to the surgical intervention. As expected, more adverse events occurred in the liposuction group, but they were mostly of mild-to-moderate intensity. No unexpected or life-threatening events occurred. These results substantially raise the level of evidence for treatments of lipoedema.

Implications of all the available evidence

The LIPLEG trial proves that liposuction offers a substantial reduction in patient-reported pain and improvements in quality of life in all lipoedema stages compared with conservative therapy. These findings align with previous case reports but provide the first high-quality evidence of a randomised controlled trial. The results have changed health-care policy in Germany, resulting in the incorporation of liposuction in the catalogue of services reimbursed by the German statutory health insurances. Further research should focus on long-term efficacy and safety of liposuction, as this study reports the results of the 12 months' analysis. Ongoing follow-up up to 36 months will be published as soon as available. Recurrence rates, and the influence of the liposuction technique used should be further elucidated. Comparable studies in health-care systems other than Germany are encouraged to investigate different study populations.

Traditional Surgery vs. Robotic Joint Replacement



Robotics
do not
improve
outcomes

Robotic-arm-assisted versus conventional total knee replacement (RACER-Knee): a pragmatic, multicentre, participant-masked and assessor-masked, superiority, randomised controlled trial

Summary

Background Robotic systems are being increasingly used to assist with total knee replacement (TKR). Whether robotic systems improve outcomes after TKR is uncertain. We aimed to ascertain the clinical efficacy and cost-effectiveness of the Mako robotic-arm system compared with conventional instruments for TKR.

Methods We conducted a participant-masked and assessor-masked pragmatic, superiority, randomised controlled trial at ten hospitals in Great Britain involving 33 surgeons. Patients with advanced knee osteoarthritis underwent TKR with conventional instruments (cTKR) or with the Mako robotic-arm-assisted system (rTKR). Key exclusion criteria were inflammatory arthropathy, previous fracture, or the need for complex implants. Participants were randomly assigned (1:1) through a remote computer system using minimisation by age, BMI, centre, surgeon, and primary knee compartment involved. Participants and assessors were masked through methods including using sham incisions, additional draping, and masked operation notes. The primary outcome was the Forgotten Joint Score (FJS) at 12 months after randomisation according to the intention-to-treat principle using a linear mixed-effects model. The prespecified target difference was 12 points. The trial is registered with ISRCTN (ISRCTN27624068), and long-term follow-up is ongoing.

Findings Between Dec 21, 2021, and Dec 13, 2023, 807 patients were screened and 339 were randomly assigned: 168 to rTKR and 171 to cTKR. The median age was 68·8 years (IQR 61·3–75·2), 167 (49%) were female, and 172 (51%) were male. At 12 months, the mean FJS was 49·2 (SD 28·4; n=154) in the rTKR group and 50·2 (29·9; n=158) in the cTKR group. The adjusted mean difference was –1·5 (95% CI –7·5 to 4·5; p=0·62) favouring cTKR. 16 participants in each group had one serious adverse event.

Interpretation In this pragmatic trial, rTKR as delivered in routine practice was more costly than cTKR and did not provide a clinically meaningful patient benefit at 12 months after randomisation. The two groups had similar safety (ie, harms) profiles.

Funding UK National Institute for Health and Care Research Health Technology Assessment Programme.

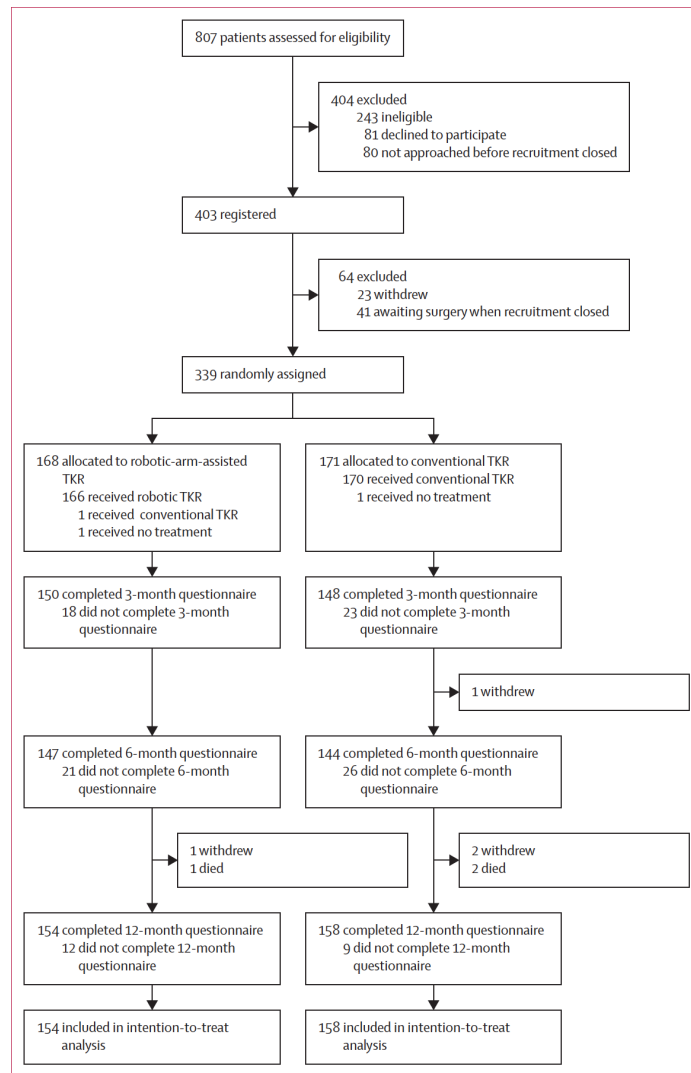


Figure 1: Trial profile
TKR=total knee replacement.

	Robotic-arm-assisted total knee replacement (n=168)	Conventional total knee replacement (n=171)
Age (years), median (IQR)	68.9 (61.4–75.3)	68.5 (61.3–75.2)
Age group		
<60 years	34 (20%)	35 (20%)
≥60 years	134 (80%)	136 (80%)
Sex		
Female	80 (48%)	87 (51%)
Male	88 (52%)	84 (49%)
BMI (kg/m ²), median (IQR)	32.0 (28.0–35.2)	31.6 (27.9–35.3)
BMI group		
<35 kg/m ²	121 (72%)	121 (71%)
≥35 kg/m ²	47 (28%)	50 (29%)
Affected knee		
Left	75 (45%)	85 (50%)
Right	93 (55%)	86 (50%)
Most-affected knee compartment		
Medial	129 (77%)	127 (74%)
Lateral	31 (18%)	31 (18%)
Patellofemoral	8 (5%)	13 (8%)
Duration of symptoms		
<1 year	2 (1%)	2 (1%)
1–5 years	76 (45%)	70 (41%)
6–10 years	41 (24%)	42 (25%)
>10 years	49 (29%)	56 (33%)
Not reported	0	1 (<1%)
Ethnicity		
White	151 (90%)	160 (94%)
Asian or Asian British	9 (5%)	7 (4%)
Black, African, Caribbean, or Black British	5 (3%)	3 (2%)
Mixed or other ethnic group	3 (<1%)	0
Missing	0	1 (<1%)
Forgotten Joint Score	9.0 (10.3)	9.2 (10.8)
EuroQol 5-Dimension 5-Level	0.392 (0.270)	0.376 (0.280)
Oxford Knee Score	19.3 (7.7)	18.7 (7.9)
Oxford Participation and Activities Questionnaire	10.5 (15.2)	9.7 (15.2)
PROMIS Pain Intensity	66.1 (7.2)	66.1 (7.3)

Data are n (%) or mean (SD) unless otherwise specified. PROMIS=Patient-Reported Outcomes Measurement Information System.

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

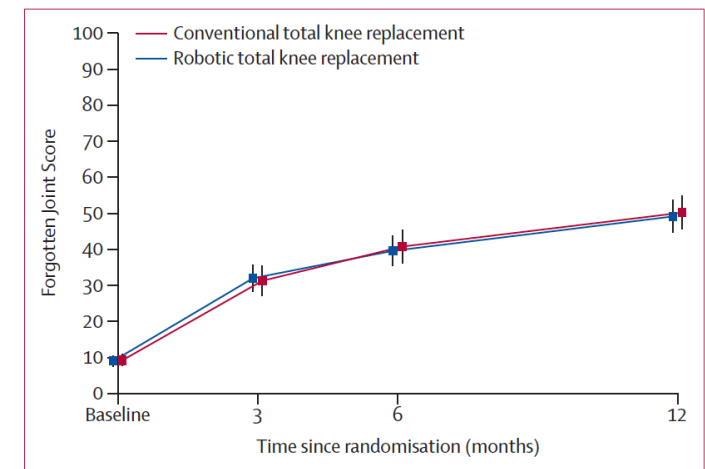


Figure 2: Forgotten Joint Score over 12 months after randomisation
Data are means; error bars show 95% CIs. Group-specific points are displaced slightly horizontally for visibility.

	Robotic-arm-assisted total knee replacement (n=168)	Conventional total knee replacement (n=171)	Adjusted effect estimate (95% CI)
Primary outcome			
Forgotten Joint Score at 12 months	49.2 (28.4); 154	50.2 (29.9); 158	-1.5 (-7.5 to 4.5), p=0.62
Secondary outcomes			
Forgotten Joint Score			
At 3 months	32.0 (22.6); 150	31.3 (25.4); 148	0.6 (-4.6 to 5.8)
At 6 months	39.6 (25.8); 147	40.8 (28.6); 144	-1.1 (-7.0 to 4.8)
Post-surgery pain averaged across days 1–3 in operated knee			
At the moment	5.3 (2.1); 161	5.5 (2.1); 162	-0.1 (-0.6 to 0.3)*
At rest over past 24 h	5.3 (1.9); 161	5.4 (1.9); 162	-0.1 (-0.5 to 0.3)*
When moving over past 24 h	7.0 (1.7); 161	6.8 (1.7); 162	0.2 (-0.2 to 0.5)*
Total opioid usage (morphine equivalent dose) days 1–3	79.8 (74.8); 165	83.0 (62.7); 170	-1.5 (-14.9 to 11.9)*
Hours from surgery completion to discharge	76.1 (113.4); 159	73.4 (54.1); 165	3.8 (-15.0 to 22.5)*
EuroQol 5-Dimension 5-Level (utility score)			
6 weeks	0.642 (0.185); 154	0.638 (0.199); 155	-0.002 (-0.043 to 0.038)
3 months	0.667 (0.208); 151	0.691 (0.192); 150	-0.025 (-0.067 to 0.018)
6 months	0.722 (0.207); 147	0.724 (0.247); 149	-0.006 (-0.051 to 0.040)
12 months	0.759 (0.198); 154	0.737 (0.270); 158	0.012 (-0.035 to 0.060)
Oxford Knee Score			
3 months	32.3 (8.5); 151	32.5 (9.0); 149	-0.2 (-2.0 to 1.7)
6 months	35.1 (8.7); 147	35.1 (9.5); 149	-0.1 (-1.9 to 1.7)
12 months	37.3 (9.1); 155	36.9 (9.9); 157	0.3 (-1.8, 1.9)
Oxford Participation and Activities Questionnaire score			
3 months	43.6 (27.8); 151	46.2 (32.9); 150	-2.4 (-9.2 to 4.3)
6 months	52.6 (29.3); 147	53.8 (33.4); 149	-1.8 (-8.7 to 5.0)
12 months	60.2 (30.6); 155	59.0 (32.1); 157	1.2 (-5.5 to 7.8)
PROMIS Pain Intensity (T-score)			
3 months	52.1 (8.9); 149	51.7 (9.6); 147	0.1 (-1.9 to 2.1)*
6 months	50.1 (10.8); 144	49.2 (10.3); 148	0.6 (-1.7 to 2.9)*
12 months	45.9 (9.6); 153	46.3 (10.6); 153	-0.6 (-2.7 to 1.5)*
Physiotherapy sessions within 12 months			
Total number of sessions	5.4 (5.3); 164	6.5 (6.4); 164	0.8 (0.6 to 1.0)†
Health economic costs			
Initial admission (including robotic system costs) per allocation group	£7814.03 (1257.97); 159	£6819.49 (261.21); 167	994.55 (795.04 to 1194.06)
Total NHS and PSS cost 0–3 months	£759.38 (1268.48); 141	£671.23 (713.06); 140	88.15 (-152.24 to 328.55)
Total NHS and PSS cost 3–6 months	£236.70 (290.62); 139	£327.72 (391.81); 140	-91.03 (-171.94 to -10.12)
Total NHS and PSS cost 6–12 months	£195.71 (354.36); 154	£297.52 (603.52); 155	-101.81 (-212.08 to 8.47)
Total NHS and PSS cost 0–12 months, mean (bootstrap SD); n‡	£8979.69 (210.38); 116	£8140.66 (109.45); 116	839.03 (370.95 to 1307.11)

(Table 2 continues on next page)

	Robotic-arm-assisted total knee replacement (n=168)	Conventional total knee replacement (n=171)	Adjusted effect estimate (95% CI)
(Continued from previous page)			
Process outcomes			
Time from skin incision to final dressing, min	92 (24.5); 165	83 (22.3); 170	10.5 (6.8 to 14.3)
Radiology: 3 months after operation			
Hip–knee–ankle angles	-0.8° (2.8); 111	-0.7° (3.7); 133	-0.1 (-0.9 to 0.7)
Absolute difference between achieved and planned hip–knee–ankle angle	2.0° (1.8); 102	2.8° (2.4); 133	-0.8 (-1.4 to -0.3)
Lateral distal femoral angle	89.9° (2.0); 111	89.1° (2.3); 133	0.8 (0.2 to 1.3)
Medial proximal tibial angle	89.5° (2.0); 111	89.6° (2.1); 133	0.0 (-0.6 to 0.5)
Tibial slope	3.1° (2.2); 143	4.4° (2.7); 149	-1.3 (-1.9 to -0.8)
Femoral rotation	3.0° (2.5); 98	3.1° (2.6); 119	0.0 (-0.7 to 0.6)
Tibial rotation	18.4° (10.0); 122	17.9° (9.2); 134	0.6 (-1.8 to 3.0)
Data are mean (SD); n, unless otherwise stated. Negative values favour conventional total knee replacement, unless otherwise indicated. NHS=UK National Health Service. PROMIS=Patient-Reported Outcomes Measurement Information System. PSS=Personal Social Services. *Positive values favour conventional total knee replacement. †Adjusted rate ratio (negative binomial model). ‡Complete-case estimates; uncertainty estimated by non-parametric bootstrapping; no imputation applied. §Negative values represent varus alignment.			
Table 2: Key trial outcomes at each follow-up point			

	Robotic-arm-assisted total knee replacement (n=168)	Conventional total knee replacement (n=171)	All participants (n=339)
Adverse events per participant			
Yes (any number)	21 (13%)	16 (9%)	37 (11%)
1 adverse event	19 (11%)	13 (8%)	32 (9%)
≥2 adverse events	2 (1%)	3 (2%)	5 (1%)
Participants with any serious adverse event			
1 serious adverse event	16 (10%)	16 (9%)	32 (9%)
Data are n (%).			
Table 3: Participants with any adverse event within 12 months of randomisation			

Research in context

Evidence before this study

Total knee replacement (TKR) is one of the most common elective operations worldwide. Robotic systems that assist the surgeon to do TKRs have been introduced into care, but whether they improve patient outcomes remains uncertain. Before this study, a systematic review and meta-analysis of 22 studies, involving 2346 participants, evaluating robotic systems for TKR identified no randomised controlled trials of robotic systems in current use. Non-randomised studies suggested improved early outcomes with robotic surgery, including less pain, shorter length of stay, and greater satisfaction at 6 months compared with TKR. In 2025, we performed an updated systematic review and meta-analysis, for which the available evidence remained predominantly observational studies and which suggested better medium-term (3–12 months) outcomes with the Mako (Stryker, Fort Lauderdale, FL, USA) robotic system, the most widely used system worldwide, than with conventional instruments. During the conduct of our trial, RACER-Knee, the unmasked ROAM randomised controlled trial, which included 50 participants assigned to robot-assisted TKR and 50 assigned to conventional TKR, reported no significant between-group differences in its primary outcome, the Western Ontario and McMaster Universities Osteoarthritis Index, at 6 or 12 months.

Added value of this study

To our knowledge, RACER-Knee is the largest participant-masked and assessor-masked randomised controlled trial of

robotic-arm-assisted TKR (rTKR). In a pragmatic comparison of rTKR versus conventional TKR (cTKR) as delivered in routine practice, we found no clinically meaningful difference in patient-reported outcomes, measured using the Forgotten Joint Score, at 12 months. rTKR was more costly and unlikely to be cost-effective. We updated our 2025 systematic review and meta-analysis of functional outcomes after Mako-assisted TKR by incorporating these results. We searched five databases up to March 1, 2026, and identified one other randomised trial, ROAM. Meta-analysis of the two available randomised trials (RACER-Knee and ROAM, involving 439 participants), showed no difference in patient-reported outcomes at 3 or 12 months. Serious adverse events were similar between groups in RACER-Knee. Both trials found that robotic TKR was unlikely to be cost-effective.

Implications of all the available evidence

Uptake of rTKR is increasing rapidly worldwide, accounting for 6% of cases in the UK, 15% in the USA, and 41% in Australia. The available evidence from randomised controlled trials shows no clinical or cost-effective benefit of rTKR over cTKR during the first year after surgery. Under the willingness-to-pay thresholds evaluated, rTKR was more costly and was unlikely to be cost-effective.

Cardiovascular Disease and Pregnancy 1

Cardiovascular disease in pregnancy: physiology, global burden, risk stratification, and opportunities in care

Cardiovascular disease remains one of the leading causes of maternal mortality worldwide and a major driver of long-term morbidity. Yet, pregnancy-related cardiovascular complications are often under-recognised and variably managed across global settings. This three-part Series examines the continuum of cardiovascular risk surrounding pregnancy—from preconception through to lifelong surveillance. In the first paper in this Series, we describe the haemodynamic changes of pregnancy and global trends of congenital and acquired heart disease before pregnancy, evaluate established risk-stratification tools, and discuss the importance of multidisciplinary care. We focus on the existing burden of cardiovascular disease during pregnancy and related maternal and fetal complications. The second paper focuses on hypertensive disorders of pregnancy—the most common cardiovascular complication during pregnancy worldwide—detailing the pathophysiology, risk factors, and innovative care-delivery models to bridge gaps in longitudinal management. Finally, the third paper examines the association between adverse pregnancy outcomes and future cardiovascular disease, delineating mechanistic pathways, early interventions, and subsequent cardiovascular care. Together, this Series underscores pregnancy as a pivotal window into women's lifelong cardiovascular health and calls for integrated, equitable strategies to prevent avoidable maternal and fetal complications, while substantially lowering the lifetime risk of cardiovascular disease across diverse populations.

Key messages

- Pregnancy poses a unique haemodynamic stress on women, with substantial metabolic and hormonal alterations that can often unmask underlying cardiovascular disease or precipitate de-novo cardiovascular disease; this paper focuses on the pathophysiological changes of high-risk cardiovascular disease, which are described as congenital heart disease, acquired pre-pregnancy cardiovascular disease, and new-onset cardiovascular conditions
- Management of high-risk cardiovascular disease during pregnancy requires a multidisciplinary pregnancy heart team (cardio-obstetrics) approach, prioritising preconception counselling, focused risk stratification (using tools such as modified WHO classes, ZAHARA, CARPREG II, etc), genetic counselling, medication reconciliation, and nuanced discussion on the timing and mode of birth, encompassing fetal and delivery risks
- There is a need for the implementation of screening protocols for all pregnant and postpartum women for early detection of cardiovascular disease, which includes patient-reported symptoms, vital signs, risk factors, and physical examinations, along with additional imaging (eg, echocardiograms), that helps distinguish between the typical physiological and haemodynamic changes of pregnancy versus cardiovascular disease, and prompts clinicians to streamline care for these high-risk conditions
- There remain global challenges in advancing equitable, system-level action across diverse care settings and in refocusing efforts on testing care models for feasibility and cost-effectiveness, particularly in resource-limited countries

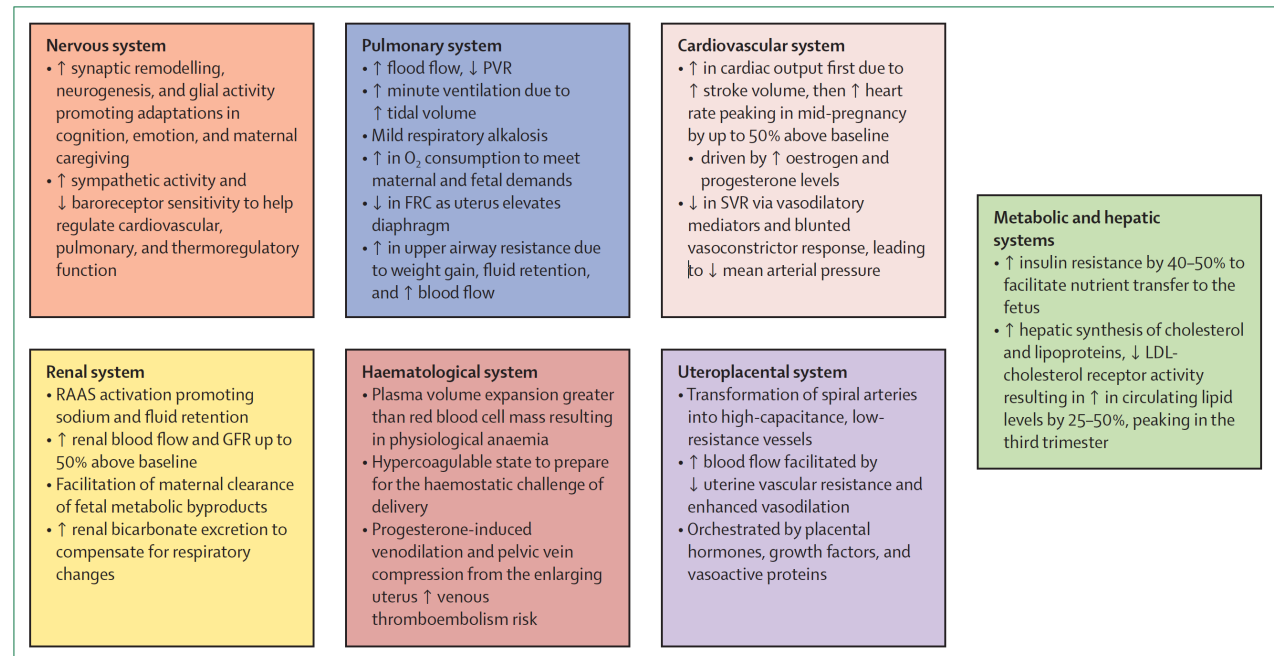


Figure 1: Haemodynamic and physiological changes during pregnancy

FRC=functional residual capacity. GFR=glomerular filtration rate. PVR=pulmonary vascular resistance. RAAS=renin-angiotensin-aldosterone system. SVR=systemic vascular resistance.

Panel 1: Epidemiological classification and key features of cardiovascular diseases in pregnancy

Congenital cardiovascular diseases: structural or functional heart lesions present from birth

Examples

- Defects of the wall or vessels of the heart: atrial septal defect, ventricular septal defect, and patent ductus arteriosus
- Complex congenital heart disease: tetralogy of Fallot, transposition of the great arteries, and single ventricle or Fontan procedure
- Outflow tract or valvular lesions: congenital aortic or pulmonary stenosis and bicuspid aortic valve
- Aortopathy: coarctation of the aorta
- Cyanotic heart disease: Eisenmenger physiology and total anomalous pulmonary venous return
- Inherited arrhythmia syndromes: long QT syndrome and Wolff-Parkinson-White syndrome

Key features

- Cause: structural or functional heart lesions present from birth (genetic or developmental)
- Primary prevention: limited; focus on genetic counselling and optimisation before pregnancy
- Epidemiology: increasing prevalence globally due to improved survival into reproductive age
- Risks: pregnancy risk depends on lesion complexity and residual haemodynamic burden (eg, heart failure, arrhythmias, and maternal-fetal complications)

Acquired cardiovascular diseases pre-dating pregnancy: pre-existing before conception (may be chronic, often known conditions)

Examples

- Valvular heart disease: rheumatic heart disease or prosthetic heart valves
- Ischaemic disease: coronary artery disease, previous myocardial infarction, and previous stroke
- Known cardiomyopathies: dilated with ventricular dysfunction, hypertrophic, restrictive, and previous peripartum cardiomyopathy
- Pulmonary hypertension: pulmonary arterial hypertension, idiopathic, or secondary causes
- Hypertensive disease: chronic hypertension
- Arrhythmias: atrial fibrillation, supraventricular tachycardia, ventricular tachycardia, heart block, and inherited channelopathies
- Aortopathy: Marfan syndrome and Loeys-Dietz syndrome
- Thromboembolic risk: previous venous thromboembolism or thrombophilia (eg, Factor V Leiden)

Key features

- Cause: chronic conditions developing before conception (eg, rheumatic, cardiometabolic, or degenerative disease)
- Primary prevention: possible for many through disease control and risk-factor modification (eg, hypertension, obesity, smoking, or diabetes)
- Epidemiology: increasing prevalence with increasing maternal age and cardiometabolic disease
- Risks: risk of decompensation during pregnancy (eg, heart failure, arrhythmias, or thromboembolism); requires preconception risk assessment

Acquired cardiovascular diseases developing or presenting during pregnancy or postpartum: conditions first diagnosed or precipitated by pregnancy itself (physiological, hormonal, or thrombotic triggers)

Examples

- Hypertensive disorders of pregnancy: gestational hypertension, pre-eclampsia, and eclampsia
- Thromboembolic disease: pregnancy-related deep-vein thrombosis and pulmonary embolism
- Infective or inflammatory endocarditis, myocarditis, and pericarditis
- Myocardial infarction including spontaneous coronary artery dissection
- Stroke
- New-onset cardiomyopathies: peripartum cardiomyopathy, stress-induced cardiomyopathy (eg, Takotsubo syndrome)
- Aortic complications: dissection
- Arrhythmias: pregnancy-related atrial fibrillation, supraventricular tachycardia, and ventricular tachycardia

Key features

- Cause: pregnancy-triggered conditions related to haemodynamic, hormonal, or thrombotic changes
- Primary prevention: possible for some (eg, hypertensive disorders and venous thromboembolism) through risk identification and prophylaxis
- Epidemiology: most common category of cardiovascular complications in pregnancy
- Risks: highest risk of acute maternal morbidity and mortality (eg, peripartum cardiomyopathy, spontaneous coronary artery dissection, and aortic dissection), often presenting late in pregnancy or postpartum

Panel 2: Overview of maternal and fetal risks of cardiovascular diseases during pregnancy

Congenital cardiovascular diseases: structural or functional heart lesions present from birth (may be repaired or unrepaired)

Maternal morbidity and mortality

Maternal cardiac complications are common and lesion specific:

- Heart failure occurs in 5–15% of pregnancies with moderate-to-severe coronary heart disease^{51,52}
- Arrhythmias (especially atrial and supraventricular) affect 5–10% of pregnancies^{51,53}
- Women with cyanosis, pulmonary hypertension, or systemic right ventricle carry the highest risk of morbidity and mortality^{51,52,54,55}
- Hypertensive disorders, caesarean delivery, preterm delivery, and postpartum haemorrhage are more common compared with the general population⁵²

Maternal mortality is low overall and concentrated in subgroups at high risk:

- Overall: 0.1–1.5% maternal mortality^{51,53}
- Mortality up to 5–10% in women with Eisenmenger physiology, severe pulmonary hypertension, or complex unrepaired lesions^{51,52,55}

Fetal and neonatal risks

Fetal and neonatal risks include obstetric complications and inherited heart disease:

- Preterm birth (<37 weeks of gestation) occurs in 20–25% of pregnancies^{52,55}
- Intrauterine growth restrictions and small for gestational age up to two times higher in women with congenital cardiovascular disease than in unaffected pregnancies^{52,53,56}
- Fetal loss and perinatal mortality are roughly two to four times higher in women with congenital cardiovascular disease than in unaffected pregnancies, especially when maternal cyanosis or heart failure are present^{52,57}
- Fetus or offspring bears higher risk of inherited congenital heart defects⁵⁶

Acquired cardiovascular diseases pre-dating pregnancy: pre-existing before conception (may be chronic, often known conditions)

Maternal morbidity and mortality

Valvular heart disease and cardiomyopathies:

- Women with rheumatic valvular disease, previous valve replacement, or cardiomyopathy are at high risk^{51,54}
- Heart failure occurs in up to 20–30% of pregnancies with mitral stenosis or cardiomyopathy^{51,54}

- Anticoagulation and prosthetic valve management pose major challenges and risk of thromboembolism^{51,54}

Chronic pre-existing cardiovascular disease: in women with chronic hypertension, ischaemic heart disease, or significant arrhythmias, pregnancy is associated with higher rates of heart failure, hypertensive crises, recurrent ischaemia, thromboembolic events, and arrhythmia exacerbation.^{36,51}

Maternal mortality is highest in some subgroups: overall mortality is 1–2%, but rises to 5–10% in severe rheumatic mitral stenosis, prosthetic valve thrombosis, or advanced cardiomyopathy.^{51,54}

Fetal and neonatal risks

Fetal and neonatal risks are substantially elevated, often from obstetric complications:

- Chronic maternal hypoxia or low cardiac output affects fetal growth⁵⁸
- Increased rates of preterm delivery (20–30%), fetal growth restriction, and perinatal mortality (two to five times more common than in the general population)^{54,58}

Acquired cardiovascular diseases developing or presenting during pregnancy or postpartum: conditions first diagnosed or precipitated by pregnancy itself (physiological, hormonal, or thrombotic triggers)

Maternal morbidity and mortality

Hypertensive diseases are the most common cardiovascular complication of pregnancy:

- Markedly increases risk of superimposed pre-eclampsia, heart failure, placental abruption, preterm birth, and perinatal growth restriction⁵⁹

Rarer conditions carry the highest risk:

- Disorders such as peripartum cardiomyopathy, pregnancy-associated myocardial infarction (including spontaneous coronary artery dissection), aortic dissection, or infective endocarditis are considered high risk for maternal and fetal complications
- Major maternal complications include heart failure, arrhythmia, and cardiogenic shock
- Severe cases require mechanical circulatory support, surgery, or heart transplantation
- Complications occur within the first 6 weeks postpartum when haemodynamic and hormonal shifts peak, and can occur up to 1 year postpartum¹⁶

(Continues on next page)

(Panel 2 continued from previous page)

Maternal mortality is substantially higher than for pre-existing disease:

- Maternal mortality ranges from 4% to 6% for pregnancy-associated myocardial infarction (up to 6–11% for peripartum cardiomyopathy and 6–11% for stroke)⁶⁰⁻⁶²
- Highest maternal mortality rates are reported for infective endocarditis (5–23%) and aortic dissection (up to 20%)^{63,64}

Fetal and neonatal risks

Fetal and neonatal risks are substantially elevated, often related to severe maternal cardiovascular complications and the need for early delivery:

- High rates of preterm delivery (>30%), fetal growth restriction, and perinatal mortality (4–8%)⁶⁵
- Rapid access to cardiology, obstetrics, cardiac imaging, and critical care expertise dramatically improves survival; postpartum follow-up is essential to prevent recurrence⁶⁹



Figure 2: Incidence, prevalence, and case-fatality rates of maternal cardiovascular diseases in pregnancy and the postpartum period

Estimates are illustrative and represent plausible ranges based on currently available literature and expert consensus. Where available, estimates were informed from the most recent systematic review reporting incidence, prevalence, or case-fatality rates in defined pregnancy populations and 95% CIs. Where recent systematic reviews were not available, representative ranges were informed from global reviews and registry summaries, prevalence estimates in women of childbearing age, and expert consensus statements. These estimates are suitable for visualisation and broad comparisons across conditions but should not be cited as meta-analysis results. Interpretation should consider the heterogeneity in study design, case definitions, reporting practices, and geographical settings of underlying studies. Estimates are displayed as colour-coded ranges and are summarised globally and by regional income group (ie, high-income countries and low-income and middle-income countries). More detail on the search strategies, data sources, and references used to derive plausible ranges are provided in the appendix (pp 6–20). Incidence and prevalence estimates are reported per pregnancy, expressed as percentages or, for rare outcomes, per 100 000 pregnancies, except for peripartum cardiomyopathy, where incidence is reported per livebirth.

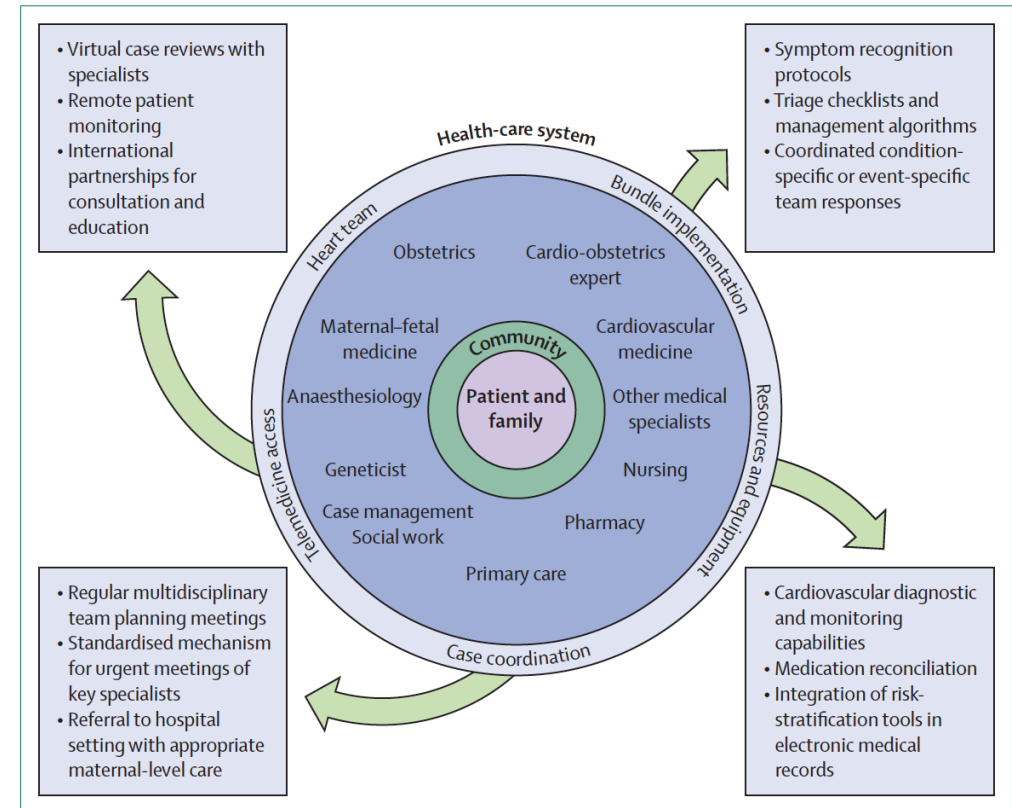


Figure 3: The pregnancy heart team within systems of care

	mWHO (2011, 2018, and 2025 [mWHO 2.0])	CARPREG I (2001)	CARPREG II (2019)	ZAHARA (2010)	DEVI (2020)
When	Pre-pregnancy; all trimesters	Pre-pregnancy; all trimesters	All trimesters	Pre-pregnancy; all trimesters	Pre-pregnancy; all trimesters
Population	All cardiovascular diseases	All cardiovascular diseases	All cardiovascular diseases	Congenital heart disease	Valvular disease
Predictors	Cardiac diagnosis, divided into classes 1–4 with increasing severity	Four predictors (1 point for each; scoring of 0, 1, and >1): previous cardiac event or arrhythmia, NYHA >2, left-ventricular outflow obstruction, and systemic ventricular dysfunction	Ten predictors (different points by severity; scoring of 0 to >4): late pregnancy assessment, no previous cardiac intervention, high-risk aortopathy, coronary artery disease, pulmonary hypertension, high-risk left-sided valve disease or obstruction, ventricular dysfunction, mechanical valve, baseline NYHA 3–4, and previous cardiac events or arrhythmias	Ten predictors (points by severity; scoring 0–13): maternal age, history of arrhythmias, cardiac medication before pregnancy, NYHA >2, left-ventricular outflow obstruction, left-ventricular dysfunction, moderate-to-severe atriocentric valve regurgitation, moderate-to-severe pulmonary valve regurgitation, mechanical valve, and cyanotic heart disease	Seven predictors (points by severity; scoring 0–12): previous cardiovascular event, pulmonary hypertension, taking cardiac medication (–1), severe mitral stenosis, moderate mitral stenosis, mild mitral stenosis, and prosthetic heart valve
Outcomes	Maternal morbidity and mortality	Cardiac-specific outcomes, most commonly pulmonary oedema and cardiac arrhythmias	Cardiac-specific outcomes, most commonly arrhythmias and left-sided heart failure	Cardiac, obstetric, and neonatal outcomes; prediction only possible for cardiac outcomes	Cardiac-specific outcomes, including heart failure, arrhythmias, and pulmonary oedema
Predictive accuracy development cohort	NA; developed through expert consensus	546 women; AUC 0.79 (95% CI 0.71–0.87)	1938 women; AUC 0.78 (95% CI 0.73–0.83)	1302 women; AUC 0.76 (no 95% CI presented)	681 women; AUC 0.80 (95% CI 0.76–0.85)
Predictive accuracy external validation	AUC 0.78, ¹³⁰ 0.77, ¹³¹ and 0.68; ¹³² LMICs: 0.79 ¹⁴ and 0.74 ¹³³	AUC 0.57, ¹³¹ 0.69, ¹³² and 0.71 ¹³⁴	AUC 0.85; ¹³⁰ LMICs: 0.81 ¹⁸	AUC 0.86, ¹³⁰ 0.71, ¹³¹ 0.81, ⁷⁸ and 0.73; ¹³² LMICs: 0.77 ¹³³	AUC 0.88 ¹⁸ and 0.75; ¹³⁴ LMICs: 0.88 ¹⁸
Absolute risk	Class 1: 3–10%; class 2: 8–22%; class 2–3: 13–18%; class 3: 21–29%; class 4: 36–50% ^{13,135}	Risk index 0: 5%; risk index 1: 27%; risk index >1: 75% ¹³⁶	Risk index 0–1: 3–5%; risk index 2: 7–10%; risk index 3: 15–16%; risk index 4: 22–25%; risk index >4: 41–45% ¹³	Risk score 0–0.50: 2.9%; risk score 0.51–1.50: 7.5%; risk score 1.51–2.50: 17.5%; risk score 2.51–3.50: 43.1%; risk score >3.51: 70.0% ^{13,137}	Multivariable model with cutoff at 20% probability and false positive rate of 12%; in the cohort, 15% of women had one or more outcomes ¹³⁸
Endorsed by	European Society of Cardiology, Society of Maternal-Fetal Medicine and American College of Cardiology/American Heart Association, and American College of Obstetrics and Gynecology	NS	Society for Maternal-Fetal Medicine and American College of Cardiology/American Heart Association	NS	NS

Classification of heart disease to predict complications in pregnancy. AUC describes the capability of a model to distinguish between classes (eg, positive vs negative) across all classification thresholds. AUC >0.7 illustrates moderate predictive performance, AUC >0.8 describes good predictive performance, and AUC >0.9 excellent predictive performance. Absolute risks describe the percentage risk in a specific risk class in the respective models for the outcome. AUC=area under the curve. CARPREG=Cardiac Disease in Pregnancy. DEVI=Events in Valvular Rheumatic Heart Disease in Pregnancy. LMIC=low-income and middle-income countries. mWHO=modified updated WHO classification. NS=not specified. NYHA=New York Heart Association. ZAHARA=Zwangerschap bij Aangeboren Hartafwijkingen.

Table: Cardiovascular risk scores to predict maternal complications during pregnancy

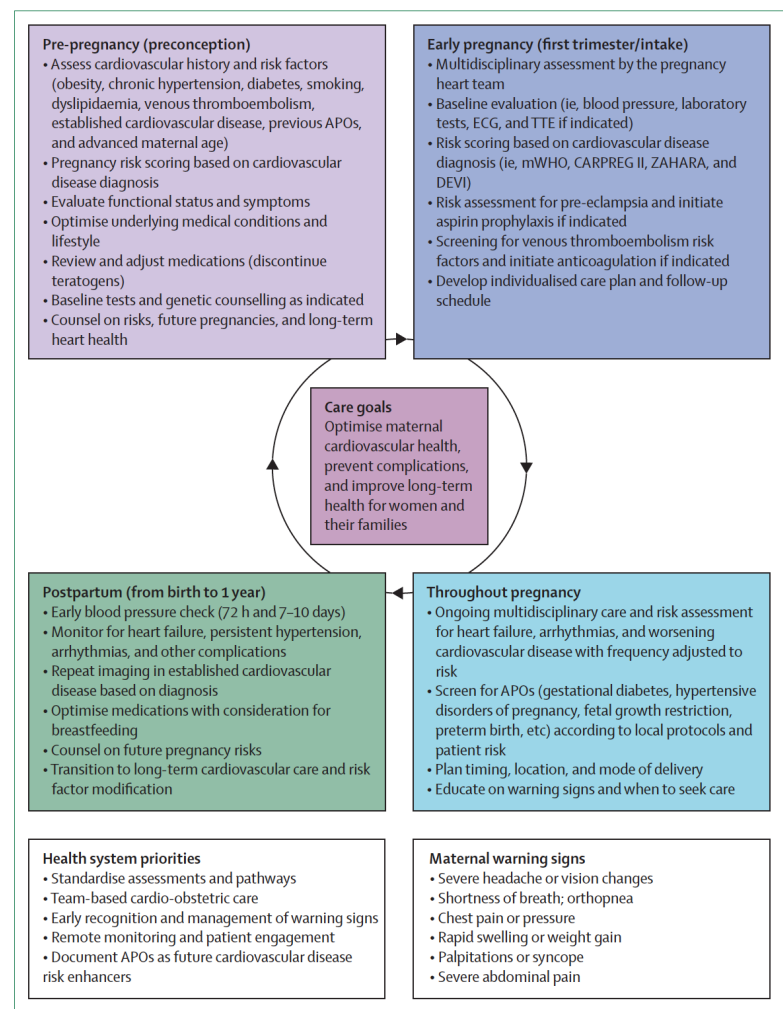


Figure 4: Cardiovascular care through every stage
APOs=adverse pregnancy outcomes. CARPREG II=Cardiac Disease in Pregnancy II. DEVI=Events in Valvular Rheumatic Heart Disease in Pregnancy. ECG=electrocardiogram. mWHO=modified updated WHO classification 2.0. TTE=transthoracic echocardiography. ZAHARA=Zwangerschap bij Aangeboren Hartafwijkingen.

Conclusion

The Cardiovascular Disease in Pregnancy Writing Group recognises certain challenges and opportunities in addressing maternal cardiovascular disease. Despite advances in risk stratification and multidisciplinary care, substantial knowledge gaps and implementation challenges continue to limit progress in maternal cardiovascular health worldwide. A substantial proportion of pregnancy-related cardiovascular complications—and up to a quarter of maternal deaths—might be preventable through earlier risk identification and improved multidisciplinary management of cardiovascular disease.^{13,184} Closing this gap requires a dual agenda: generating stronger evidence to define risk and effective interventions, and translating that evidence into equitable, system-level action across diverse care settings.

At an individual level, engaging in preventive care, preconception risk stratification, and contraception counselling is essential. At the health-system level, strengthening workforce training, including dedicated cardio-obstetrics programmes, alongside quality improvement systems and equitable access to diagnostics and therapies, is crucial to reducing fragmentation and delayed recognition.¹⁸⁵ In addition, digital health and telemedicine innovations, including the use of machine-learning algorithms for early prediction and detection of decompensation, offer important opportunities for improving maternal and fetal outcomes. At the population and policy levels, building trust and engaging under-represented communities in research, strengthening data analytics in maternal surveillance systems, and increasing research funding and regulatory support are also key opportunities.



Cardiovascular Disease and Pregnancy 3

Adverse pregnancy outcomes and long-term cardiovascular disease risk

Pregnancy provides a unique physiological stress test for the cardiovascular system, during which, adverse pregnancy outcomes (APOs) can unmask latent susceptibility to future disease. Common complications, including hypertensive disorders of pregnancy (HDP), gestational diabetes, and preterm birth (delivery before 37 weeks' gestation), identify women at substantially higher long-term risk of cardiovascular morbidity and mortality compared with women without a history of APOs. These excess risks likely reflect the combined effects of pre-existing cardiometabolic and genetic susceptibility, as well as the haemodynamic and metabolic stressors of pregnancy, heralding accelerated risk factor trajectories, relative impairment in endothelial and microvascular function, and early disease onset. This final Review in the Series extends the focus from cardiovascular disease during pregnancy and HDP to the long-term cardiovascular implications of APOs after delivery. We synthesise epidemiological data quantifying cardiovascular risk across major APO phenotypes and emerging evidence linking maternal APO history with cardiometabolic risk trajectories in offspring. We also delineate putative mechanistic pathways and summarise guidelines and consensus-informed recommendations for short-term and long-term follow-up after APOs. Finally, we propose practical approaches for integrating APO history into cardiovascular disease risk assessment and guideline-directed prevention across the female life course. We highlight key knowledge gaps, including uncertainty about optimal follow-up models, the limitations of current risk-stratification tools, and the absence of APO-specific prevention trials. We also outline priorities for mechanistic and implementation research. Positioning APOs as early, sex-specific indicators of cardiovascular risk offers a key window of opportunity to shift prevention upstream and improve cardiovascular health outcomes for women.

Hypertension, gestational diabetes, preterm birth (low birthweight) = followup

Key messages

- Cardiovascular disease in pregnancy is a major global contributor to maternal morbidity and mortality, with substantial variation in disease phenotype, recognition, access to specialist care, and outcomes across health system and resource settings
- Hypertensive disorders of pregnancy are the most common cardiovascular complication of pregnancy and require risk-stratified, resource-adapted approaches to prediction, prevention, treatment, and postpartum blood pressure management
- Adverse pregnancy outcomes identify women with increased long-term cardiovascular risk—pregnancy history should be documented and communicated beyond obstetric care to support life course prevention through risk-based surveillance and guideline-directed management of established modifiable risk factors

	Cardiovascular mortality	Chronic hypertension	Heart failure	Coronary heart disease	Stroke
Gestational hypertension	1.7	6	1.8	1.5–1.8	1.2–1.8
Pre-eclampsia	2*	3.1*	2.5–3.5	1.5–2.1	1.7–2
Gestational diabetes	1.6–2.3†	1.8	1.6	1.4–1.7	1.5
Preterm birth	1.9	1.2–2.2*†	2.9*†	1.5	1.7
Stillbirth	1.8–2.2	1.15†	1.2–1.4*	1.3–1.5	1.4–1.7
Miscarriage	1.2	1.05†	No association	1.3–1.5	1.1‡
Placental abruption	2.7	1.1†	1.7†	1.6†	1.4†

Figure 1: Relative risk of future cardiovascular disease after adverse pregnancy outcomes

Values represent approximate ranges of relative effect estimates (ie, relative risk, hazard ratio, or odds ratio) derived primarily from meta-analyses. APO=adverse pregnancy outcome. *Estimates vary by APO severity, timing, or clustering of other APOs (eg, severe or preterm phenotypes confer increased risk). †Estimates taken from large cohort studies in the absence of meta-analysis. ‡Other meta-analyses showed no association.

Panel 1: Definitions of adverse pregnancy outcomes*

Hypertensive disorders of pregnancy (HDP)

Spectrum of conditions characterised by sustained hypertension (ie, blood pressure $\geq 140/90$ mm Hg) during pregnancy or the postpartum period, including:

- Chronic hypertension: pre-existing hypertension or diagnosed before 20 weeks' gestation.
- Gestational hypertension: the American College of Obstetricians and Gynecologists (ACOG) and the International Society for the Study of Hypertension in Pregnancy (ISSHP) define gestational hypertension as de novo hypertension at 20 weeks' gestation or more in the absence of proteinuria or other signs of pre-eclampsia.
- Pre-eclampsia: ACOG define this as new-onset hypertension ($\geq 140/90$ mm Hg) after 20 weeks' gestation, with either proteinuria or evidence of end-organ dysfunction (see later; pre-eclampsia with severe features). ISSHP define pre-eclampsia as new-onset hypertension ($\geq 140/90$ mm Hg) at 20 weeks' gestation or more, with proteinuria or maternal end-organ dysfunction or uteroplacental dysfunction (including placental abruption, angiogenic imbalance, fetal growth restriction, altered umbilical artery Doppler waveform analysis, or intrauterine fetal death).
- Chronic hypertension with superimposed pre-eclampsia.
- Pre-eclampsia with severe features: pre-eclampsia with any of the following features—severe hypertension (blood pressure $\geq 160/110$ mm Hg), thrombocytopenia (platelets $<100\,000/\mu\text{L}$), impaired liver function (aminotransferases >2 times normal limits, or severe persistent right upper quadrant or epigastric pain), renal insufficiency (creatinine >1.1 mg/dL [per ACOG] or ≥ 90 $\mu\text{mol/L}$ [per ISSHP]), pulmonary oedema, new-onset headache unresponsive to medication, or visual disturbances.
- Eclampsia: new-onset generalised tonic-clonic seizures in a woman with pre-eclampsia, which cannot be attributed to other causes.
- Haemolysis, elevated liver enzymes, low platelets syndrome: pre-eclampsia accompanied by lactate dehydrogenase ≥ 600 IU/L, aspartate aminotransferase and alanine aminotransferase elevated more than twice the upper limit of normal, or a platelet count $<100\,000 \times 10^9/\text{L}$.

Gestational diabetes

Glucose intolerance with onset or first recognition during pregnancy. Diagnostic criteria are as follows:

- US (ACOG and ADA): two-step approach (50 g screen, 100 g diagnostic). Diagnosis requires ≥ 2 times normal limits.
- WHO and ISSHP: one-step approach (75 g diagnostic). Diagnosis requires ≥ 1 normal limits.

Preterm birth

Any birth before 37 completed weeks of gestation (<259 days).

Stillbirth

- US (ACOG and Centers for Disease Control and Prevention): fetal death at 20 weeks' gestation or more (or fetal weight ≥ 350 g if gestational age unknown).
- WHO: fetal death at 28 weeks or more (or fetal weight ≥ 1000 g) to ensure consistency with low-resource settings. Definitions in Europe vary by country.

Small for gestational age (SGA)

Statistical definition of size expressed as a birthweight below the tenth percentile for gestational age. Includes both constitutionally small (ie, healthy) infants and those with pathological growth restriction.

Placental abruption

Premature separation of a normally implanted placenta from the uterine wall (ie, decidua) before delivery of the fetus.

Miscarriage

- ACOG: loss of pregnancy before 20 weeks' gestation.
- WHO: loss of pregnancy before 22 weeks' gestation or a fetal weight of 500 g. Definitions in Europe varies by country.

*Adverse pregnancy outcome categories are not mutually exclusive. Preterm birth, SGA, placental abruption, and stillbirth might co-occur with HDP or reflect overlapping placental vascular pathology. SGA is a birthweight-based definition that includes both constitutionally small infants and infants with fetal growth restriction due to placental dysfunction or other pathology; consider source studies distinguishing fetal growth restriction from SGA when interpreting long-term cardiovascular disease risk. Detailed definitions of HDP and guideline variation are reviewed in the second paper in this Series.⁹

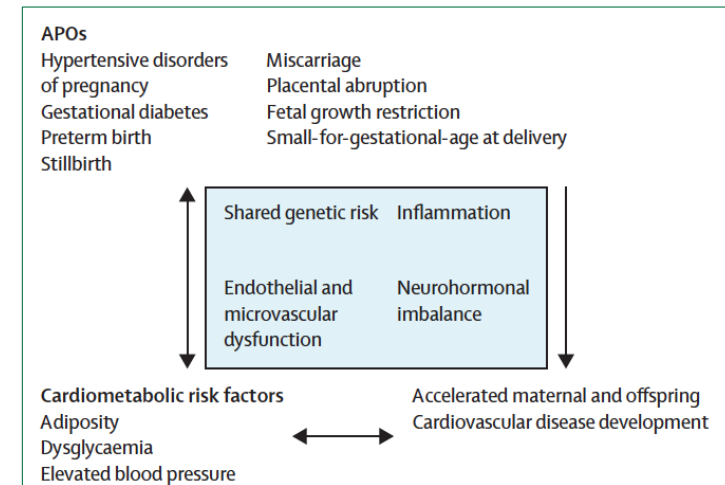


Figure 2: Potential mechanistic pathways linking APOs and cardiovascular disease

The outer arrows depict the dynamic relationships between cardiometabolic risk factors, APOs, and accelerated maternal and offspring cardiovascular disease development. The central pathways—ie, shared genetic risk, inflammation, endothelial and microvascular dysfunction, and neurohormonal imbalance—represent overlapping mechanisms that might pre-dispose to APOs and contribute to persistent postpartum cardiometabolic risk and later cardiovascular disease. APO=adverse pregnancy outcome.

	0–6 months postpartum: recovery and linkage to care	6–12 months postpartum: structured cardiometabolic risk assessment	Beyond 12 months: ongoing CVD prevention and future pregnancy planning
Objectives	To manage residual complications, ensure a safe transition from maternity to primary care, and establish awareness of APO–CVD links and the need for ongoing follow-up	To detect and treat emerging cardiometabolic risk factors early, strengthen coordination between services, and maintain continuity of care with primary care providers	To embed CVD prevention into routine adult care, maintain long-term engagement of women with previous APOs and optimise cardiovascular health before and between pregnancies
Where	Hospital and community-based postnatal and maternity clinics; coordinated with paediatric visits; transition towards primary care or community clinics	Primary care settings; integrated mother–child clinics; specialist postpregnancy or cardiometabolic clinics reserved for patients identified as high risk and requiring specialised care	Primary care clinics as usual site of care; community health programmes; home or digital monitoring platforms when available
Who	Obstetricians, maternal–fetal medicine specialists, midwives, primary care providers, nursing staff, and allied health professionals (eg, dietitians, physiotherapists, and social workers)	Primary care providers; specialist input as required for patients at high risk (eg, cardiologists, endocrinologists, and nephrologists)	Primary care provider as long-term coordinator; obstetrician for reproductive counselling and future pregnancy planning; specialists as needed
Key tasks	Comprehensive postpartum visit at around 6 weeks to review pregnancy outcomes and manage residual complications; document APO history and BP in the medical record; do basic screening (eg, BP, weight, mood, and anaemia), summarise cardiovascular risk, identify women needing extended follow-up, communicate long-term risks, and initiate handover to a primary care provider	Primary care-led visits focused on structured cardiometabolic risk assessment (eg, BP, BMI, waist circumference, lipids, glucose, and renal indices), integration of screening into routine care, adjustment or initiation of treatment as indicated, referral to cardiology, endocrinology, or nephrology for women at high risk, and development of individualised lifestyle and preventive care plans	Ongoing preventive care in primary care, with periodic reassessment of cardiovascular risk factors, optimisation of antihypertensive, lipid-lowering, and glucose-lowering therapies as needed, reinforcement of healthy lifestyle, linkage to community or workplace health resources, and re-engagement of obstetric or cardio-obstetric specialists for preconception counselling and planning of future pregnancies

APO=adverse pregnancy outcome. BP=blood pressure. CVD=cardiovascular disease.

Table 1: Postpartum continuity-of-care framework after adverse pregnancy outcomes

	Timing postpartum	Ongoing follow-up
HDP test		
BP	Daily	Home BP monitoring at least daily initially, then taper frequency once BP is controlled or medications are stable; continue until BP is consistently normalised and medications are discontinued if started; thereafter, assess BP at least annually when feasible; prioritise closer follow-up for higher-risk APO phenotypes, elevated BP, or antihypertensive therapy
Gestational diabetes test		
75 g OGTT	4–12 weeks	If within normal limits, screen for diabetes or prediabetes with fasting glucose or HbA _{1c} every 1–3 years; if prediabetes, intensify lifestyle therapy and consider metformin, with at least annual glycaemic testing
All adverse pregnancy outcome tests		
Weight, height, BMI, and waist circumference	3–6 months	Repeat at ~12 months to assess return to pre-pregnancy weight; at least annually thereafter in primary care, especially if excess adiposity persists
BP	3–6 months as part of a comprehensive evaluation	At least annually for all women with previous APO; more frequently if elevated or on antihypertensive therapy
Fasting lipid profile with or without lipoprotein(a) once, per local guidelines	3 months after pregnancy-related lipid changes have regressed	If outside normal limits, repeat lipid test after 6–12 months of lifestyle intervention; thereafter per guideline-directed intervals
Serum creatinine:eGFR; urine albumin:creatinine; or protein:creatinine ratios	3–6 months	Particularly in women with HDP and kidney injury during pregnancy; if outside normal limits, repeat at least yearly; if within normal limits, repeat based on clinical risk (eg, every 1–3 years after HDP)
Edinburgh Postnatal Depression Scale or other validated depression or anxiety screening tool	3–6 months and earlier as part of routine postpartum care	Screen at each clinical visit in the first postpartum year or whenever symptoms are suspected; refer for treatment as indicated
APO=adverse pregnancy outcome. BP=blood pressure. eGFR=estimated glomerular filtration rate. HDP=hypertensive disorders of pregnancy. OGTT=oral glucose tolerance test.		
Table 2: Suggested cardiometabolic and mental health screening after adverse pregnancy outcomes		

Panel 2: Future research priorities

Clarify mechanisms and causal pathways

Better delineate causal pathways linking adverse pregnancy outcomes (APOs) to later cardiovascular disease to define mechanistically distinct APO subtypes and enable more targeted prevention strategies

Define optimal postpartum and longitudinal care

Determine the ideal structure, timing, and intensity of follow-up after APOs, including which women—and offspring—benefit most from longer-term specialist involvement

Test scalable care pathways in real-world settings

Do pragmatic implementation and comparative effectiveness trials of alternative postpartum and longitudinal care models to identify approaches that are effective, scalable, and resource-conscious

Generate trial evidence for prevention strategies

Address the scarcity of randomised trials by leveraging alternative designs (eg, pragmatic or registry-based randomised trials and cluster randomisation) and rigorously validated imaging or biomarker endpoints to accelerate actionable evidence

Assess durability of early postpartum interventions

Extend follow-up of trials testing early postpartum interventions (eg, intensive early postpartum blood pressure control following hypertensive disorders of pregnancy) to determine the duration and clinical relevance of benefit

Evaluate contemporary obesity and metabolic therapies

Test the safety and efficacy of GLP-1 receptor agonists and SGLT2 inhibitors in women with previous APOs, with outcomes spanning cardiometabolic risk factors and longer-term cardiovascular endpoints

Young adulthood and pre-pregnancy	Pregnancy	Postpartum 0–12 months	Interpregnancy and early midlife	Midlife and beyond
Optimise cardiovascular health • Screen and treat hypertension, dyslipidaemia (including lipoprotein[a]), obesity, and diabetes • Counsel on lifestyle, contraception, and pregnancy planning • Change to pregnancy-compatible pharmacotherapies when appropriate	Identify APOs • Diagnose and manage APOs • Record APO history, document type and severity, and communicate to longitudinal clinicians and general practitioner	Early postpartum risk assessment • BP follow-up after HDP and 75 g OGTT after GDM • Baseline weight, BP, lipids (~3 months postpartum), and renal function, as well as supporting breastfeeding and mental health	Interpregnancy and early midlife (age 20–40 years) • Comprehensive cardiovascular risk assessment • Annual BP, as well as glycaemia and lipids every 1–3 years • Intensify lifestyle and therapies based on APO history and other risk enhancers	Comprehensive CVD prevention • Treat hypertension, LDLc, and diabetes aggressively • Consider CAC to refine risk

Figure 3: Strategies to integrate adverse pregnancy outcomes into life course cardiovascular disease prevention

APO=adverse pregnancy outcome. BP=blood pressure. CAC=coronary artery calcification. CVD=cardiovascular disease. GDM=gestational diabetes. HDP=hypertensive disorders of pregnancy. LDLc=low-density lipoprotein cholesterol. OGTT=oral glucose test.

Conclusion

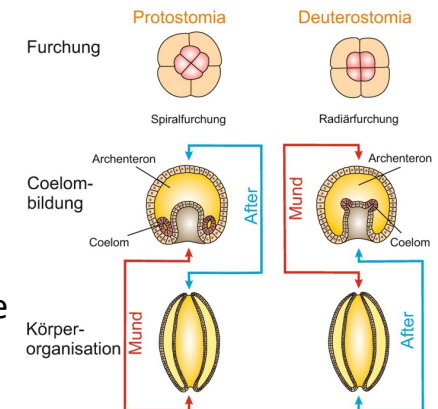
This three-part Series examined cardiovascular disease across the spectrum of pregnancy and beyond. The preceding Reviews define the burden and management of cardiovascular disease in pregnancy, with attention focused on HDP as the most common pregnancy-specific cardiovascular disorder, and a major contributor to maternal morbidity and mortality. This final Review carries this framework forward, emphasising that APOs should not be treated as isolated obstetric events, but as early markers of long-term cardiovascular risk (figure 3). Together, these perspectives come together on a key message: pregnancy reveals latent cardiovascular risk and offers an important window for prevention. However, APOs are treated as transient obstetric complications, rather than signals of long-term cardiovascular risk in most health systems. Cardiovascular disease is a leading cause of maternal morbidity and mortality worldwide,⁴ and even for HDP—in which structured risk assessment, aspirin prophylaxis, and biomarker-guided evaluation have reshaped clinical practice—risk prediction is imprecise, preventive strategies are only partially effective, and disease-modifying therapies are absent. Integrating pregnancy history into cardiovascular risk assessment might identify women at high risk early, and improve prevention across the life course.

⁴ The Working Group of Cardiovascular Disease in Pregnancy recognises that the evidence associating APOs with increased long-term cardiovascular disease risk is now robust, but clinical interpretation requires nuance. APOs should not be regarded simply as isolated obstetric exposures or as fully established causal mediators of later cardiovascular disease. An immediate clinical opportunity for improvement would be to ensure that APO history is consistently documented, communicated beyond obstetric care, and used to prompt early recognition and guideline-directed management of established, modifiable risk factors, including blood pressure, dysglycaemia, adiposity, dyslipidaemia, and kidney dysfunction. This approach should extend beyond the so-called fourth trimester into life course prevention, while adapting follow-up intensity to APO severity, recurrence, persistent cardiometabolic abnormalities, and local resources. A major opportunity exists in research to move from documenting associations to defining what APO phenotypes identify the greatest risk, clarifying the relative contributions of shared susceptibility versus pregnancy-related vascular dysfunction, improving risk stratification in young women, and testing whether structured APO-informed prevention improves cardiovascular health. Progress will require prospective pre-pregnancy and postpartum phenotyping, causal-triangulation designs, and pragmatic implementation trials.

Die Tierstämme im Überblick

Sowohl Protostomier als auch Deuterostomier umfassen eine gewaltige Vielfalt an Lebewesen. Hier ist die Zuordnung der bekanntesten Tierstämme:

- **Protostomia (Urmünder):**
 - **Gliederfüßer (Arthropoda):** Insekten, Spinnentiere, Krebstiere und Tausendfüßer (die artenreichste Gruppe der Erde).
 - **Weichtiere (Mollusca):** Schnecken, Muscheln und Tintenfische.
 - **Ringelwürmer (Annelida):** Regenwürmer und Blutegel.
 - **Fadenwürmer (Nematoda) & Plattwürmer (Plathelminthes).**
- **Deuterostomia (Neumünder):**
 - **Chordatiere (Chordata):** Alle Wirbeltiere (Säugetiere, Vögel, Reptilien, Amphibien, Fische) sowie Lanzettfischchen und Manteltiere.
 - **Stachelhäuter (Echinodermata):** Seesterne, Seeigel, Seewalzen und Schlangensterne.
 - **Kiemenlochtere (Hemichordata):** Eichelwürmer.



Die räumliche Transkriptomik (engl. *Spatial Transcriptomics*) ist eine moderne molekularbiologische Technik, mit der die Genexpression direkt in einer Gewebeprobe gemessen und gleichzeitig der genaue räumliche Ort der RNA-Moleküle bestimmt werden kann.

Spatially resolved single-cell atlas reveals the macroevolutionary trajectory of animal hearts



INTRODUCTION: The heart represents a key evolutionary innovation in the rise of complex animal life. Yet the **cellular and molecular basis of heart diversity**, its deep evolutionary origins, and the modes of convergent versus divergent evolution across phyla are largely unresolved. Addressing these fundamental questions is critical not only for understanding metazoan organ evolution but also for providing evolutionary context to human cardiac biology and disease. However, existing cardiac research leans narrowly on humans and a limited set of classic model organisms, leaving key groups, such as mollusks, arthropods, and basal chordates, severely underrepresented, which hinders **a holistic view of cardiac origins and evolutionary principles**. A comprehensive understanding of these unresolved questions therefore depends on integrating multimodal data from evolutionarily diverse species, an approach that remains challenging when applied to studies that involve nonmodel species across deep evolutionary timescales.

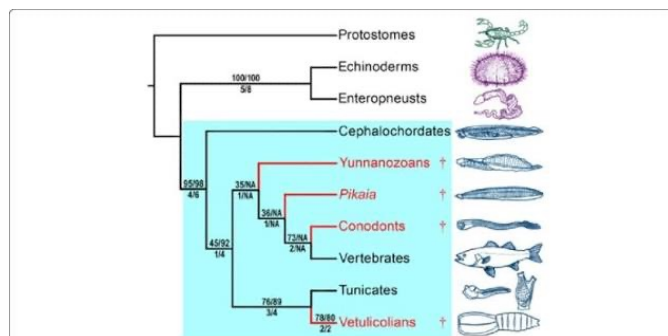
RATIONALE: To address these gaps, we integrated comparative genomics with bulk, single-cell, and spatial transcriptomics to profile adult hearts across a broad range of evolutionarily diverse taxa. Our sampling spanned protostomes (fruit fly, horseshoe crab, shrimp, crab, scallop, oyster, snail, and octopus) and deuterostomes (amphioxus, sea squirt, lamprey, skate, bamboo shark, zebrafish, lungfish, axolotl, tropical clawed frog, *Xenopus*, gecko, turtle, red junglefowl, zebra finch, mouse, rat, tree shrew, and human). This design enabled systematic interrogation of conserved, divergent, and convergently evolved features of the heart at the molecular, cellular, and tissue architecture levels. To empower the broader community, we have established an open database,

HEART

(<https://db.genomics.cn/stomics/heart/>), which offers both a resource and an analytical framework for cross-species exploration of cardiac molecular profiles.

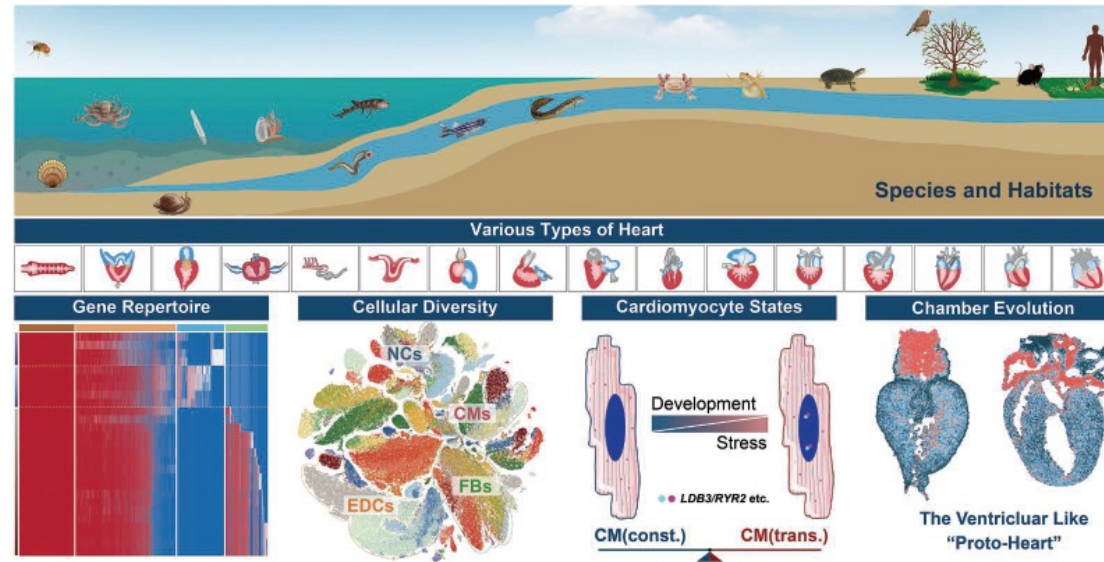
RESULTS: Our analysis revealed that animal hearts share more than 60% of gene modules and a conserved cellular foundation. Notably, certain atrial and ventricular characteristics were inherited by both protostomes and deuterostomes, pointing to an ancient origin possibly traceable to the last common bilaterian ancestor. The early expansion of cardiac genes in chordates aligns with early chordate whole-genome duplication events.

The diversity in cardiac architecture reflects lineage-specific genetic innovations, flexible cell-type combinations, and molecular-level functional adaptations, with both gene loss and gain events shaping cardiac evolution. Leveraging **spatial transcriptomics**, we identified an evolutionary conserved cardiomyocyte state that correlates with cardiac development and stress. Finally, our evidence suggests that the ancestral “proto-heart” consisted primarily of ventricular-like myocardium.



CONCLUSION: Our work reveals the macroevolutionary trajectory of animal hearts and illuminates the ancestral origin of their pumping function. By tracing distinct molecular trajectories across major cardiac cell types and identifying conserved chamber features shared by protostomes and deuterostomes, this study offers a framework for decoding heart evolution across bilaterians. Collectively, this work provides an open resource and a scalable research paradigm for investigating the evolutionary mechanisms of complex organs, exemplified by the heart, across deep evolutionary timescales.

Well-known examples of protostomes are **arthropods, molluscs, annelids, flatworms and nematodes**. In deuterostomes, **the developing embryo's first opening (the blastopore) becomes the anus and cloaca**, while the mouth is formed at a different site later on.

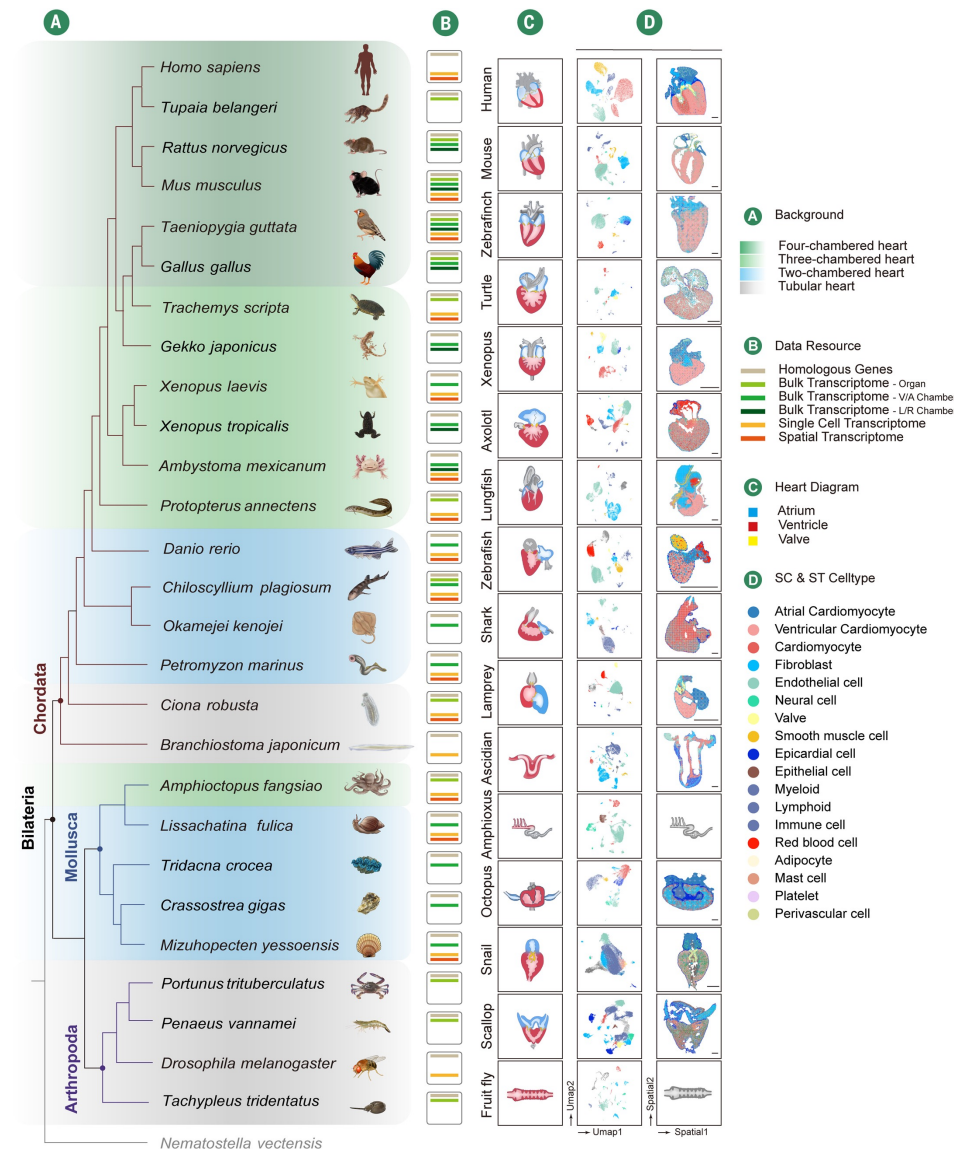


Bilaterian heart evolution. Animal hearts evolved diverse anatomical structures and physiological functions to adapt to their habitats. A multiomics analysis across chordates, arthropods, and mollusks revealed that **bilaterian hearts share a core gene repertoire**, combined with evolutionary gained genes, driving cardiac cellular diversity and the emergence of atria from a ventricular foundation, along with an evolutionarily conserved cardiomyocyte state in response to cardiac development and stress. CM, cardiomyocyte; CM(const.), constitutive cardiomyocyte state; CM(trans.), transient cardiomyocyte state; EDC, endothelial cell; FB, fibroblast; NC, neural cell.

The study highlights a **stepwise "add-on" strategy**. Bilateria hearts share an ancient, common cellular and genetic foundation, with ancestral "proto-hearts" primarily consisting of a ventricular-like myocardium. Lineage-specific complexities and architectural changes (such as multi-chamber evolution) developed over time by introducing flexible combinations and expression adaptations rather than full genomic rewrites.

The multi-omics atlas:

- The **27 specific animal species** profiled (including chordates, arthropods, and mollusks).
- The discovered **hypoxia-stimulated cardiomyocyte state** linked to regeneration.
- How **whole-genome duplication events** in early chordates shaped cardiac architecture





How one smart man lives without a phone

The iPhone isn't even 20 years old yet and it and its smartcousins have already rewired modern life — people's behavior, expectations, even the way they pay attention. It has remade mental landscapes much as, a century ago, the automobile remade physical ones.

Which is one of the reasons I treasure my friendship with Adrian: He has never owned a cellphone. Never. Not an iPhone, not a BlackBerry, not even a Nokia.

I should clarify that Adrian is not a man who “doesn't have a phone” because an assistant six feet behind him has two. He genuinely does not have a mobile phone. He is living, essentially, in a parallel world.

Adrian's phonelessness has, at times, been annoying for his friends.

He once came to visit my family in Amagansett, New York, coming from Brooklyn. He took the train but didn't realize he needed to change at Jamaica in Queens. Train announcements seem to have dwindled on public transportation because it is increasingly assumed that every traveler is being personally shepherded across the planet by a small glowing screen.

Not Adrian.