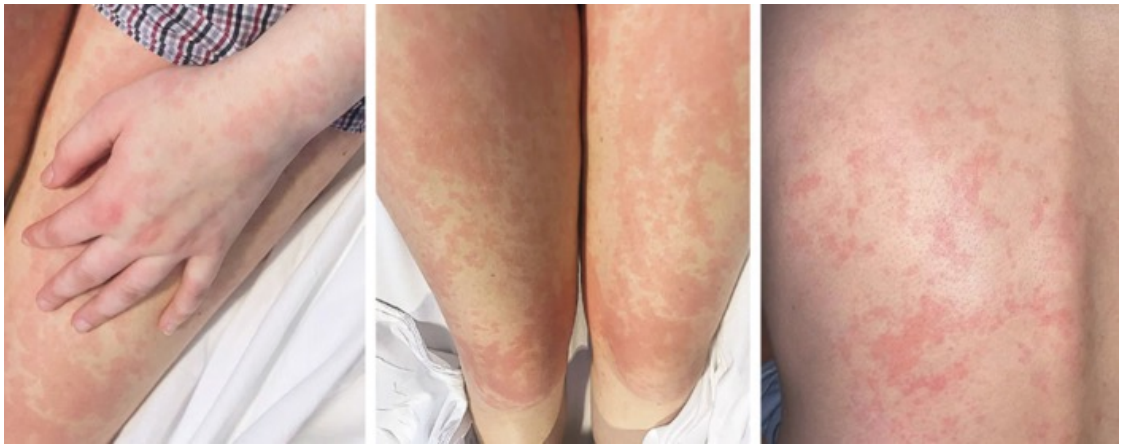
https://www.mdc-berlin.de/de/veroeffentlichungstypen/clinical-journal-club

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



A 27-year-old woman presented with a 2-week history of joint pain, fever, sore throat, and a nonpruritic rash that worsened during febrile episodes. Physical examination was notable for generalized lymphadenopathy and swelling of the wrists, knees, and ankles. Laboratory studies showed neutrophilic leukocytosis, an elevated C-reactive protein level and erythrocyte sedimentation rate, and ferritin level of 4053 µg per liter (reference range, 10 to 200). An antinuclear antibody was negative. Which of the following is the most likely diagnosis?

Testing for autoimmune and infectious conditions was negative and a diagnosis of adult-onset Still's disease was made. Still's disease is an uncommon autoinflammatory disorder characterized by fever, polyarthritis, and an evanescent rash that may resolve when the patient is afebrile. The diagnosis is made in patients who have typical clinical findings and elevated levels of inflammatory markers and ferritin, after infectious, malignant, and autoimmune conditions have been ruled out.

Adult-onset Still's disease

Drug reaction with eosinophilia and systemic symptoms

Parvovirus B-19

Sarcoidosis

Scarlet fever

Der **Morbus Still des Erwachsenen** (Adult-onset Still's disease, AOSD) ist eine seltene autoinflammatorische Erkrankung, die durch eine Kombination aus hohem Fieber, einem lachsfarbenen Hautausschlag und Gelenkschmerzen gekennzeichnet ist. Sie gilt als die Erwachsenenform der systemischen juvenilen idiopathischen Arthritis (Still-Syndrom bei Kindern).

Kernsymptome

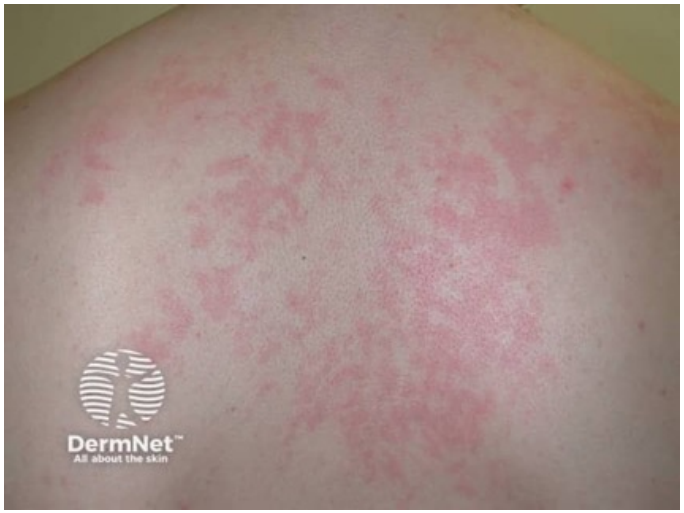
Die Erkrankung tritt oft schubweise auf und zeigt meist folgende typische Merkmale:

•**Fieber:** Plötzlich auftretendes, hohes Fieber (oft > 39 °C), das meist einmal oder zweimal täglich (häufig abends) spitzt und dann wieder abfällt.

•**Hautausschlag:** Ein flüchtiger, lachsrosa oder rötlicher Ausschlag, der meist während der Fieberschübe auftritt und danach wieder verschwindet.

•**Gelenkschmerzen:** Entzündungen und Schmerzen in den Gelenken (Arthritis/Arthralgie), die oft chronisch werden können. Besonders häufig betroffen sind Knie, Handgelenke und Knöchel.

•**Halsschmerzen:** Ein häufiges frühes Symptom, oft begleitet von geschwollenen Lymphknoten im Halsbereich.



Diagnose

Da es keinen einzelnen spezifischen Test gibt, ist AOSD eine **Ausschlussdiagnose**. Ärzte nutzen oft die sogenannten **Yamaguchi-Kriterien** zur Einordnung.

Typische Laborbefunde sind:

•Extrem erhöhte **Ferritin-Werte** (ein Eisen-Speicherprotein).

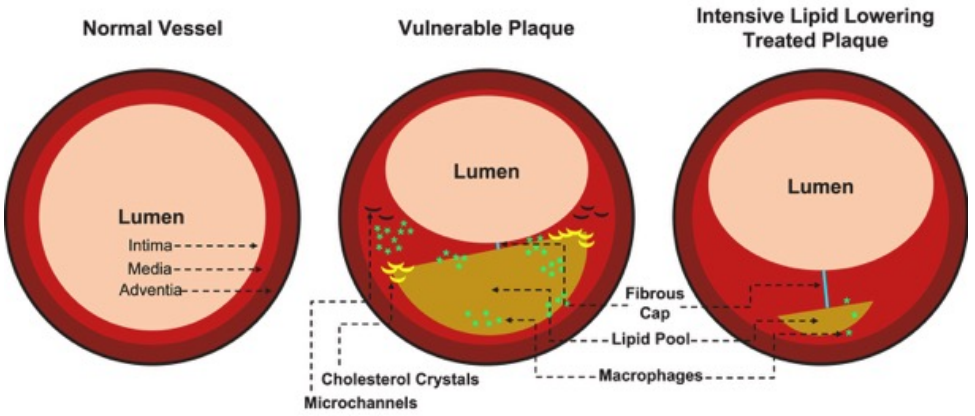
•Stark erhöhte Anzahl weißer Blutkörperchen (**Leukozytose**).

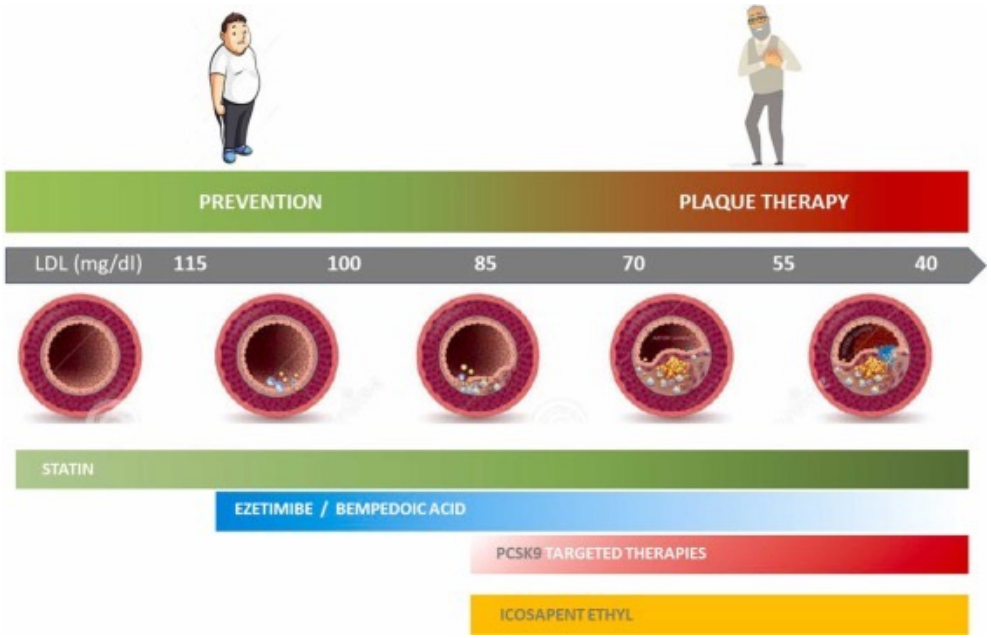
•Negative Ergebnisse bei Tests auf Rheumafaktoren und antinukleäre Antikörper (ANA).

LDL <70 mg/dL?

oder

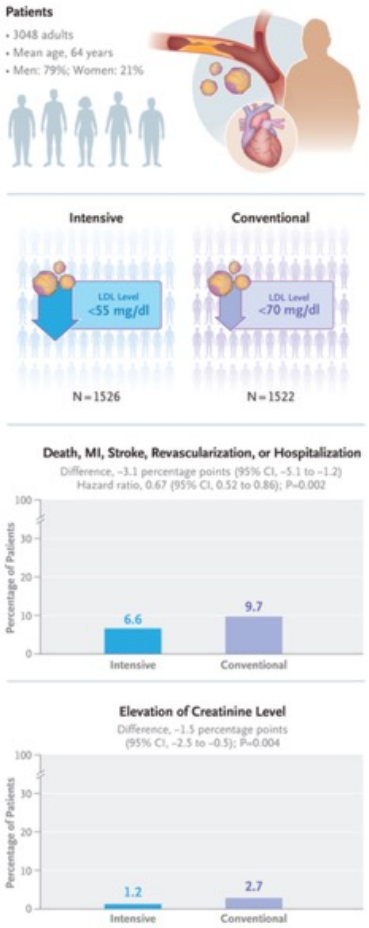
LDL <55 mg/dL?





Intensive LDL Cholesterol Targeting in Atherosclerotic Cardiovascular Disease

Despite guideline recommendations, evidence from randomized trials evaluating the appropriate low-density lipoprotein (LDL) cholesterol target for secondary prevention in patients with atherosclerotic cardiovascular disease remains limited. In this open-label superiority trial conducted in South Korea, we randomly assigned patients with atherosclerotic cardiovascular disease in a 1:1 ratio to a target LDL cholesterol level of less than 55 mg per deciliter (1.4 mmol per liter) (intensive-targeting group) or less than 70 mg per deciliter (1.8 mmol per liter) (conventional-targeting group). The primary end point was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, any revascularization, or hospitalization for unstable angina at 3 years. Safety was also assessed.



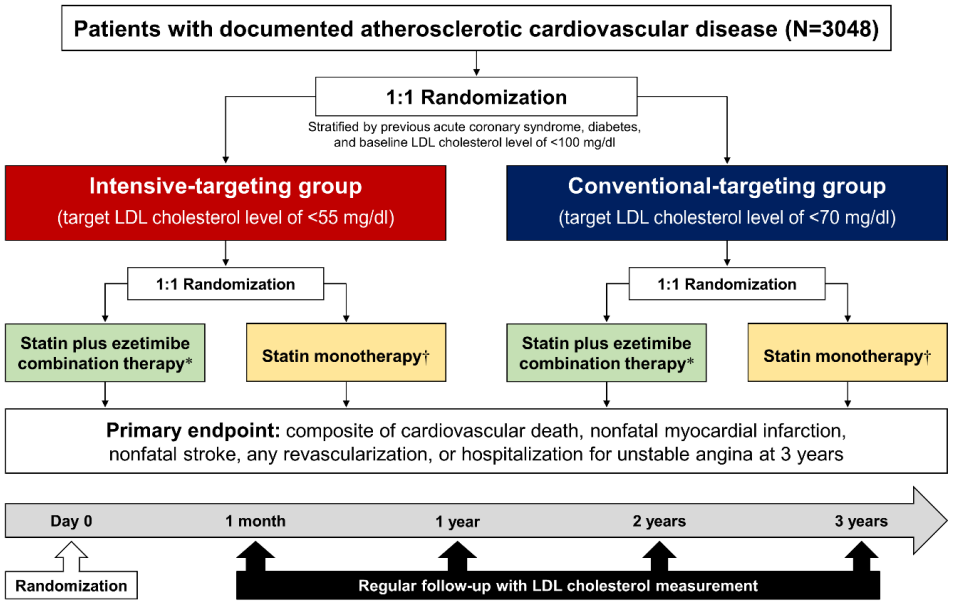
Patients with atherosclerotic cardiovascular disease are at high risk or very high risk for future cardiovascular events. Low-density lipoprotein (LDL) cholesterol is the primary target for management of dyslipidemia, and intensive lowering of LDL cholesterol levels is recommended in these patients. These recommendations are based on data from previous randomized trials showing that high-intensity statins or the addition of ezetimibe or proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitors to statins reduces LDL cholesterol levels and the risk of cardiovascular events. However, these trials aimed primarily to evaluate the effects of intensive lipid-lowering drugs rather than to determine specific targets for LDL cholesterol levels. Therefore, the Ez-PAVE trial (Effects of Ezetimibe Combination Therapy for Patients with Atherosclerotic Cardiovascular Disease — Randomized Comparison of LDL Cholesterol Targeting <70 mg per Deciliter vs. <55 mg per Deciliter) was designed to investigate whether targeting an LDL cholesterol level of less than 55 mg per deciliter is superior to targeting a level of less than 70 mg per deciliter for preventing recurrent major cardiovascular events in patients with atherosclerotic

Trial Population

Patients were eligible to participate in the trial if they were 19 to 80 years of age and had documented atherosclerotic cardiovascular disease, which was defined as the previous occurrence or presence of at least one of the following: previous acute coronary syndrome (myocardial infarction or unstable angina), stable angina with imaging or functional studies, coronary revascularization or other arterial revascularization, stroke or transient ischemic attack, or peripheral artery disease.

Randomization and Treatment

Eligible patients were randomly assigned in a 1:1 ratio to a target LDL cholesterol level of less than 55 mg per deciliter (intensive-targeting group) or less than 70 mg per deciliter (conventional-targeting group). A Web response system with permuted-block randomization (with mixed blocks of 4 or 6) was used at each participating site for randomization, with stratification according to previous acute coronary syndrome (yes or no), the presence of diabetes (yes or no), and baseline LDL cholesterol level (<100 mg per deciliter [<2.6 mmol per liter] or ≥100 mg per deciliter). Furthermore, the patients in each group underwent a second random assignment in a 1:1 ratio to one of two treatment regimens: statin monotherapy or combination therapy with statin plus ezetimibe. The patients assigned to the statin-monotherapy group were further randomly assigned in a 1:1 ratio to receive one of two statin types: rosuvastatin or atorvastatin.



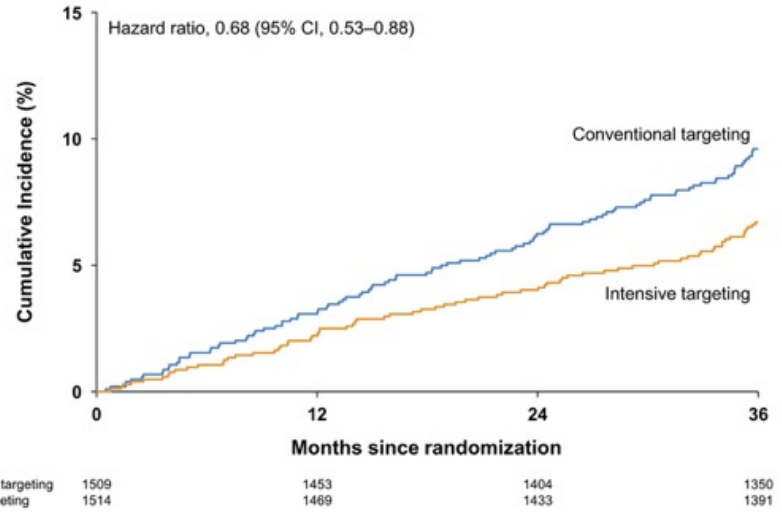
Eligible patients were randomly assigned in a 1:1 ratio to a target LDL cholesterol level of less than 55 mg per deciliter (intensive-targeting group) or less than 70 mg per deciliter (conventional-targeting group), stratified by previous acute coronary syndrome, presence of diabetes, and baseline LDL cholesterol level of less than 100 mg per deciliter. Furthermore, patients in each group were secondarily randomly assigned in a 1:1 ratio to receive one of two therapy regimens: statin monotherapy or statin plus ezetimibe combination therapy. Basic instructions (Section S4) were provided to guide initial and follow-up therapy for achieving the assigned target LDL cholesterol levels. LDL denotes low-density lipoprotein.

* For patients assigned to receive statin plus ezetimibe combination therapy, they received rosuvastatin as the statin component.

† For patients assigned to receive statin monotherapy, they were further randomly assigned in a 1:1 ratio to receive either rosuvastatin or atorvastatin.

Composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, any revascularization, or hospitalization for unstable angina at 3 years.

Figure S5. Primary end point in the per-protocol population



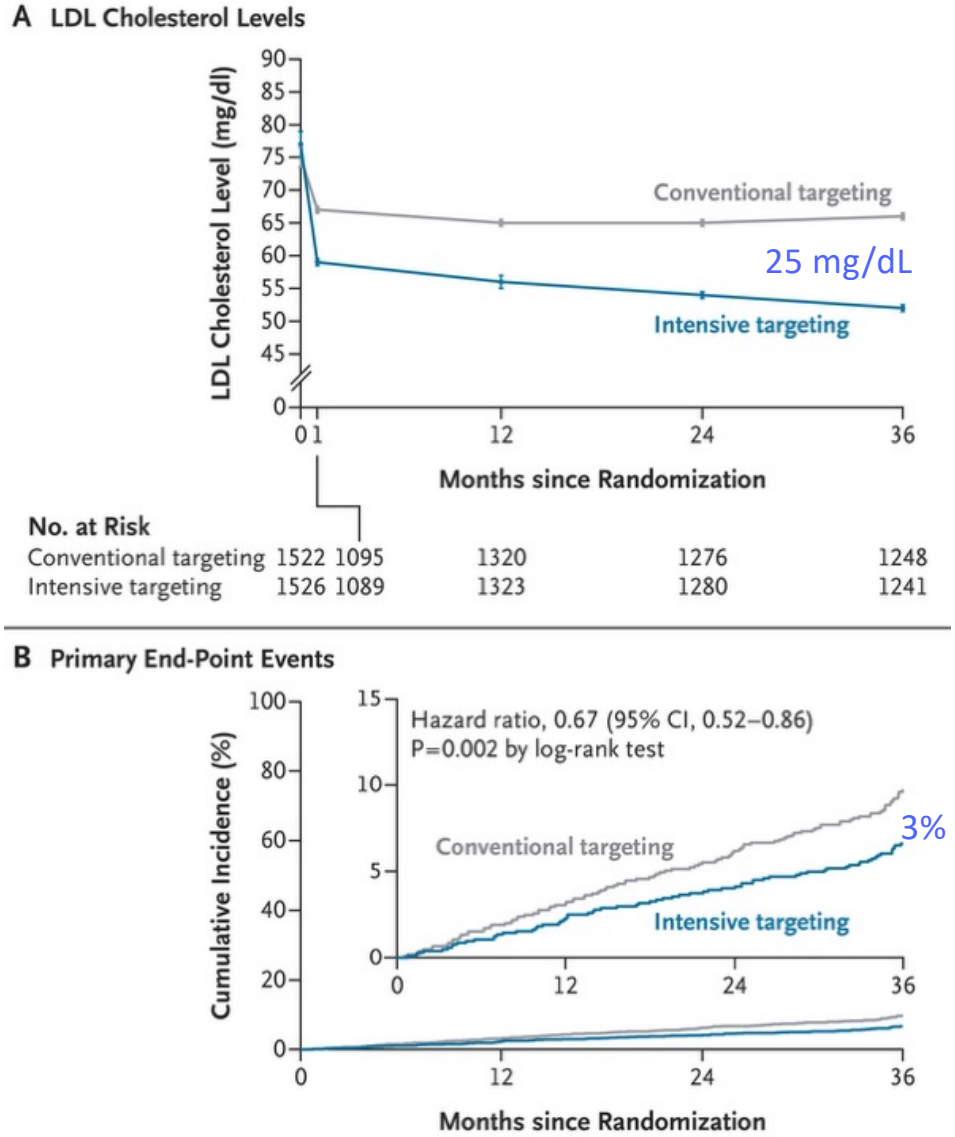
Characteristic	Intensive Targeting (N=1526)	Conventional Targeting (N=1522)
Age — yr	64.2±9.1	64.6±9.0
Male sex — no. (%)	1204 (78.9)	1206 (79.2)
Median height (IQR) — cm	167 (160–171)	166 (160–170)
Median weight (IQR) — kg	68 (62–75)	68 (61–75)
Median body-mass index (IQR)†	24.9 (23.0–26.8)	24.7 (23.1–26.8)
Type of atherosclerotic cardiovascular disease — no. (%)‡		
Previous acute coronary syndrome	827 (54.2)	867 (57.0)
Myocardial infarction	460 (30.1)	481 (31.6)
Unstable angina	367 (24.0)	386 (25.4)
Stable angina with imaging or functional studies§	744 (48.8)	730 (48.0)
Coronary or other arterial revascularization	1015 (66.5)	1034 (67.9)
Percutaneous coronary intervention	884 (57.9)	900 (59.1)
Coronary-artery bypass grafting	58 (3.8)	71 (4.7)
Other arterial revascularization	88 (5.8)	82 (5.4)
Stroke or transient ischemic attack	57 (3.7)	60 (3.9)
Peripheral artery disease	132 (8.7)	134 (8.8)
Hypertension — no. (%)	1136 (74.4)	1103 (72.5)
Diabetes — no. (%)	605 (39.6)	602 (39.6)
Chronic kidney disease — no. (%)¶	91 (6.0)	87 (5.7)
Current smoker — no. (%)	348 (22.8)	388 (25.5)
Median lipid level (IQR) — mg/dl		
LDL cholesterol	77 (60–96)	75 (61–97)
HDL cholesterol	46 (40–55)	47 (39–54)
Total cholesterol	143 (123–167)	143 (123–167)
Triglycerides	117 (87–159)	115 (83–163)
Lipid-lowering therapy — no. (%)		
Statin‖		
High intensity	352 (23.1)	349 (22.9)
Moderate intensity	1036 (67.9)	1038 (68.2)
Low intensity	10 (0.7)	1 (0.1)
None	128 (8.4)	134 (8.8)
Ezetimibe	454 (29.8)	421 (27.7)

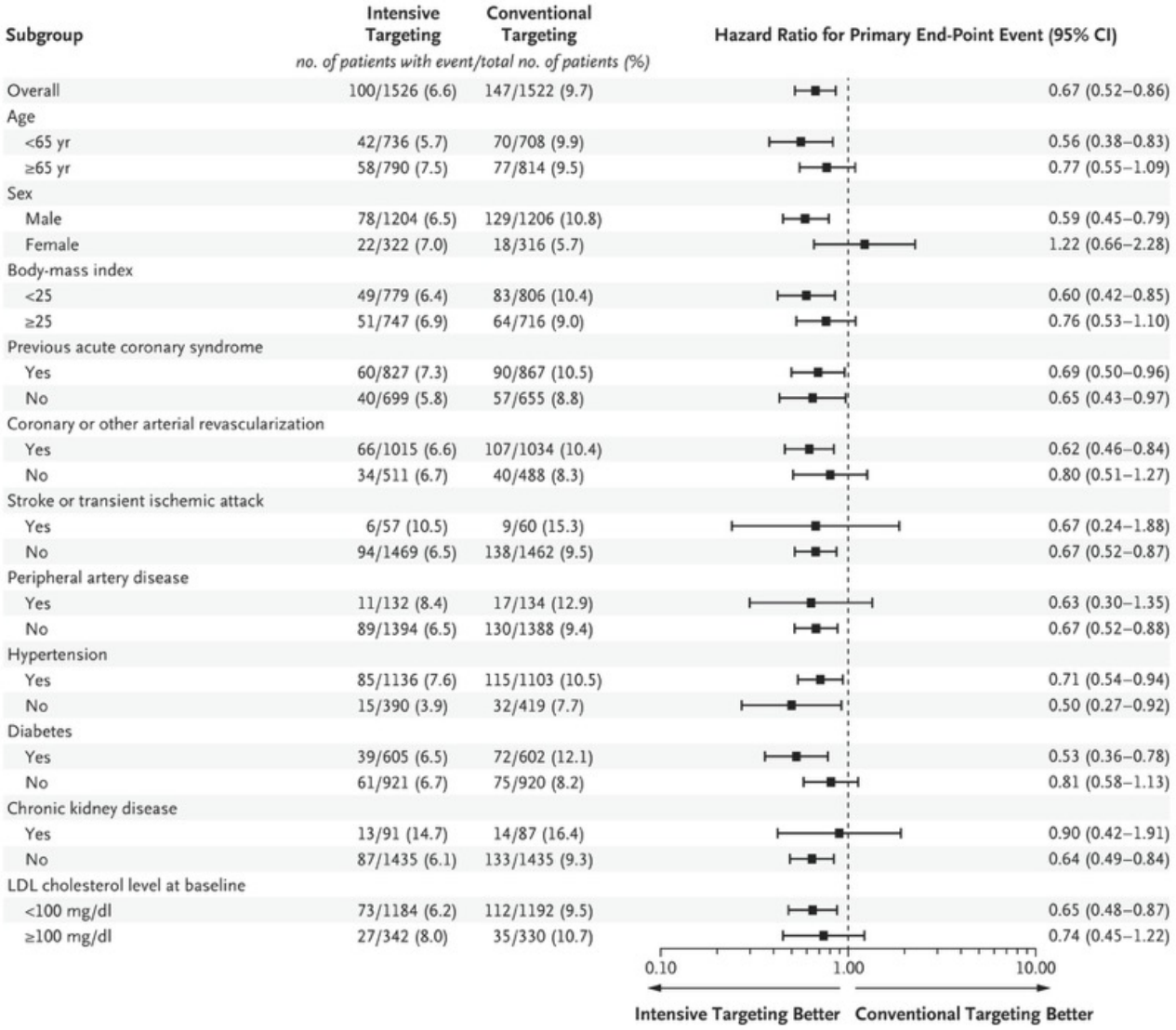
Primary and Secondary End Points.

End Point	Intensive Targeting (N=1526)	Conventional Targeting (N=1522)	Difference (95% CI)	Hazard Ratio (95% CI)
	no. of patients (%)		*percentage points*	
Primary end point				
Composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, any revascularization, or hospitalization for unstable angina	100 (6.6)	147 (9.7)	−3.1 (−5.1 to −1.2)	0.67 (0.52 to 0.86)†
Secondary end points				
Components of the primary end point				
Death from cardiovascular causes	15 (1.0)	18 (1.2)	−0.2 (−0.9 to 0.5)	0.83 (0.42 to 1.65)
Nonfatal myocardial infarction	12 (0.8)	26 (1.7)	−0.9 (−1.7 to −0.1)	0.46 (0.23 to 0.91)
Nonfatal stroke	8 (0.5)	10 (0.7)	−0.1 (−0.7 to 0.4)	0.80 (0.32 to 2.03)
Ischemic stroke	7 (0.5)	7 (0.5)	−0.0 (−0.5 to 0.5)	1.00 (0.35 to 2.85)
Hemorrhagic stroke	1 (0.1)	3 (0.2)	−0.1 (−0.4 to 0.1)	0.33 (0.03 to 3.20)
Any revascularization	72 (4.8)	113 (7.5)	−2.7 (−4.5 to −1.0)	0.63 (0.47 to 0.84)
Percutaneous coronary intervention	67 (4.5)	99 (6.6)	−2.2 (−3.8 to −0.5)	0.67 (0.49 to 0.91)
Coronary-artery bypass grafting	1 (0.1)	7 (0.5)	−0.4 (−0.8 to −0.0)	0.14 (0.02 to 1.15)
Other arterial revascularization	6 (0.4)	9 (0.6)	−0.2 (−0.7 to 0.3)	0.67 (0.24 to 1.87)
Hospitalization for unstable angina	22 (1.5)	36 (2.4)	−0.9 (−1.9 to 0.1)	0.61 (0.36 to 1.03)
Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	34 (2.3)	54 (3.6)	−1.3 (−2.5 to −0.1)	0.63 (0.41 to 0.96)
Composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or any revascularization	95 (6.3)	141 (9.3)	−3.0 (−5.0 to −1.1)	0.66 (0.51 to 0.86)
Composite of death from cardiovascular causes, nonfatal myocardial infarction, or any revascularization	88 (5.8)	132 (8.7)	−2.9 (−4.8 to −1.1)	0.66 (0.50 to 0.86)
Composite of death from any cause, nonfatal myocardial infarction, nonfatal stroke, any revascularization, or hospitalization for unstable angina‡	116 (7.6)	157 (10.4)	−2.7 (−4.8 to −0.7)	0.73 (0.57 to 0.92)

Safety End Points.

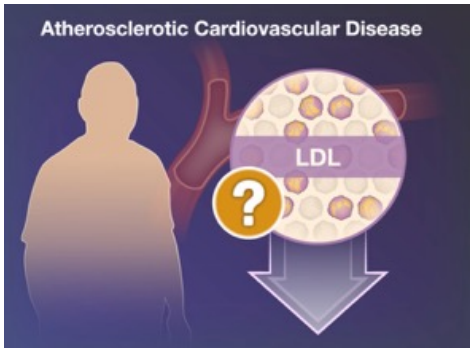
End Point	Intensive Targeting (N=1526)	Conventional Targeting (N=1522)	Difference (95% CI)	P Value
			percentage points	
New-onset diabetes among patients without diabetes at baseline — no. of patients/total no. (%)	153/921 (16.6)	148/920 (16.1)	0.5 (−2.9 to 3.9)	0.81
Worsening of glycemic control among patients with diabetes at baseline — no. of patients/total no. (%)	295/605 (48.8)	305/602 (50.7)	−1.9 (−7.5 to 3.7)	0.55
Statin-associated muscle symptoms leading to changes in therapy dose or regimen — no. of patients (%)	15 (1.0)	9 (0.6)	0.4 (−0.2 to 1.0)	0.31
Diagnosis of cancer — no. of patients (%)	36 (2.4)	40 (2.6)	−0.3 (−1.4 to 0.8)	0.72
Cataract surgery — no. of patients (%)	20 (1.3)	16 (1.1)	0.3 (−0.5 to 1.0)	0.62
Laboratory abnormalities at any time				
Aminotransferase elevation — no. of patients (%)†	37 (2.4)	23 (1.5)	0.9 (−0.1 to 1.9)	0.09
Creatinine elevation — no. of patients/total no. (%)‡	18/1517 (1.2)	41/1515 (2.7)	−1.5 (−2.5 to −0.5)	0.004
Creatine kinase elevation — no. of patients (%)§	4 (0.3)	4 (0.3)	0.0 (−0.4 to 0.4)	1.00

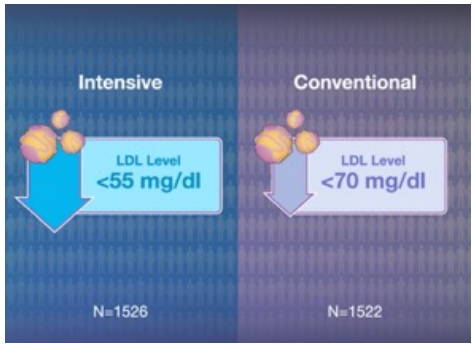


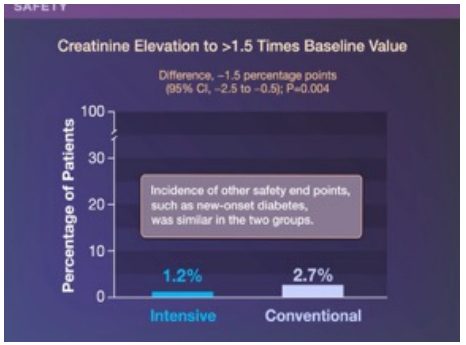


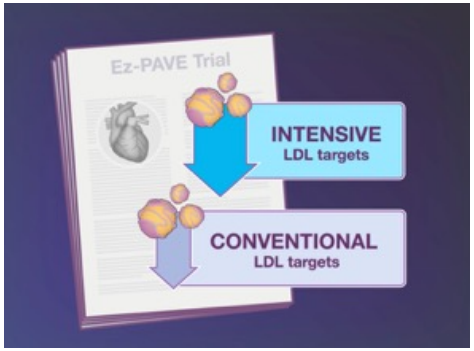
Subgroup Analyses of the Primary End Point.

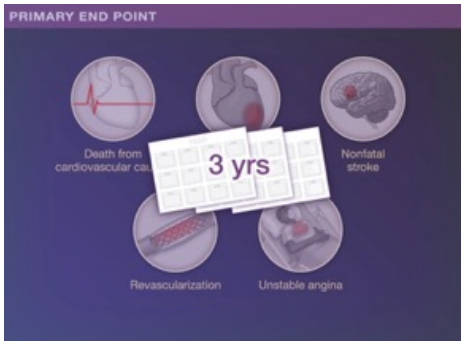
Shown are hazard ratios (intensive targeting vs. conventional targeting) for primary end-point events across prespecified subgroups. Percentages are cumulative incidences at 3 years calculated with the Kaplan–Meier method; therefore, the percentages may not reflect the ratio of the numerator and the denominator. The widths of the confidence intervals have not been adjusted for multiple comparisons and should not be used to infer definitive treatment effects. Body-mass index is the weight in kilograms divided by the square of the height in meters.

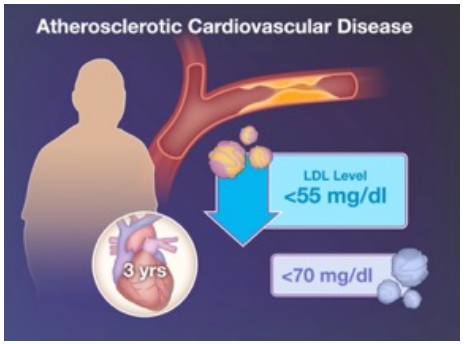

Atherosclerotic Cardiovascular Disease
LDL
?

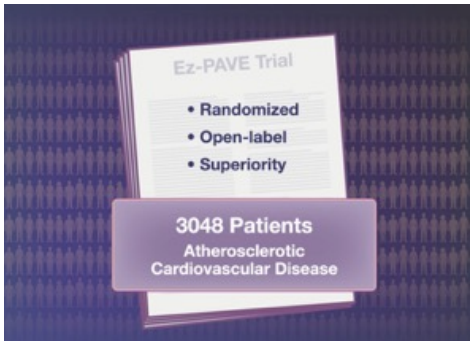

Intensive
Conventional
LDL Level
<55 mg/dl
LDL Level
<70 mg/dl
N=1526
N=1522

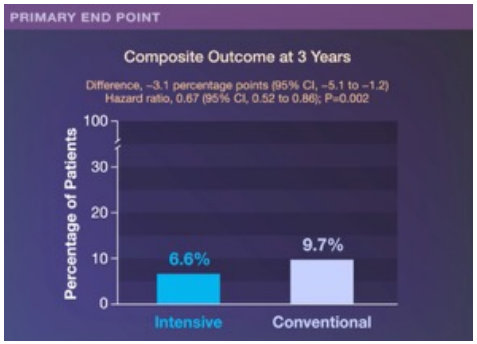

SAFETY
Creatinine Elevation to >1.5 Times Baseline Value
Difference, −1.5 percentage points
(95% CI, −2.5 to −0.5); P=0.004
Percentage of Patients
100
30
20
10
0
Incidence of other safety end points, such as new-onset diabetes, was similar in the two groups.
1.2%
2.7%
Intensive
Conventional


Ez-PAVE Trial
INTENSIVE
LDL targets
CONVENTIONAL
LDL targets

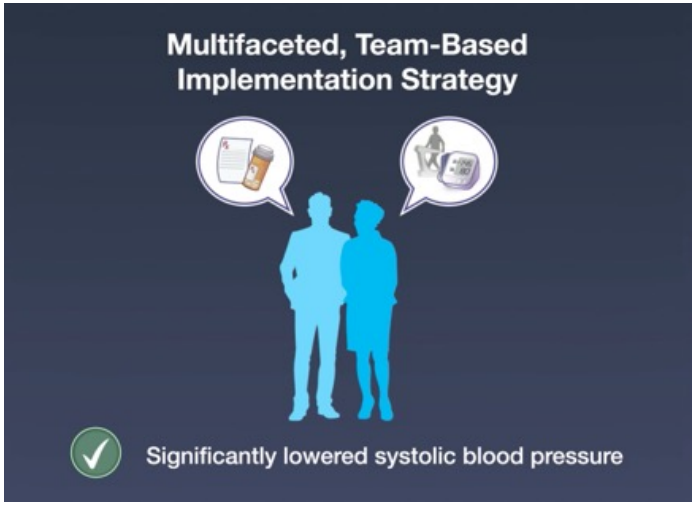

PRIMARY END POINT
Death from cardiovascular ca
3 yrs
Nonfatal stroke
Revascularization
Unstable angina


Atherosclerotic Cardiovascular Disease
LDL Level
<55 mg/dl
3 yrs
<70 mg/dl


Ez-PAVE Trial
• Randomized
• Open-label
• Superiority
3048 Patients
Atherosclerotic Cardiovascular Disease


PRIMARY END POINT
Composite Outcome at 3 Years
Difference, −3.1 percentage points (95% CI, −5.1 to −1.2)
Hazard ratio, 0.67 (95% CI, 0.52 to 0.86); P=0.002
Percentage of Patients
100
30
20
10
0
6.6%
9.7%
Intensive
Conventional

Blood Pressure Lowering in the low SDI Setting



Der **Socio-demographic Index (SDI)** ist eine zusammenfassende Kennzahl, die den Entwicklungsstand eines Landes oder einer Region auf einer Skala von **0 bis 1** misst. Er wurde von Forschern des **Institute for Health Metrics and Evaluation (IHME)** im Rahmen der *Global Burden of Disease* (GBD) Studie entwickelt.

Federally Qualified Health Centers (FQHCs) sind gemeinnützige, primärversorgende Kliniken in den USA, die umfassende Gesundheitsleistungen für unterversorgte Bevölkerungsgruppen anbieten. Sie erhalten Bundesförderung (330-Grant), bieten Behandlungen unabhängig von der Zahlungsfähigkeit an und nutzen eine gestaffelte Gebührenordnung (Sliding Fee Scale). FQHCs verbessern den Zugang zu Pflege, senken Kosten und behandeln über 31 Millionen Menschen.

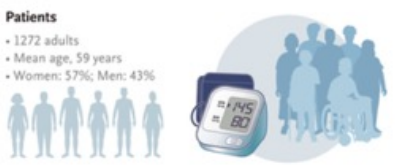
Hauptmerkmale und Vorteile von FQHCs:

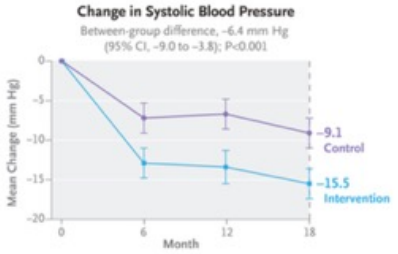
- **Dienstleistungen:** Bieten primäre medizinische Versorgung, Zahnpflege, psychische Gesundheit, Verhaltensberatung und oft Apothekenleistungen an.
- **Zugang:** Behandeln Patienten ohne Rücksicht auf Versicherungsstatus, Einkommen oder Einwanderungsstatus.
- **Finanzierung & Struktur:** Erhalten Zuschüsse von der HRSA und qualifizieren sich für eine verbesserte Erstattung durch Medicare und Medicaid.
- **Verwaltung:** Werden von einem Patientenbeirat geleitet (Consumer Governance), wobei mindestens 51 % der Vorstandsmitglieder Patienten des Zentrums sein müssen.
- **Standorte:** Finden sich sowohl in städtischen als auch in ländlichen Gebieten mit medizinischer Unterversorgung.
- **FQHC Look-Alikes:** Einrichtungen, die alle Programmstandards eines FQHC erfüllen, aber keine direkten 330-Grants erhalten, jedoch berechtigt für Medicaid/Medicare-Erstattungen sind.

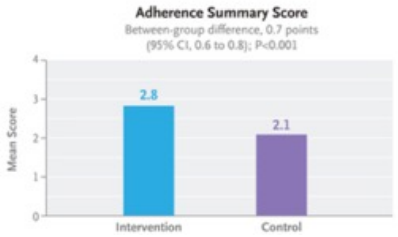
COMMUNITY HEALTH CENTER®
FQHC
QUALITY

Multifaceted Strategies for Hypertension Control in Low-Income Patients

Uncontrolled hypertension disproportionately affects populations that have substantial health disparities. Data regarding the effectiveness and implementation of multifaceted, team-based strategies for hypertension control among low-income patients are lacking. We randomly assigned federally qualified health center clinics in Louisiana and Mississippi to use either a multifaceted implementation strategy (intervention group) or enhanced usual care (control group) for hypertension control. The intervention included team-based care, protocol-based intensive blood-pressure management, blood-pressure audit and feedback, health coaching on lifestyle changes and medication adherence, and home blood-pressure monitoring. Enhanced usual care involved educating physicians about clinical guidelines for hypertension. The primary effectiveness outcome was the mean change in systolic blood pressure from baseline to 18 months. The primary implementation outcome was the adherence summary score (on a scale of 0 to 4, with higher scores indicating better adherence to blood-pressure management).







The Systolic Blood Pressure Intervention Trial (SPRINT) showed that intensive antihypertensive treatment targeting a systolic blood pressure of less than 120 mm Hg resulted in a significantly lower incidence of cardiovascular events or death from any cause than a target of less than 140 mm Hg. Several subsequent randomized trials have confirmed these benefits across diverse populations. Traditionally, marginalized ethnic groups and low-income populations have been underrepresented in clinical trials and often benefit less from clinical research. There is a critical need to develop and test effective, scalable implementation strategies to translate evidence-based interventions into real-world primary care, particularly for underserved populations. We assessed the effectiveness and implementation outcomes of a multifaceted, team-based strategy to deliver an intensive blood-pressure control protocol adapted from SPRINT among low-income patients receiving care at FQHC clinics.

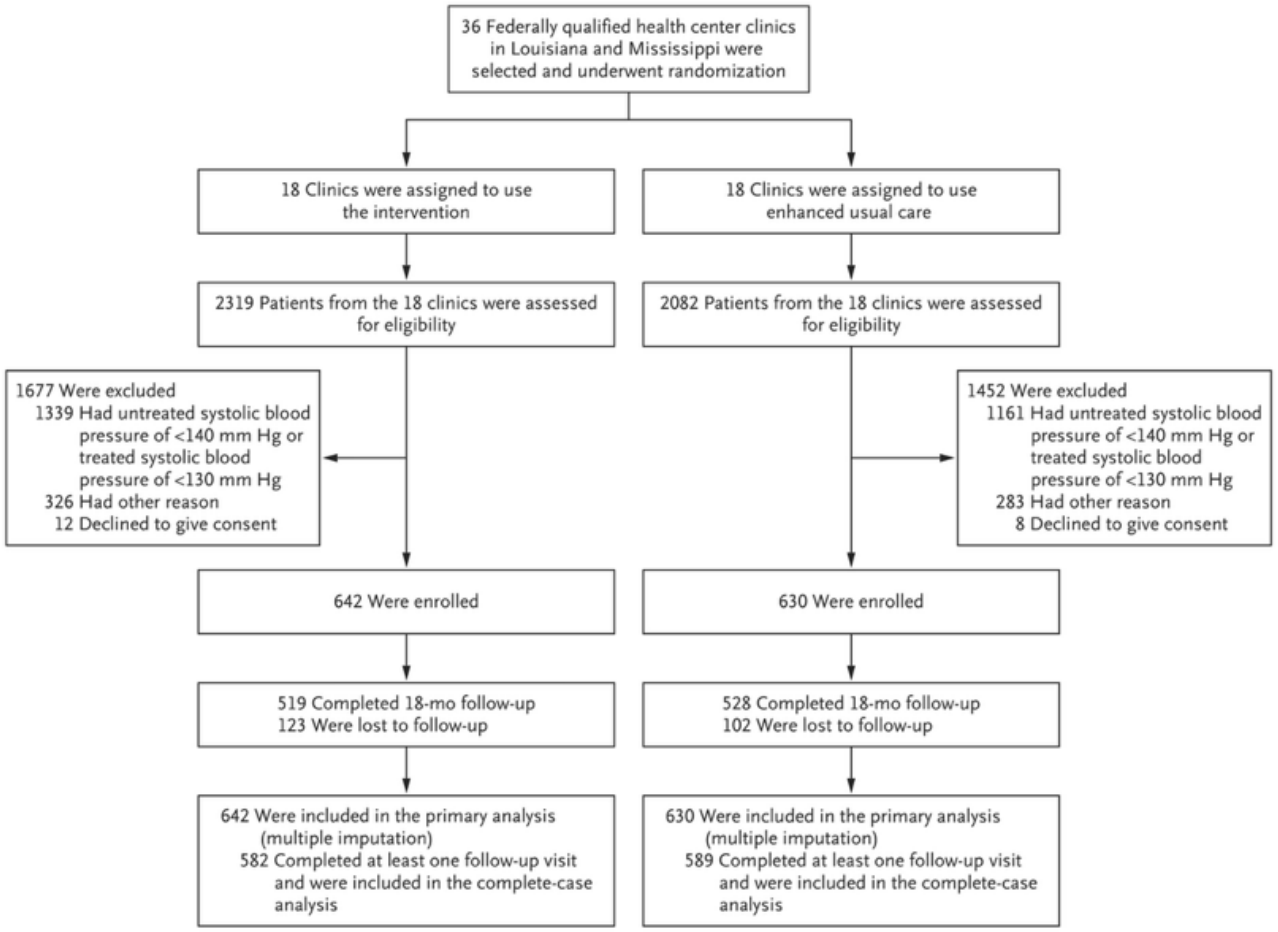
Trial Procedures

The multifaceted implementation strategy that was used in the intervention clinics involved team-based care, protocol-based intensive blood-pressure management, blood-pressure audit and feedback, health coaching, and home blood-pressure monitoring. In addition, findings from SPRINT were disseminated to care teams, patients, and administrators. Initial and annual interactive training for providers focused on protocol-based intensive blood-pressure management. Nurses and medical assistants were trained to deliver health coaching on lifestyle changes and medication adherence. Providers and clinic staff also received training in standardized techniques for blood-pressure measurement.

Primary and Secondary Outcomes

The primary effectiveness outcome was the mean change in systolic blood pressure from baseline to 18 months, based on six measurements taken at two visits at each time point (baseline, 6 months, 12 months, and 18 months). Secondary clinical outcomes included a systolic blood pressure of less than 120 mm Hg and less than 130 mm Hg, a reduction in systolic blood pressure of more than 30 mm Hg at 18 months, and the mean change in diastolic blood pressure and mean change in physical and mental SF-12 scores from baseline to 18 months.

Tender Loving Care (oft als **TLC** abgekürzt) ist eine englische Redewendung, die im Deutschen am ehesten mit **„liebevolle Zuwendung“**, **„Pflege“** oder **„Streicheleinheiten“** übersetzt wird.



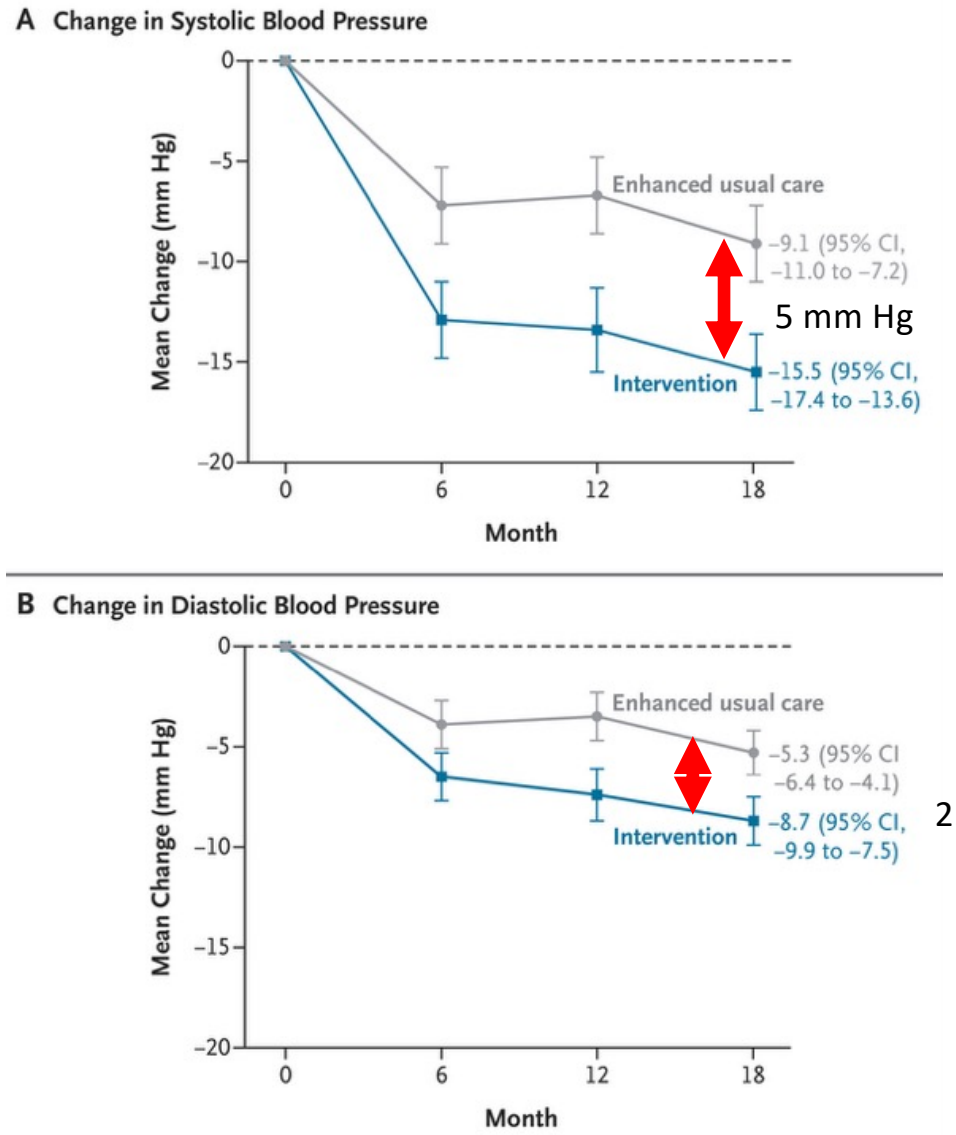
Enrollment, Randomization, and Follow-up.

The intervention consisted of team-based care, protocol-based intensive blood-pressure management, blood-pressure audit and feedback, health coaching on lifestyle changes and medication adherence, and home blood-pressure monitoring. Enhanced usual care involved educating physicians about clinical guidelines for hypertension. The complete-case analysis included only patients with complete data.

Variable	Intervention	Enhanced Usual Care
Clinics		
Total no. of clinics	18	18
Median no. of providers per clinic (IQR)	2 (1–3)	2 (2–3)
Median no. of nurses or medical assistants per clinic (IQR)	4 (2–7)	3 (2–4)
Median no. of adult primary care patients per clinic (IQR)	1937 (1206–2974)	1442 (811–2180)
Median no. of patients with hypertension per clinic (IQR)	619 (461–1108)	420 (334–771)
Median no. of patients in trial per clinic (IQR)	35 (27–40)	32 (25–46)
Trial Patients		
Total no. of patients	642	630
Age — yr	59.1±8.9	58.5±9.0
Female sex — no. (%)	377 (58.7)	344 (54.6)
Race or ethnic group — no. (%)†		
Non-Hispanic White	171 (26.7)	203 (32.2)
Non-Hispanic Black	430 (67.1)	376 (59.7)
Hispanic	29 (4.5)	24 (3.8)
Other	11 (1.7)	27 (4.3)
Missing data	1 (0.2)	0
Not a high school graduate — no. (%)	162 (25.2)	174 (27.6)
Unemployed — no. (%)	484 (75.4)	482 (76.5)
Annual family income <$25,000 — no./total no. (%)	468/638 (73.4)	460/626 (73.5)
No private health insurance — no. (%)	535 (83.5)	531 (84.3)
Duration of hypertension >10 yr — no. (%)	277 (44.0)	252 (41.2)
Use of antihypertensive medications — no. (%)	605 (94.2)	589 (93.5)
Median no. of antihypertensive medications per patient (IQR)	2 (1–3)	2 (1–2)
MMAS-8 score‡	6.5±1.6	6.4±1.7
Satisfaction with antihypertensive medications — no. (%)	424 (70.2)	437 (74.2)
Satisfaction with hypertension-related care — no. (%)	568 (88.6)	570 (90.6)
History of myocardial infarction or stroke — no. (%)	101 (15.7)	105 (16.7)
History of diabetes — no. (%)	255 (39.7)	248 (39.4)
History of chronic kidney disease — no. (%)	22 (3.4)	17 (2.7)
Systolic blood pressure — mm Hg	148.4±12.9	146.7±12.1
Diastolic blood pressure — mm Hg	85.1±11.1	84.2±10.8

Effectiveness, Implementation, and Adverse Outcomes.

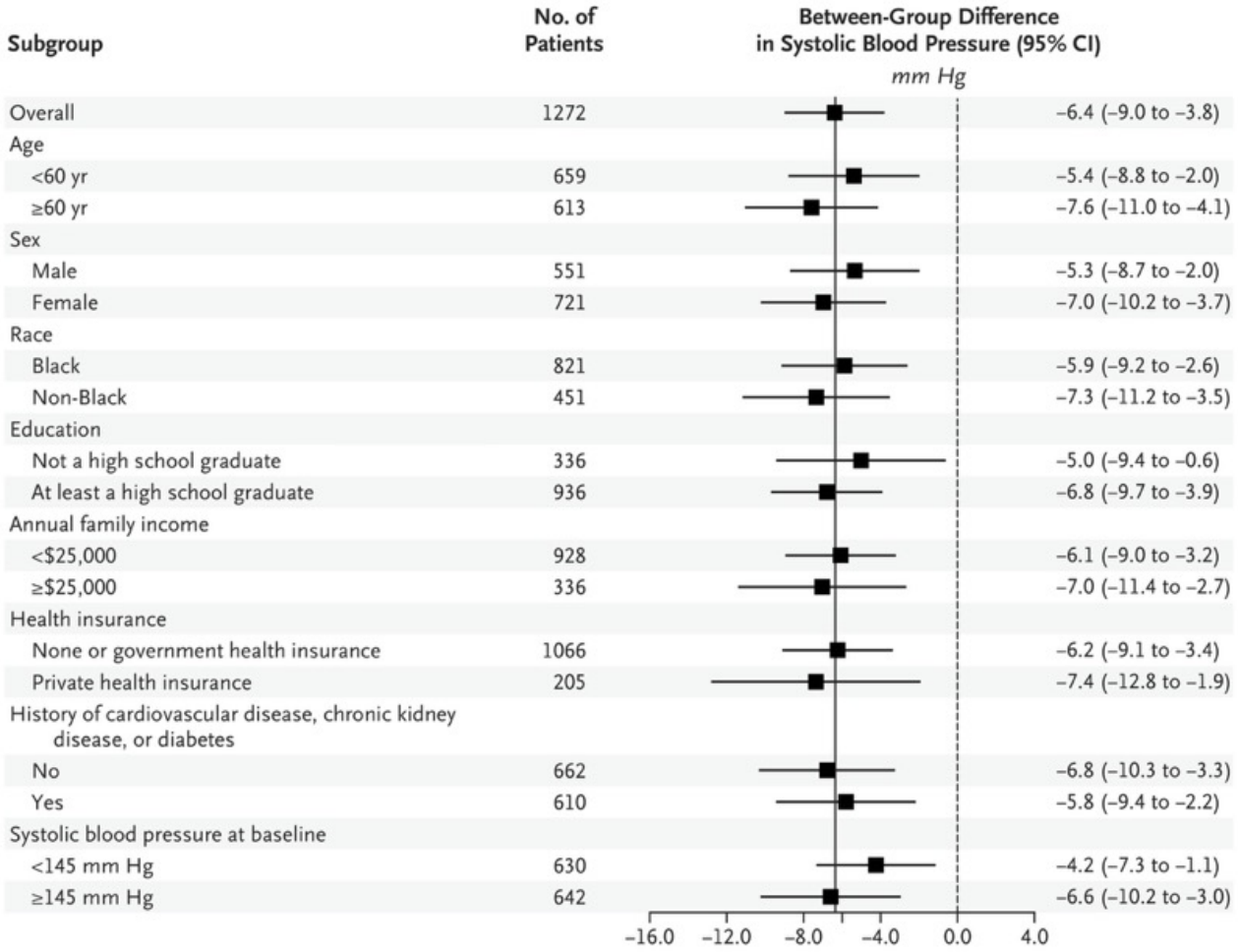
Outcome	Mean Value or Percentage of Patients (95% CI)		Between-Group Difference (95% CI)	P Value for Difference	Adjusted Between-Group Difference (95% CI)††	P Value for Adjusted Difference
	Intervention	Enhanced Usual Care				
Effectiveness outcomes						
Primary outcome						
Change in systolic blood pressure from baseline to 18 mo — mm Hg	−15.5 (−17.4 to −13.6)	−9.1 (−11.0 to −7.2)	−6.4 (−9.0 to −3.8)	<0.001	−5.6 (−8.1 to −3.0)	<0.001
Secondary outcomes						
Systolic blood pressure <120 mm Hg at 18 mo — % of patients	21.8 (17.6 to 26.0)	15.1 (11.6 to 18.6)	6.7 (1.2 to 12.1)		6.7 (−1.7 to 15.1)	
Systolic blood pressure <130 mm Hg at 18 mo — % of patients	47.7 (42.2 to 53.2)	36.4 (31.3 to 41.4)	11.3 (3.9 to 18.8)		14.2 (3.3 to 25.2)	
Reduction of >30 mm Hg in systolic blood pressure from baseline to 18 mo — % of patients	18.7 (15.0 to 22.4)	10.9 (8.0 to 13.8)	7.8 (3.1 to 12.5)		5.3 (−0.8 to 11.5)	
Change in diastolic blood pressure from baseline to 18 mo — mm Hg	−8.7 (−9.9 to −7.5)	−5.3 (−6.4 to −4.1)	−3.4 (−5.1 to −1.8)		−3.2 (−4.7 to −1.6)	
Change in physical SF-12 score from baseline to 18 mo — points‡	1.2 (0.3 to 2.2)	1.1 (0.2 to 2.0)	0.2 (−1.1 to 1.4)		0.3 (−1.0 to 1.5)	
Change in mental SF-12 score from baseline to 18 mo — points‡	1.9 (0.9 to 2.9)	2.1 (1.2 to 3.0)	−0.1 (−1.4 to 1.1)		−0.1 (−1.4 to 1.1)	
Implementation outcomes						
Primary outcome						
Adherence summary score over the 18-mo follow-up period§	2.8 (2.7 to 2.9)	2.1 (2.0 to 2.2)	0.7 (0.6 to 0.8)	<0.001	0.7 (0.6 to 0.8)	<0.001
Secondary outcomes — % of patients						
Patient-reported high adherence to antihypertensive medications at 18 mo	37.4 (33.4 to 41.5)	41.0 (37.0 to 45.1)	−3.6 (−9.3 to 2.1)		−3.4 (−13.4 to 6.6)	
Receipt of treatment intensification during the 18-mo follow-up period¶	90.4 (87.8 to 93.1)	71.5 (67.3 to 75.7)	18.9 (14.0 to 23.9)		20.6 (11.8 to 29.3)	
Blood pressure monitored at home during the 18-mo follow-up period¶	97.8 (95.4 to 100)	77.6 (72.8 to 82.3)	20.2 (14.9 to 25.5)		23.7 (14.8 to 32.6)	
Receipt of health education during the 18-mo follow-up period¶	96.6 (93.0 to 100)	85.8 (80.9 to 90.8)	10.7 (4.6 to 16.8)		13.8 (4.9 to 22.8)	
Satisfaction with antihypertensive medications at 18 mo	84.5 (75.1 to 93.8)	83.1 (78.1 to 88.1)	1.4 (−9.2 to 12.0)		1.9 (−10.6 to 14.3)	
Satisfaction with blood pressure–related care at 18 mo	89.2 (81.4 to 97.1)	89.5 (84.4 to 94.5)	−0.2 (−9.6 to 9.1)		−0.1 (−11.9 to 11.8)	
Adverse outcomes — % of patients						
Serious adverse event‖	20.9 (15.5 to 26.3)	21.7 (18.1 to 25.4)	−0.8 (−7.4 to 5.7)	0.80	−0.9 (−9.9 to 8.1)	0.85
Injurious fall**	7.7 (3.1 to 12.2)	6.6 (3.7 to 9.5)	1.1 (−4.4 to 6.5)	0.70	1.2 (−5.3 to 7.6)	0.72
Syncope††	3.7 (0.0 to 7.4)	2.6 (0.1 to 5.2)	1.0 (−3.5 to 5.5)	0.66	1.4 (−4.6 to 7.3)	0.65
Kidney transplantation or dialysis‡‡	0.9 (−0.1 to 1.8)	0.7 (−0.2 to 1.6)	0.2 (−1.1 to 1.5)	0.76		
Hypotension‡‡	1.0 (0.0 to 1.9)	0.6 (−0.1 to 1.3)	0.4 (−0.8 to 1.6)	0.51		



Protocol-based intensive blood-pressure management, blood-pressure audit and feedback, health coaching, and home blood-pressure monitoring.

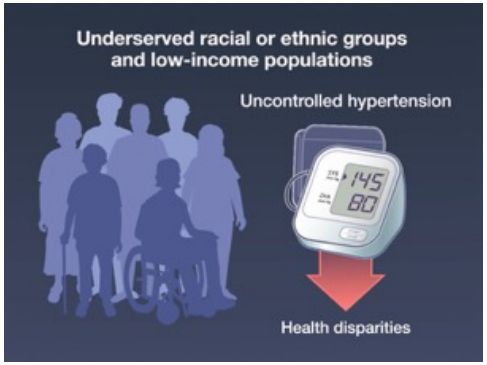
Change in Blood Pressure over 18 Months.

The primary analysis used multiple imputation for missing outcomes, on the assumption that data were missing at random. The widths of the confidence intervals were not adjusted for multiplicity and should not be used as a substitute for hypothesis testing. I bars indicate 95% confidence intervals.

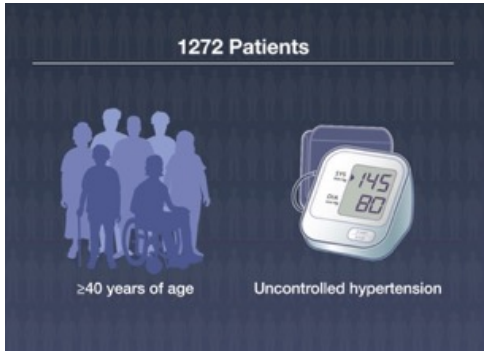


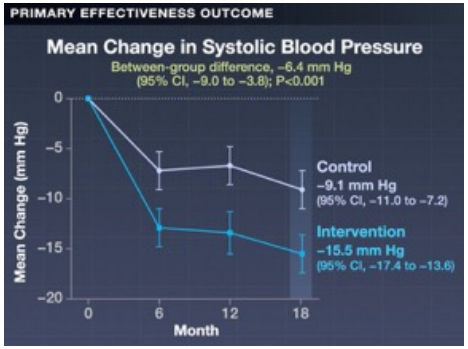
Between-Group Difference in the Change in Systolic Blood Pressure over 18 Months According to Subgroup.

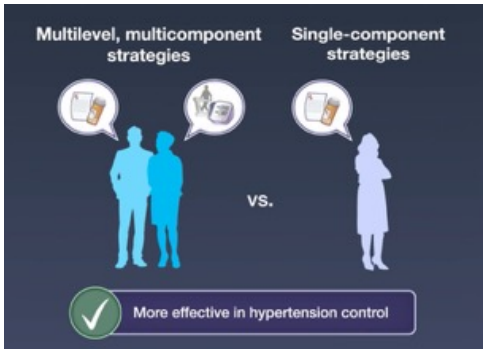
Shown is the mean change in systolic blood pressure from baseline to 18 months in the intervention group minus the mean change in the control group. The primary analysis used multiple imputation for missing outcomes, on the assumption that data were missing at random. The widths of the confidence intervals were not adjusted for multiplicity and should not be used as a substitute for hypothesis testing. The solid vertical line shows the difference in the mean change in systolic blood pressure from baseline to 18 months between the intervention group and the control group among all the patients in the trial. I bars indicate 95% confidence intervals.


Underserved racial or ethnic groups and low-income populations
Uncontrolled hypertension
145
80
Health disparities


IMPACTS-BP Trial
• Cluster-randomized
• Louisiana and Mississippi

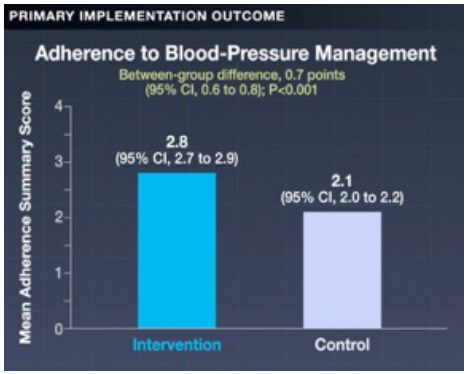

1272 Patients
≥40 years of age
Uncontrolled hypertension
145
80

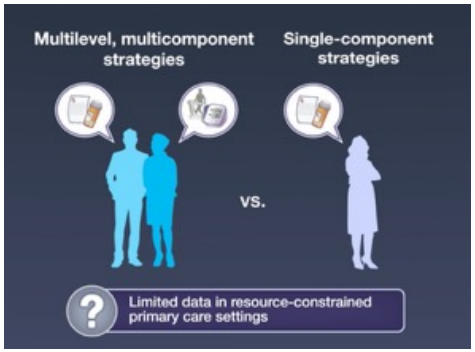

PRIMARY EFFECTIVENESS OUTCOME
Mean Change in Systolic Blood Pressure
Between-group difference, −6.4 mm Hg
(95% CI, −9.0 to −3.8); P<0.001
Mean Change (mm Hg)
0
−5
−10
−15
−20
0
6
12
18
Month
Control
−9.1 mm Hg
(95% CI, −11.0 to −7.2)
Intervention
−15.5 mm Hg
(95% CI, −17.4 to −13.6)

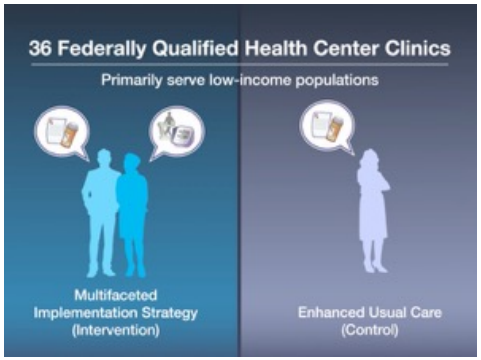

Multilevel, multicomponent strategies
Single-component strategies
vs.
More effective in hypertension control


36 Federally Qualified Health Center Clinics
Primarily serve low-income populations

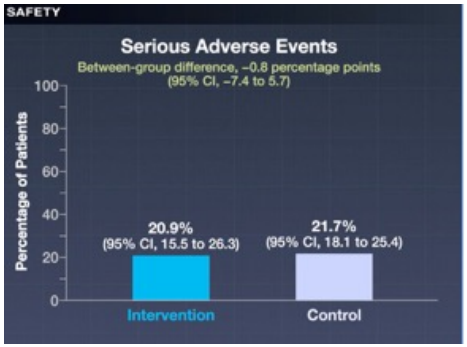

Multifaceted Implementation Strategy
• Team-based care
• Protocol-based blood-pressure management
• Blood-pressure audit and feedback
• Health coaching
• Home blood-pressure monitoring


PRIMARY IMPLEMENTATION OUTCOME
Adherence to Blood-Pressure Management
Between-group difference, 0.7 points
(95% CI, 0.6 to 0.8); P<0.001
Mean Adherence Summary Score
4
3
2
1
0
2.8
(95% CI, 2.7 to 2.9)
2.1
(95% CI, 2.0 to 2.2)
Intervention
Control


Multilevel, multicomponent strategies
Single-component strategies
vs.
Limited data in resource-constrained primary care settings


36 Federally Qualified Health Center Clinics
Primarily serve low-income populations
Multifaceted Implementation Strategy (Intervention)
Enhanced Usual Care (Control)


Enhanced Usual Care
Involved educating providers about clinical guidelines for hypertension
Clinical Guidelines
145
80


SAFETY
Serious Adverse Events
Between-group difference, −0.8 percentage points
(95% CI, −7.4 to 5.7)
Percentage of Patients
100
80
60
40
20
0
20.9%
(95% CI, 15.5 to 26.3)
21.7%
(95% CI, 18.1 to 25.4)
Intervention
Control

EDITORIAL

Systems-Based Success for Hypertension

The trial patients, who had uncontrolled hypertension, were already taking a median of two blood pressure–lowering medications at baseline. Despite the effectiveness of the intervention, the between-group difference in the change in systolic blood pressure from baseline to 18 months was modest; in addition, at the end of the trial, less than half the patients in the intervention group had a systolic blood pressure of less than 130 mm Hg, and approximately one fifth had a systolic blood pressure < 120 mm Hg. For context, most patients who had been enrolled in SPRINT were taking three or more drugs in order for their systolic blood pressure to reach a target of less than 120 mm Hg. Therefore, single-pill combination therapy, which includes three- and four-drug combinations, may offer an effective, efficient, and scalable strategy that can improve adherence and side-effect profiles.

Although the current trial showed that systems-based strategies can improve hypertension control, implementation requires coordinated, intensive, and costly efforts. Although the current trial showed that systems-based strategies can improve hypertension control, implementation requires coordinated, intensive, and costly efforts. Programs for lowering blood pressure that include the key elements discussed here represent an ideal starting point, but future efforts should focus on refining processes to prepare systems and provide incentives for the use of team-based models. For example, tiered federal benchmarks could be applied to create a payment environment that rewards hypertension control without penalizing resource-limited FQHCs.

Only 20% met SPRINT goals.

Die **idiopathische thrombozytopenische Purpura (ITP)**, heute meist als **Immunthrombozytopenie** bezeichnet, ist eine Autoimmunerkrankung, bei der das Immunsystem die körpereigenen Blutplättchen (Thrombozyten) zerstört. Da Thrombozyten für die Blutgerinnung zuständig sind, führt ein Mangel zu einer erhöhten Blutungsneigung.

•**Definition:** Ein Abfall der Thrombozytenzahl auf unter 100.000/µl Blut ohne erkennbare andere Ursache.

•**Symptome:**

- **Petechien:** Punktförmige, stecknadelkopfgroße Hauteinblutungen, oft an den Beinen.
- **Hämatome:** Neigung zu blauen Flecken schon bei leichten Stößen.
- **Schleimhautblutungen:** Häufiges Nasen- oder Zahnfleischbluten sowie verstärkte Regelblutungen.

•**Formen:**

- **Akute ITP:** Tritt oft bei Kindern nach einem Infekt auf und heilt meist von selbst wieder aus.
- **Chronische ITP:** Betrifft häufiger Erwachsene und bleibt oft dauerhaft bestehen, was eine langfristige medizinische Begleitung erfordert.

•**Behandlung:** Eine Therapie ist meist erst notwendig, wenn die Thrombozytenzahl sehr niedrig ist oder starke Blutungen auftreten. Klassische Erstmaßnahmen sind Kortikosteroide (Cortison) oder Immunglobuline.

•**Lebensführung:** Bei niedrigen Werten sollten Sportarten mit hohem Verletzungsrisiko (z. B. Fußball oder Kampfsport) gemieden werden. Die Lebenserwartung ist bei korrekter Behandlung in der Regel normal.

Paul Gottlieb Werlhof

Die wichtigsten Zielantigene sind bestimmte **Glykoproteinkomplexe** auf der Thrombozytenmembran:

•**GP IIb/IIIa** (Fibrinogenrezeptor): Dies ist das am häufigsten betroffene Antigen-Ziel.

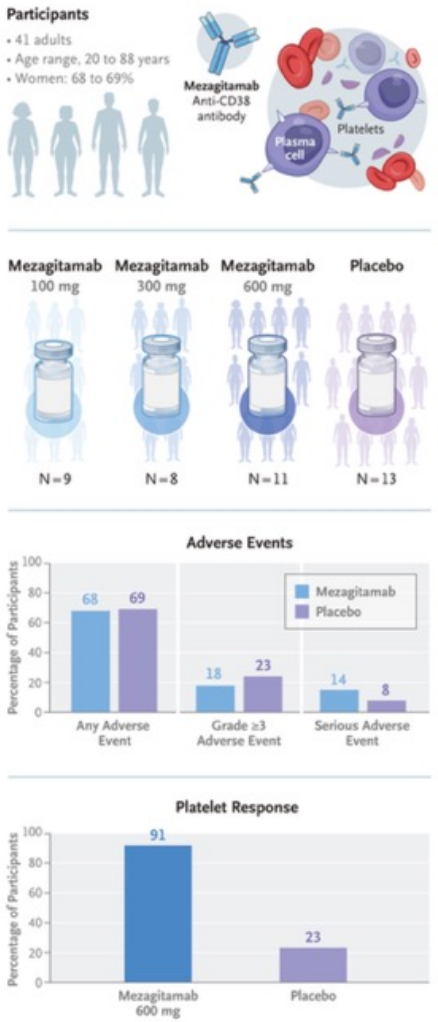
•**GP Ib/IX/V** (vWF-Rezeptor): Ein weiteres häufiges Ziel der Autoantikörper.

•**GP Ia/IIa** sowie **GP IV** und **GP V**: Diese können ebenfalls als Antigene fungieren.

A Phase 2 Randomized Trial of Mezagitamab in Primary Immune Thrombocytopenia

Immune thrombocytopenia (ITP) is a disorder of increased platelet destruction and reduced platelet production and is associated with an increased bleeding risk and a compromised quality of life. Available therapies are ineffective in at least 20% of cases. Mezagitamab is an anti-CD38 antibody that targets plasma cells, plasmablasts, and natural killer cells.

We conducted this multicenter, double-blind, randomized, placebo-controlled trial to assess the safety and efficacy of mezagitamab at a dose of 100 mg, 300 mg, or 600 mg, as compared with placebo, administered subcutaneously once weekly for 8 weeks in adults with persistent or chronic ITP (mean platelet count on ≥2 measurements, <30,000 per microliter). The primary end point was adverse events. A key secondary efficacy end point was a platelet response (defined by a platelet count of ≥50,000 per microliter and ≥20,000 per microliter above the baseline value) on at least two visits at any time through week 16.



Primary immune thrombocytopenia (ITP) is an autoimmune disease characterized by a decreased platelet count and a consequent increased risk of bleeding, which can be severe and life-threatening. Many patients also report a substantial adverse effect on their health-related quality of life owing to accompanying symptoms such as fatigue and anxiety.

ITP is a heterogeneous disease that may involve various pathophysiological mechanisms and result in varied disease trajectories and therapeutic responses. ITP is generally attributed to the binding of autoantibodies to platelets and megakaryocytes, which leads to platelet destruction by FcγR-mediated cellular cytotoxicity, as well as impairment of platelet production. However, autoantibodies cannot be detected in all patients; this suggests that other mechanisms may be involved, including CD8+ T cells or natural killer (NK) cells.

Mezagitamab (TAK-079) is a fully human IgG1 monoclonal antibody that targets CD38 with high affinity. CD38 is highly expressed on the surface of plasma cells and to a lesser extent on NK cells and subsets of T cells and B cells. Anti-CD38 therapy is commonly used for the treatment of multiple myeloma, and its efficacy in the treatment of autoimmune diseases shows promise.

We conducted a multicenter, randomized, placebo-controlled trial to evaluate the safety and efficacy of subcutaneous mezagitamab in participants with persistent or chronic primary ITP.

Eligibility

Eligible participants were at least 18 years of age and had primary ITP that had persisted for at least 3 months. The diagnosis of ITP was supported by documentation of a previous response to an ITP therapy (other than a thrombopoietin-receptor agonist). Participants were required to have a mean platelet count of less than 30,000 per microliter (and individual measurements of ≤35,000 per microliter) based on at least two measurements at least 1 week apart during screening.

Key exclusion criteria were the use of rituximab within 4 months before the first administration of mezagitamab or placebo, previous use of rituximab with a CD19 count outside the normal range at screening, a history of thrombotic or embolic events in the previous 12 months, splenectomy in the previous 3 months, and recent or anticipated use of certain medications or treatments.

End Points and Assessments

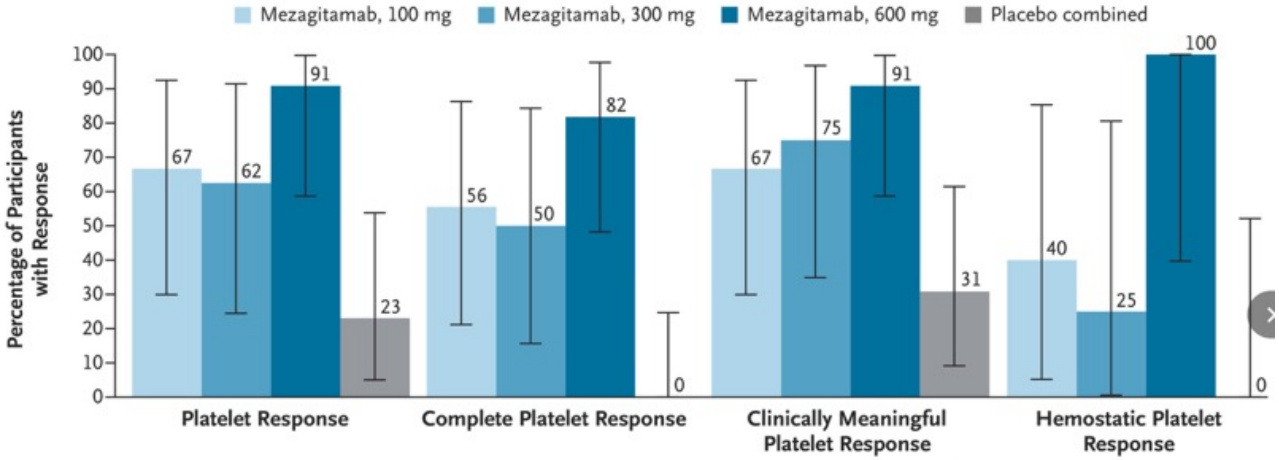
The primary end point was adverse events, including adverse events of grade 3 or higher, serious adverse events, and adverse events leading to discontinuation of mezagitamab or placebo.

Secondary efficacy end points were the following outcomes on at least two visits at any time through week 16: a platelet response (defined by a platelet count of ≥50,000 per microliter and ≥20,000 per microliter above the baseline value),

Characteristic	Placebo Combined (N=13)	Mezagitamab Combined (N=28)	Mezagitamab 100 mg (N=9)	Mezagitamab 300 mg (N=8)	Mezagitamab 600 mg (N=11)
Age — yr					
Mean	39±16	50±17	49±14	52±17	48±20
Range	20–65	24–88	32–80	24–79	24–88
Female sex — no. (%)	9 (69)	19 (68)	5 (56)	5 (62)	9 (82)
Race — no. (%)†					
Asian	1 (8)	2 (7)	0	0	2 (18)
White	11 (85)	26 (93)	9 (100)	8 (100)	9 (82)
Not reported	1 (8)	0	0	0	0
Ethnic group — no. (%)†					
Not Hispanic or Latino	12 (92)	26 (93)	9 (100)	8 (100)	9 (82)
Hispanic or Latino	1 (8)	0	0	0	0
Not reported	0	2 (7)	0	0	2 (18)
Time since ITP diagnosis — yr	11.3±10.9	10.8±10.8	13.4±12.1	15.4±13.1	5.5±5.0
Platelet count — per microliter	17,300±10,400	19,100±12,800	17,900±14,500	19,600±14,400	19,800±11,400
No. of previous ITP treatments					
Mean	4±3	4±2	4±3	4±2	4±2
Range	1–13	1–9	1–9	1–6	2–9
Participants previously treated with thrombopoietin-receptor agonists — no. (%)	8 (62)	18 (64)	5 (56)	5 (62)	8 (73)
No. of categories of previous ITP treatments	2.8±1.6	2.7±1.4	2.9±2.0	2.6±1.3	2.6±1.1
Participants receiving stable background ITP treatment — no. (%)‡	7 (54)	17 (61)	3 (33)	5 (62)	9 (82)
Previous splenectomy — no. (%)	3 (23)	6 (21)	3 (33)	2 (25)	1 (9)

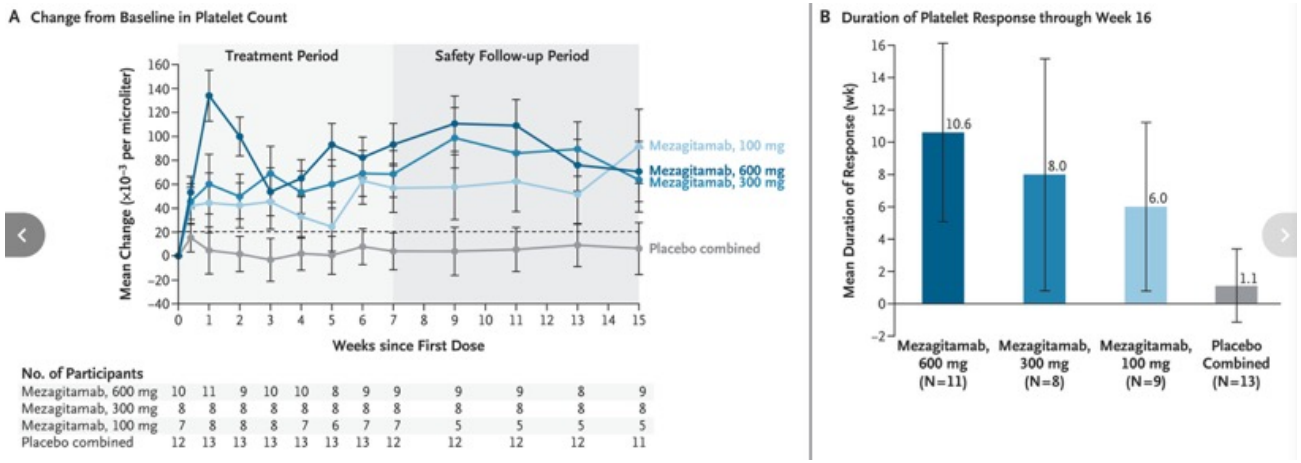
Adverse Events.

Event	Placebo Combined (N=13)	Mezagitamab Combined (N=28)	Mezagitamab 100 mg (N=9)	Mezagitamab 300 mg (N=8)	Mezagitamab 600 mg (N=11)
	number of participants (percent)				
Any adverse event	9 (69)	19 (68)	7 (78)	5 (62)	7 (64)
Adverse event related to mezagitamab or placebo	5 (38)	9 (32)	2 (22)	4 (50)	3 (27)
Serious adverse event	1 (8)	4 (14)	2 (22)	0	2 (18)
Serious adverse event related to mezagitamab or placebo	0	2 (7)	1 (11)	0	1 (9)
Adverse event leading to discontinuation of mezagitamab or placebo	0	4 (14)	2 (22)	0	2 (18)
Grade ≥3 adverse event	3 (23)	5 (18)	2 (22)	0	3 (27)
Grade ≥3 adverse event related to mezagitamab or placebo	0	2 (7)	1 (11)	0	1 (9)
Adverse events reported in ≥10% of participants in either combined group					
Injection-site hematoma	3 (23)	2 (7)	0	2 (25)	0
Coronavirus disease 2019	1 (8)	3 (11)	2 (22)	0	1 (9)
Conjunctival hemorrhage	2 (15)	1 (4)	1 (11)	0	0
Asthenia	2 (15)	0	0	0	0
Contusion	2 (15)	0	0	0	0
Petechiae	2 (15)	0	0	0	0
Infection-related adverse event	2 (15)	6 (21)	3 (33)	0	3 (27)



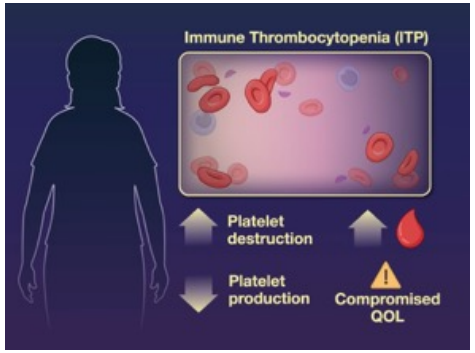
Platelet Responses at Week 16.

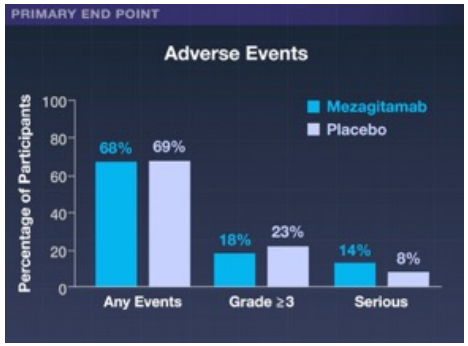
Shown are the results for the secondary efficacy end points. A platelet response was defined by a platelet count of at least 50,000 per microliter and at least 20,000 per microliter above the baseline value on at least two visits at any time through week 16. A complete platelet response was defined by a platelet count of at least 100,000 per microliter on at least two visits at any time through week 16. A clinically meaningful platelet response was defined by a platelet count of at least 20,000 per microliter above the baseline value on at least two visits at any time through week 16. A hemostatic platelet response was defined by a platelet count of at least 30,000 per microliter and at least 20,000 per microliter above the baseline value on at least two visits at any time through week 16, with a baseline platelet count of less than 15,000 per microliter. At any visit, platelet counts were not considered for these end points if a permitted rescue treatment had been administered in the previous 4 weeks or if a previous rescue therapy that was not permitted had been administered. The 95% confidence intervals (CIs) for the percentage-point differences were calculated with the use of the exact method described by Santner and Snell.[21] I bars indicate 95% confidence intervals, which were calculated with the use of the Clopper–Pearson method.

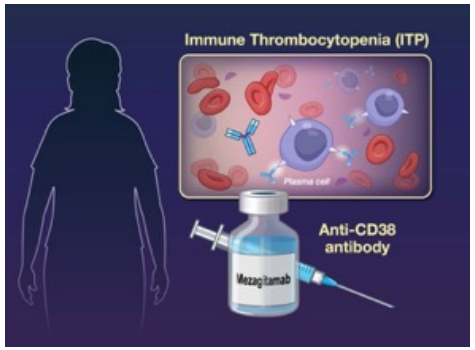


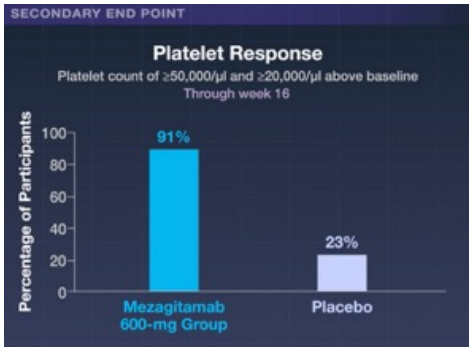
Change from Baseline in Platelet Count and Duration of Platelet Response through Week 16 (Exploratory End Points).

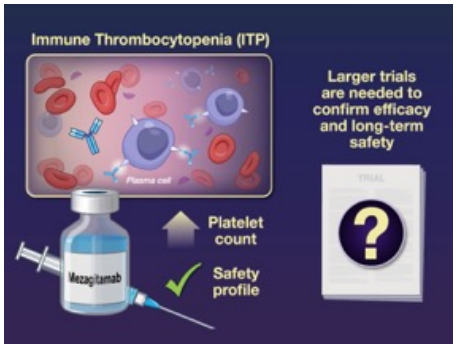
Panel A shows the mean change from baseline in the platelet count, which was derived from a mixed-effects model for repeated measures. The time after the first dose was based on the time of the scheduled visit, which could occur within a 2-day window. The dashed horizontal reference line delineates a change from baseline of at least 20,000 per microliter. I bars indicate standard errors. Panel B shows the mean cumulative duration of the platelet response, which was defined as the number of weeks with a platelet count of at least 50,000 per microliter, through week 16. I bars indicate standard deviations.

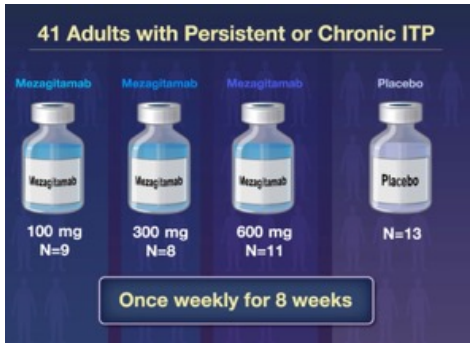

Immune Thrombocytopenia (ITP)
Platelet destruction
Platelet production
Compromised QOL

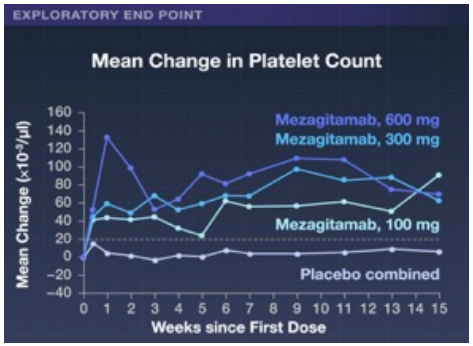

PRIMARY END POINT
Adverse Events
Percentage of Participants
Mezagitamab
Placebo
68%
69%
18%
23%
14%
8%
Any Events
Grade ≥3
Serious


Immune Thrombocytopenia (ITP)
Anti-CD38 antibody
Mezagitamab


SECONDARY END POINT
Platelet Response
Platelet count of ≥50,000/µl and ≥20,000/µl above baseline
Through week 16
Percentage of Participants
91%
23%
Mezagitamab 600-mg Group
Placebo


Immune Thrombocytopenia (ITP)
Larger trials are needed to confirm efficacy and long-term safety
Platelet count
Safety profile
Mezagitamab


41 Adults with Persistent or Chronic ITP
Mezagitamab
Mezagitamab
Mezagitamab
Placebo
100 mg N=9
300 mg N=8
600 mg N=11
N=13
Once weekly for 8 weeks

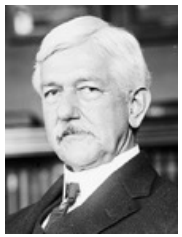

EXPLORATORY END POINT
Mean Change in Platelet Count
Mean Change (x10⁻³/µl)
Mezagitamab, 600 mg
Mezagitamab, 300 mg
Mezagitamab, 100 mg
Placebo combined
Weeks since First Dose

Gelbfieber ist eine schwere, durch tagaktive Mücken übertragene Viruserkrankung in tropischen Gebieten Afrikas und Südamerikas. Sie äußert sich durch hohes Fieber, Schmerzen und Gelbsucht. Es gibt keine spezifische medikamentöse Therapie, die das Virus direkt bekämpft. Die wirksamste Maßnahme ist eine einmalige Impfung, die meist lebenslangen Schutz bietet.

Medikament gegen Gelbfieber

- **Keine ursächliche Therapie:** Es existiert kein Medikament, das das Gelbfieber-Virus direkt abtötet.
- **Symptomatische Behandlung:** Die Therapie beschränkt sich auf die Linderung der Symptome, wie Fiebersenkung und Flüssigkeitszufuhr. Schwere Verläufe erfordern eine intensivmedizinische Betreuung.
- **Impfung:** Die Impfung (Stamm 17D) ist der effektivste Schutz, oft zwingend für die Einreise in Endemiegebiete erforderlich und muss mindestens 10 Tage vor Reiseantritt erfolgen.

Carlos Finlay, Walter Reed, William Gorgas



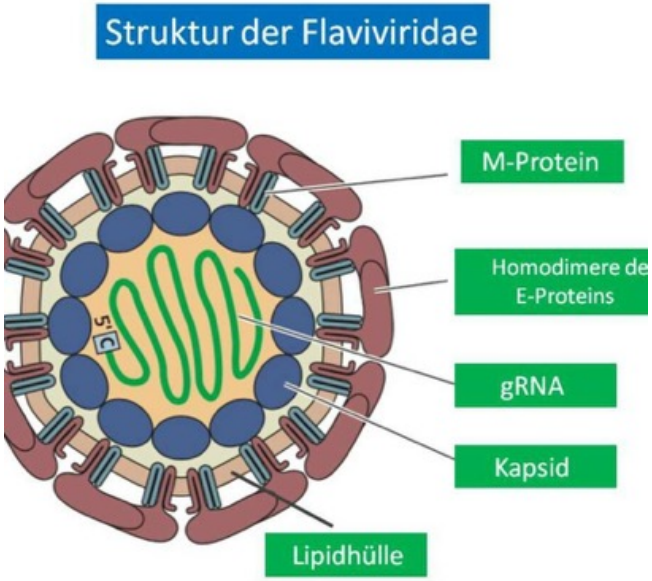
Die Gelbfieber-Impfung ist eine hocheffektive Schutzmaßnahme für Reisen in tropische Gebiete Afrikas sowie Mittel- und Südamerikas. Sie erfolgt mit einem **Lebendimpfstoff** (meist Stamaril®), der eine lebenslange Immunität vermitteln kann.

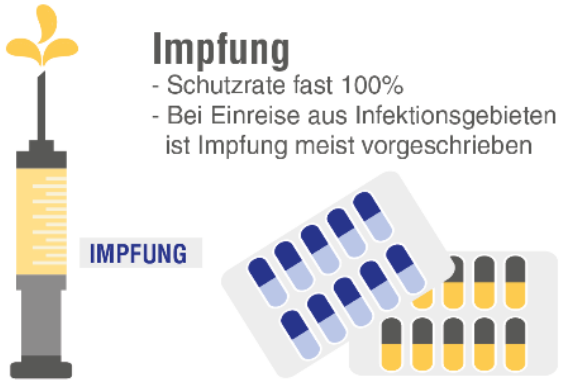
Besonderheiten & Risiken

Da es sich um einen Lebendimpfstoff handelt, gibt es Einschränkungen für bestimmte Personengruppen:

- **Schwangere und Stillende** sowie Personen mit **Immunschwäche** sollten nur nach strenger Nutzen-Risiko-Abwägung geimpft werden.
- Bei über 60-jährigen Erstgeimpften besteht ein leicht erhöhtes Risiko für schwere Nebenwirkungen, weshalb eine ausführliche Beratung in einer Gelbfieberimpfstelle notwendig ist.

Brasilien ist der Gelbfieber-Impfstoff **nicht vollständig ausgegangen**, das Land sah sich jedoch in den letzten Jahren wiederholt mit kritischen Engpässen konfrontiert, insbesondere während großer Ausbrüche.

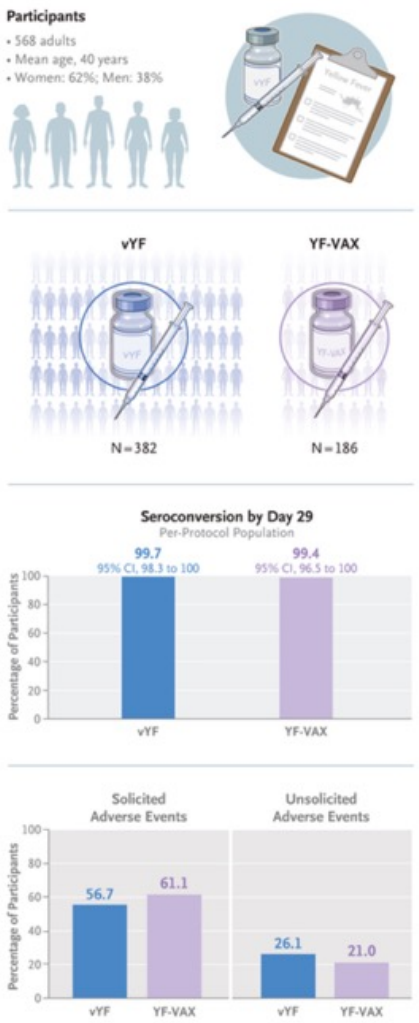




Immunogenicity and Safety of vYF, a Yellow Fever Vaccine — A Phase 2 Trial

A next-generation, live-attenuated yellow fever vaccine, vYF, was developed in Vero cells to improve vaccine supply and availability. The safety of and immune response to vYF as compared with those of the licensed yellow fever vaccine, YF-VAX, are unclear.

In this year 1 interim analysis of a phase 2, observer-blinded, randomized, active-controlled trial, we randomly assigned healthy adults 18 to 60 years of age in a 2:1 ratio to receive vYF or YF-VAX as a single vaccine injection on day 1. Neutralizing antibody titers were measured on day 29, month 6, and year 1. The primary analysis focused on the per-protocol population, which included participants with no history of yellow fever infection or vaccination and with no protocol deviations. Noninferiority would be shown if the lower limit of the two-sided 95% confidence interval of the between-group difference in the percentage of participants with seroconversion was greater than −5 percentage points on day 29.



A next-generation yellow fever vaccine, vYF (Sanofi), has been developed to address the need for a safe, effective vaccine that can be upscaled rapidly in an outbreak. This live-attenuated vaccine is derived from the YF-17D 204 substrain of YF-VAX (Sanofi); vaccines based on this substrain have been shown to trigger broad immune responses by engaging innate, humoral, and cellular immunity. The vYF vaccine is produced in high yields in Vero cells, in accordance with international Good Manufacturing Practice standards, to help ensure a sustainable vaccine supply.

The vYF substrain has five nucleotide differences relative to its parent; however, only two result in amino acid changes. In small-animal models, vYF showed immunogenicity and viscerotropism similar to those of the 17D strain used in YF-VAX but lower neurovirulence. In addition, vYF protected against high viremia after lethal challenge with yellow fever virus. Studies in cynomolgus macaques suggest that vYF would offer protection against yellow fever virus infection similar to that of currently marketed YF-17D vaccines. Recently, a phase 1 clinical trial showed that vYF had safety and immunogenicity similar to that of YF-VAX. This follow-up phase 2 trial assessed the safety and immunogenicity of vYF in adults 18 to 60 years of age with no history of yellow fever infection or vaccination, with YF-VAX used as a comparator. Participants are currently in the third year of follow-up and will be followed up to 5 years after vaccination. Here, we report the interim analysis of the safety and primary immunogenicity end points for up to 1 year after vaccination.

Methods

Trial Design and Oversight

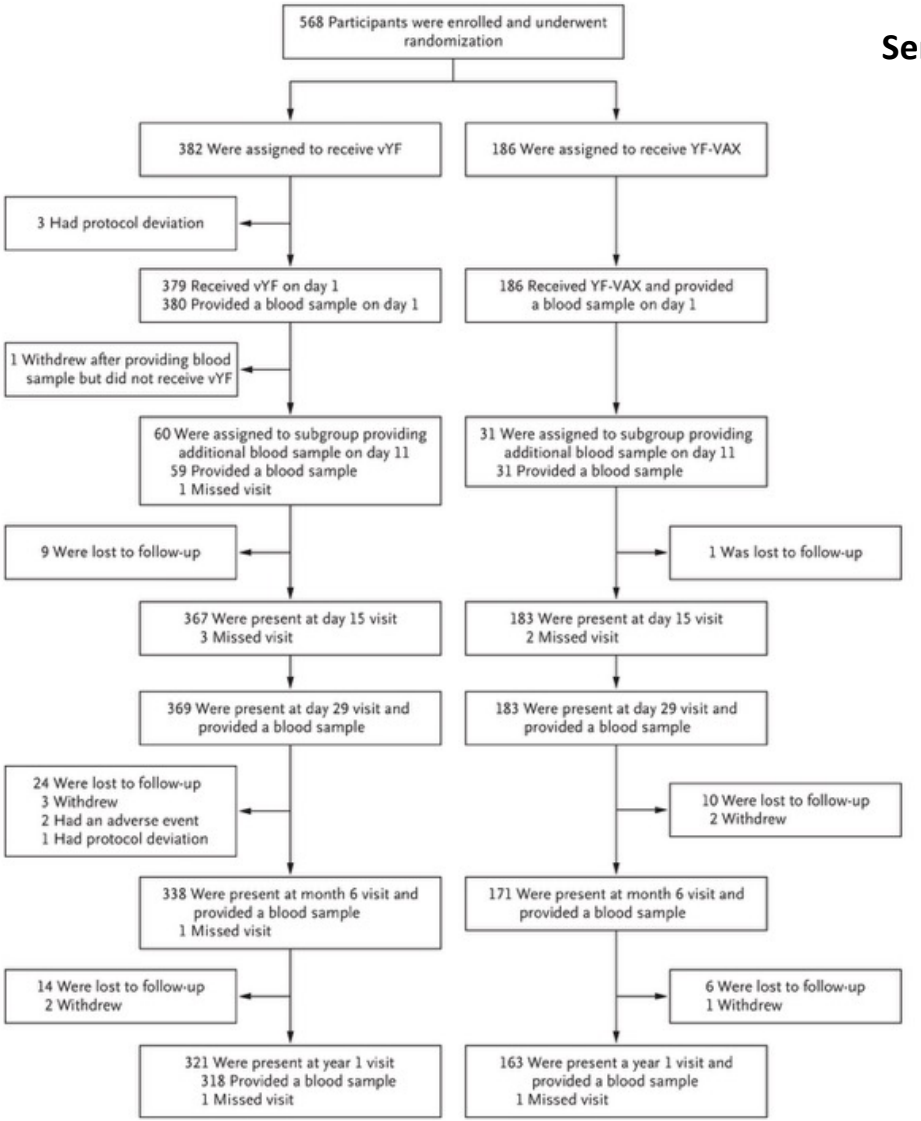
This phase 2, observer-blind, randomized, active-controlled, noninferiority trial was conducted at 11 centers across the United States, with participants enrolled between July 1, 2021, and May 27, 2022. Participants will be monitored annually until the conclusion of the trial (year 5). Healthy adults 18 to 60 years of age were eligible for inclusion.

Trial Objectives

The primary objective was to determine the noninferiority of the antibody response to vYF in terms of seroconversion at day 29 as compared with the antibody response to YF-VAX in participants with no history of yellow fever infection or vaccination. Secondary objectives were to describe the immune response to both vaccines at successive time points from day 1 to year 1, describe the immune response according to participants' orthoflavivirus serostatus at baseline, and compare the safety profiles.

Randomization and Blinding

Participants were randomly assigned in a 2:1 ratio to receive one dose of vYF or YF-VAX. The trial vaccinator oversaw preparation and administration of the vaccine products but was not authorized to collect safety data. All the participants, investigators, safety assessors, laboratory staff, and the sponsor were unaware of the vaccine-group assignments.

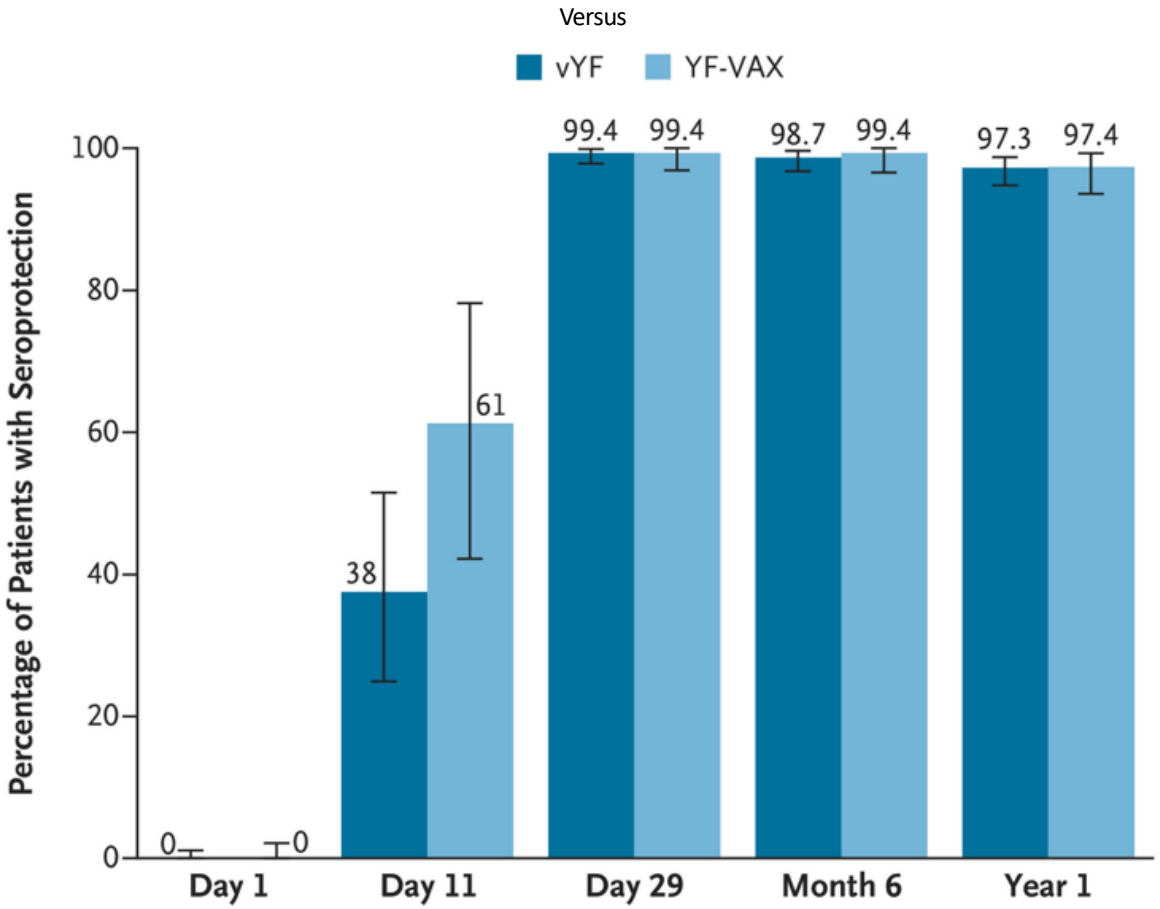


Seroconversion by Day 29 (Per-Protocol Analysis Population).

Variable	vYF	YF-VAX
No. of participants with available data	329	156
No. of participants with seroconversion	328	155
Percentage of participants with seroconversion (95% CI)	99.7 (98.3 to 100)	99.4 (96.5 to 100)
Between-group difference (two-sided 95% CI) — percentage points	0.3 (−1.2 to 3.2)†	

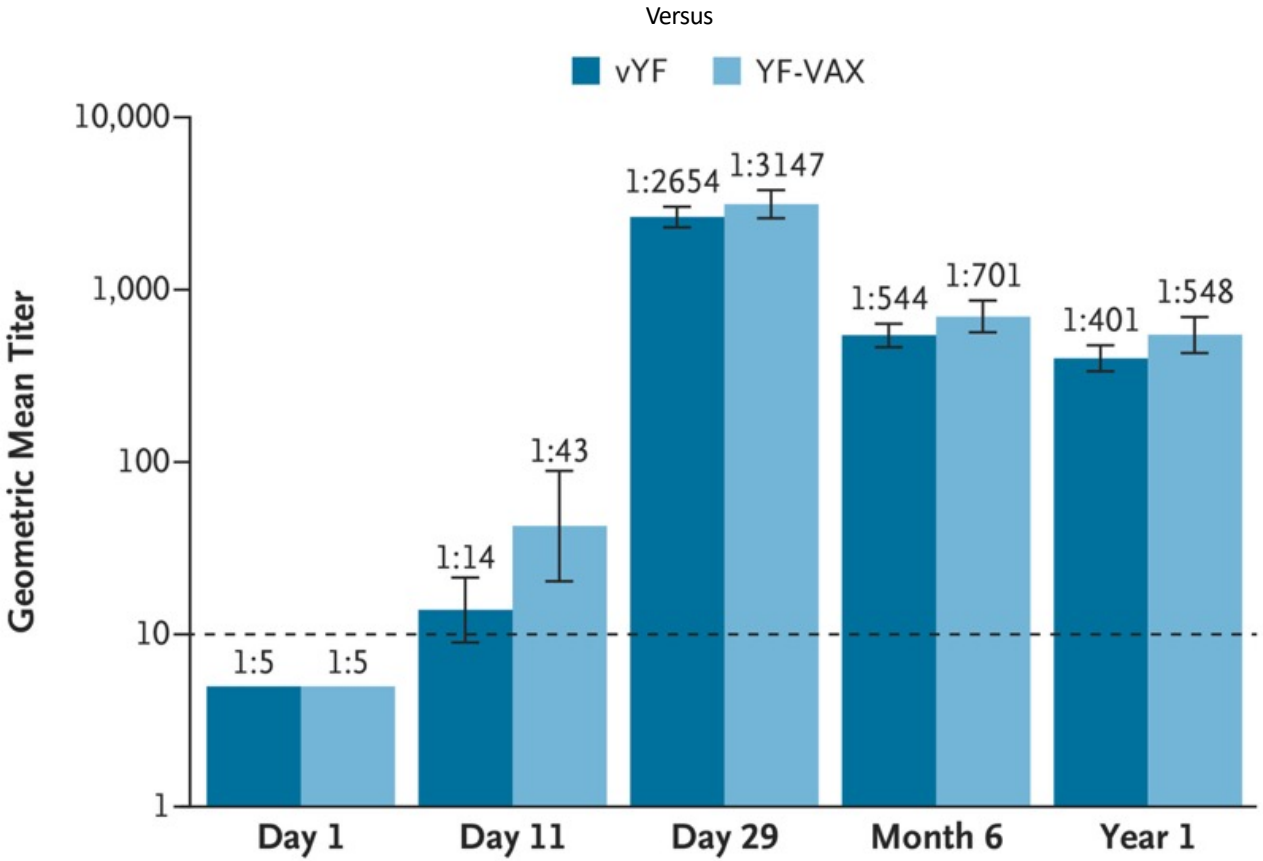
Safety Overview after One Dose of Yellow Fever Vaccine (Safety Analysis Population).

Adverse Event	vYF		YF-VAX	
	no. of participants/ total no.	*% (95% CI)*	*no. of participants/ total no.*	*% (95% CI)*
Within 30 minutes after vaccine injection				
Immediate unsolicited adverse event	1/379	0.3 (0.0–1.5)	0/186	0.0 (0.0–2.0)
Immediate unsolicited adverse reaction	0/379	0.0 (0.0–1.0)	0/186	0.0 (0.0–2.0)
Solicited reaction within solicited period after vaccine injection	208/367	56.7 (51.4–61.8)	113/185	61.1 (53.7–68.1)
Solicited injection-site reaction	115/367	31.3 (26.6–36.4)	64/185	34.6 (27.8–41.9)
Solicited systemic reaction	178/367	48.5 (43.3 –53.7)	102/185	55.1 (47.7–62.4)
Within 28 days after vaccine injection				
Unsolicited adverse event	99/379	26.1 (21.8–30.9)	39/186	21.0 (15.4–27.5)
Unsolicited adverse reaction	32/379	8.4 (5.8–11.7)	11/186	5.9 (3.0–10.3)
Adverse event leading to discontinuation from trial	0/379	0.0 (0.0–1.0)	0/186	0.0 (0.0–2.0)
Serious adverse event	0/379	0.0 (0.0–1.0)	2/186	1.1 (0.1–3.8)
Death	0/379	0.0 (0.0–1.0)	0/186	0.0 (0.0–2.0)
Adverse event of special interest	0/379	0.0 (0.0–1.0)	0/186	0.0 (0.0–2.0)
Medically attended adverse event	14/379	3.7 (2.0–6.1)	10/186	5.4 (2.6–9.7)
During 6-month follow-up period†				
Serious adverse event	6/379	1.6 (0.6–3.4)	2/186	1.1 (0.1–3.8)
Death	2/379	0.5 (0.1–1.9)	0/186	0.0 (0.0–2.0)
Adverse event of special interest	0/379	0.0 (0.0–1.0)	0/186	0.0 (0.0–2.0)
Medically attended adverse event	4/379	1.1 (0.3–2.7)	2/186	1.1 (0.1–3.8)



Seroprotection among Participants with No History of Yellow Fever Infection or Vaccination (Full Analysis Population).

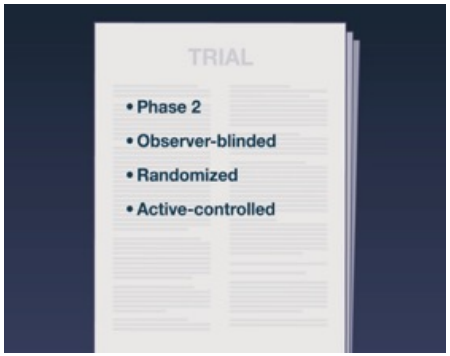
Seroprotection was considered likely to be achieved at neutralizing antibody titers of at least 1:10. Values at day 11 are for a subgroup of participants who provided an additional blood sample on day 11 only. I bars indicate 95% confidence intervals.

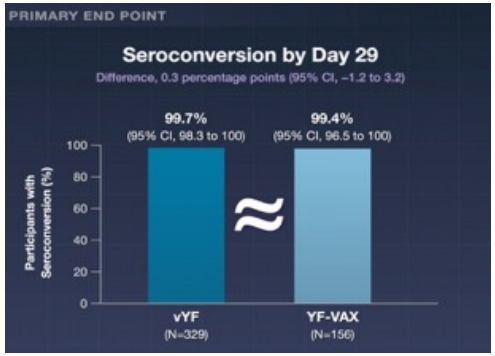


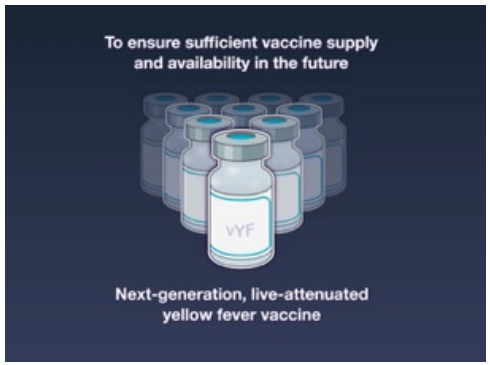
Geometric Mean Titers in Participants with No History of Yellow Fever Infection or Vaccination (Full Analysis Population).

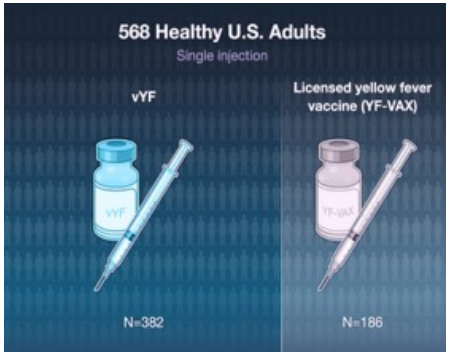
Values at day 11 are for a subgroup of participants who provided an additional blood sample on day 11 only. The dashed line represents the threshold for seroprotection (1:10). I bars indicate 95% confidence intervals.

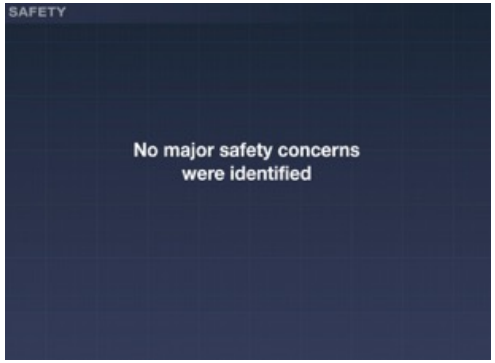

Yellow Fever Outbreaks
Brazil
Central Africa


TRIAL
• Phase 2
• Observer-blinded
• Randomized
• Active-controlled

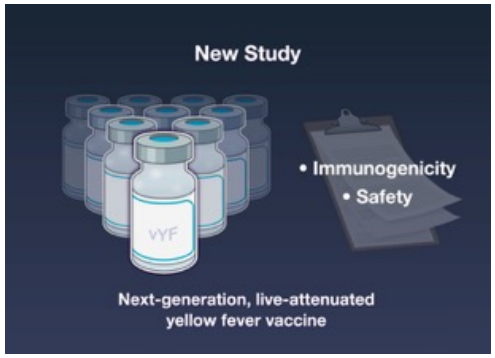

PRIMARY END POINT
Seroconversion by Day 29
Difference, 0.3 percentage points (95% CI, −1.2 to 3.2)
99.7%
(95% CI, 98.3 to 100)
99.4%
(95% CI, 96.5 to 100)
Participants with Seroconversion (%)
100
80
60
40
20
0
≈
vYF
(N=329)
YF-VAX
(N=156)


To ensure sufficient vaccine supply and availability in the future
vYF
Next-generation, live-attenuated yellow fever vaccine

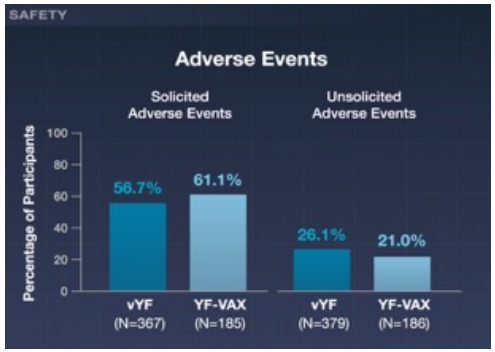

568 Healthy U.S. Adults
Single injection
vYF
Licensed yellow fever vaccine (YF-VAX)
N=382
N=186


SAFETY
No major safety concerns were identified


vYF
≈
YF-VAX


New Study
vYF
• Immunogenicity
• Safety
Next-generation, live-attenuated yellow fever vaccine


PRIMARY END POINT
Seroconversion by Day 29
99.7%
(95% CI, 98.3 to 100)
99.4%
(95% CI, 96.5 to 100)
Participants with Seroconversion (%)
100
80
60
40
20
0
vYF
(N=329)
YF-VAX
(N=156)


SAFETY
Adverse Events
Solicited Adverse Events
Unsolicited Adverse Events
Percentage of Participants
100
80
60
40
20
0
56.7%
61.1%
26.1%
21.0%
vYF
(N=367)
YF-VAX
(N=185)
vYF
(N=379)
YF-VAX
(N=186)

KRAS (Kirsten Rat Sarcoma Virus) bezeichnet primär ein Gen und das dazugehörige Protein, das als zentraler Schalter für das Zellwachstum fungiert.

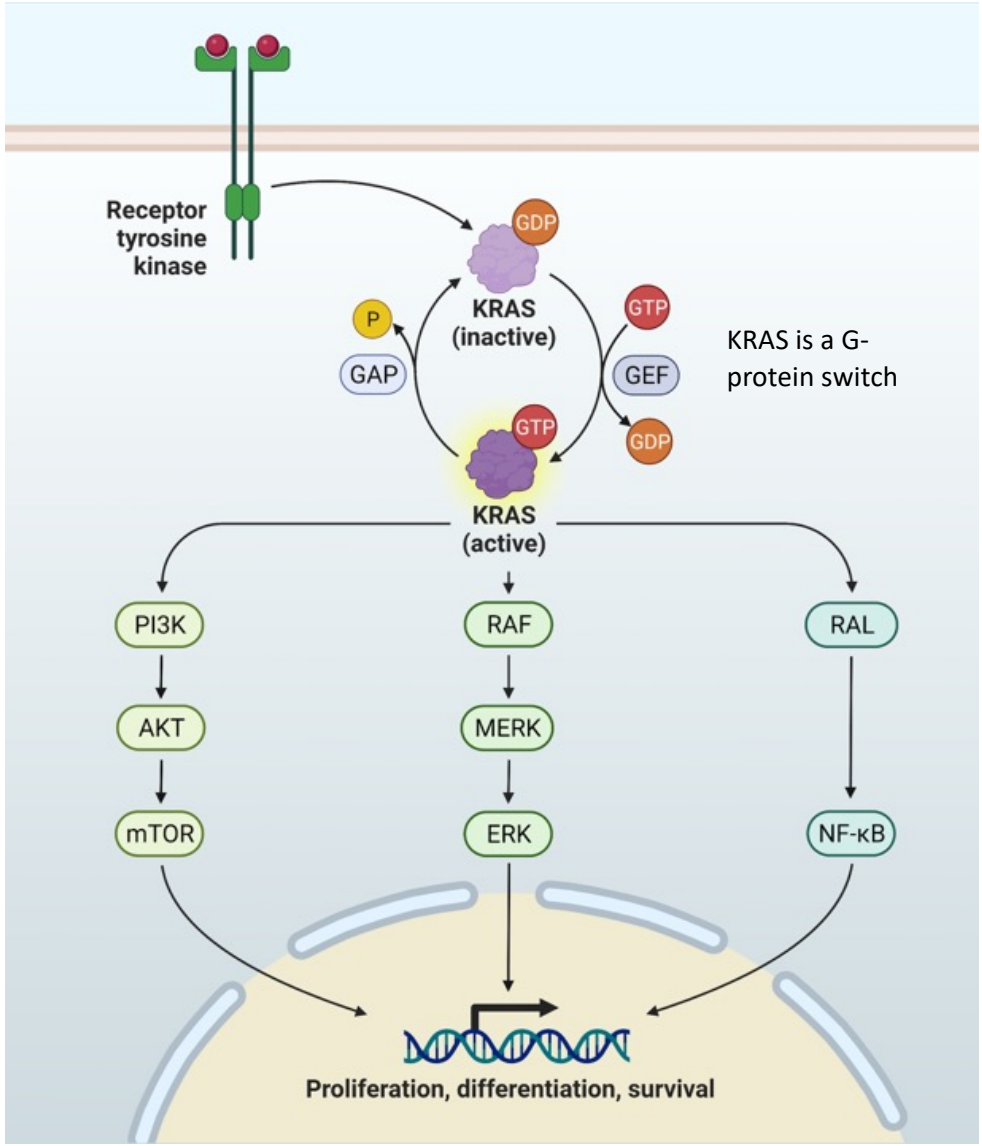
Biologische Funktion

Das KRAS-Protein ist ein sogenanntes monomeres G-Protein. Es leitet Signale von der Zelloberfläche an den Zellkern weiter, um der Zelle mitzuteilen, wann sie wachsen, sich teilen oder spezialisieren soll. In gesundem Zustand schaltet sich KRAS nach der Signalübertragung selbstständig wieder aus.

Bedeutung bei Krebserkrankungen

Mutationen im KRAS-Gen führen dazu, dass der "Schalter" dauerhaft in der "Ein"-Position verbleibt. Dies verursacht ein unkontrolliertes Zellwachstum, was die Entstehung und Ausbreitung von Tumoren fördert.

Der „Kirsten“ im Namen des **Kirsten Rat Sarcoma Virus** (Ki-RSV) bezieht sich auf **Werner H. Kirsten** (1925–1992), einen deutsch-amerikanischen Pathologen und Krebsforscher.
Hier sind die wichtigsten Details zu seiner Person und seiner Entdeckung:
•**Werner H. Kirsten**: Er wurde in Leipzig geboren und wanderte in den 1950er Jahren in die USA aus. Er verbrachte einen Großteil seiner Karriere an der **University of Chicago**, wo er 1967 das Virus entdeckte, das heute seinen Namen trägt.



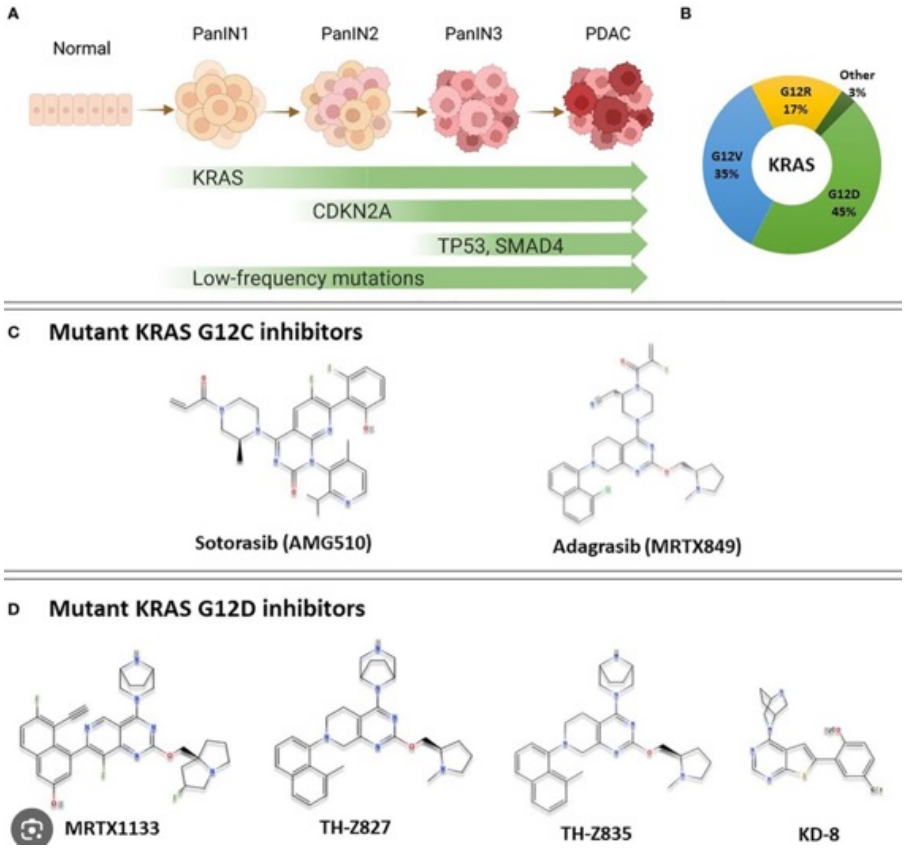
KRAS is a G-protein switch

Die **KRAS p.G12D**-Variante ist eine der häufigsten und klinisch bedeutsamsten Onkogen-Mutationen beim Menschen. Sie entsteht durch eine Punktmutation im *KRAS*-Gen (Austausch von Guanin gegen Adenin), die an Position 12 der Proteinkette zum Austausch der Aminosäure Glycin gegen Asparaginsäure führt.

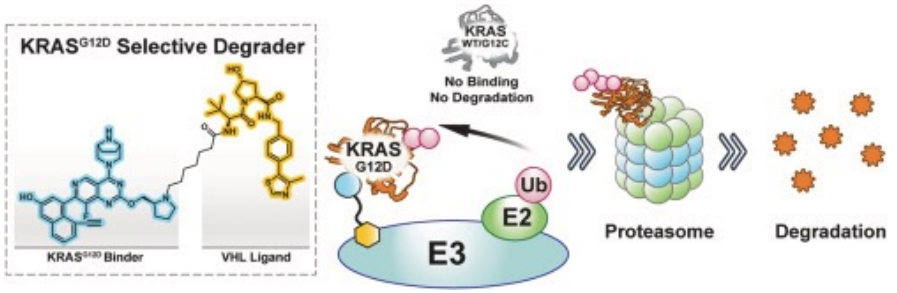
Klinische Bedeutung und Häufigkeit

Diese Variante ist ein zentraler Treiber für das Tumorwachstum und tritt besonders häufig bei folgenden Krebsarten auf:

- **Bauchspeicheldrüsenkrebs (PDAC):** Hier ist G12D die vorherrschende Mutation und wird bei etwa **40 %** der Patienten gefunden.
- **Darmkrebs (CRC):** Ebenfalls eine sehr häufige Treibermutation.
- **Nicht-kleinzelliges Lungenkarzinom (NSCLC):** Betrifft etwa **5 %** der Patienten insgesamt, ist aber mit ca. **46 %** die häufigste *KRAS*-Mutation bei Nichtrauchern.

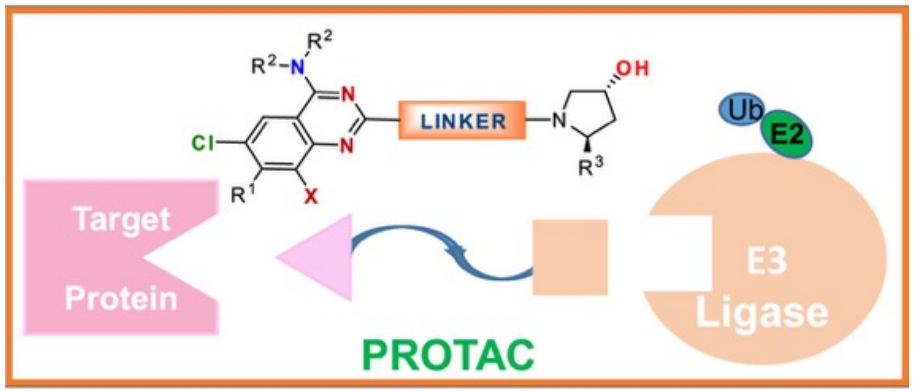


Selektive **KRAS G12D-gezielte Protein-Degrader** sind eine neuartige Klasse von Therapeutika, die darauf abzielen, das mutierte KRAS-Protein direkt abzubauen, anstatt es nur vorübergehend zu blockieren. Da KRAS G12D eine der häufigsten Mutationen bei Bauchspeicheldrüsen-, Darm- und Lungenkrebs ist, gelten diese Degrader (oft als PROTACs konzipiert) als vielversprechende Lösung, um die bisherige „Undruggability“ dieses Ziels zu überwinden.



•**ASP3082 (Astellas Pharma)**: Der am weitesten fortgeschrittene Wirkstoff in klinischen Studien (NCT05382559).**Status**: Befindet sich in **Phase I**-Studien für fortgeschrittene solide Tumoren (Bauchspeicheldrüse, Darm, Lunge).

•**Wirkungsweise**: Ein selektiver **VHL-basierter PROTAC**, der das KRAS G12D-Protein mit hoher Präzision abbaut und im Vergleich zu herkömmlichen Inhibitoren eine dauerhaftere Unterdrückung des Signalwegs zeigt.



PROTACs (Proteolysis Targeting Chimeras) bestehen aus drei Komponenten: einem Liganden für das Zielprotein (POI), einem Linker und einem Liganden für eine E3-Ligase.
•**Mechanismus**: Der PROTAC bringt das Zielprotein und die VHL-E3-Ligase in räumliche Nähe, wodurch ein **Ternärkomplex** entsteht.

Setidegrasib in Advanced Non–Small-Cell Lung Cancer and Pancreatic Cancer

The *KRAS* p.G12D variant occurs in 5% of patients with non–small-cell lung cancer (NSCLC) and is the most common substitution variant in pancreatic ductal adenocarcinoma, occurring in 40% of patients, but no targeted therapies directed against this variant are currently approved for clinical use. Setidegrasib (ASP3082) is a first-in-class KRAS G12D–targeted protein degrader.

We conducted this phase 1 study to evaluate the safety, pharmacokinetics, pharmacodynamics, and antitumor activity of setidegrasib in patients with previously treated advanced solid tumors harboring *KRAS* p.G12D variants. The primary objectives were to evaluate the safety profile, as indicated by dose-limiting toxic effects and adverse events (the primary end points), and to determine the phase 2 dose. Setidegrasib was administered intravenously once weekly at doses of 10 to 800 mg.

Conclusions

Setidegrasib was associated with antitumor activity and a low incidence of treatment discontinuation due to adverse events in patients with previously treated advanced *KRAS* p.G12D–mutated NSCLC or pancreatic ductal adenocarcinoma.

The *KRAS* p.G12D variant occurs in 5% of patients with non–small-cell lung cancer (NSCLC) and is the most common substitution variant in pancreatic ductal adenocarcinoma, occurring in approximately 40% of patients. In contrast to the number of therapies approved for use against KRAS G12C, no targeted therapies directed against KRAS G12D are currently approved for clinical use. The challenge in classic inhibition of KRAS G12D reflects structural distinctions between the two alleles: whereas KRAS G12C has a reactive cysteine residue that enables covalent inhibitor binding, KRAS G12D lacks this feature and possesses only a shallow switch II pocket, which renders it difficult to target. Recent advances have permitted KRAS G12D targeting despite these structural constraints. Several KRAS G12D inhibitors are in development and have been shown to have clinical activity in patients with *KRAS* p.G12D–mutated NSCLC or pancreatic ductal adenocarcinoma.

Targeted protein degradation represents a method of treatment that is distinct from small-molecule inhibition and enables catalytic elimination of oncogenic proteins. Setidegrasib (ASP3082) is a first-in-class KRAS G12D–targeted protein degrader that forms a ternary complex among KRAS G12D, a proteolysis-targeting chimera, and von Hippel–Lindau E3 ligase, resulting in selective degradation of KRAS G12D and inhibition of downstream signaling pathways. Here, we report the safety, pharmacokinetics, pharmacodynamics, and preliminary antitumor activity of setidegrasib monotherapy from a first-in-human phase 1 study involving patients with advanced solid tumors, including those with NSCLC and those with pancreatic ductal adenocarcinoma.

Patients

Eligible patients were adults who had documented locally advanced unresectable or metastatic solid tumors harboring *KRAS* p.G12D variants, had previously received at least one systemic anticancer therapy but not KRAS G12D or pan-RAS inhibitors or degraders; and did not have symptomatic or untreated central nervous system metastases.

Study Design

This phase 1, open-label, international, multicenter study included dose-escalation and dose-expansion cohorts.

Assessments

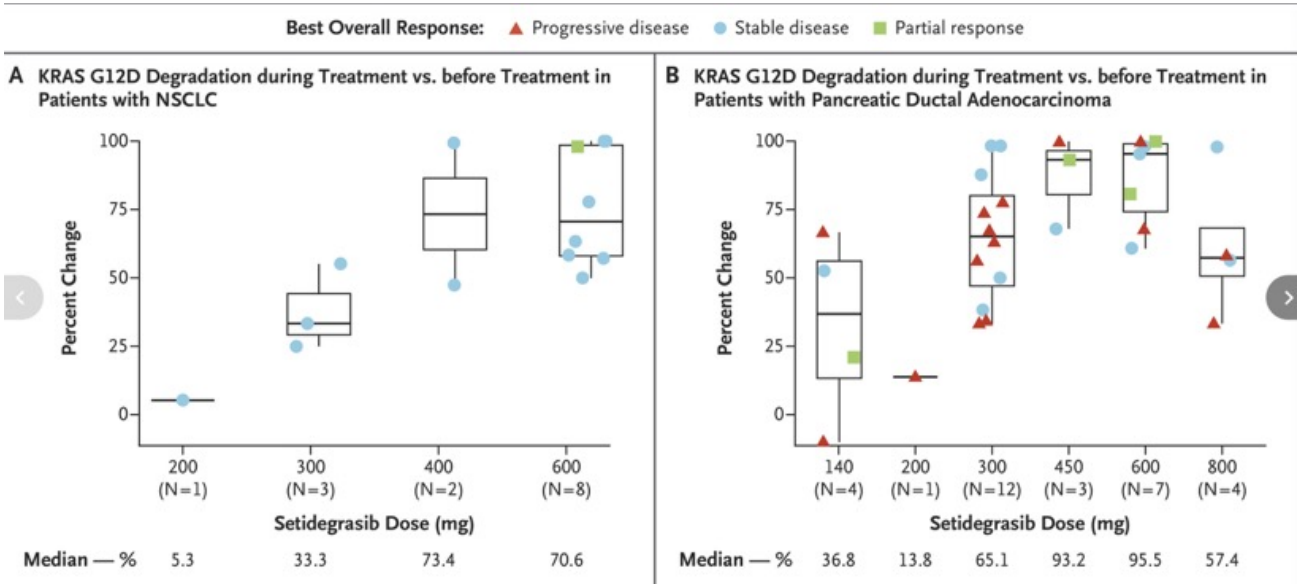
Tumors were assessed by computed tomography or magnetic resonance imaging at screening, every 6 weeks during treatment, and every 9 weeks during follow-up until the occurrence of disease progression, the receipt of new anticancer therapy, death, withdrawal from the study, or loss to follow-up.

End Points

The primary objectives were to evaluate the safety profile, as indicated by dose-limiting toxic effects and adverse events (the primary end points), and to determine the maximum tolerated dose and the recommended phase 2 dose of setidegrasib. Secondary end points were objective response (partial or complete response), duration of response, and disease control.

Characteristic	All Patients (N=76)	NSCLC (N=45)	PDAC (N=31)
Median age (range) — yr	66 (36–81)	68 (36–81)	65 (36–79)
Female sex — no. (%)	41 (54)	28 (62)	13 (42)
Race — no./total no. (%)†			
White	31/54 (57)	23/33 (70)	8/21 (38)
Asian	22/54 (41)	10/33 (30)	12/21 (57)
Black or African American	1/54 (2)	0	1/21 (5)
ECOG performance-status score of 1 — no. (%)‡	56 (74)	35 (78)	21 (68)
Median lines of previous anticancer therapy (range)	2 (1–5)	2 (1–5)	2 (1–5)
Lines of previous anticancer therapy — no. (%)			
1	26 (34)	19 (42)	7 (23)
2	27 (36)	13 (29)	14 (45)
≥3	23 (30)	13 (29)	10 (32)
Disease stage IV — no. (%)§	74 (97)	43 (96)	31 (100)
Distant metastasis — no. (%)¶			
Bone	—	17 (38)	—
Lymph node	—	17 (38)	—
Liver	—	9 (20)	23 (74)
Brain	—	6 (13)	—
Type of previous anticancer therapy — no. (%)‖			
Platinum-based chemotherapy and immune checkpoint inhibitor	—	42 (93)	—
Gemcitabine plus paclitaxel or nab-paclitaxel	—	—	26 (84)
Modified FOLFIRINOX	—	—	16 (52)

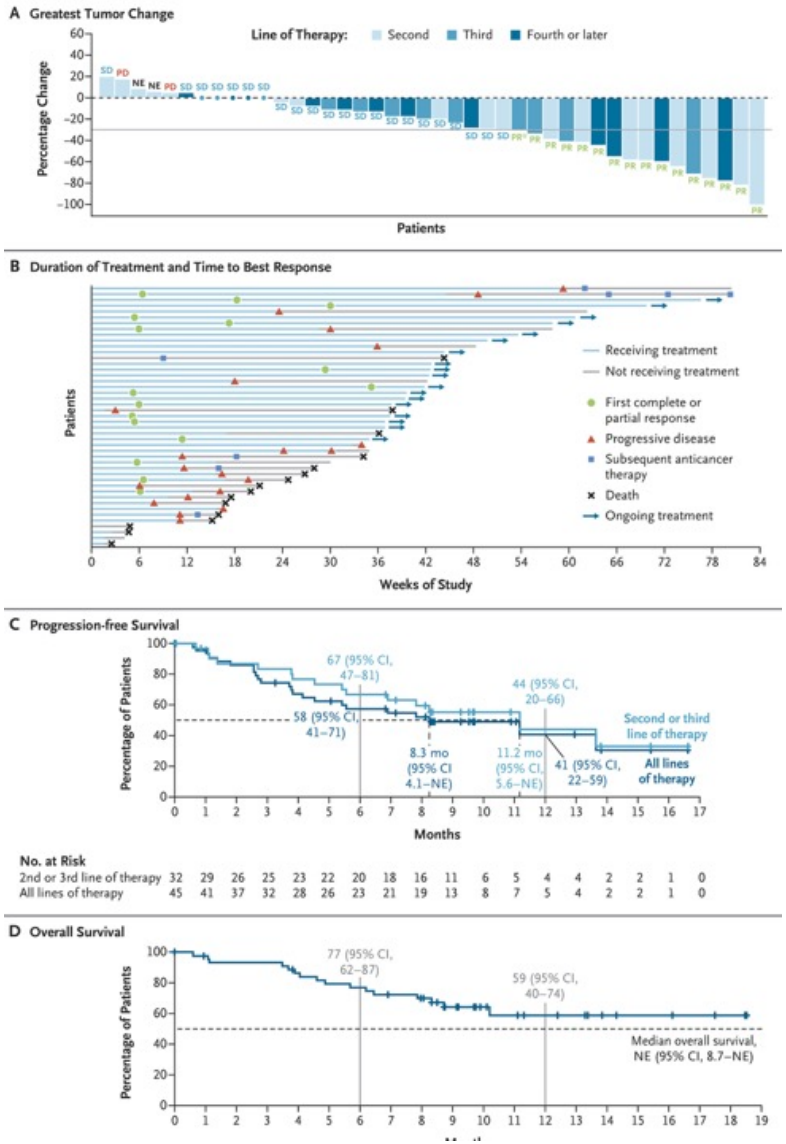
Event	Patients (N=76)
Adverse events that emerged during treatment — no. (%)	
Any	76 (100)
Grade ≥3	32 (42)
Serious	25 (33)
Leading to treatment interruption	59 (78)
Leading to dose reduction	4 (5)
Leading to permanent discontinuation	2 (3)
Treatment-related adverse events — no. (%)	
Any	71 (93)
Grade ≥3	7 (9)
Alanine aminotransferase increased	2 (3)
Neutropenia*	2 (3)
Neutrophil count decreased	2 (3)
Iron deficiency anemia	1 (1)
Cholangitis*	1 (1)
Serious	4 (5)
Leading to treatment interruption	53 (70)
Infusion-related reactions	48 (63)
Noninfusion-related-reaction adverse events	8 (11)
Leading to dose reduction	4 (5)
Leading to permanent discontinuation	0
Occurring in ≥20% of patients	
Infusion-related reactions	61 (80)
Nausea	23 (30)



KRAS G12D Protein Degradation.

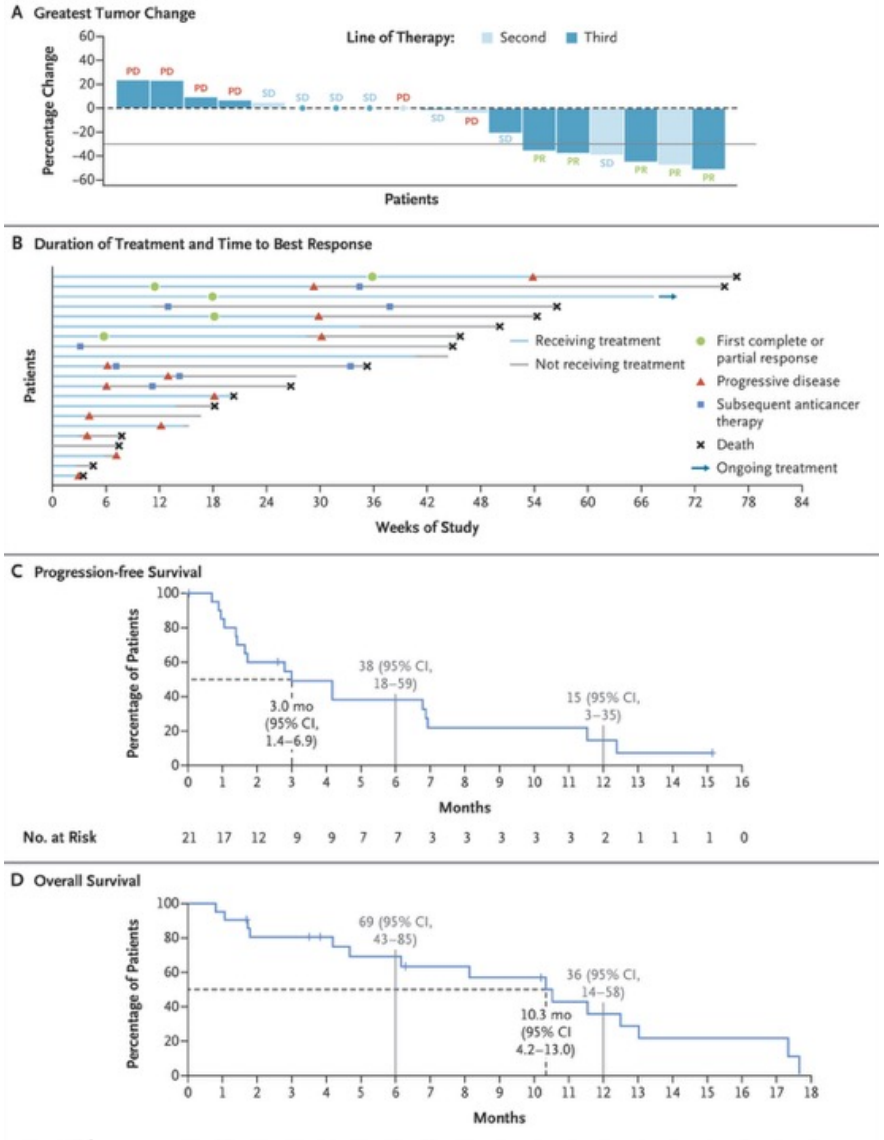
Shown is the level of KRAS G12D degradation in patients with non–small-cell lung cancer (NSCLC) and in those with pancreatic ductal adenocarcinoma. The horizontal lines within the boxes indicate the medians, and the lower and upper box limits represent quartile 1 and quartile 3, respectively. The lower whiskers represent 1.5 times the quartile 1 value or the minimum if within that range, and the upper whiskers represent 1.5 times the quartile 3 value or the maximum if within that range.

Stage IV disease



Efficacy in Patients with NSCLC.

Data are shown for patients with NSCLC who received 600 mg of setidegrasib monotherapy as second-line treatment or later. Panel A shows the greatest tumor change from baseline, Panel B the time to response and duration of treatment, Panel C progression-free survival, and Panel D overall survival. The gray line in Panel A represents partial response according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. The asterisk indicates an unconfirmed partial response according to RECIST, version 1.1. The dashed line in Panels C and D represents the median. NE denotes could not be estimated, PD progressive disease, PR partial response, and SD stable disease.



Stage IV disease

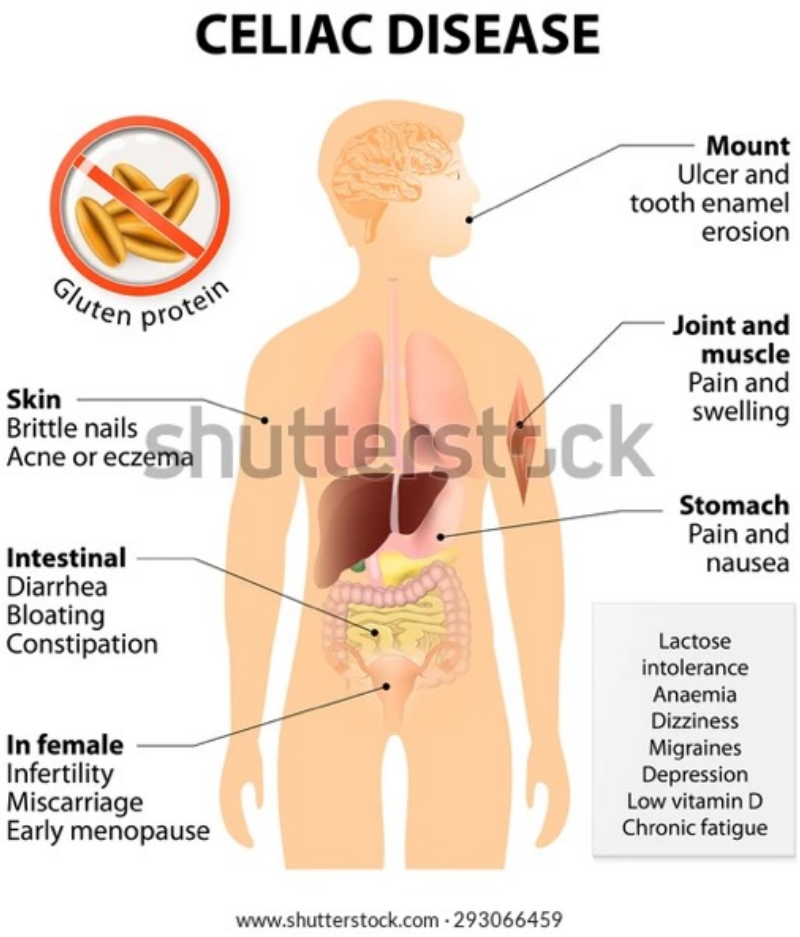
Efficacy in Patients with Pancreatic Ductal Adenocarcinoma.

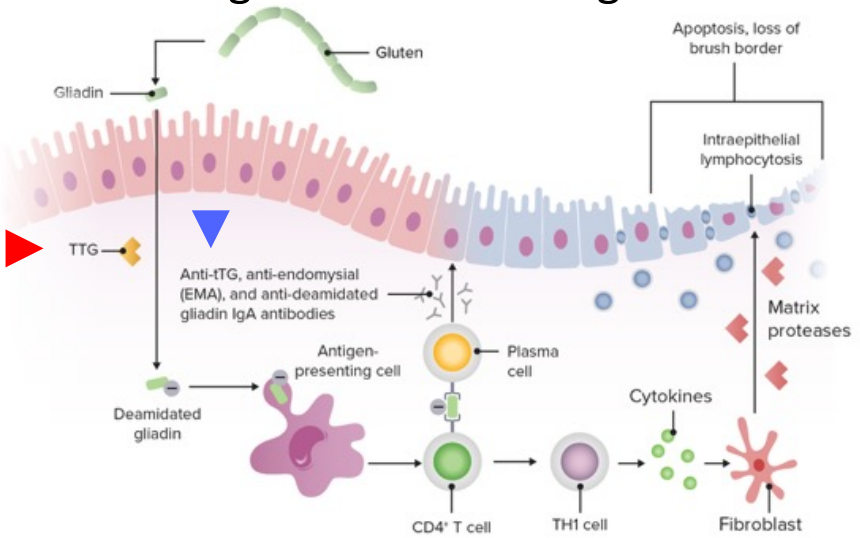
Data are shown for patients with pancreatic ductal adenocarcinoma who received 600 mg of setidegrasib monotherapy as second- or third-line treatment. Panel A shows the greatest tumor change from baseline, Panel B the time to response and duration of treatment, Panel C progression-free survival, and Panel D overall survival. The gray line in Panel A represents partial response according to RECIST, version 1.1. The dashed line in Panels C and D represents the median.

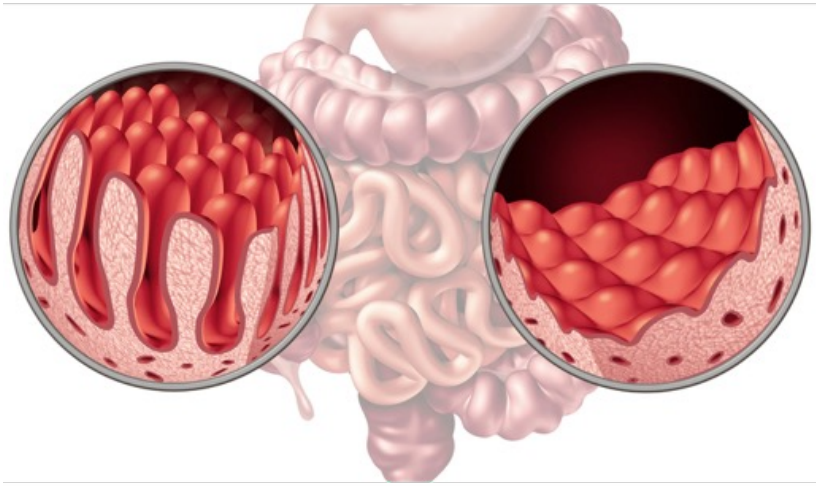
Discussion

This phase 1, first-in-human study involving patients with advanced, previously treated NSCLC or pancreatic ductal adenocarcinoma evaluated the safety profile and clinical activity of setidegrasib, a first-in-class, selective KRAS G12D–targeted protein degrader, administered at a dose of 600 mg intravenously once weekly. Overall, 42% of the patients who received setidegrasib at a dose of 600 mg had adverse events of grade 3 or higher; adverse events led to discontinuation in 2 patients. Infusion-related reactions were the most common treatment-related adverse events (occurring in 80% of the patients). All were events of grade 1 or 2, occurred predominantly during the first infusion, and were managed during subsequent infusions with protocol-specified measures, including infusion-rate modification, temporary interruption, and antihistamine administration. None of the patients discontinued treatment owing to infusion-related reactions. Most of the other treatment-related adverse events were also of grade 1 or 2. Overall, 9% of the patients had treatment-related adverse events of grade 3 or higher with setidegrasib at a dose of 600 mg; no treatment-related gastrointestinal or dermatologic adverse events of grade 3 or higher were noted. In phase 1–2 studies of KRAS G12D inhibitors in patients with *KRAS* p.G12D–mutated solid tumors, the incidence of treatment-related adverse events of grade 3 or higher ranged widely, from approximately 1 to 30%. In a phase 1 study of the pan-RAS inhibitor daraxonrasib in patients with *KRAS* p.G12X mutations, the incidence of treatment-related adverse events of grade 3 or higher was approximately 35% in patients with pancreatic ductal adenocarcinoma and 16% in patients with NSCLC. Cross-trial comparisons should be interpreted with caution.

Tissue transglutaminase and IgA antibodies against tissue transglutaminase







Die Gewebe-Transglutaminase (**tTG** oder **TG2**) ist ein körpereigenes Enzym, das bei Zöliakie eine doppelte Schlüsselrolle spielt: Sie ist sowohl der entscheidende Akteur bei der Krankheitsentstehung (Pathogenese) als auch das wichtigste Ziel für die Diagnose (Autoantigen).

Zentrale Funktionen bei Zöliakie

- **Verstärkung der Immunreaktion (Deamidierung):** tTG verändert Gluten-Bestandteile (Gliadin) durch die Umwandlung von Glutamin in Glutaminsäure. Diese sogenannten „deamidierten" Gliadin-Peptide binden deutlich stärker an die Risiko-Gene **HLA-DQ2** und **HLA-DQ8**, was eine heftige Entzündungsreaktion im Darm auslöst.
- **Haupt-Autoantigen:** Das Immunsystem von Zöliakie-Betroffenen erkennt die tTG fälschlicherweise als Feind und bildet Antikörper gegen sie (**tTG-Antikörper**). Diese Antikörper können die Darmzellen schädigen und zu den typischen Gewebeveränderungen wie Zottenatrophie führen.

Bedeutung für die Diagnose

Der Nachweis von tTG-Antikörpern im Blut ist heute der Standard-Screeningtest auf Zöliakie.

- **tTG-IgA-Test:** Dies ist das bevorzugte Verfahren mit einer Sensitivität von etwa 93–98 % und einer Spezifität von über 90 %.
- **Voraussetzung:** Für ein korrektes Testergebnis muss man sich zum Zeitpunkt der Blutentnahme **glutenhaltig ernähren**.
- **Verzicht auf Biopsie:** Nach den aktuellen ESPGHAN-Leitlinien kann bei Kindern (und zunehmend auch bei Erwachsenen) auf eine Darmbiopsie verzichtet werden, wenn der tTG-IgA-Wert mehr als das **10-fache des Grenzwertes** beträgt und weitere Kriterien erfüllt sind.

Celiac Disease

At presentation, an 18-year-old woman reports a 1-year history of daily abdominal bloating and malodorous flatulence. She also reports fatigue and recurrent mouth ulcers. Her complete blood count shows a normal hemoglobin level but a low mean corpuscular volume (65 fl [reference range, 76 to 100]) and a low ferritin level (6 ng per milliliter [reference range, 6 to 175). Additional blood tests reveal mild iron deficiency without anemia and mildly elevated liver-enzyme levels (alanine aminotransferase level, 70 U per liter [reference range, 7 to 45], and aspartate aminotransferase level, 56 U per liter [reference range, 8 to 43]). Oral iron therapy is initiated, but her symptoms and hypoferritinemia persist. Her family history is notable for a 10-year-old brother with type 1 diabetes mellitus and celiac disease. A celiac serologic test for IgA antibodies against tissue transglutaminase (tTG-IgA) is performed, and the results are positive (150 IU per milliliter [reference value, <15). How would you proceed?

Celiac Disease

- Celiac disease is a common autoimmune disease with a prevalence of approximately 1%.
- Celiac disease occurs at all ages, provided that gluten is part of the diet, and can be a major cause of malabsorption of key nutrients.
- A gluten-free diet is the mainstay of treatment.
- The presence of genes encoding HLA-DQ2 or HLA-DQ8 is a prerequisite for celiac disease.
- Celiac antibodies in serum, mainly IgA antibodies against tissue transglutaminase, are used for first-line screening in patients with symptoms consistent with celiac disease. Endomysial antibodies are more specific and are used as a confirmatory test in those with a positive screening result.
- Histologic evaluation of a duodenal-biopsy sample is needed to confirm the diagnosis in most adults and in children who do not meet nonbiopsy diagnostic criteria.
- Celiac disease often occurs in conjunction with other autoimmune diseases such as type 1 diabetes mellitus and autoimmune thyroid disease.
- Nonresponsive celiac disease occurs in adults and should be followed regularly owing to the risk of malignant conditions if refractory celiac disease occurs.

Extragastrointestinal Manifestations of Celiac Disease.

Manifestation (Special Features)

Common manifestations

Neuropsychiatric system
- Peripheral neuropathy (distal, symmetric, predominantly sensory neuropathy)
- Cerebellar ataxia
- Migraine
- Seizure disorder (associated with occipital calcification)
- Movement disorder (associated with myoclonus)
- Cognitive impairment (ranging from brain fog to dementia)
- Depression, anxiety, eating disorders, attention deficit–hyperactivity disorder, autism spectrum disorders, and irritability

Reproductive system
- Delayed menarche
- Unexplained female or male infertility
- Premature menopause
- Miscarriage
- Secondary amenorrhea

Mucocutaneous system
- Dermatitis herpetiformis
- Recurrent aphthous ulceration
- Xerosis
- Urticaria
- Alopecia
- Skin pigmentation

Musculoskeletal system
- Arthralgias
- Muscle pain or weakness
- Increased fracture risk
- Rickets and osteoporosis

Hepatic system
- Hepatic steatosis
- Isolated elevation of liver enzymes
- Portal hypertension
- Granulomatous hepatitis

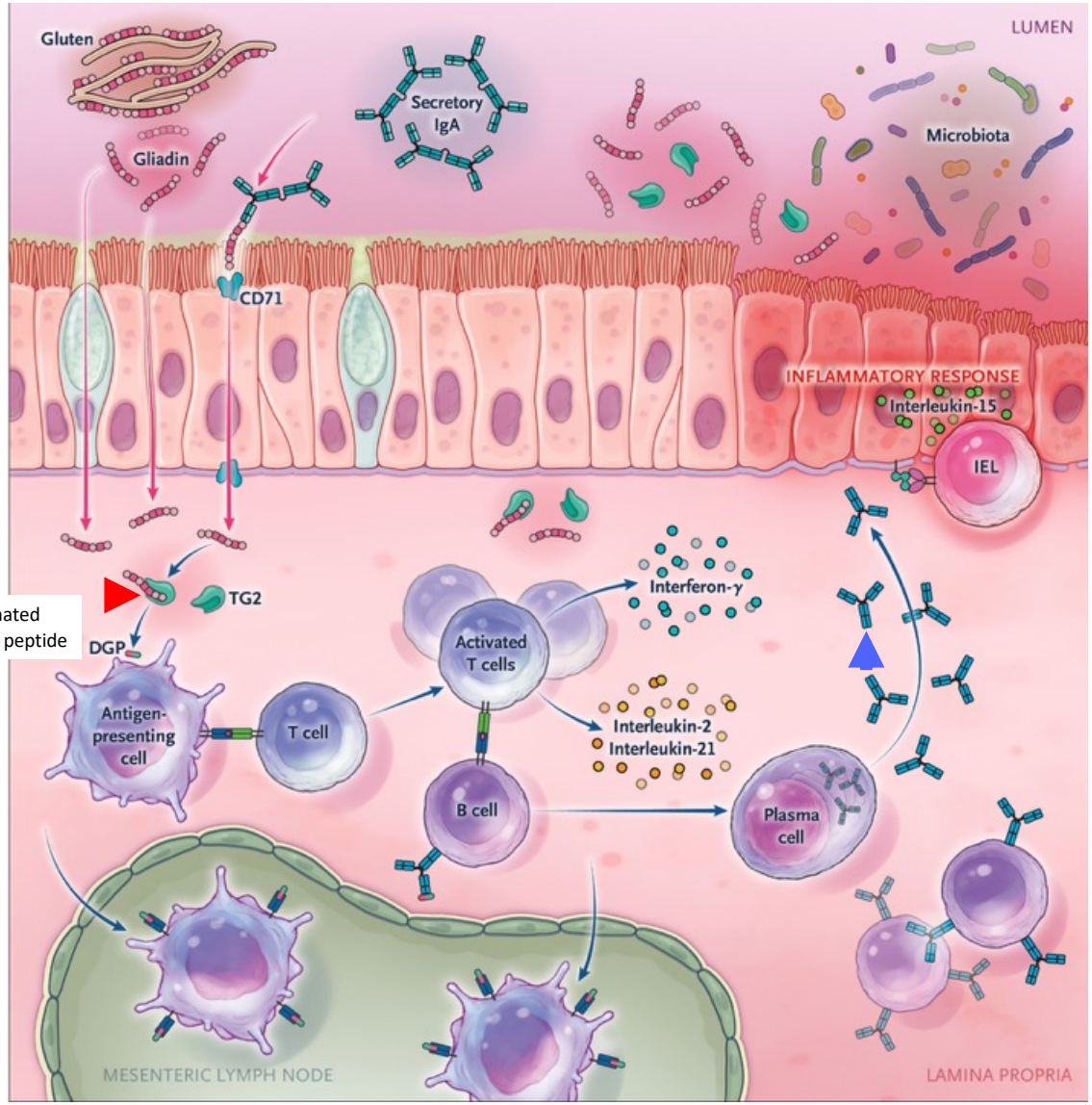
Hematologic system
- Anemia (iron deficiency, vitamin B_{12} deficiency, folate deficiency, copper deficiency)
- Hyposplenism
- IgA deficiency
- Neutropenia
- Hemophagocytic lymphohistiocytosis

Rare manifestations

Cardiovascular system
- Myocarditis
- Pericarditis
- Deep venous thromboembolism
- Dyslipidemia

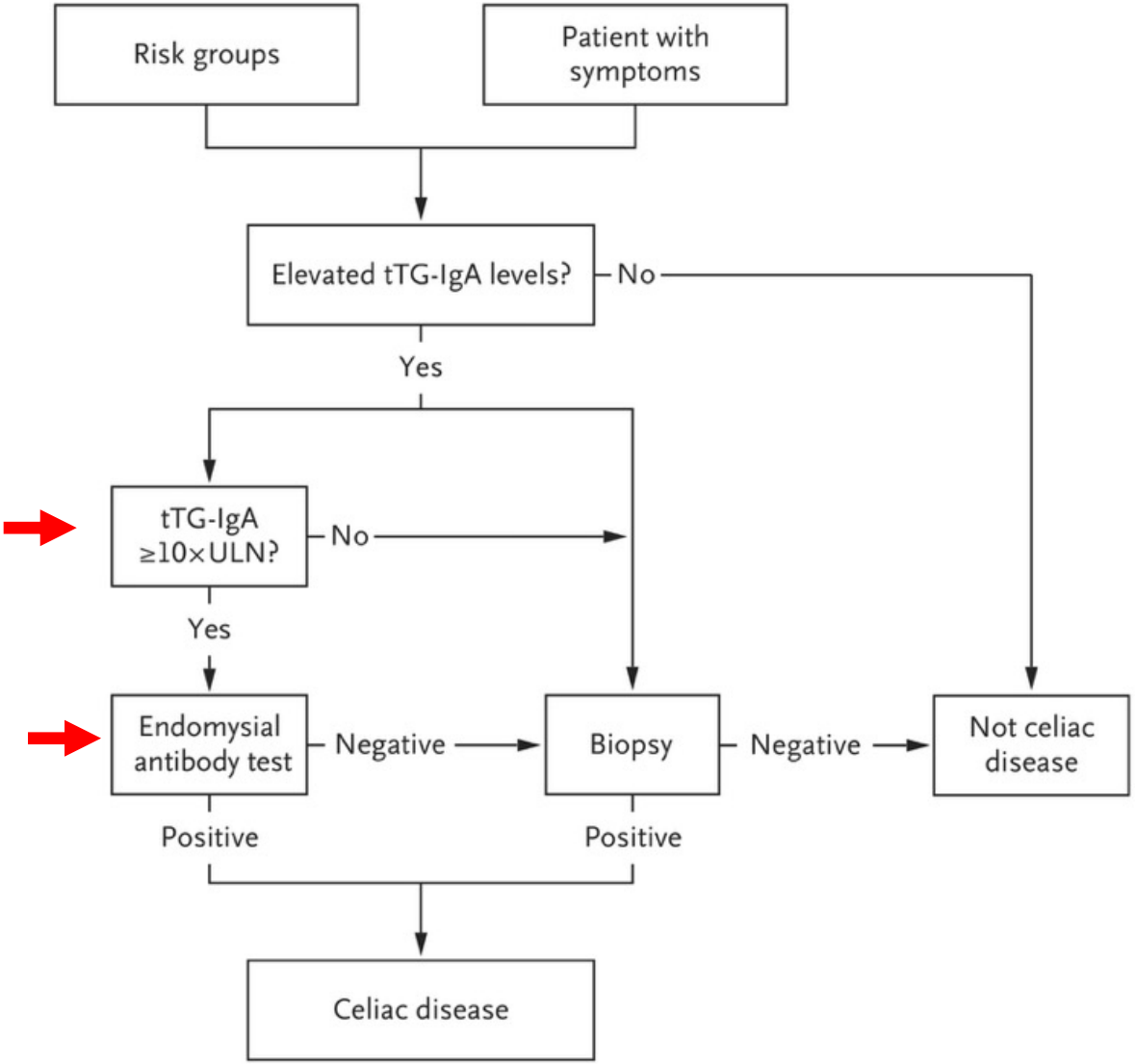
Respiratory system
- Lane–Hamilton syndrome (pulmonary hemosiderosis)
- Bronchiectasis
- Pneumococcal pneumonia[9]
- Interstitial lung disease
- Nocardia infection

Oncologic conditions[10]
- Enteropathy-associated T-cell lymphoma
- Adenocarcinoma of the small intestine
- Head and neck cancers
- Esophageal cancer



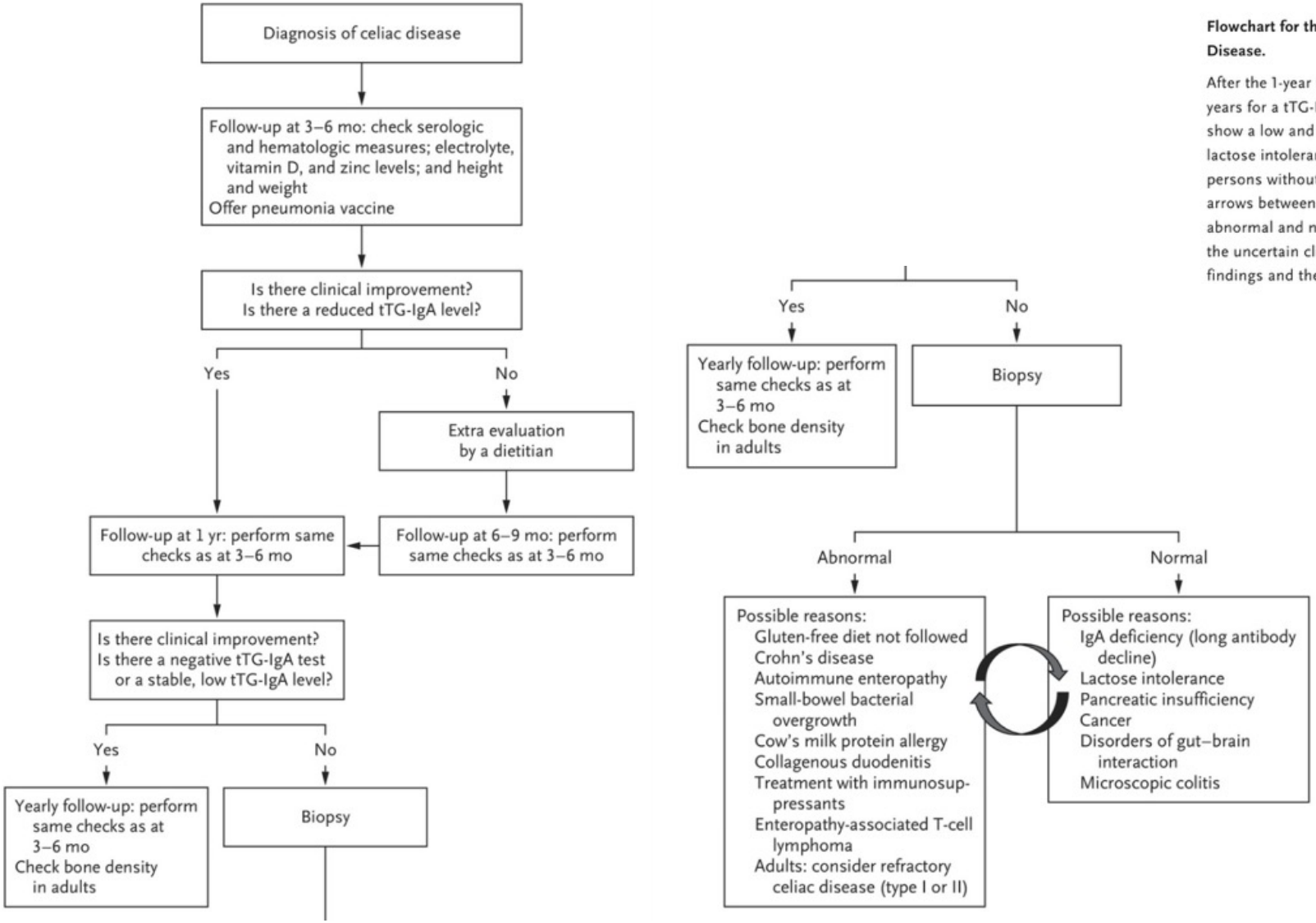
Elements of the Pathogenesis of Celiac Disease in the Small Intestine.

Gluten is incompletely digested into peptide fragments. These peptides transit the epithelium by several pathways and interact with tissue transglutaminase 2 (TG2). The peptides are deamidated and taken up by antigen-presenting cells (especially B cells) to engage with CD4 T cells driving the release of cytokines, including interleukin-2 and interferon-γ, and expansion of inflammatory cells. B cells develop into plasma cells that produce primarily IgA antibodies. Intraepithelial lymphocytes (IELs) expressing the natural killer cell receptors NKG2D and NKG2C recognize HLA-E and class I major histocompatibility complex–related molecules and target enterocytes for cytolysis, which leads to mucosal destruction. DGP denotes deamidated gliadin peptide.



Flowchart for the Diagnosis of Celiac Disease.

Risk groups are those with a family history of celiac disease or autoimmune diseases associated with celiac disease. Testing for IgA antibodies against tissue transglutaminase (tTG-IgA) is the primary serologic test in patients with normal total serum IgA. ULN denotes upper limit of the normal range.



Flowchart for the Management of Celiac Disease.

After the 1-year follow-up, it may take 1 to 2 years for a tTG-IgA test to become negative or show a low and stable level. The symptoms of lactose intolerance may not differ from those in persons without celiac disease. The rotating arrows between the possible reasons for abnormal and normal biopsy results indicate the uncertain clinical significance of histologic findings and the fact that disorders can coexist.

Conclusions and Recommendations

Our practice regarding celiac disease has changed dramatically over the past decades. Health professionals now consider celiac disease in a far broader range of patients, both in terms of demographic characteristics (i.e., age, geographic region, and ethnic group) and across a much wider spectrum of clinical manifestations.

In the introductory vignette, the patient has an increased tTG-IgA level (10 times the ULN) on celiac serologic testing. On the basis of the American College of Gastroenterology guidelines, we recommend performing a gastroscopy with duodenal biopsies and, if the results are confirmatory for celiac disease, prescribing a gluten-free diet. However, because the patient is still a teenager, a no-biopsy diagnostic approach is possible. This strategy involves the use of an endomysial antibody test, which, if positive, would confirm the diagnosis. If the test is negative, we would then recommend duodenal biopsy.

Many patients struggle to adhere to a gluten-free diet and are exposed to gluten at a level sufficient to cause ongoing inflammation, placing them at risk for symptoms and complications. Therefore, once the patient is confirmed to have celiac disease and placed on a gluten-free diet, we would establish regular follow-up with routine surveillance of recurrent symptoms, extragastrointestinal manifestations, and cancer surveillance as appropriate, especially if the patient does not have a response to a gluten-free diet.

Case 10-2026: A 70-Year-Old Woman with a Racing Heart, Fatigue, and Dyspnea

Presentation of Case

A 70-year-old woman was evaluated at this hospital because of a racing heart, fatigue, dyspnea, and leg edema.

Five months before the current admission, the patient was evaluated by a cardiologist at this hospital for frequent episodes of palpitations and lightheadedness that did not resolve with cessation of alcohol and caffeine use. Outpatient rhythm monitoring showed paroxysmal atrial tachycardia and atrial fibrillation events that constituted a total tachycardia burden of 6%, with heart rates of up to 180 beats per minute. Treatment with apixaban and flecainide was started; however, the symptoms did not abate, and flecainide was discontinued.

One month before the current admission, percutaneous catheter ablation was performed with the patient under general anesthesia. The procedure included pulsed-field ablation for pulmonary-vein isolation and posterior-wall isolation, as well as radiofrequency ablation in the coronary sinus, the slow pathway of the atrioventricular node, and the basal septum because ectopic beats from these sites had been observed to provoke paroxysmal atrial fibrillation. The patient was discharged home on the same day.

The next day, the patient called her cardiologist to report 2.0 kg of weight gain since the procedure and new edema in both legs. Oral furosemide was prescribed. Eleven days later, the patient called her cardiologist to report intermittent episodes of palpitations and sharp, "cramping" pain on the left side of the chest that were accompanied by a sensation of heartburn; ibuprofen was prescribed. The next day, myalgias in the neck, arms, and torso developed, along with a mild nonproductive cough. Point-of-care testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was positive, and the patient took acetaminophen for symptom relief.

Sixteen days after the ablation procedure and 2 weeks before the current admission, the patient had extreme fatigue, persistent pedal edema, increasing dyspnea occurring with minor exertion, and an additional 2.8 kg of weight gain. She contacted her primary care physician and was subsequently admitted to another hospital with a diagnosis of heart failure.

On evaluation at the other hospital, the patient was afebrile, with a temporal temperature of 36.6°C. The heart rate was 90 beats per minute and regular, but paroxysmal atrial fibrillation occurred with a heart rate of up to 140 beats per minute. The blood pressure was 179/81 mm Hg, the respiratory rate 27 breaths per minute, and the oxygen saturation 95% while the patient was breathing ambient air. Laboratory test results are shown. An electrocardiogram (ECG) reportedly showed sinus rhythm, PR-interval depression, and inferolateral ST-segment elevation.

Variable	Reference Range, Adults, Other Hospital	10 Days before Current Admission, Other Hospital	Day of Current Admission, Other Hospital	Reference Range, Adults, This Hospital†	On Current Admission, This Hospital
Hemoglobin (g/dl)	11.2–15.7	10.1	12.3	12.0–16.0	12.0
Hematocrit (%)	34.1–44.9	31.4	37.9	36.0–46.0	37.9
White-cell count (per μl)	4000–10,000	13,100	16,200	4500–11,000	12,390
Differential count (per μl)					
Neutrophils	—	—	—	1800–7700	10,900
Lymphocytes	—	—	—	1000–4800	740
Platelet count (per μl)	182,000–369,000	413,000	507,000	150,000–400,000	325,000
Sodium (mmol/liter)	136–145	129	132	135–145	135
Potassium (mmol/liter)	3.5–5.1	4.4	4.6	3.4–5.0	4.8
Chloride (mmol/liter)	98–107	98	102	98–108	98
Carbon dioxide (mmol/liter)	20–31	21	20	23–32	17
Urea nitrogen (mg/dl)	9–23	34	34	8–25	29
Creatinine (mg/dl)	0.55–1.52	0.71	1.11	0.60–1.50	1.10
Glucose (mg/dl)	74–106	106	177	70–110	121
Albumin (g/dl)	3.4–5.0	3.0	2.8	3.3–5.0	3.2
Alanine aminotransferase (U/liter)	7–40	170	71	7–33	53
Aspartate aminotransferase (U/liter)	13–40	71	44	9–32	45
Alkaline phosphatase (U/liter)	46–116	451	301	45–115	280
Total bilirubin (mg/dl)	0.2–1.1	1.7	1.6	0.0–1.0	1.2
Troponin I (ng/liter)	<45	7	7	—	—
B-type natriuretic peptide (pg/ml)	<100	196	518	—	—
Lactate (mmol/liter)	0.5–1.6	—	4.3	0.5–2.2	2.7
Prothrombin time (sec)	—	—	—	10.0–13.0	27.8
International normalized ratio	—	—	—	0.9–1.1	2.5
Partial-thromboplastin time (sec)	—	—	—	24.0–37.5	26.4

Echocardiography showed normal ventricular function, a small left ventricular cavity, pleural effusions, moderate pericardial effusion, and a dilated inferior vena cava. Oral amiodarone, oral colchicine, intravenous furosemide, intravenous and oral metoprolol, and intravenous diltiazem were administered. After 2 days, the patient was maintaining sinus rhythm and had lost 3.0 kg of weight; she was discharged from the hospital.

Five days later, the patient stopped taking colchicine because of diarrhea. She had a telehealth visit with her cardiologist and reported that the dyspnea on exertion had abated somewhat, but she also reported difficulty and pain with swallowing.

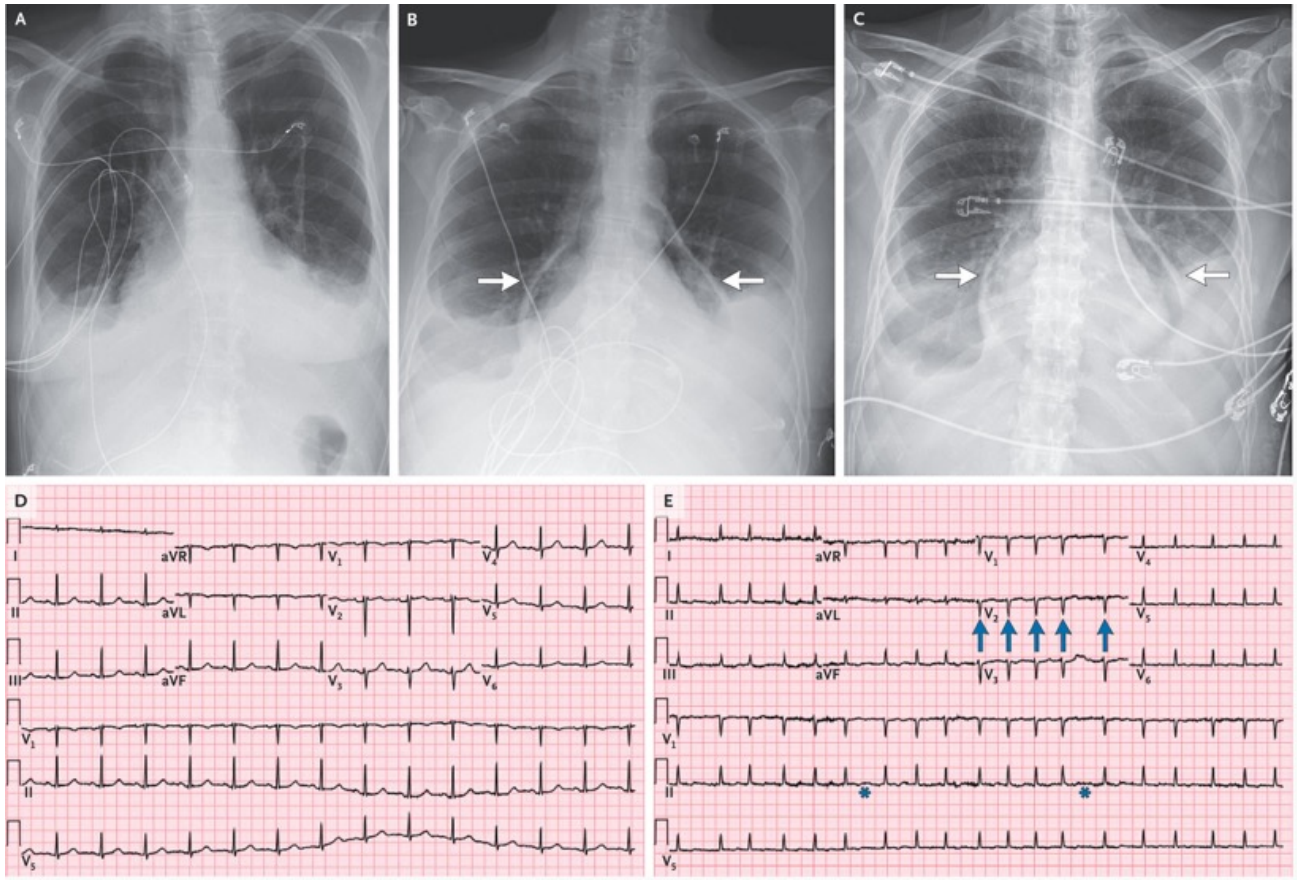
Three days later, on the day of the current admission, the patient was evaluated in the emergency department of the other hospital for marked dyspnea with the inability to catch her breath, a racing heart, and fatigue.

She was afebrile, with a temporal temperature of 36.4°C. The heart rate was 131 beats per minute and irregular, the blood pressure 131/92 mm Hg, the respiratory rate 26 breaths per minute, and the oxygen saturation 95% while she was breathing ambient air. The examination revealed decreased breath sounds at the lung bases and edema in the legs. A chest radiograph obtained on admission to the other hospital showed new pneumopericardium with pericardial thickening and persistent pleural effusions.

Blood was obtained for culture, and empirical treatment with intravenous vancomycin and piperacillin–tazobactam was administered. The patient was transferred to the cardiac intensive care unit (ICU) of this hospital. On admission to the cardiac ICU, review of systems was notable for leg edema, dyspnea, and anorexia. The patient reported that difficulty swallowing had started after the ablation procedure. She reported no fever, chills, emesis, nausea, abdominal pain, chest pain, bleeding, or dizziness.

The patient's medical history included carotid artery disease (for which she had undergone right carotid endarterectomy), hyperlipidemia, torticollis (for which she had received botulinum toxin injections), osteoarthritis (for which she had undergone right hip arthroplasty), and anxiety. Medications included apixaban, amiodarone, colchicine, metoprolol, pravastatin, and famotidine, as well as acetaminophen and diazepam as needed. Sulfonamides had caused nausea and vomiting. She had received vaccinations against SARS-CoV-2.

On examination, the temporal temperature was 36.6°C, the heart rate 113 beats per minute and irregular, the blood pressure 163/77 mm Hg, and the oxygen saturation 94% while the patient was breathing ambient air. She appeared anxious. Auscultation of the chest revealed irregular tachycardia, a friction rub, tachypnea, and diminished basilar breath sounds. Edema in the legs was noted.



Initial Chest Radiographs and Electrocardiograms.

Percutaneous catheter ablation was performed 1 month before the current admission. A chest radiograph obtained 20 days after the procedure (Panel A) shows moderate pleural effusions. Chest radiographs obtained 28 days after the procedure (Panels B and C), on the day of the current admission, show new pneumopericardium with diffuse pericardial thickening (arrows). A 12-lead electrocardiogram obtained immediately after the ablation procedure (Panel D) shows sinus rhythm and normal findings overall. A 12-lead electrocardiogram obtained 28 days after the procedure (Panel E), on the day of the current admission, shows atrial fibrillation with a rapid ventricular response, as evidenced by an undulating baseline (blue asterisks) with irregularly irregular RR intervals. As compared with the tracing obtained 1 month earlier, this tracing shows that the QRS amplitude no longer exceeds 1 mV across leads V_1 through V_6, including lead V_2 (blue arrows). Low QRS voltage, particularly when it develops over a relatively short time frame (days or weeks), may indicate fluid accumulation in the pericardial or pleural space.

Differential Diagnosis

This 70-year-old woman with a long-standing coexisting condition (atrial fibrillation) had recently undergone an intervention (percutaneous catheter ablation) and did not receive the intended benefit. Instead, the day after her procedure, she had evidence of fluid retention, which began a cascade of symptoms in the subsequent weeks that culminated in admission to the cardiac ICU approximately 4 weeks after the procedure.

My immediate concern is that the patient had a complication after percutaneous catheter ablation, which seems to be the inciting event. Postablation complications can include acute vascular injury (bleeding or stroke), cardiac perforation (cardiac tamponade), pulmonary-vein stenosis, heart failure, new arrhythmias, and damage to nearby structures such as the esophagus, vagus nerve, or phrenic nerve. Because the patient is presenting a month after her procedure, our list narrows to complications that are not immediately evident during the procedure.

The patient is afebrile, has an elevated heart rate and increased blood pressure, and reports dysphagia. An ECG shows atrial fibrillation and low QRS voltage in the precordial leads. Chest radiography shows air in the pericardium, an enlarged heart, and pleural effusions, with more fluid present on the left side than on the right. In developing a differential diagnosis to explain this patient's presenting symptoms, I will consider six possible diagnoses: heart failure syndrome, esophageal perforation, barotrauma, paraesophageal hernia, atrioesophageal fistula, and esophageal–pericardial fistula.

Heart Failure Syndrome

When this patient was first admitted to the other hospital, her symptom complex included fatigue, pedal edema, worsening dyspnea on exertion, and weight gain. All these signs and symptoms are consistent with heart failure. However, the development of difficulty swallowing, which had occurred after her procedure, and the findings on chest radiography performed on transfer to this hospital are not consistent with a diagnosis of heart failure.

Esophageal Perforation

Esophageal perforation is a rare but well-known complication of ablation procedures and should be considered as a possible diagnosis in this patient, especially given her difficulty swallowing. In patients with perforation of the esophagus, chest imaging is often notable for bilateral pleural effusions, which were present in this patient. However, patients also typically have sepsis.

Barotrauma

Barotrauma is another uncommon but well-known complication of ablation procedures. Barotrauma typically causes a clinically significant pneumothorax, which is usually easy to identify on chest imaging and was not noted in this patient.

Paraesophageal Hernia

A paraesophageal hernia can appear on chest imaging as a retrocardiac mass or opacity, which may contain an air–fluid level and, sometimes, a gas-filled lucency. In the absence of trauma, a paraesophageal hernia would not be associated with such rapid progression on imaging and is thus an unlikely diagnosis in this patient.

Atrioesophageal Fistula

An atrioesophageal fistula often appears 2 to 6 weeks after an ablation procedure. However, the symptoms are rather severe and include chest pain, dysphagia, hematemesis, and melena. Although this patient had difficulty swallowing, she had no other symptoms at the time of the current evaluation that were suggestive of an atrioesophageal fistula. However, it is important to consider this diagnosis because it is a medical emergency associated with high mortality.

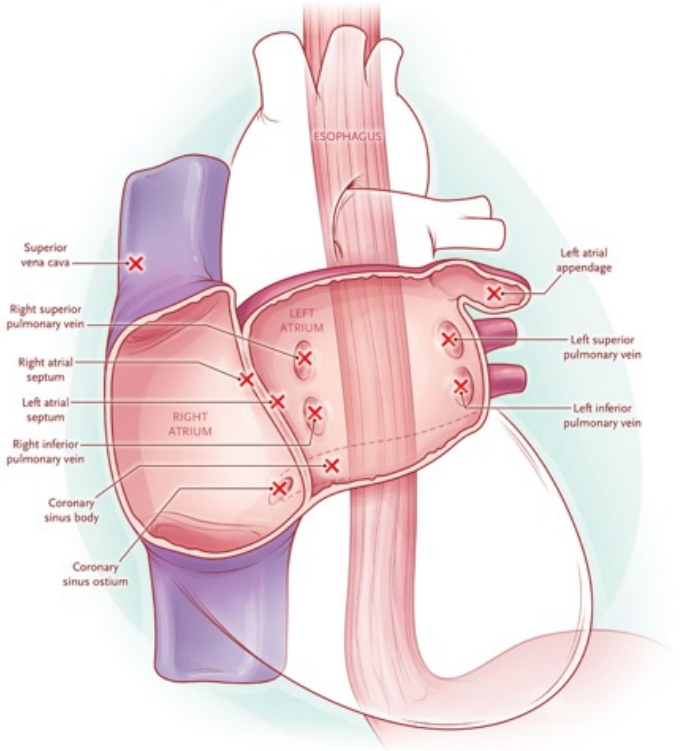
Esophageal–Pericardial Fistula

Finally, an esophageal–pericardial fistula stemming from the procedure should be considered. The patient's clinical presentation was notable for a mix of esophageal and cardiac symptoms, particularly shortness of breath, difficulty swallowing, and air in the pericardial sac — the classic sign of an esophageal–pericardial fistula. On the basis of these findings, I think that the most likely diagnosis in this patient is an esophageal–pericardial fistula. I would recommend that contrast-enhanced computed tomography (CT) of the chest and abdomen be performed to establish the diagnosis.

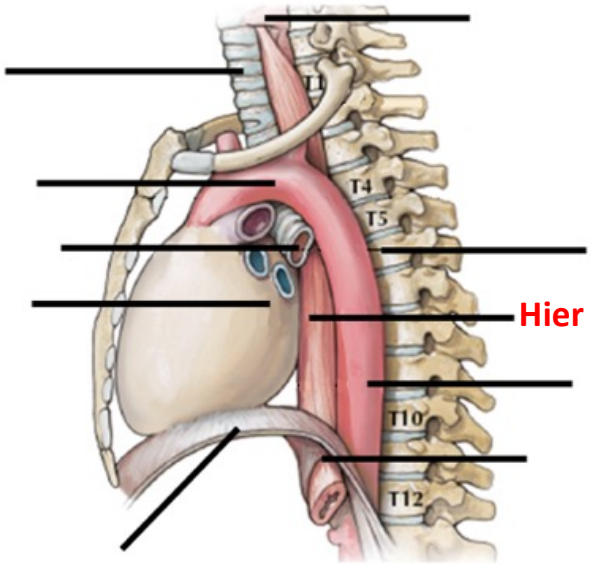
Clinical Impression

Esophageal perforation with or without a fistula to the atrium (atrioesophageal fistula) or pericardium (esophageal–pericardial fistula) is a rare complication of ablation for atrial fibrillation that is performed with radiofrequency or cryothermal energy, with an incidence of 0.10 to 0.25%.

PA view

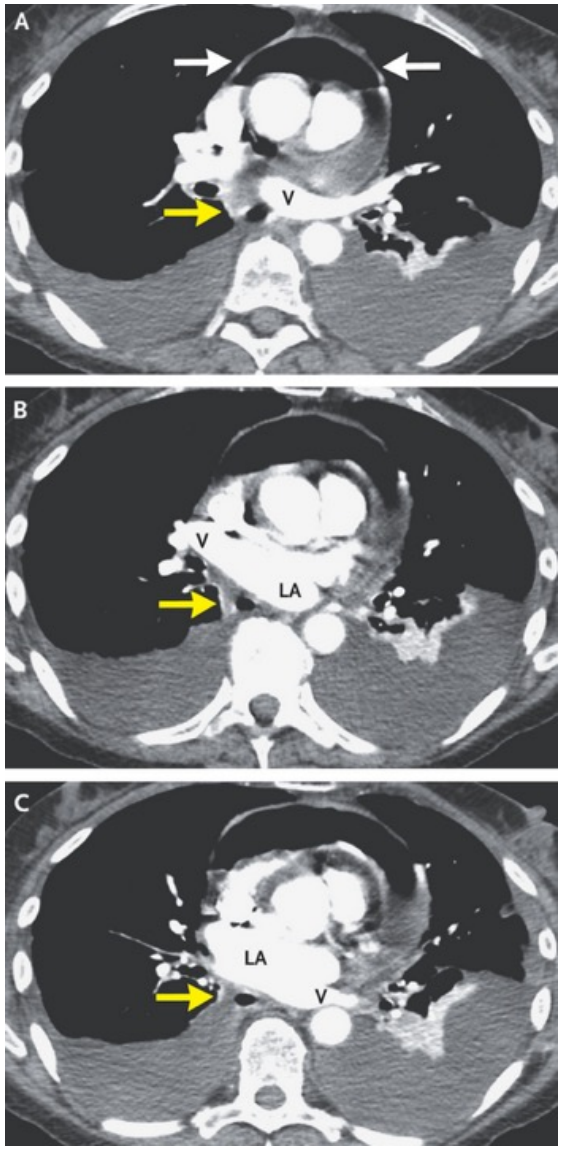


Lateral view



Relationship between the Esophagus and Targets Used in Ablation for Atrial Fibrillation.

Shown are common targets (red X symbols) used in ablation for atrial fibrillation and their typical anatomical relationship with the usual course of the esophagus in an approximate left anterior oblique projection. The relationship of the esophagus to the left atrium varies substantially, particularly within the coronal plane. Factors that affect heating of the esophagus (radiofrequency) or cooling of the esophagus (cryotherapy) are multiple and complex. In addition to anatomical proximity, such factors include pericardial fat volume; the number, duration, and sequence of energy applications; contact force; and catheter stability.

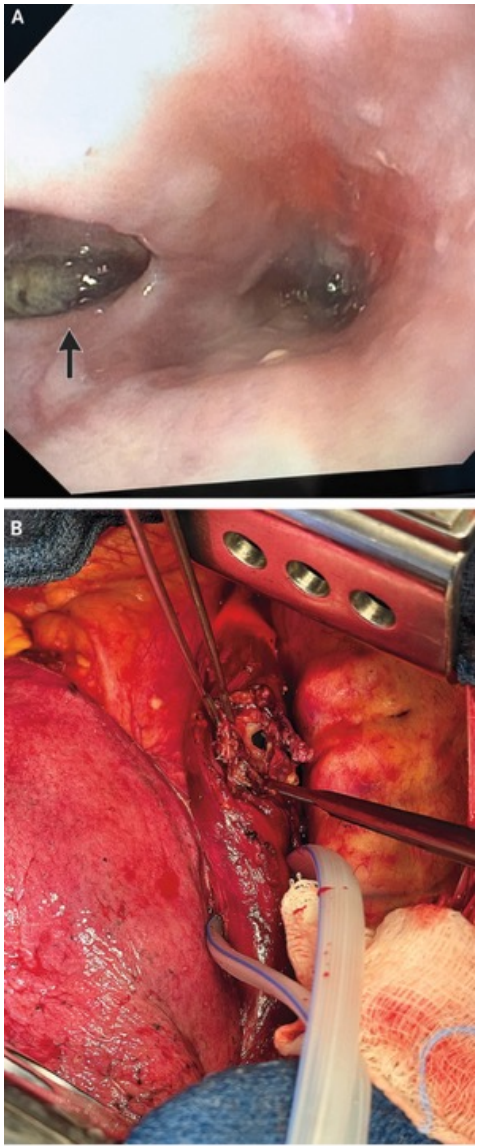


Chest CT Images.

Chest CT images obtained after the administration of intravenous contrast material show moderate layering effusions and basilar atelectasis. Moderate hydropneumopericardium (Panel A, white arrows) is present with diffuse pericardial thickening. Circumferential thickening of the esophagus (Panels A, B, and C; yellow arrows) is present adjacent to the left atrium (LA), at the level of the superior and inferior pulmonary veins (V) as they enter the left atrium. No air is visible within the cardiac chambers or in the mediastinum.

Intraoperative Images.

An intraoperative endoscopic image, obtained after a fistula to the left atrium or pulmonary veins was ruled out, shows a clear fistula from the esophageal lumen to the pericardial sac (Panel A, arrow). An intraoperative photograph, obtained once the esophagus was separated from the pericardium, shows a 2-cm defect involving the full thickness of the esophageal wall with a fibrotic rind (Panel B).



Follow-up

For the first 2 weeks after the procedure, the patient remained in critical condition in the surgical ICU. Trials of extubation were unsuccessful, and tracheostomy was performed, with subsequent discontinuation of ventilatory support. Drainage occurred through the nasogastric tube and the gastric port of the gastrojejunal tube, and total enteral nutrition was administered through the jejunal port. Chest and pericardial drains were removed sequentially.

Three weeks after the procedure, the patient was transferred out of the surgical ICU to the surgical floor, where she received physical therapy and speech and language therapy for rehabilitation. Decannulation was performed, and the nasogastric tube was removed. A barium swallow examination performed 8 weeks after the procedure showed no evidence of a leak at the surgical site. An oral diet was advanced slowly, and the gastrojejunal tube was capped.

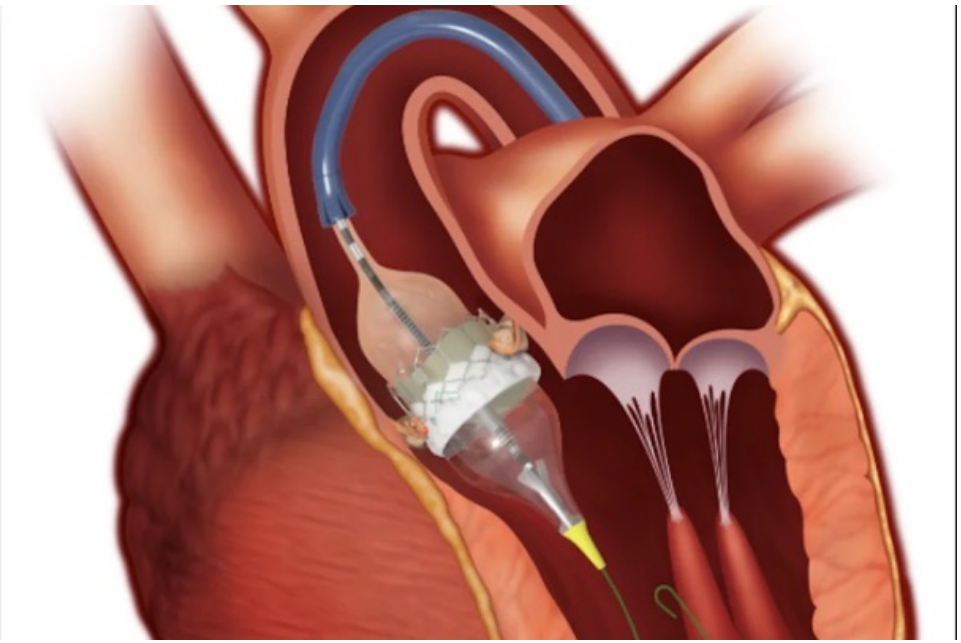
The patient completed the 4-week course of cefepime, metronidazole, fluconazole, and meropenem for the treatment of sepsis and empyema. She continued to receive apixaban, amiodarone, and metoprolol for atrial fibrillation. The patient was discharged to a skilled nursing facility for 1 week and then returned home. At a follow-up visit 12 weeks after the procedure, she was able to maintain a diet of soft solid foods and to walk without assistance, and all tubes and catheters were removed. At a later follow-up visit, she had returned to her baseline functional status and active lifestyle.

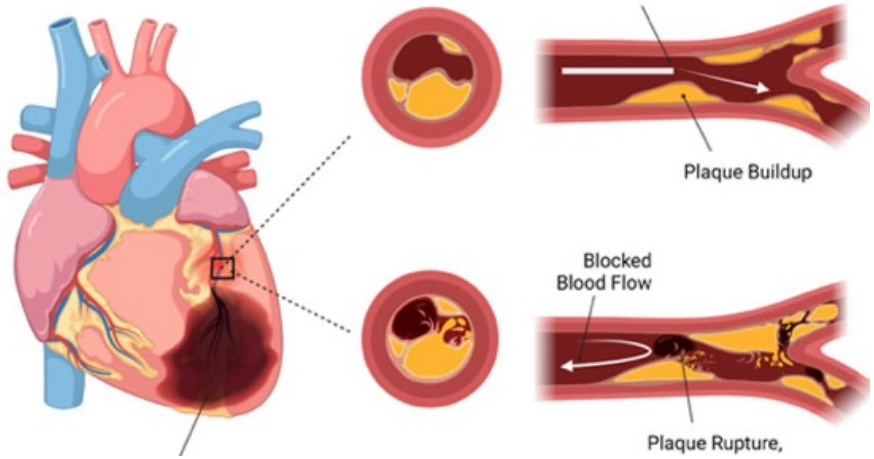
Final Diagnosis

Esophageal–pericardial fistula after percutaneous catheter ablation for atrial fibrillation.

THE LANCET

Old people with aortic steonosis commonly have coronary artery disease





Deferral of percutaneous coronary intervention in patients undergoing transcatheter aortic valve implantation (PRO-TAVI): an investigator-initiated, multicentre, open-label, non-inferiority, randomised controlled trial

Summary

Background Coronary artery disease is common in patients undergoing transcatheter aortic valve implantation (TAVI). We aimed to assess whether deferral of percutaneous coronary intervention (PCI) is non-inferior to routine PCI before TAVI in patients with coronary artery disease.

Methods In this investigator-initiated, open-label, randomised controlled trial, done at 12 hospitals in the Netherlands, TAVI patients with coronary artery disease were randomly assigned in a 1:1 ratio to deferral of PCI or PCI before TAVI. Randomisation was done by use of a web-based system with random block sizes of 2 and 4, and stratification by presence of coronary artery disease involving proximal left anterior descending artery. The primary endpoint was a composite of all-cause mortality, myocardial infarction, stroke, and major bleeding at 1 year. Non-inferiority testing was done in the intention-to-treat population against the prespecified margin of 11 percentage points. The study is registered with ClinicalTrials.gov (NCT05078619) and long-term follow-up is ongoing.

Findings Between Oct 7, 2021, and Nov 19, 2024, 466 patients were enrolled: 233 were assigned to deferral of PCI and 233 to PCI before TAVI. Median age was 81 years (IQR 78–84), and 166 (36%) of 466 patients were female. The primary endpoint occurred in 56 (24%) of 233 patients in the deferral group as compared with 60 (26%) of 233 patients in the PCI group (rate difference –1·7% [95% CI –9·5 to 6·2]; hazard ratio 0·89 [95% CI 0·62–1·28]; p=0·0008 for non-inferiority; p=0·68 for superiority).

Interpretation In patients with coronary artery disease undergoing TAVI, deferral of PCI was non-inferior to PCI before TAVI for the 1-year composite of all-cause mortality, myocardial infarction, stroke, and major bleeding. These findings suggest that an initial conservative strategy can be appropriate in selected patients, although patient-tailored treatment decisions remain essential.

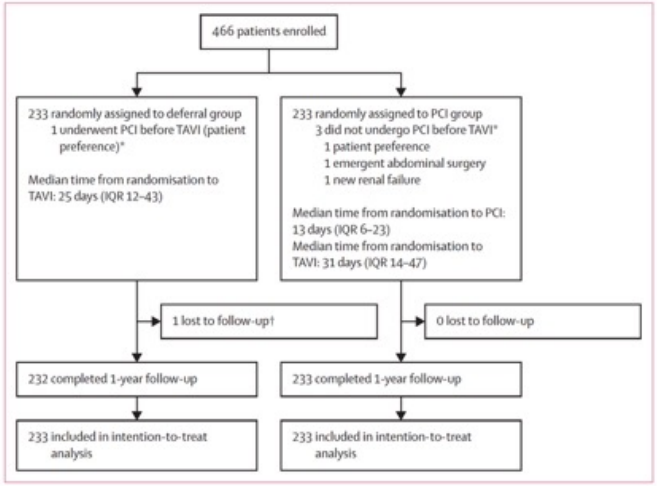


Figure 1: **Trial profile**
PCI=percutaneous coronary intervention. TAVI=transcatheter aortic valve implantation. *Not included in the per-protocol analysis. †Patient lost to follow-up at day 150.

	Deferral group (n=233)	PCI group (n=233)
Patient characteristics		
Age, years	81 (77–84)	81 (78–84)
Sex		
Female	84 (36%)	82 (35%)
Male	149 (64%)	151 (65%)
BMI, kg/m²	25·9 (23·6–29·0)	26·0 (23·8–29·3)
New York Heart Association functional class		
I or II	110 (47%)	117 (50%)
III or IV	123 (53%)	116 (50%)
Angina	85 (36%)	103 (44%)
Frailty*	34 (15%)	45 (19%)
Medical history		
Previous myocardial infarction	46 (20%)	57 (24%)
Previous PCI	47 (20%)	51 (22%)
Previous coronary artery bypass graft	13 (6%)	19 (8%)
Previous surgical aortic valve replacement	5 (2%)	8 (3%)
Previous stroke	19 (8%)	22 (9%)
Atrial fibrillation	80 (34%)	82 (35%)
Peripheral vascular disease	41 (18%)	40 (17%)
Diabetes	75 (32%)	75 (32%)
Hypertension	154 (66%)	157 (67%)
Hypercholesterolaemia	148 (64%)	151 (65%)
Oral anticoagulants	83 (36%)	86 (37%)
Risk scores		
STS-PROM score	3·1 (1·9–4·9)	3·1 (2·0–5·2)
EuroSCORE II	2·9 (1·9–4·3)	2·9 (2·1–4·9)
Echocardiographic characteristics		
Aortic valve area, cm²	0·8 (0·7–0·9)	0·8 (0·7–0·9)
Peak pressure gradient, mm Hg	68 (55–84)	66 (52–78)
Mean pressure gradient, mm Hg	41 (33–49)	39 (31–46)
Left ventricular ejection fraction		
Preserved ejection fraction, ≥50%	175 (75%)	166 (71%)
Mildly reduced ejection fraction, 41–49%	28 (12%)	25 (11%)
Reduced ejection fraction, ≤40%	30 (13%)	42 (18%)
Bicuspid aortic valve†	7/232 (3%)	5 (2%)
Moderate or severe aortic regurgitation†	38/231 (16%)	44 (19%)
Angiographic characteristics		
SYNTAX score	10 (6–17)	10 (5–17)
Invasive physiological assessment	32 (14%)	33 (14%)
Triple-vessel disease	30 (13%)	29 (12%)
Proximal left anterior descending artery	50 (21%)	50 (21%)
Proximal lesion	133 (57%)	136 (58%)
Coronary stenosis severity		
Coronary lesion with stenosis >90%	139 (60%)	139 (60%)
Coronary lesion with stenosis 70–90%	77 (33%)	80 (34%)
Coronary lesion with stenosis 40–70%	17 (7%)	14 (6%)

Data are median (IQR), n (%), or n/N (%). EuroSCORE=European System for Cardiac Operative Risk Evaluation. PCI=percutaneous coronary intervention. STS-PROM=Society of Thoracic Surgeons Predicted Risk of Mortality. SYNTAX=Synergy between PCI with TAXUS and Cardiac Surgery. TAVI=transcatheter aortic valve implantation. *Frailty was assessed using the Edmonton frailty scale, ranging from 0 to 18 and frailty defined as a score above 5. †Denominators vary due to missing echocardiography data at baseline.

Table 1: **Baseline characteristics**

	Deferral group (n=233)	PCI group (n=233)
PCI*		
Time from randomisation to PCI procedure, days	..	13 (6–23)
Timing of PCI procedure†		
Before TAVI procedure	..	213/229 (93%)
Concomitantly with TAVI procedure	..	15/229 (7%)
Multivessel PCI	..	63/229 (28%)
Median total length of stents, mm	..	28 (18–44)
Drug-eluting stent	..	209/229 (91%)
Calcium modification	..	16/229 (7%)
Residual SYNTAX score	..	0 (0–6)
TAVI procedure characteristics		
TAVI performed‡	229 (98%)	230 (99%)
Time from randomisation to TAVI procedure, days	25 (12–43)	31 (14–47)
Transfemoral access route	214/229 (93%)	214/230 (93%)
Local anaesthesia without conscious sedation	198/229 (86%)	191/230 (83%)
Balloon-expandable transcatheter heart valve§	125/228 (55%)	117/229 (51%)
Cerebral protection	6/229 (3%)	3/230 (1%)
Predilatation	125/229 (55%)	130/230 (57%)
Postdilatation	38/229 (17%)	38/230 (17%)

Data are median (IQR), n/N (%), or n (%). PCI=percutaneous coronary intervention. SYNTAX=Synergy between PCI with TAXUS and Cardiac Surgery. TAVI=transcatheter aortic valve implantation. *Four patients did not undergo PCI (one patient died before PCI; one patient chose not to undergo PCI; one patient underwent emergent abdominal surgery; and one patient due to new renal failure). †One patient underwent elective PCI after urgent non-transfemoral TAVI. ‡Seven patients did not undergo TAVI (six died before TAVI, whereas one patient in the deferral group chose not to undergo TAVI). §Two TAVI procedures were not accompanied by the implantation of a transcatheter heart valve due to procedural difficulties.

Table 2: **Characteristics of the PCI and TAVI procedures**

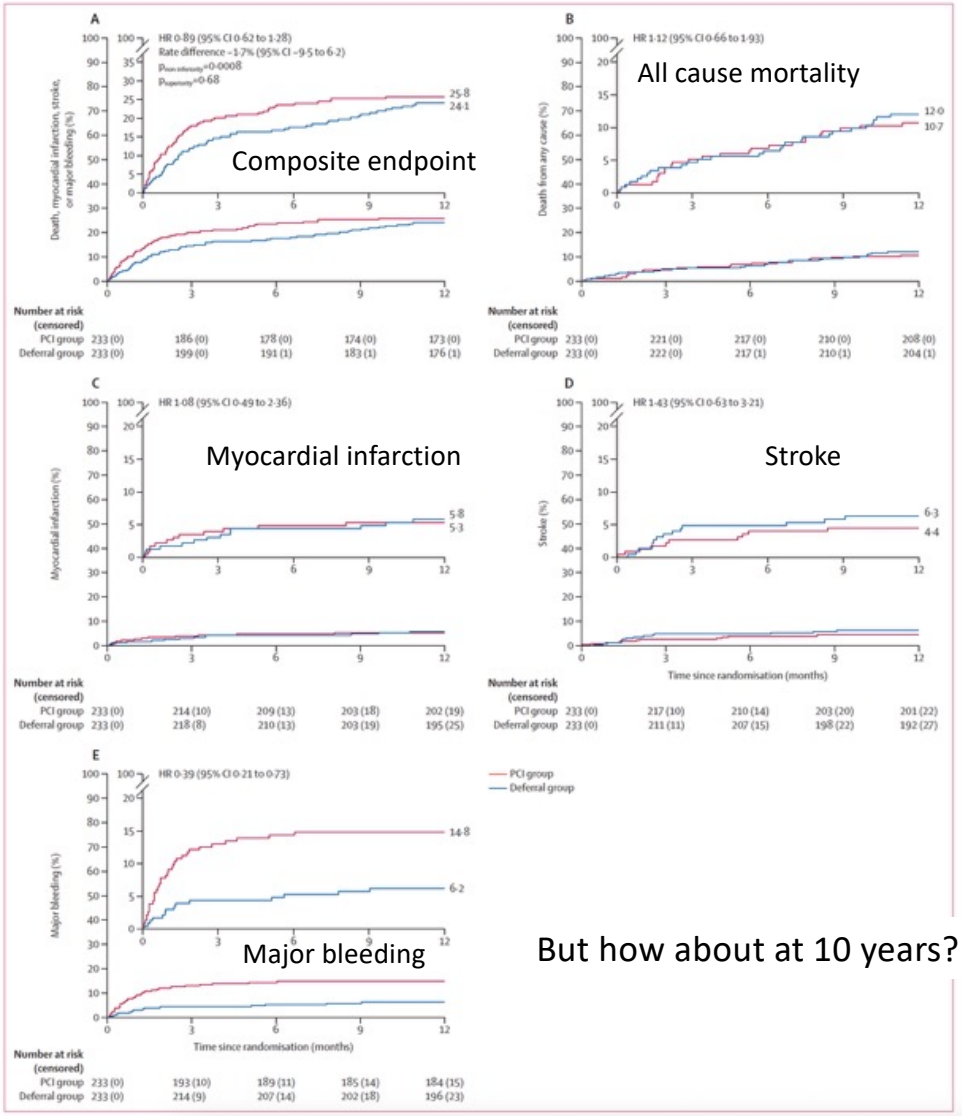


Figure 2: **Time-to-event Kaplan–Meier curves for the primary composite endpoint and its individual components**

Kaplan–Meier curves show the primary composite endpoint of all-cause mortality, myocardial infarction, stroke, or major bleeding (A), and the individual components of all-cause mortality (B), myocardial infarction (C), stroke (D), and major bleeding (E), in patients with significant coronary artery disease undergoing TAVI with deferral of PCI or PCI before TAVI. Event rates were based on Kaplan–Meier estimates in time-to-first-event analyses. HR=hazard ratio. PCI=percutaneous coronary intervention. TAVI=transcatheter aortic valve implantation.

But how about at 10 years?

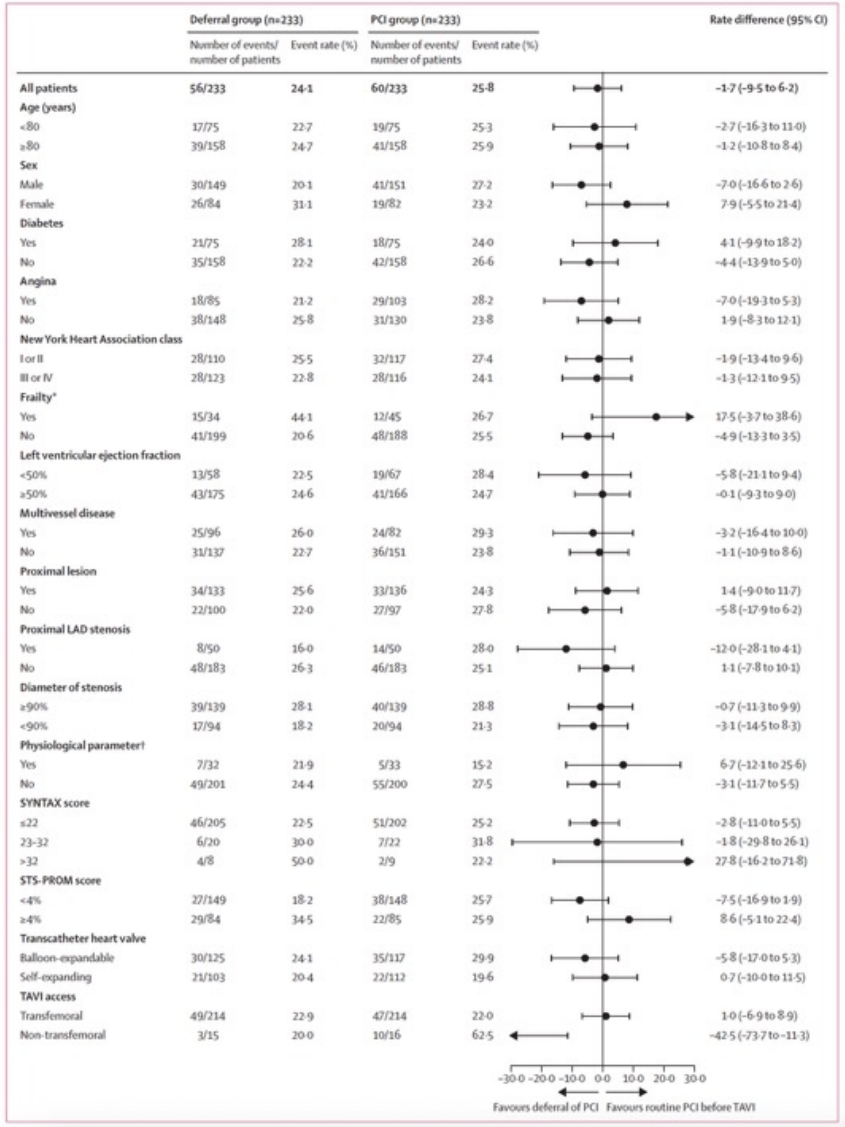


***Figure 3*: Subgroup analyses of the primary composite endpoint of all-cause mortality, myocardial infarction, stroke, and major bleeding**

Subgroup analyses are shown for prespecified baseline and procedural characteristics. All percentages are Kaplan-Meier estimates. Patients were included in subgroup analyses if they had at least one lesion that fulfilled subgroup criteria. LAD=left anterior descending artery. PCI=percutaneous coronary intervention. STS-PROM=Society of Thoracic Surgeon Predicted Risk of Mortality. SYNTAX=Synergy between PCI with TAXUS and Cardiac Surgery. TAVI=transcatheter aortic valve implantation. *Frailty was assessed using the Edmonton frailty scale, ranging from 0 to 18 and frailty defined as a score above 5. †Physiological parameters included fractional flow reserve, and instantaneous wave-free ratio.

	Deferral group (n=233)*		PCI group (n=233)		Rate difference (95% CI)	Hazard ratio (95% CI)
	Events, n	Event rate,† %	Events, n	Event rate,† %		
Primary endpoint‡						
Composite of all-cause mortality, myocardial infarction, stroke, or major bleeding	56	24%	60	26%	−1·7 (−9·5 to 6·2)	0·89 (0·62 to 1·28)
Secondary endpoints						
Composite of all-cause mortality, myocardial infarction, or stroke	48	21%	38	16%	4·3 (−2·7 to 11·4)	1·28 (0·84 to 1·96)
Death from any cause	28	12%	25	11%	1·3 (−4·5 to 7·1)	1·12 (0·66 to 1·93)
Cardiovascular death	17	7%	16	7%	0·4 (−4·3 to 5·2)	1·07 (0·54 to 2·11)
Myocardial infarction§	13	6%	12	5%	0·5 (−3·7 to 4·8)	1·08 (0·49 to 2·36)
Stroke	14	6%	10	4%	1·8 (−2·3 to 6·0)	1·43 (0·63 to 3·21)
Any bleeding, VARC-3 types I–IV	40	18%	98	43%	−25·1 (−33·2 to −17·0)	0·34 (0·24 to 0·50)
I	26	11%	73	32%	..	..
II	4	2%	15	7%	..	..
III	8	4%	18	8%	..	..
IV	2	1%	3	1%	..	..
Major bleeding, VARC-3 types II, III, IV	14	6%	34	15%	−8·6 (−14·2 to −3·1)	0·39 (0·21 to 0·73)
Any revascularisation¶	24	11%	11	5%	6·0 (1·0 to 10·9)	2·20 (1·08 to 4·50)
Urgent revascularisation‖	13	6%	7	3%	2·7 (−1·1 to 6·5)	1·86 (0·74 to 4·66)
Study lesion revascularisation**	18	8%	7	3%	5·0 (0·8 to 9·3)	2·59 (1·08 to 6·21)
Acute kidney injury stage 3 and 4	1	<1%	3	1%	−0·9 (−2·6 to 0·8)	0·33 (0·03 to 3·18)
Hospitalisation	72	32%	79	35%	−2·4 (−11·2 to 6·3)	0·88 (0·64 to 1·21)

PCI=percutaneous coronary intervention. TAVI=transcatheter aortic valve implantation. VARC-3=third Valve Academic Research Consortium. *One patient was lost to follow-up (day 150) without any event prior to this date. †Event rates based on 1-year Kaplan-Meier estimates in time-to-first-event analyses. ‡p=0·0008 for non-inferiority; hazard ratio should be interpreted as exploratory given that the proportional hazard assumption was violated. §Type 4 and 5 myocardial infarction in three patients (1·3%) in the deferral group, and in two patients (0·9%) in the PCI group. ¶Excluding index PCI procedures (one procedure due to protocol violation in the deferral group, 229 procedures in the PCI group). ‖Urgent revascularisation included all procedures that were done in an urgent, emergent, or salvage setting, adjudicated in accordance with the American College of Cardiology's and American Heart Association's Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials. **Study lesion was defined as the study segment including the 5 mm margin proximal and distal to stent. In the deferral group, study lesion revascularisation was defined as a PCI of the study lesion. In the PCI group, study lesion revascularisation was defined as (recurrent) PCI of the study lesion.

***Table 3*: Primary and secondary endpoints**

Research in context

Evidence before this study

The initiation of the PRO-TAVI trial was accompanied by a systematic review of the literature. We searched PubMed and Embase on July 20, 2022 using terms related to transcatheter aortic valve implantation (TAVI) and percutaneous coronary intervention (PCI) using the search terms: tavi*[Title/Abstract] OR tavr*[Title/Abstract] OR Percutaneous aortic valve*[Title/Abstract] OR Transcatheter Aortic Valve implant*[Title/Abstract] OR transcatheter aortic valve replacement*[Title/Abstract] OR "Transcatheter Aortic Valve Replacement"[MeSh] AND PCI[Title/Abstract] OR percutaneous coronary*[Title/Abstract] OR coronary stenting[Title/Abstract] OR coronary revascularization[Title/Abstract] OR coronary revascularisation[Title/Abstract] OR coronary angioplasty[Title/Abstract] OR PTCA[Title/Abstract] OR percutaneous transluminal coronary angioplasty[Title/Abstract] OR percutaneous coronary intervention[MeSH] and repeated the search on Jan 11, 2026. The only eligible randomised controlled trial initially identified, ACTIVATION, did not show a benefit of PCI in patients with concomitant coronary artery disease undergoing TAVI, but its findings should be interpreted with caution because the trial was prematurely terminated. More recently, a second randomised controlled trial, NOTION-3, showed superiority of PCI in patients with concomitant coronary artery disease undergoing TAVI, primarily driven by a reduction in myocardial infarction and urgent revascularisation. Deferral of PCI has not been investigated by other randomised trials.

Added value of this study

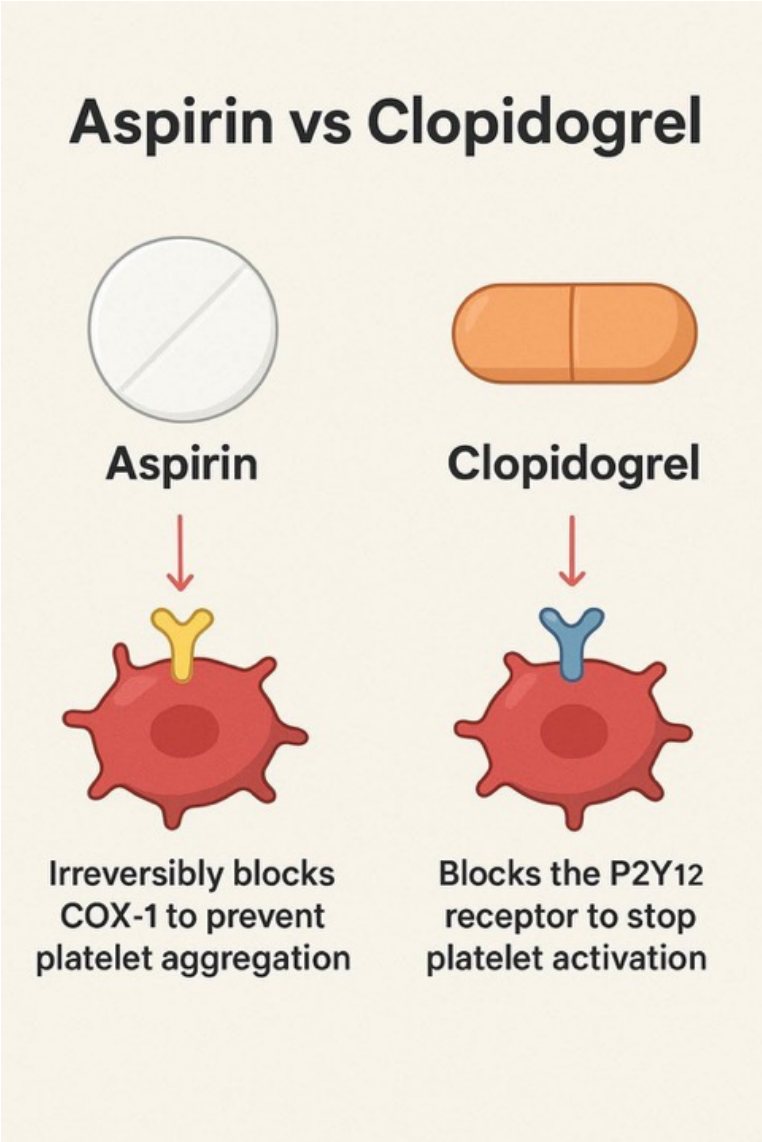
The PRO-TAVI trial provides robust data on the treatment of patients with concomitant coronary artery disease undergoing TAVI, showing non-inferiority of deferral of PCI in patients with concomitant coronary artery disease undergoing TAVI compared with routine PCI before TAVI with respect to the primary composite endpoint of all-cause mortality, myocardial infarction, stroke, and major bleeding. We observed a substantial reduction in major bleeding with deferral of PCI. A small proportion of patients assigned to deferral of PCI ultimately underwent PCI after TAVI, all without major periprocedural complications. This trial adds an important dimension to the results of previous studies.

Implications of all the available evidence

The results of the PRO-TAVI trial indicate that an initial strategy of deferring PCI is a viable option for patients with concomitant coronary artery disease undergoing TAVI. These findings support a more selective, patient-centred approach to revascularisation, enabling heart teams to tailor decisions to individual anatomy, comorbidities, and clinical priorities rather than defaulting to routine PCI before TAVI. Contemporary TAVI practice—including advances in valve design and implantation techniques that facilitate commissural alignment and preserve coronary access—further supports the feasibility and safety of revascularisation after TAVI when clinically indicated. Together, the available evidence broadens the therapeutic options for this population and provides a clearer framework for balancing ischaemic and bleeding risks in routine care.

THE LANCET

Maintenance
after PCI



Aspirin versus clopidogrel for chronic maintenance monotherapy after percutaneous coronary intervention: 10-year follow-up of the HOST-EXAM trial

Summary

Background The long-term clinical outcomes of clopidogrel monotherapy versus aspirin monotherapy after percutaneous coronary intervention (PCI) remain uncertain. We conducted a 10-year follow-up of the HOST-EXAM trial to assess the very long-term effects of clopidogrel versus aspirin monotherapy in this setting.

Methods In HOST-EXAM, patients who had completed dual antiplatelet therapy without clinical events for 6–18 months after PCI were randomly assigned to receive clopidogrel 75 mg once daily or aspirin 100 mg once daily. This study is an investigator-initiated 10-year extended follow-up of the HOST-EXAM trial. The primary endpoint was a composite of all-cause death, non-fatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and Bleeding Academic Research Consortium type ≥3 bleeding. The primary analysis was done in the intention-to-treat population. The study is registered with ClinicalTrials.gov (NCT02044250) and is complete.

Findings From March 26, 2014, to May 29, 2018, 5530 patients were enrolled and 5438 were randomly assigned to the aspirin group (n=2728) or the clopidogrel group (n=2710). Clinical follow-up status was ascertained on May 1, 2025, resulting in a median follow-up duration of 10·5 years (IQR 9·4–11·4) after PCI and a completion rate of 92·8%. Clopidogrel was associated with a lower rate of the primary composite endpoint than aspirin (Kaplan–Meier estimate 25·4% for the clopidogrel group *vs* 28·5% for the aspirin group; hazard ratio 0·86 [95% CI 0·77–0·96]; log-rank p=0·0050). Clopidogrel was also associated with a lower rate of the thrombotic endpoint (17·3% *vs* 20·0%; log-rank p=0·0024) and bleeding endpoint (9·1% *vs* 10·8%; log-rank p=0·020). All-cause mortality was similar between groups.

Interpretation During 10 years of follow-up, clopidogrel monotherapy, compared with aspirin monotherapy, was associated with lower rates of the primary composite, ischaemic, and bleeding outcomes, but not all-cause mortality after PCI. These findings support consideration of clopidogrel as an alternative to aspirin for long-term antiplatelet monotherapy during the chronic maintenance phase after PCI.

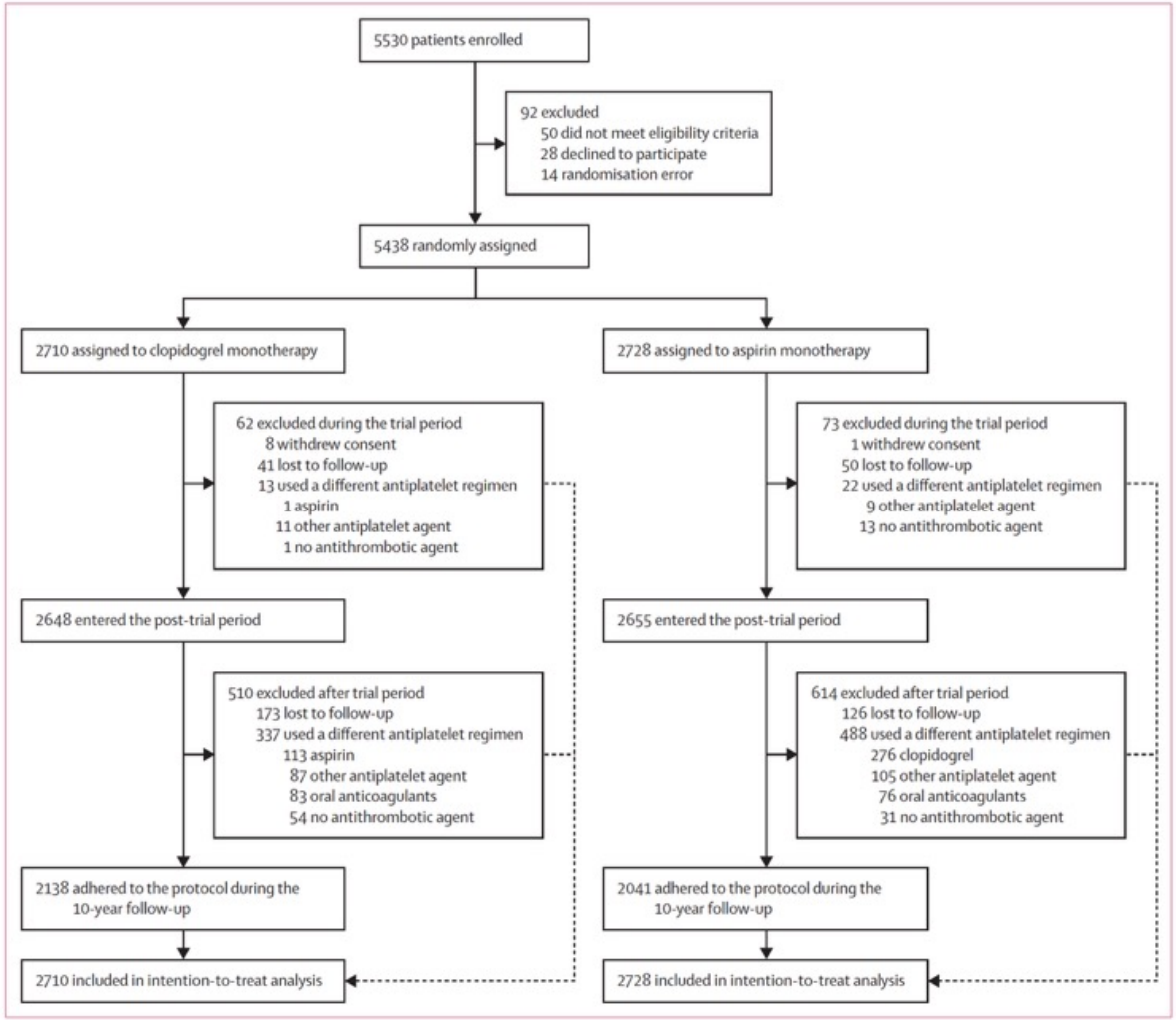
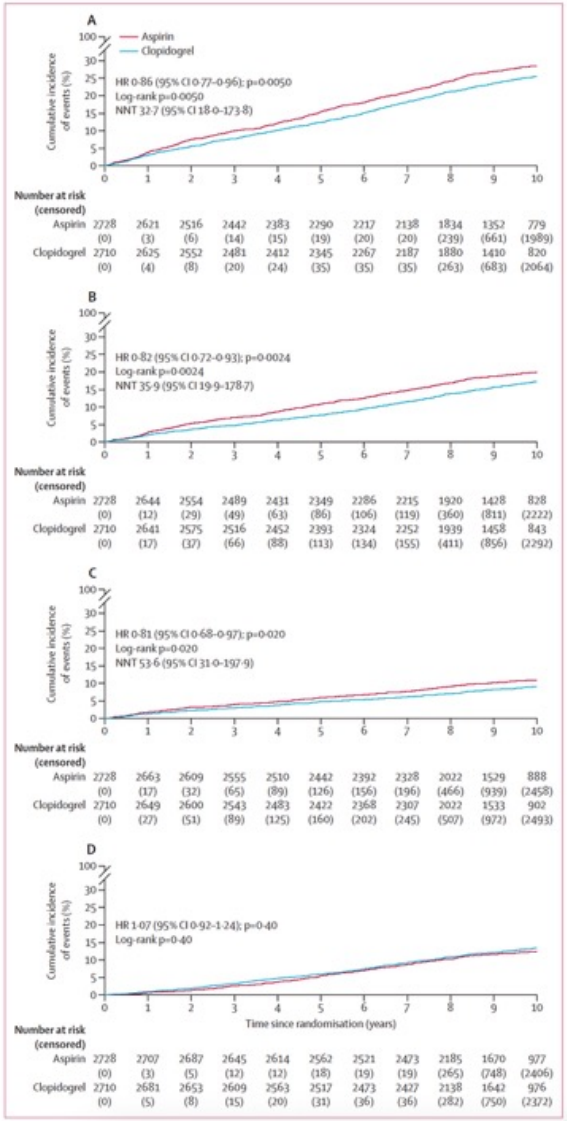


Figure 1: **Trial profile**

Patients who underwent PCI with a drug-eluting stent and maintained dual antiplatelet therapy without any clinical events within 6–18 months after the index PCI were eligible for enrolment in the HOST-EXAM trial. Patients were followed up for up to 10 years. The primary endpoint was analysed in the intention-to-treat population. PCI=percutaneous coronary intervention.

Figure 2: **Cumulative incidence of the primary composite endpoint, secondary composite endpoints, and all-cause death in the intention-to-treat population**

(A) Cumulative incidence of the primary composite endpoint, consisting of all-cause death, non-fatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and major bleeding (Bleeding Academic Research Consortium type ≥3 bleeding). (B) Cumulative incidence of the secondary composite thrombotic endpoint, consisting of cardiac death, non-fatal myocardial infarction, ischaemic stroke, readmission due to acute coronary syndrome, or definite or probable stent thrombosis. (C) Cumulative incidence of any bleeding. (D) Cumulative incidence of all-cause death. HRs are for clopidogrel monotherapy versus aspirin monotherapy. NNTs are shown only when the absolute risk difference excludes zero. HR=hazard ratio. NNT=number needed to treat.



Composite endpoint

Tiny bit better

Secondary composit thrombotic endpoint

Tiny bit better

Any bleeding

Tiny bit better

All cause deaths

No better

	Clopidogrel (n=2710)	Aspirin (n=2728)	Hazard ratio (95% CI)	p value	Absolute risk reduction (95% CI)	Number needed to treat (95% CI)
Primary composite endpoint*	646 (25·4%)	739 (28·5%)	0·86 (0·77–0·96)	0·0050	3·1 (0·6 to 5·6)	32·7 (18·0–173·8)
Thrombotic composite endpoint†	418 (17·3%)	506 (20·0%)	0·82 (0·72–0·93)	0·0024	2·8 (0·6 to 5·0)	35·9 (19·9–178·7)
Any bleeding (BARC type ≥2)‡	217 (9·1%)	270 (10·8%)	0·81 (0·68–0·97)	0·020	1·7 (0·0 to 3·4)	..
All-cause death§	338 (13·4%)	322 (12·5%)	1·07 (0·92–1·24)	0·40	−0·9 (−2·8 to 0·9)	..
Cardiovascular death	167 (7·1%)	171 (6·9%)	0·99 (0·80–1·23)	0·95	−0·1 (−1·6 to 1·4)	..
Non-cardiovascular death	171 (6·9%)	151 (6·0%)	1·15 (0·93–1·43)	0·21	−0·9 (−2·3 to 0·5)	..
Non-fatal myocardial infarction	85 (3·6%)	105 (4·2%)	0·82 (0·62–1·09)	0·17	0·6 (−0·5 to 1·7)	..
Stroke	110 (4·6%)	154 (6·4%)	0·72 (0·56–0·92)	0·0081	1·8 (0·4 to 3·1)	57·2 (32·7–228·5)
Ischaemic stroke	85 (3·6%)	104 (4·3%)	0·81 (0·61–1·08)	0·16	0·8 (−0·4 to 1·9)	..
Haemorrhagic stroke	25 (1·0%)	50 (2·1%)	0·50 (0·31–0·81)	0·0050	1·1 (0·4 to 1·8)	92·5 (55·5–279·1)
Readmission due to acute coronary syndrome	208 (8·7%)	277 (11·0%)	0·75 (0·63–0·90)	0·0017	2·3 (0·6 to 4·0)	42·9 (24·8–158·5)
Percutaneous coronary intervention	157 (6·8%)	207 (8·5%)	0·76 (0·62–0·93)	0·0084	1·7 (0·1 to 3·2)	59·1 (30·9–690·3)
Coronary artery bypass surgery	5 (0·2%)	8 (0·3%)	0·62 (0·20–1·90)	0·41	0·1 (−0·2 to 0·4)	..
Medical treatment	46 (1·8%)	62 (2·4%)	0·74 (0·51–1·09)	0·13	0·6 (−0·2 to 1·4)	..
Major bleeding (BARC type ≥3)	133 (5·6%)	190 (7·7%)	0·71 (0·57–0·88)	0·0019	2·1 (0·7 to 3·5)	47·5 (28·3–148·4)

Data are n (%), unless otherwise specified. Number needed to treat is shown only when the 95% CI for the absolute risk reduction excludes 0. BARC=Bleeding Academic Research Consortium. *Primary composite endpoint is defined as a composite of all-cause death, non-fatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and major bleeding (BARC type ≥3). †Thrombotic composite endpoint is defined as cardiac death, non-fatal myocardial infarction, ischaemic stroke, readmission due to acute coronary syndrome, and definite or probable stent thrombosis. ‡Any bleeding defined as any BARC type ≥2 bleeding events. § The specific causes of mortality events are described in the appendix (pp 23–24).

Table: **Clinical outcomes during the 10-year follow-up in the intention-to-treat population**

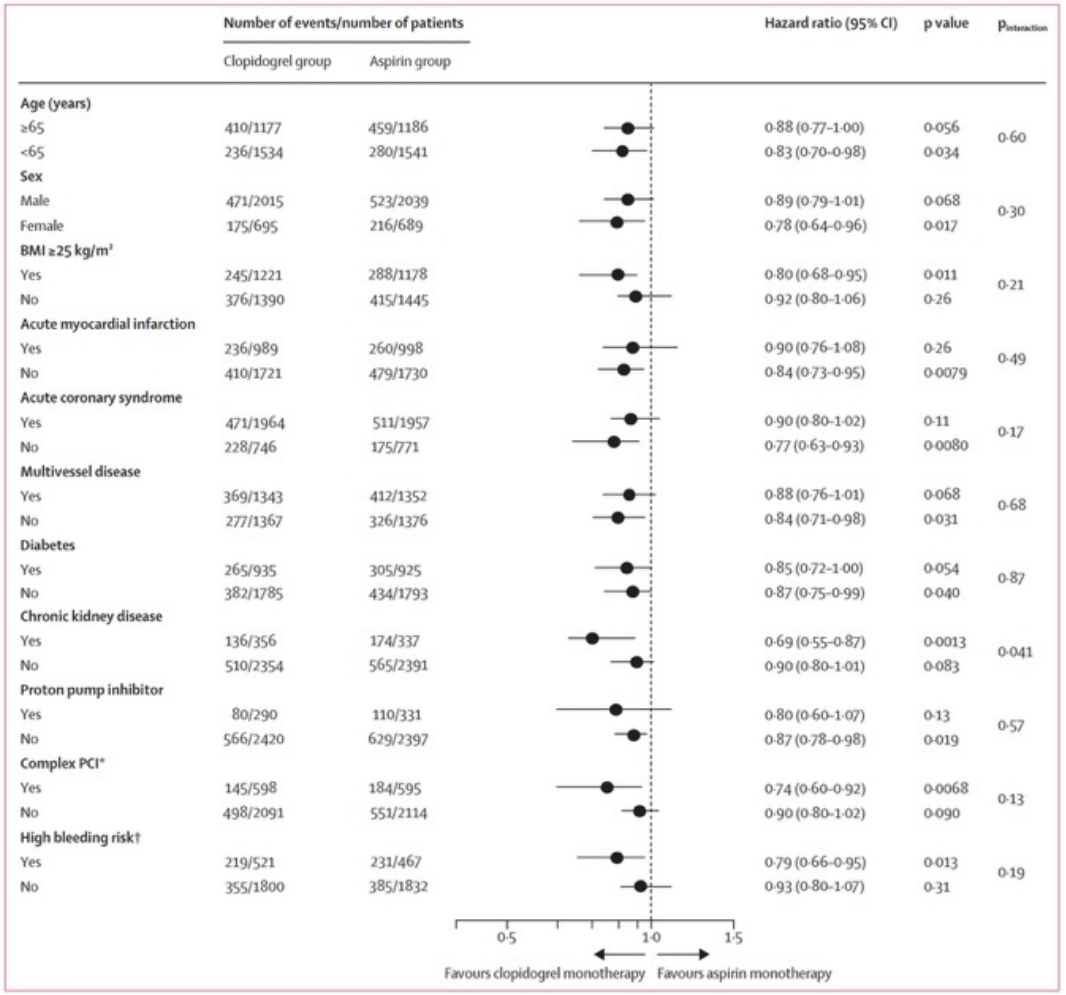


***Figure 3*: Subgroup analysis of the primary composite endpoint in the intention-to-treat population**

Hazard ratios for the primary composite endpoint (all-cause death, non-fatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and major bleeding [Bleeding Academic Research Consortium type ≥3]) in the two groups are shown according to prespecified subgroups. *Complex PCI was defined as having at least one of the following features: three vessels treated, three or more stents implanted, three or more lesions treated, bifurcation with two stents implanted, total stent length greater than 60 mm, or chronic total occlusion. †High bleeding risk was defined according to the Academic Research Consortium for High Bleeding Risk definition. PCI=percutaneous coronary intervention.

Research in context

Evidence before this study

We searched PubMed, MEDLINE, and the Cochrane Library for randomised controlled trials and meta-analyses comparing P2Y12 inhibitor monotherapy with aspirin monotherapy for long-term secondary prevention after percutaneous coronary intervention (PCI), published from database inception to Dec 31, 2025, using the keywords "clopidogrel", "aspirin", "antiplatelet monotherapy", "percutaneous coronary intervention", "drug-eluting stent", and "secondary prevention", with no language restrictions. Evidence from randomised trials before this study was limited to studies with short or intermediate duration of follow-up. The STOPDAPT-2 and SMART-CHOICE 3 trials reported lower rates of clinical events with clopidogrel than with aspirin, and a 2025 individual patient data meta-analysis reported that clopidogrel monotherapy was superior to aspirin monotherapy for prevention of major adverse cardiovascular or cerebrovascular events. Nevertheless, no randomised trial had previously assessed antiplatelet monotherapy beyond 5 years after PCI.

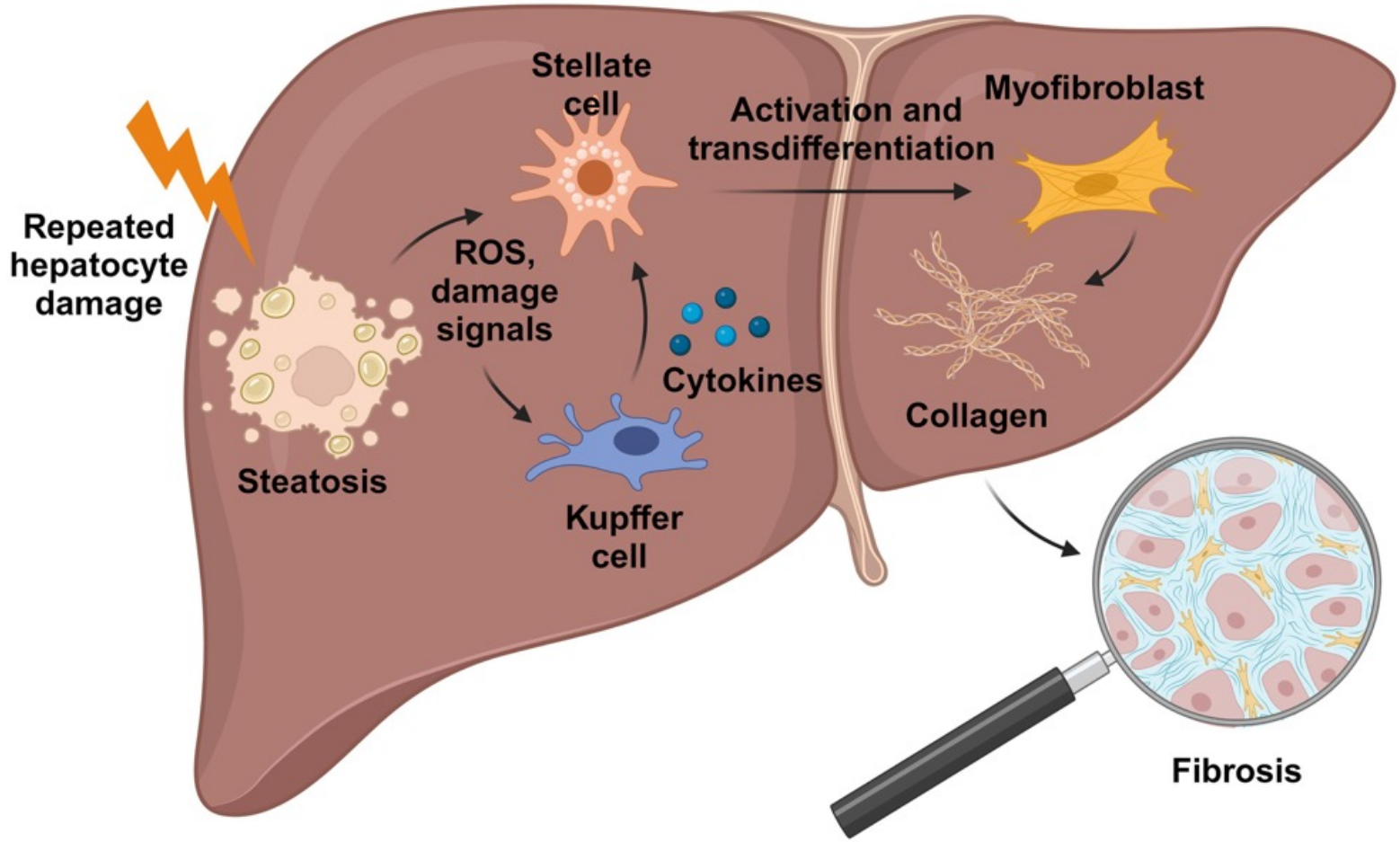
Added value of this study

This study reports the 10-year follow-up of the HOST-EXAM randomised trial, providing the longest randomised comparison of antiplatelet monotherapy after PCI with drug-eluting stents. Clopidogrel monotherapy was associated with sustained reductions in the primary composite endpoint compared with aspirin monotherapy over 10 years, extending the longest previous randomised follow-up of 5 years. The cumulative long-term benefit was reflected in a lower number needed to treat at 10 years compared with that at 2 years. Treatment adherence was higher in the clopidogrel group than in the aspirin group, in which gastrointestinal discomfort was a common cause of treatment discontinuation, highlighting the role of tolerability in long-term therapy.

Implications of all the available evidence

Combined with data from previous randomised trials and meta-analyses, our results strengthen the evidence supporting the superiority of clopidogrel monotherapy over aspirin monotherapy for long-term secondary prevention after PCI. The continued divergence of the event curves and the decreasing number needed to treat over time suggests that the clinical benefit of clopidogrel is cumulative. The totality of contemporary evidence suggests that the role of aspirin as the first-line lifelong antiplatelet therapy after PCI warrants reconsideration, especially in health-care systems where clopidogrel is accessible and inexpensive.

THE LANCET


Stellate cell
Activation and transdifferentiation
Myofibroblast
Repeated hepatocyte damage
ROS, damage signals
Cytokines
Collagen
Steatosis
Kupffer cell
Fibrosis

Prevalence of liver fibrosis in the general population (the LiverScreen project): a multinational European cohort study

Summary

Background Small scale, single-country studies suggest that undiagnosed liver fibrosis is prevalent in the general population; however, its true burden and main risk factors remain unclear. We aimed to assess the prevalence of undiagnosed liver fibrosis and its relationship with metabolic factors or alcohol consumption in a large prospective population-based multinational cohort study.

Methods We enrolled individuals from the general population who were aged 40 years and older across 35 sites, including primary health centres and screening units, and their 16 affiliated tertiary hospitals in nine European countries. Liver fibrosis was estimated using the liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE). A positive test was defined as an LSM of 8 kPa and greater or an alanine aminotransferase concentration of at least 1·5 the upper limit of normal, or a combination of both. Individuals with at least one criterion were referred for hepatology consultation to confirm chronic liver disease with fibrosis. The primary outcome was the prevalence of LSM of 8 kPa and greater.

Findings We enrolled 30 199 individuals (mean age 58 years; 57% [17 203 of 30 199] women, 89% [24 440 of 27 481] White) from nine European countries. Metabolic factors were present in 70% (21 084 of 30 024) of participants, and 59% (15 107 of 25 488) of participants reported alcohol use, with 6·1% (1771 of 29 081) of participants reporting harmful consumption. The positive screening rate was 6·9% with a prevalence of 4·6% with an LSM of 8 kPa and greater. Elevated LSM was strongly associated with obesity, type 2 diabetes, and harmful alcohol use. Of the participants referred, 61% (1491 of 2457) completed a hepatology evaluation, and chronic liver disease with fibrosis was confirmed in 32% (477 of 1491) of participants, yielding an overall estimated prevalence of 1·6% (477 of 30 199). Steatotic liver disease accounted for 93% (443 of 477) of cases.

Interpretation Undiagnosed liver fibrosis is common in the general population in Europe and is primarily driven by metabolic factors and alcohol consumption. Early detection is pivotal as it could allow personalised interventions that can prevent progression to cirrhosis and complications.

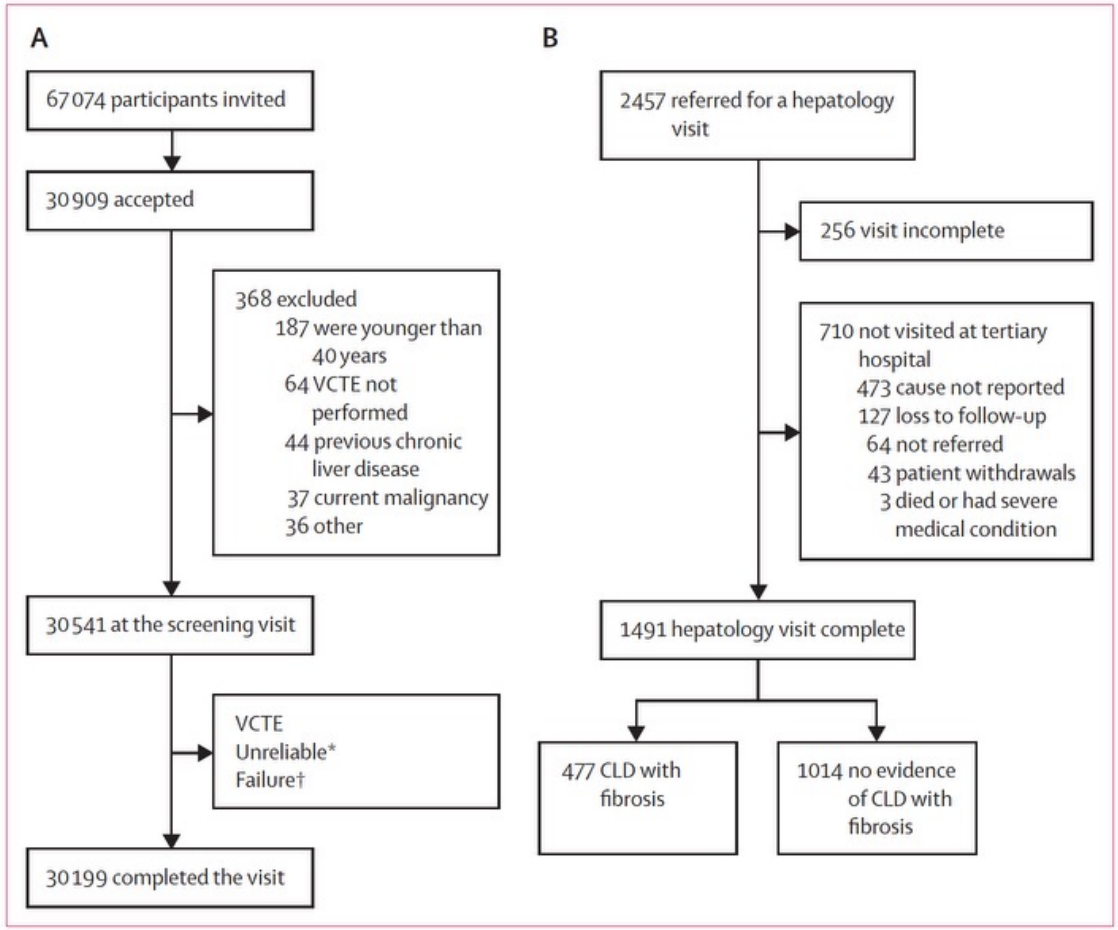


Figure 1: **Trial profile**

The invitation and enrolment process for the screening visit (A), and referral for hepatology consultation and final evaluation (B). CLD=chronic liver disease. VCTE=vibration-controlled transient elastography. *273 (0·9%) of 30 541 participants had an interquartile range-to-median ratio (IQR/P50) of at least 30% for median liver stiffness (P50 ≥7·1 kPa). †For 69 (0·2%) of 30 541 participants, we could not obtain any valid liver stiffness measurement.

	Overall cohort (N=30 199)
Age (years)	58 (10)
Sex	
Female	17 203 (57%)
Male	12 996 (43%)
Ethnicity	
White	24 440 (89%)
African	1171 (4·2%)
Latin-American	985 (3·6%)
Asian	537 (2·0%)
Mixed	94 (0·3%)
Other	140 (0·5%)
Smoking	4273 (15%)
BMI (kg/m²)*	27 (5)
Normal	10 259 (34%)
Overweight	11 857 (40%)
Obese	8065 (26%)
Abdominal obesity†	14 071 (47%)
Metabolic risk factors	
Arterial hypertension	10 488 (35%)
Type 2 diabetes	3140 (10%)
Dyslipidaemia	16 031 (53%)
At least one metabolic risk factor	21 084 (70%)
Harmful alcohol use‡	1771 (6·1%)
Glucose (mg/dL)	99 (27)
Glycated haemoglobin (%)	5·6 (0·8)
Total cholesterol (mg/dL)	205 (43)
HDL cholesterol (mg/dL)	59 (16)
LDL cholesterol (mg/dL)	124 (37)
Triglycerides (mg/dL)	106 (75)
AST (IU/L)	24 (9)
ALT (IU/L)	22 (13)
GGT (IU/L)	22 (19)
AP (IU/L)	72 (24)
Platelet count (10⁹/L)	247 (61)

Continuous variables with normal distribution are expressed as mean (SD) and non-normal variables are expressed as P50 (IQR). ALT=alanine aminotransferase. AP=alkaline phosphatase. AST=aspartate aminotransferase. GGT=gamma-glutamyl-transpeptidase. *BMI categories used: normal (BMI <25·0 kg/m²); overweight (BMI ≥25·0 kg/m² and <29·9 kg/m²; obese (BMI ≥30·0 kg/m²; Asian origin BMI ≥25·0 kg/m²). †Abdominal obesity was defined as a waist circumference of at least 88 cm for women and 102 cm for men. ‡Harmful alcohol use was defined as individuals who reported current alcohol consumption equal to or greater than 14 units per week for women and 21 units per week for men. For the participants in whom the standard drinking units questionnaire was not available, the Alcohol Use Disorders Identification Test-Concise (AUDIT-C) responses were changed to units. Missing data: ethnicity (9% missing); smoking (6% missing); alcohol consumption (4% missing); glucose (11% missing), glycated haemoglobin (39% missing); total cholesterol (10% missing); HDL cholesterol (12% missing); LDL cholesterol (14% missing), triglycerides (10% missing); AST (13% missing); ALT (9% missing); GGT (10% missing); AP (16% missing); and platelet count (16% missing). Ethnicity data were not collected for participants from the Slovakian cohort.

Table 1: **Baseline characteristics**

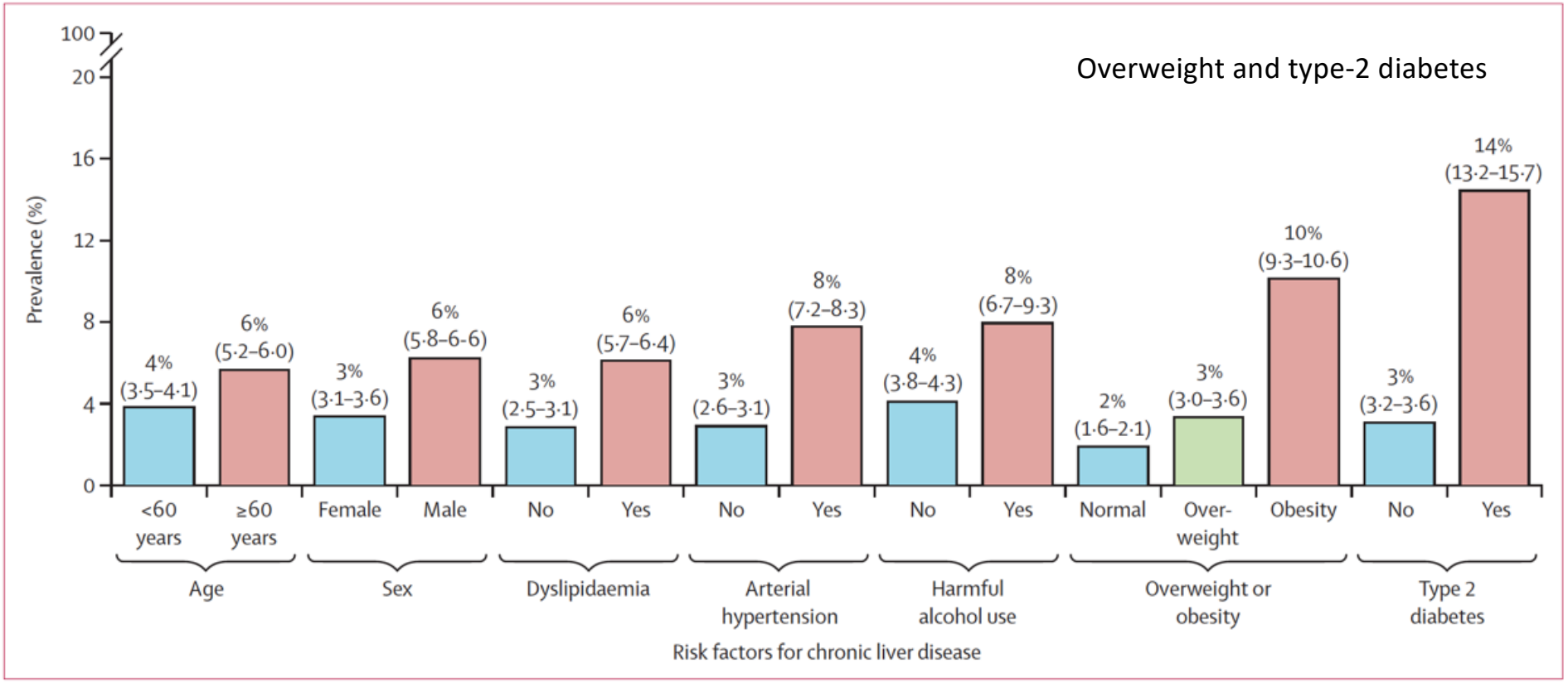


Figure 2: **Prevalence of liver stiffness measurement (LSM; ≥8 kPa) according to age, sex, and presence or absence of metabolic conditions and harmful alcohol use**
Data show the prevalence of LSM of 8 Kpa and greater and 95% CI in brackets for each condition.

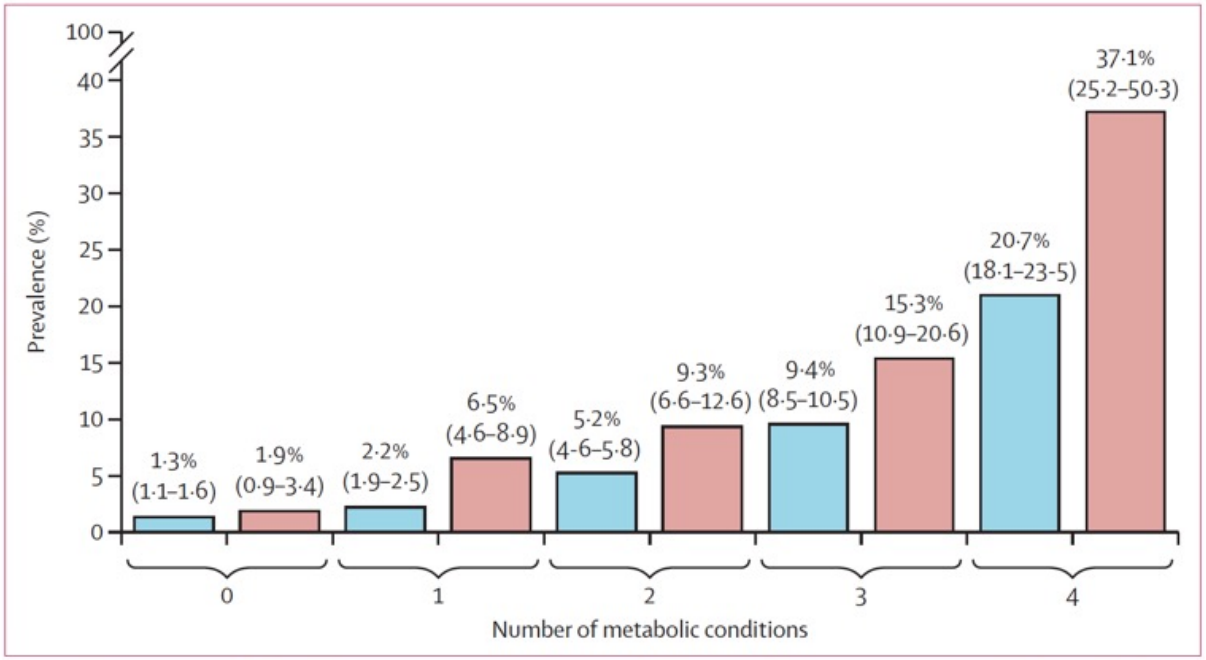


Figure 3: **Prevalence of liver stiffness measurement (LSM; ≥8 kPa) according to the number of metabolic conditions and its association with harmful alcohol use**

The numbers equate to the following: 0 is no metabolic condition; 1 is one metabolic condition; 2 is two metabolic conditions; 3 is three metabolic conditions; 4 is four metabolic conditions. The blue bars indicate no harmful alcohol use and pink bars indicate harmful alcohol use. Data show the prevalence of LSM of 8Kpa and greater and 95% CI in brackets for each condition. Odds ratios for the association between harmful alcohol use and LSM of 8 kPa and greater were calculated within each stratum of metabolic conditions, comparing participants with harmful alcohol use to those without harmful alcohol use but with the same number of metabolic conditions. The odds ratio was 1·41 in participants with no metabolic conditions, 2·97 in those with one metabolic condition, 1·79 in those with two metabolic conditions, 1·62 in those with three metabolic conditions, and 1·79 in those with four metabolic conditions. The interaction between harmful alcohol use and the number of metabolic conditions was not statistically significant, with a p value of 0·072.

	LSM≥8 kPa		LSM≥10 kPa		LSM≥15 kPa	
	n (aOR)	95% CI	n (aOR)	95% CI	n (aOR)	95% CI
No risk factors	340 (1 [ref])	..	167 (1 [ref])	..	54 (1 [ref])	..
Type 2 diabetes	106 (3·4)	2·7–4·3	67 (4·0)	3·0–5·4	28 (4·8)	3·0–7·8
Harmful alcohol use	52 (2·6)	1·9–3·5	29 (2·8)	1·9–4·2	15 (4·8)	2·7–8·7
Obesity	386 (3·8)	3·3–4·5	186 (3·6)	2·9–4·5	45 (2·6)	1·8–3·9
Type 2 diabetes and harmful alcohol use	18 (12·5)	7·2–21·6	12 (14·2)	7·4–27·0	6 (20·9)	8·6–51·2
Type 2 diabetes and obesity	273 (11·7)	9·8–14·0	168 (12·7)	10·1–16·0	57 (11·5)	7·7–17·0
Harmful alcohol use and obesity	40 (5·6)	4·0–8·0	26 (7·0)	4·5–10·8	9 (7·9)	3·8–16·3
Type 2 diabetes, harmful alcohol use and obesity	30 (25·9)	16·3–41·1	17 (22·5)	12·8–39·4	5 (18·7)	7·2–48·7

Data are n (aOR) and 95% CI, adjusted by age, sex, and country. aOR=adjusted odds ratio. LSM=liver stiffness measurement.

Table 2: **Logistic regression analysis of individual and combined risk factors with increased LSM (≥8, ≥10, and ≥15 kPa)**

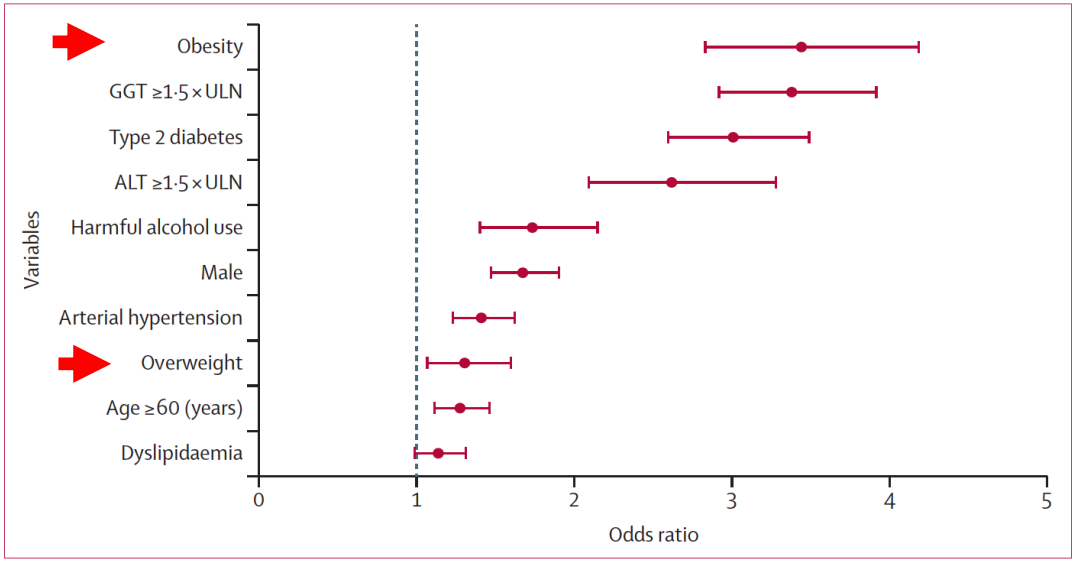


Figure 4: **Multivariable analysis of factors related to increased liver stiffness measurement (LSM; ≥8 kPa)**
Values shown are adjusted odds ratio and 95% CI, adjusted by country, sex, and all variables included in the model. ALT=alanine aminotransferase. GGT=gamma-glutamyl-transpeptidase. ULN=upper limit of normal.

Research in context

Evidence before this study

Chronic liver disease is a leading cause of premature mortality worldwide. Liver fibrosis—the principal determinant of disease progression—is often undetected until advanced stages when there is little hope for cure. Although non-invasive tests and guideline recommendations for earlier detection are increasingly available, population-level evidence to support liver fibrosis screening in the general population remains to be poor. We searched PubMed on Oct 20, 2025, using the search terms "liver fibrosis screening", "assessment of liver fibrosis", and "liver fibrosis tests", together with "general population". We searched for prospective studies published between Jan 1, 2010, to Oct 20, 2025, for English-language studies assessing liver fibrosis screening in unselected populations using invasive or non-invasive methods. Of the 605 records identified, 66 contained relevant information and were assessed in detail. Most studies were excluded because they were restricted to selected high-risk populations, had small sample sizes, did not report relevant prevalence estimates, or lacked protocolised confirmatory diagnostic assessment of chronic liver disease following screening.

Added value of this study

This is the largest prospective population-based liver fibrosis screening study that has included more than 30 000 individuals from nine European countries. Unlike previous studies, screen-positive participants underwent complete hepatology evaluation. Metabolic risk factors and alcohol use were present in more than 70% of the population. Type 2 diabetes and harmful alcohol use were the strongest predictors of positive screening and confirmed chronic liver disease, with a clear dose–response to elevated liver stiffness (≥8 kPa), which rose from 1·3% (no risk factors) to 21·0% (four metabolic factors) and 37·0% when combined with harmful alcohol use. Notably, nearly half of referred participants had lower liver stiffness measurements at hepatology assessment, underscoring the importance of confirmatory testing for accurately establishing a diagnosis of chronic liver disease. Overall, the prevalence of chronic liver disease with fibrosis in the screened population was 1·6%.

Implications of all the available evidence

Early detection of liver fibrosis is essential to enable timely, personalised interventions that can prevent disease progression. However, confirmatory testing is crucial to accurately diagnose chronic liver disease. Future screening strategies should be adapted to local epidemiological patterns and health-care system capacities to maximise effectiveness and equity in liver disease prevention. Given the high prevalence of metabolic and alcohol-related risk factors in the general population, effective screening approaches should extend beyond narrowly defined high-risk groups and include a broad segment of the population.

Zeit vor der Empfängnis (Medizin)
Im medizinischen Bereich bezieht sich der Begriff auf den Zeitraum, *bevor* eine Frau schwanger wird.

More equitable preconception health: paternal life course opportunities for better pregnancy, child, and family outcomes

Men and partners are important contributors to the health of future generations, yet their own preconception health and wellbeing remain secondary considerations in research, practice, and policy. Siloed research has exacerbated this deficit. Clinical research typically has a narrow focus on proximal behavioural factors related to periconceptional events (eg, paternal dietary influences on the sperm epigenome), with social research focusing largely on postnatal parenting. Here, we update and reappraise the evidence for men's role in preconception health through a transdisciplinary review. Across biological and behavioural research, young men's early life course experiences have been shown to shape their own and their partner's preconception physical, emotional, and behavioural health. Moreover, focusing on men's preconception health offers a corrective for legacies of sexism, which place responsibility for intergenerational health solely on the birthing parent, and of racism and colonialism, which have disproportionately disrupted the familial and societal roles of Black and Brown men. We provide three case studies illustrating these ethical concerns and conclude that greater attention to young men would lead to more equitable and holistic preconception health interventions and policy.

Key messages

- Boys and young men are an important but persistently underappreciated population for preconception interventions to improve intergenerational health
- Social and biological factors over the male life course influence male health and wellbeing at reproductive ages, and have important influences on maternal preconception health
- Supporting male preconception health is integral to health equity and reproductive justice, expanding the scope of interventions towards shared responsibility for parenthood
- Greater attention to the life course health and wellbeing of boys and young men is an important part in addressing intergenerational disparities arising from legacies of colonialism and racism
- Recognition of the broader implications of male health and behaviours across the life course on male and female preconception health is informing new targets for intervention and monitoring of preconception health indicators
- Greater appreciation for preconception social and biological roles of males calls for policy makers, public health agencies, clinicians, and men themselves to prioritise the roles and responsibilities of men in a more equitable vision to improve pregnancy, child, and family outcomes

Measuring progress in pregnancy planning and preconception health

As efforts to support pregnancy planning and improve preconception health are increasing at scale, appropriate systems to monitor progress are required. Despite developments in a few countries, no surveillance systems currently in operation are using a comprehensive set of indicators for monitoring preconception health. This Review describes relevant indicators, reflecting both system-level and individual-level factors, that can be drawn from routine data sources to form the basis for developing new surveillance systems. We present a new framework for national and international surveillance that incorporates, for the first time, community perspectives on the factors that matter most before pregnancy and parenthood. Finally, we describe an international collaboration working towards a core set of indicators that can be compared across low-income, middle-income, and high-income countries, and discuss future directions to enhance and expand international monitoring of pregnancy planning and preconception health.

Zeit vor der Empfängnis (Medizin)
Im medizinischen Bereich bezieht sich der Begriff auf den Zeitraum, *bevor* eine Frau schwanger wird.

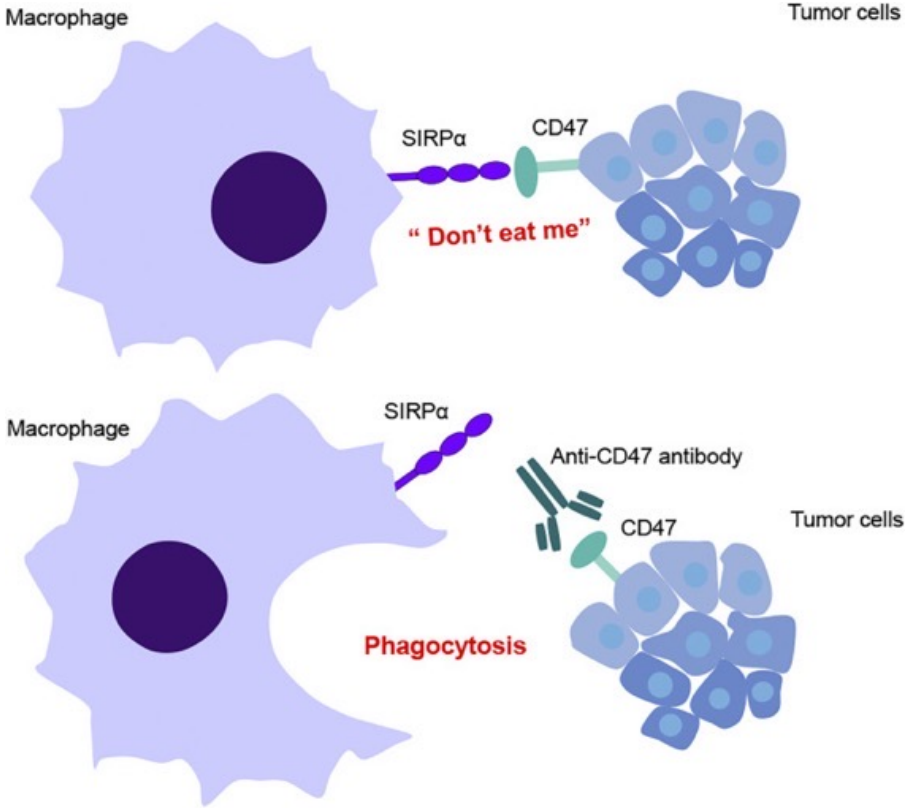
Key messages

- The growing number of preconception health interventions and policies being developed and implemented globally require monitoring to guide future targeted investments.
- Changes in pregnancy planning and preconception health should be measured at both system and individual levels by use of robust indicators that reflect the needs of communities, practitioners, and policy makers.
- Many indicators of pregnancy planning and preconception health can already be measured through a range of existing data sources.
- An internationally agreed core set of priority preconception health indicators does not currently exist but is being developed to facilitate global comparisons of progress and identification of effective preconception health strategies.
- Some countries are establishing systems for routine surveillance of pregnancy planning and preconception health, which can provide case studies to follow or adapt.
- Measuring and monitoring preconception health is a prime opportunity to support governments, health systems, and policy makers to tackle inequalities in intergenerational issues in population health.
- When proposing a new surveillance system to monitor preconception health (or updating an existing one), costs and benefits should be outlined in a business case.

Word cloud representation of community views on important factors to have in place before pregnancy

CD47 (Leukozyten-Oberflächenantigen CD47) ist ein Protein auf der Oberfläche fast aller Zellen im menschlichen Körper, das als essentielles Schutzsignal für das Immunsystem fungiert.
Die Hauptfunktion: Das „Friss-mich-nicht“-Signal
Die wichtigste Aufgabe von CD47 ist die Übermittlung eines **„Don't eat me“-Signals** an Fresszellen (Makrophagen):

- **Schutz gesunder Zellen:** Wenn CD47 an den Rezeptor **SIRPα** auf einem Makrophagen bindet, wird dessen Aktivität gehemmt. Die Fresszelle erkennt die Zielzelle als „eigen“ und gesund an und verschont sie.
- **Regulierung der Zelllebensdauer:** Junge rote Blutkörperchen haben viel CD47. Mit zunehmendem Alter verlieren sie das Protein, bis das Signal zu schwach wird und Makrophagen sie schließlich abbauen.

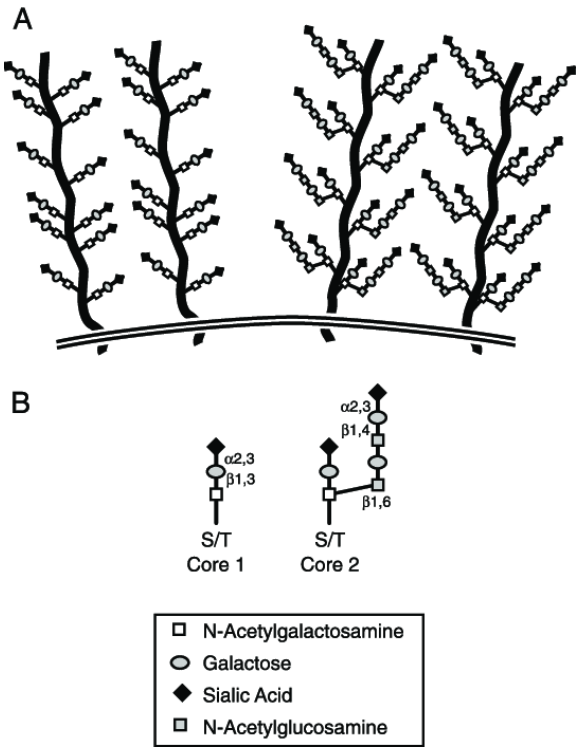


Signal-regulatory protein alpha (**SIRPα**), auch bekannt als **CD172a**, ist ein Membranprotein, das eine entscheidende Rolle als „Bremse“ im Immunsystem spielt. Es wird vor allem auf myeloiden Zellen wie **Makrophagen** (Fresszellen), dendritischen Zellen und Neutrophilen exprimiert

CD43 (auch bekannt als **Sialophorin** oder **Leukosialin**) ist ein Oberflächenprotein, das auf fast allen weißen Blutkörperchen (Leukozyten) vorkommt. In der Biologie und Medizin dient es primär als wichtiger Marker zur Identifizierung bestimmter Zelltypen und deren Entwicklungsstadien.
Wichtige Eigenschaften und Funktionen
•**Vorkommen**: Es wird auf T-Zellen, Granulozyten, Monozyten und Makrophagen exprimiert. Ein markantes Merkmal ist, dass es auf **ruhenden B-Zellen fehlt**, jedoch auf unreifen oder aktivierten B-Zellen vorhanden sein kann.
•**Struktur**: Es handelt sich um ein stark glykosyliertes Membranprotein (Sialoglykoprotein) mit einer Masse von etwa 95 bis 135 kDa.
•**Biologische Rollen**:

- **Zelladhäsion**: Es wirkt als Adhäsionsmolekül und hilft Zellen, aneinander oder an Oberflächen zu haften.
- **Signalübertragung**: Es ist an der Weiterleitung von Signalen in das Zellinnere beteiligt, was die Aktivierung von Immunzellen (insbesondere T-Zellen) beeinflusst.
- **Immunmodulation**: Es kann die Interaktion zwischen T-Zellen und anderen Zellen regulieren.

„glycocalyx“



CRISPR-Screens sind eine leistungsstarke Methode in der modernen Biologie, um die Funktion tausender Gene gleichzeitig zu untersuchen. Forscher nutzen dabei die „Genschere“ CRISPR-Cas9, um gezielt Mutationen in einer Zellpopulation zu erzeugen und herauszufinden, welche Gene für bestimmte Merkmale (Phänotypen) verantwortlich sind, etwa die Resistenz gegen Medikamente oder das Überleben von Krebszellen.

Grundprinzipien und Formate

Es gibt zwei Hauptarten, wie diese Screens durchgeführt werden:

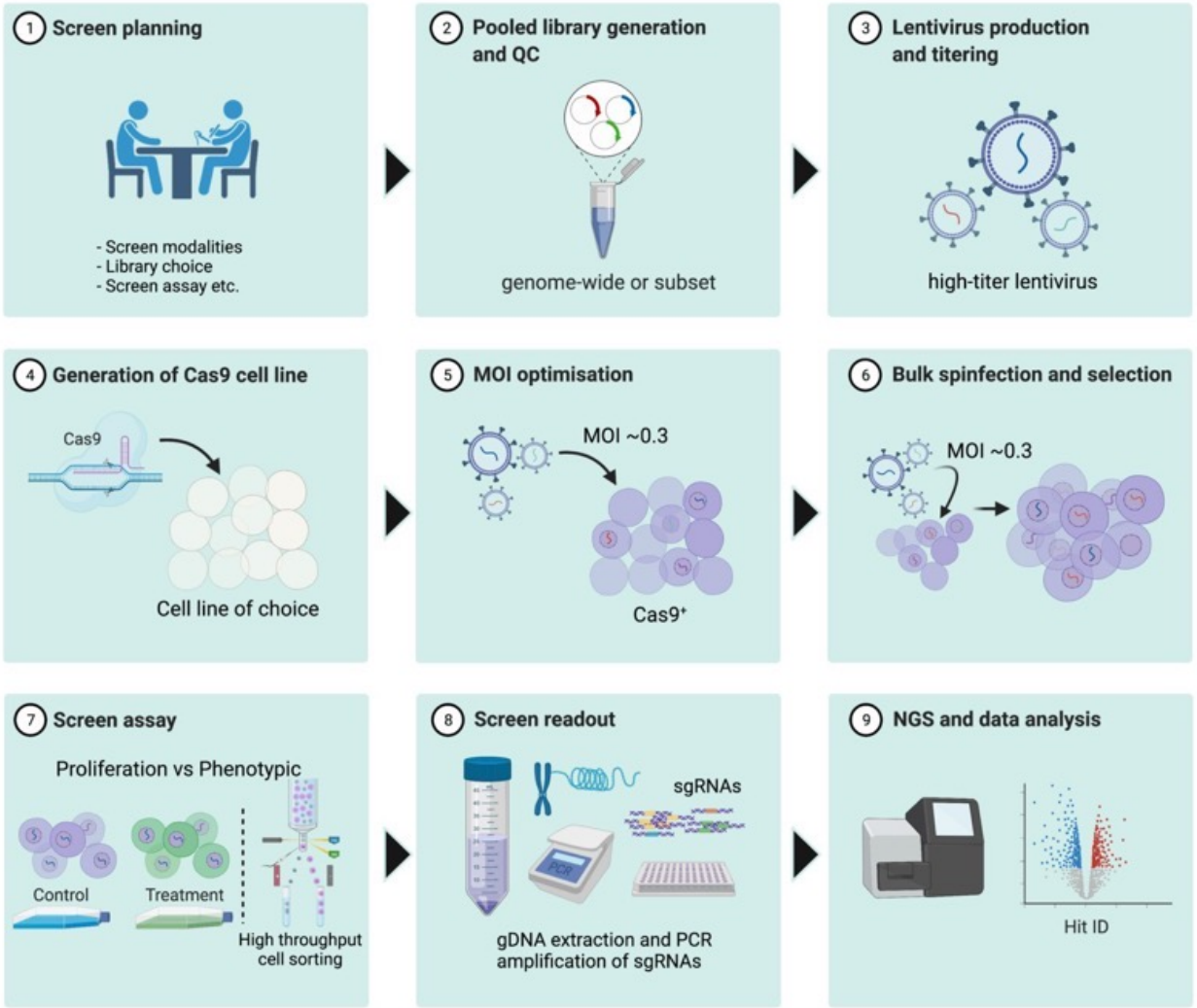
•**Gepoolte Screens (Pooled Screens):** Hierbei wird eine Mischung aus tausenden verschiedenen Guide-RNAs (sgRNAs) gleichzeitig in eine große Gruppe von Zellen eingebracht.

- **Vorteil:** Man kann das gesamte Genom auf einmal untersuchen (unbiased).
- **Readout:** Nach einer Selektion (z. B. Überleben nach Giftzugabe) wird mittels **Next-Generation-Sequencing (NGS)** analysiert, welche Gene in den überlebenden Zellen ausgeschaltet waren.

•**Arrayed Screens:** Jedes Gen wird separat in einer eigenen Vertiefung einer Multiwell-Platte verändert.

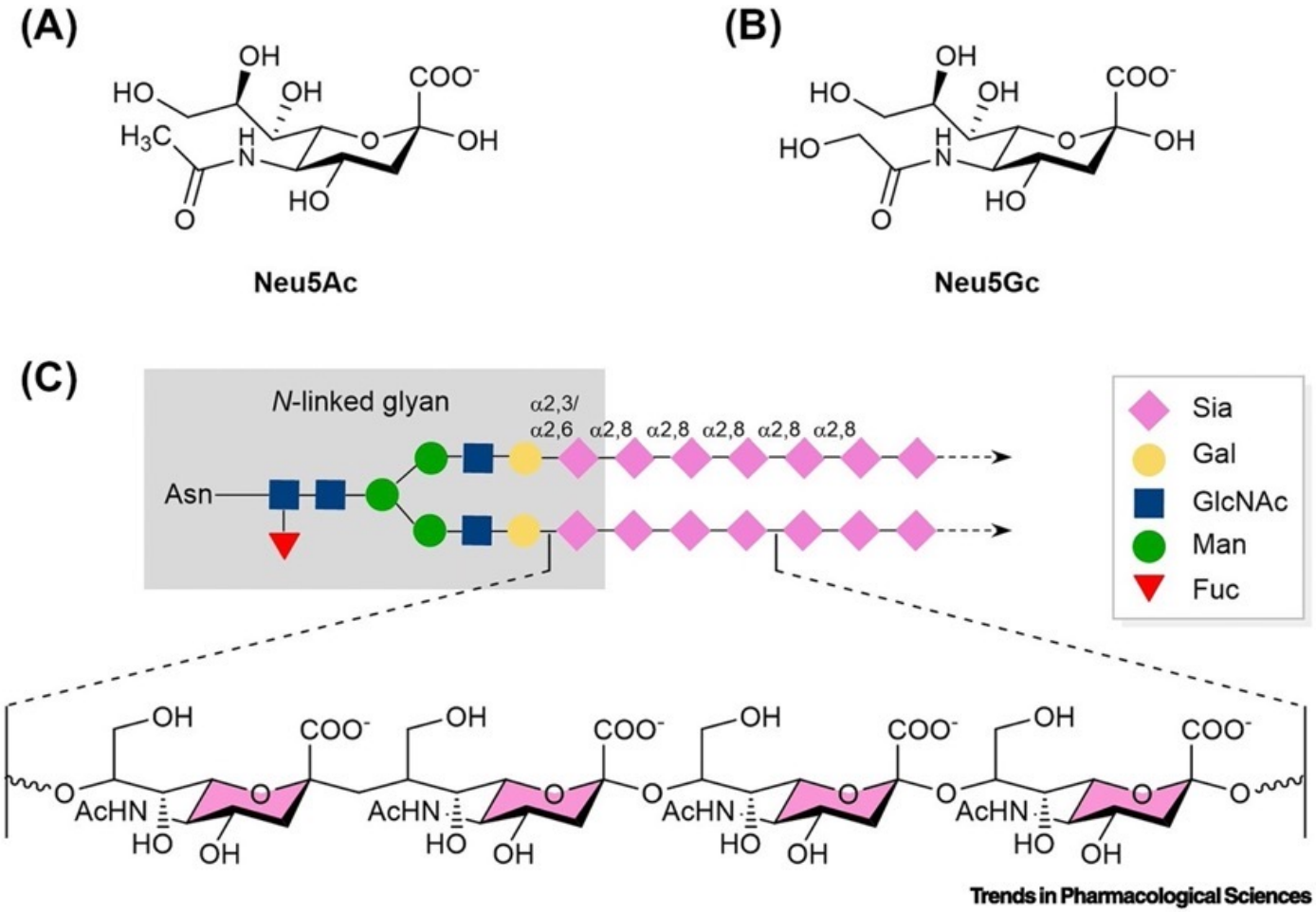
- **Vorteil:** Man kann komplexere Merkmale beobachten, wie z. B. Veränderungen in der Zellform oder die Bewegung von Proteinen unter dem Mikroskop.
- **Readout:** Bildgebende Verfahren oder direkte Messungen pro Well.

Die gRNA ermöglicht es, Gene gezielt auszuschalten (**Knockout**) oder neue Sequenzen einzufügen (**Knock-in**).



Sialylierung ist ein biologischer Prozess, bei dem Sialinsäuren als terminale Zuckerreste an Glykoproteine, Glykolipide oder Oligosaccharide gebunden werden. Dieser Vorgang, oft mit der N-Acetylneuraminsäure (NeuNAc) beim Menschen, spielt eine entscheidende Rolle bei der Zellerkennung, Signalübertragung und Stabilität von Proteinen. Sie findet hauptsächlich im Golgi-Apparat statt.
Hier sind die wichtigsten Aspekte der Sialylierung:

•**Funktion:** Sialinsäuren befinden sich meist am Ende von Zuckerseitenketten und maskieren darunterliegende Zucker, was die Zellerkennung (z.B. durch Lectine) beeinflusst.
•**Biologische Bedeutung:** Wichtig für Zell-Zell-Interaktionen, Immunantwort, Virusinfektionen (z.B. Influenza bindet an Sialinsäuren) und die Halbwertszeit von Proteinen im Blut
.
•**Medizinische Relevanz:** Änderungen im Sialylierungsmuster sind oft bei Krebs und entzündlichen Erkrankungen zu beobachten.
•**Enzyme:** Die Übertragung erfolgt durch spezifische Sialyltransferasen.

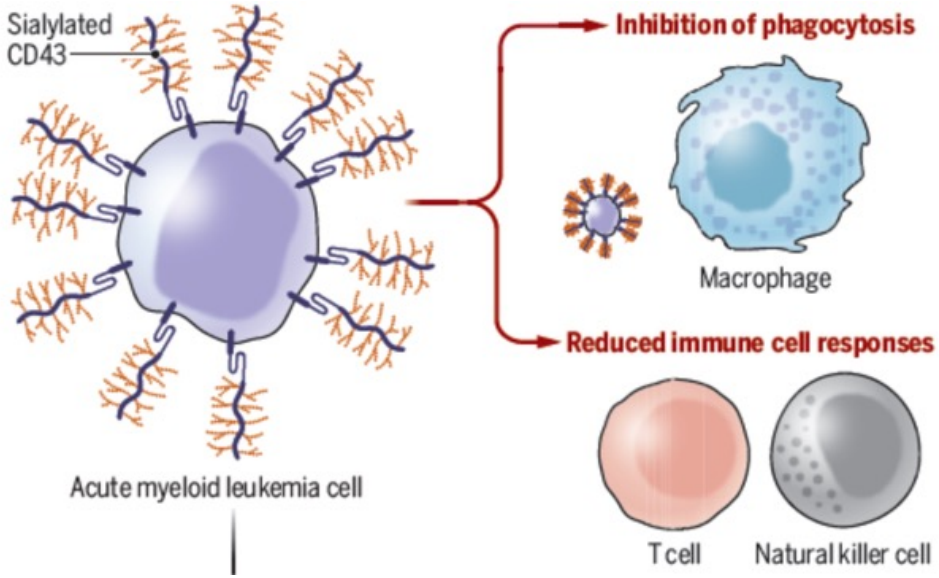

(A)
Neu5Ac
(B)
Neu5Gc
(C)
N-linked glyan
Asn
α2,3/
α2,6
α2,8
Sia
Gal
GlcNAc
Man
Fuc
Trends in Pharmacological Sciences

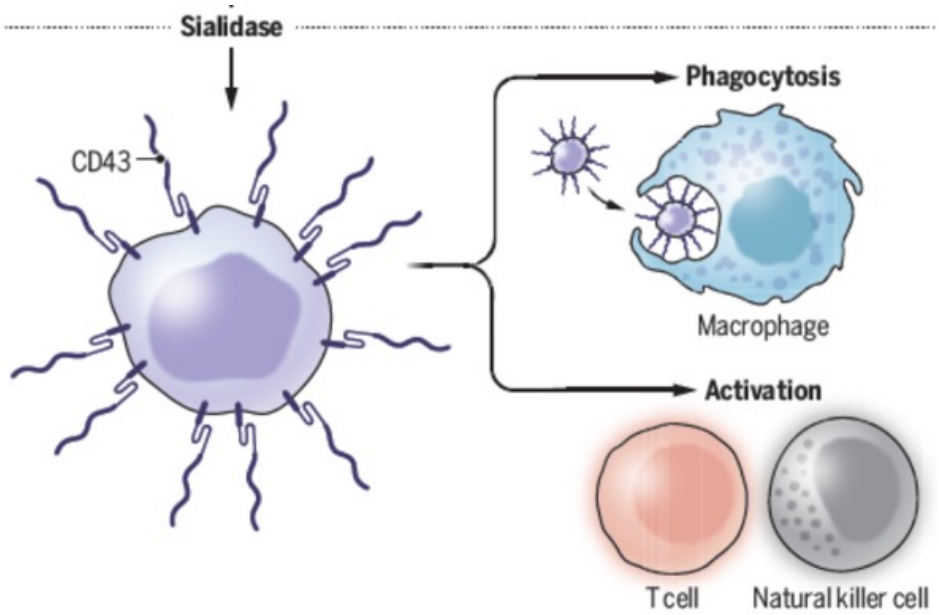
The sialic shield of leukemia cells

A coat of sialylated protein protects human leukemia cells from destruction

A “don’t-eat-me” barrier around leukemia cells

After CD47 is eliminated with neutralizing antibodies





A “don’t-eat-me” barrier around leukemia cells

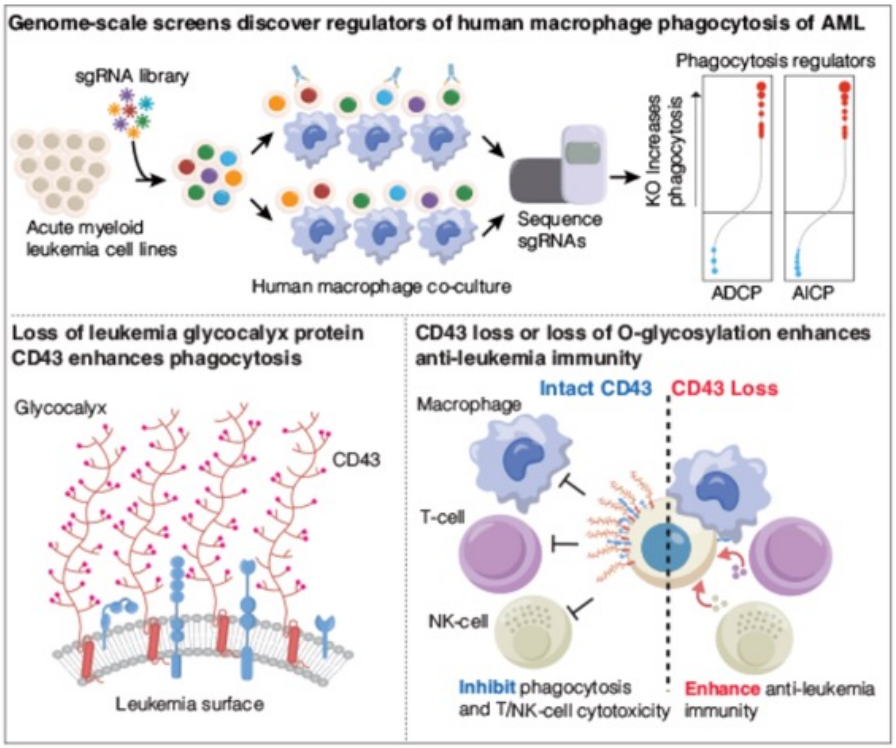
Sialylation of the sugar (glycan) portions of cluster of differentiation 43 (CD43) on the surface of acute myeloid leukemia cells acts as a don’t-eat-me signal for immune cells. Sialic acid–binding immunoglobulin-type lectin (SIGLEC) receptors, which recognize sialylation and regulate immune cell responses in other settings, are not involved in this process. Instead, sialic acids form a physical shield around the cancer cells that prevents contact and phagocytosis by macrophages and blunts T cell and natural killer cell responses. Removing this shield with the enzyme sialidase promotes phagocytosis and activates T cells and natural killer cells.

Sialylated CD43 forms a glyco-immune barrier that restrains antileukemic immunity

INTRODUCTION: Macrophages in the tumor microenvironment exert antitumorigenic effects through phagocytosis and/or direct tumoricidal activity. Phagocytosis of tumor cells occurs through both antibody-dependent cellular phagocytosis (ADCP) and antibodyindependent cellular phagocytosis (AICP) mechanisms. Despite the strong evidence that macrophages can mediate tumor control in acute myeloid leukemia (AML) and other diseases, therapeutic agents that enhance macrophage phagocytosis, including anti-CD47 neutralizing antibodies, have not led to improved clinical outcomes. Thus, a more comprehensive understanding of the tumor-intrinsic factors that suppress human macrophage phagocytosis is needed.

RATIONALE: To systematically identify the key pathways that regulate phagocytosis by human macrophages, we performed genome-scale knockout CRISPR screens in human AML cell lines cocultured with human monocyte-derived macrophages.

RESULTS: We performed in vitro genome-wide loss-of-function CRISPR screens to identify the major pathways that regulate ADCP and AICP by human macrophages. Unexpectedly, we found that the classic “don’t eat me” signal CD47 has minimal impact on human macrophage phagocytosis. By contrast, CD47 strongly suppressed mouse macrophage phagocytosis. Additionally, we identified the major histocompatibility class I complex (MHC class I) as the most potent negative regulator of ADCP. By integrating results from the AICP and ADCP screens, we discovered that the O-linked glycosylation and sialylation pathways negatively regulate both AICP and ADCP. CD43, a heavily sialylated cell surface glycoprotein, was the major mediator of the inhibitory effects of the O-linked glycosylation and sialylation pathways. The inhibitory activity of CD43 was dependent on its sialic acid residues and the length of its ectodomain but independent of the canonical sialic acid–binding receptors SIGLEC-1, SIGLEC-7, and SIGLEC-9. CD43 expression reduced the avidity of interactions between immune effector cells and leukemia cells, consistent with a model where CD43 forms a steric or electrostatic glycocalyx barrier that reduces interactions with the leukemia cell surface. We found that CD43 is overexpressed in AML patient samples, and inhibition of CD43 with antibodies enhances phagocytosis of AML cell lines and patient-derived samples. Finally, we found that CD43 not only restrains human macrophage phagocytosis but also human natural killer (NK) and human T cell cytotoxicity.

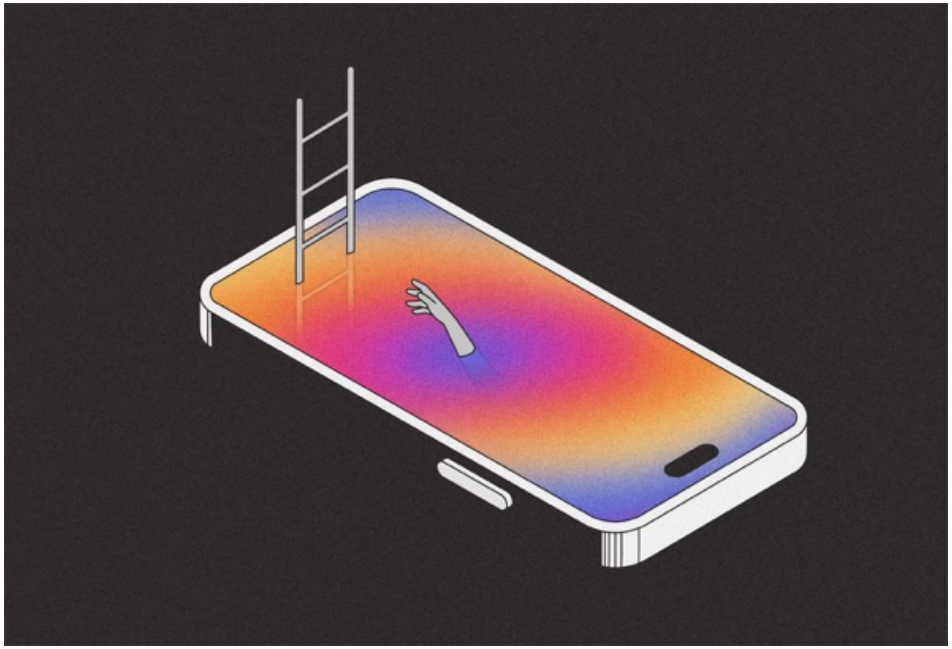


Genome-scale phagocytosis screens identify sialylated CD43 as a potent inhibitor of antileukemic immunity. Genome-scale CRISPR screens of human AML cocultured with human macrophages enabled the discovery of regulators of antibodydependent and antibody-independent phagocytosis. Cell surface Oglycosylation of the glycoprotein CD43 is a potent inhibitor of macrophage phagocytosis. Genetic deletion of CD43 enhances both innate and adaptive antileukemic immunity. sgRNA, single guide RNA; KO, knockout.

Macrophages exert antitumorigenic activity through phagocytosis, but phagocytosis-enhancing therapeutics have not improved acute myeloid leukemia (AML) outcomes. To identify phagocytosis regulators, we performed CriSpr knockout screens in human AML cells cocultured with human macrophages. We found that the “don’t eat me” signal CD47 inhibited mouse but not human macrophage phagocytosis. However, O-linked glycosylation and sialylation were strong negative regulators of phagocytosis. In AML, the cell surface mucin-like glycoprotein CD43 was the major effector of these pathways. Inhibition of phagocytosis by CD43 was dependent on the length of its ectodomain and independent of the macrophage sialic acid receptors SIGLEC-1, SIGLEC-7, and SIGLEC-9. The inhibitory effects of CD43 extended beyond human macrophages to natural killer and T cells. Thus, CD43 forms a glyco-immune barrier that restrains both innate and adaptive antileukemic immunity.

CONCLUSION: The cell surface glycoprotein CD43 is a potent inhibitor of innate and adaptive antileukemic immunity. The inhibitory activity of CD43 on immune cells is dependent on posttranslational sialic acid modifications that are added through the O-linked glycosylation and sialylation pathways. Thus, sialylated CD43 is a potential therapeutic target for the treatment of AML.

This detox may erase 10 years of social media brain damage, researchers say



The young woman described to a jury what it was like to lose control of her life to social media.

She began as a child, she said, and over time the habit expanded to fill nearly every available hour — late nights bleeding into early mornings, sleep gradually displaced. She would try to stop and find herself returning in a loop she could not escape. As her use intensified, so did her distress: anxiety, depression and a growing fixation on her appearance.

"I wanted to be on it all the time," the 20-year-old testified in the landmark trial against Meta and YouTube, before a jury found the companies negligent and ordered them to pay her $6 million in damages.

The verdict in California and another case in New Mexico in March mark a turning point in the long-running effort to hold Silicon Valley companies accountable for products critics say are engineered to be as addictive as tobacco or gambling.

The science has been moving in parallel with the court's recognition. A growing body of research links heavy social media use not only to declines in mental health but to measurable cognitive effects — on attention, memory and focus — that in some studies resemble accelerated aging.

Science also suggests we have more control than we realize when it comes to reversing this damage, and the solution is surprisingly simple: Take a break.

The average American spends roughly 4½ to 5 hours on their phone a day, according to surveys, and even if someone's use is on the lower side of two to three hours a day, that still adds up to 1½ months in a year not doing something else.

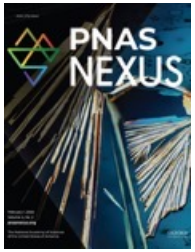
"All of us have a somewhat unhealthy relationship with our phones," said Kostadin Kushlev, an associate professor of psychology at Georgetown University.

"Digital detoxes" can sound like a fad. But in one of the largest studies to date, published in PNAS Nexus and involving more than 467 participants with an average age of 32, even a short time away produced striking results — effectively erasing a decade of age-related cognitive decline.

Noah Castelo, an associate professor at the University of Alberta School of Business, said the study grew out of his own experience. Now 35, he got his first smartphone in college and began to notice how it reshaped his time: "These technologies can interfere with activities that were otherwise engaging, like having dinner with friends."

For 14 days, participants used a commercially available app, Freedom, to block internet access on their phones. They were still allowed calls and text messages, essentially turning a smartphone into a dumb phone.

Their time online decreased from 314 minutes to 161 minutes, and by the end of the period the participants had improvements in sustained attention, mental health as well as self-reported well-being.

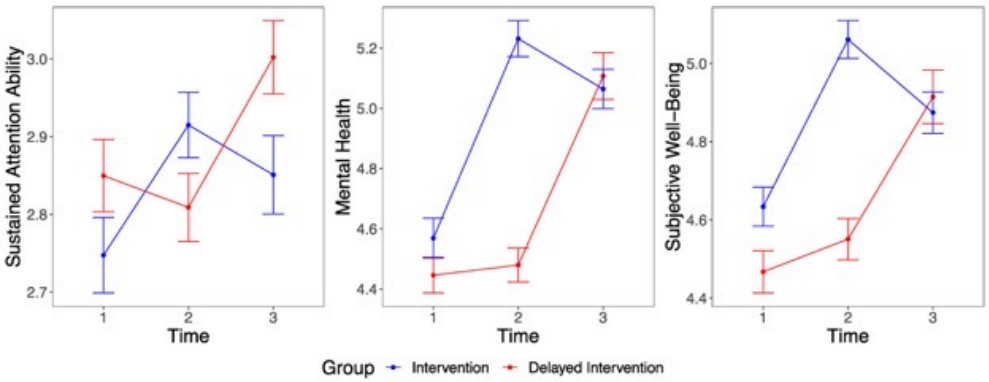


Blocking mobile internet on smartphones improves sustained attention, mental health, and subjective well-being

Abstract

Smartphones enable people to access the online world from anywhere at any time. Despite the benefits of this technology, there is growing concern that smartphone use could adversely impact cognitive functioning and mental health. Correlational and anecdotal evidence suggests that these concerns may be well-founded, but causal evidence remains scarce. We conducted a month-long randomized controlled trial to investigate how removing constant access to the internet through smartphones might impact psychological functioning. We used a mobile phone application to block all mobile internet access from participants' smartphones for 2 weeks and objectively track compliance. This intervention specifically targeted the feature that makes smartphones "smart" (mobile internet) while allowing participants to maintain mobile connection (through texts and calls) and nonmobile access to the internet (e.g. through desktop computers). The intervention improved mental health, subjective well-being, and objectively measured ability to sustain attention; 91% of participants improved on at least one of these outcomes. Mediation analyses suggest that these improvements can be partially explained by the intervention's impact on how people spent their time; when people did not have access to mobile internet, they spent more time socializing in person, exercising, and being in nature. These results provide causal evidence that blocking mobile internet can improve important psychological outcomes, and suggest that maintaining the status quo of constant connection to the internet may be detrimental to time use, cognitive functioning, and well-being.

Von Smartphone zu Nokia Handy



Attention, mental health, and SWB improve after 2 weeks of blocking mobile internet. In the Intervention group the three variables improved. In the delayed intervention group, improvement was delayed but occurred when the intervention was applied.