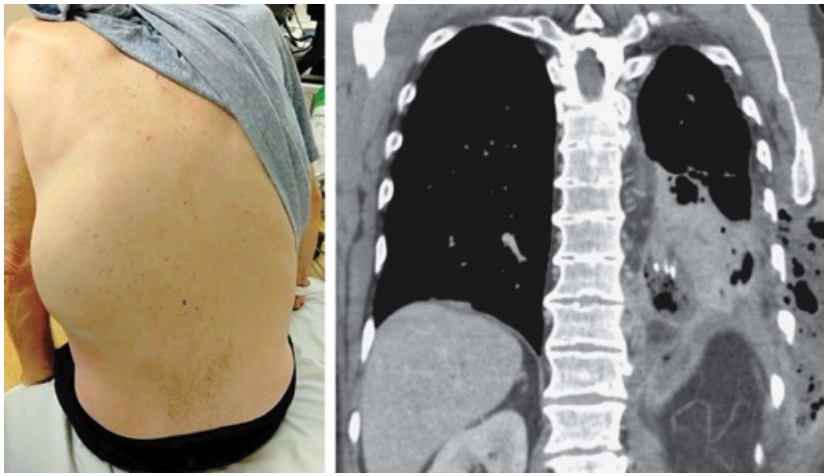
https://www.mdc-berlin.de/de/veroeffentlichungstypen/clinical-journal-club

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 66-year-old man with chronic obstructive pulmonary disease presented to the emergency department with a 2-week history of shortness of breath and cough and 5 days of left flank pain. Two days before presentation, he had noted the appearance and rapid expansion of a mass on his left side. Computed tomography of the chest is shown. What is the underlying etiology?

Autoimmune pleuritis

Empyema necessitans

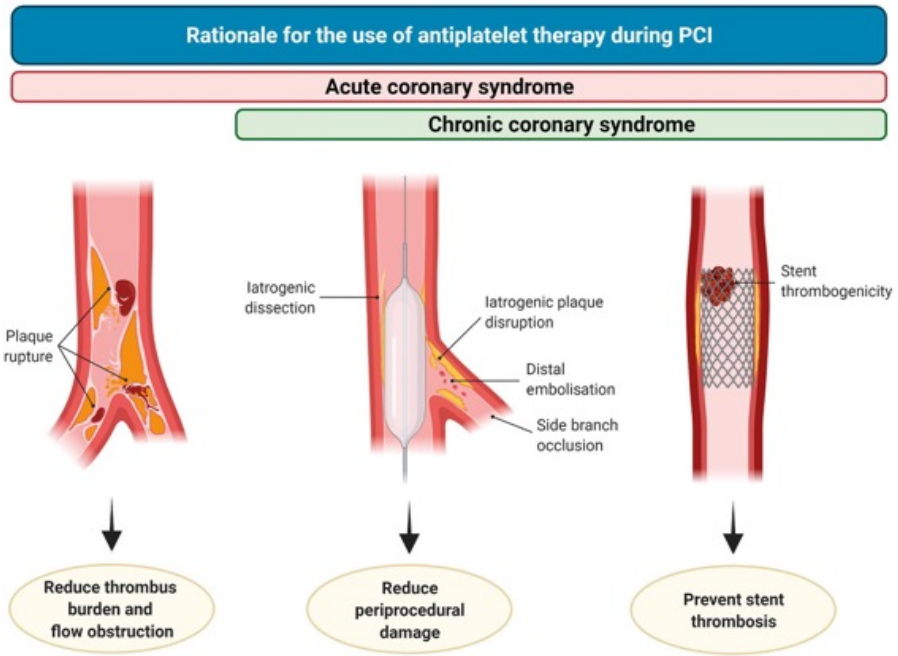
Hematoma

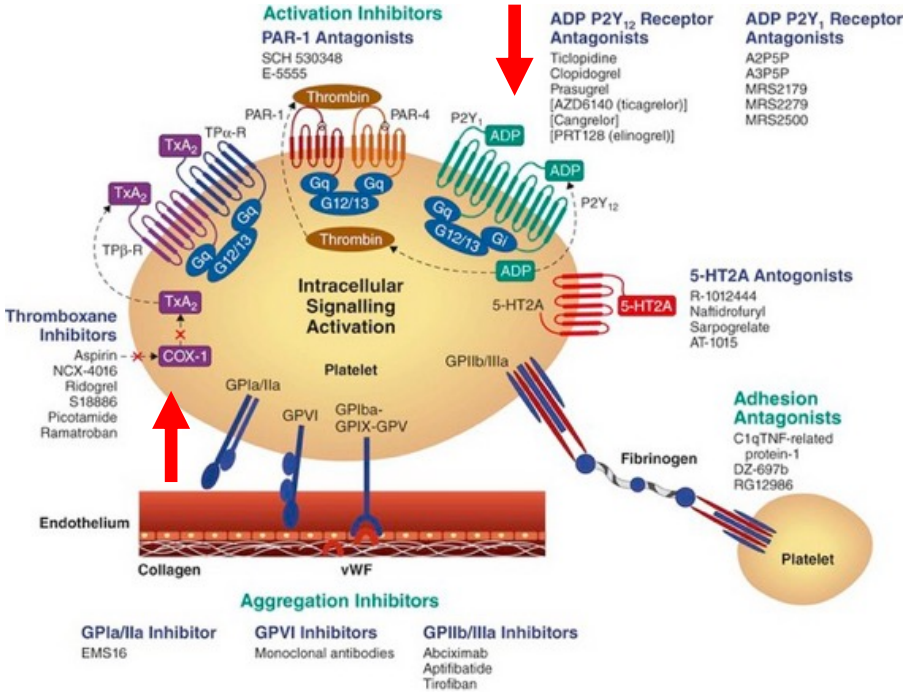
Mesothelioma

Soft tissue sarcoma of the chest wall

A diagnosis of empyema necessitans — a rare complication of empyema in which the infection extends beyond the parietal pleural into the chest wall — was made. Incision and drainage of the chest-wall mass was performed. Cultures of pleural fluid grew Streptococcus intermedius. The patient completed a prolonged course of antibiotic therapy.

Modern stenting and antiplatelet therapy

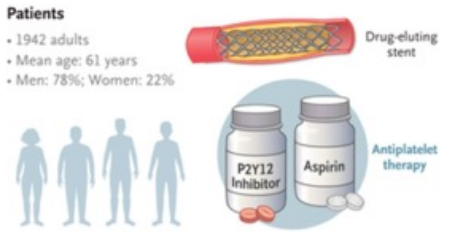




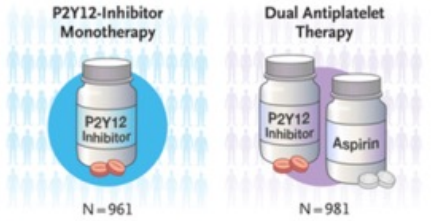
Early Discontinuation of Aspirin after PCI in Low-Risk Acute Myocardial Infarction

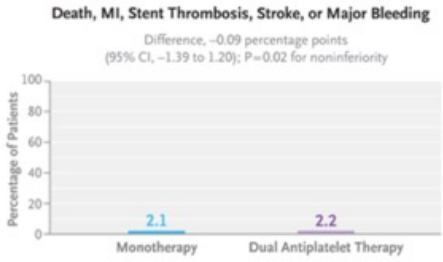
An appropriate duration of dual antiplatelet therapy after percutaneous coronary intervention for acute myocardial infarction that has been treated with guideline-recommended complete revascularization and a contemporary drug-eluting stent remains unclear.

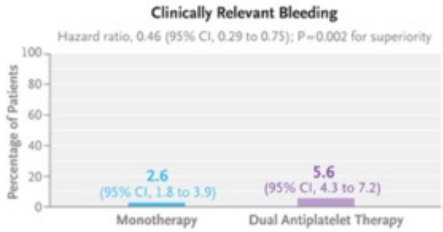
We conducted a multicenter, open-label, randomized trial at 40 European sites. Adults with acute myocardial infarction who had undergone successful complete revascularization within 7 days after the infarction and had subsequently completed 1 month of dual antiplatelet therapy with no ischemic or major bleeding events were randomly assigned to transition to a P2Y12 inhibitor as monotherapy or to continue dual antiplatelet therapy for an additional 11 months. The primary outcome was a composite of death from any cause, myocardial infarction, stent thrombosis, stroke, or major bleeding (defined by the Bleeding Academic Research Consortium [BARC] as a bleeding event of type 3 or 5) at 11 months after randomization (tested for noninferiority with a margin of 1.25 percentage points). The main secondary outcome was BARC type 2, 3, or 5 bleeding (clinically relevant bleeding) at 11 months after randomization (tested for superiority).



Both groups got dual therapy for the first month







The advent of drug-eluting stents revolutionized the management of ischemic heart disease by substantially reducing the risk of restenosis. However, first-generation stents were associated with late thrombotic complications, which led to recommendations for prolonged dual antiplatelet therapy, particularly in patients with increased platelet activation and thrombotic risk associated with acute coronary syndrome. Despite its effectiveness, dual antiplatelet therapy increases the risk of bleeding across the spectrum of patients with ischemic heart disease, including those who are not at high risk for bleeding. Observational studies, such as ADAPT-DES (Assessment of Dual Antiplatelet Therapy with Drug-Eluting Stents), have linked dual antiplatelet therapy to complications and death after percutaneous coronary intervention (PCI) in all-comer populations. The introduction of newer-generation drug-eluting stents, with lower doses of drugs and improved biocompatibility, has markedly reduced the risk of late stent thrombosis; there has been a renewed interest in refining antiplatelet strategies, including earlier de-escalation to monotherapy on the basis of individual risk profiles. Although abbreviated dual antiplatelet therapy has been studied in patients with a high bleeding risk, in unselected patient populations, and in East Asian patients with an acute coronary syndrome, only a few trials have evaluated early discontinuation of aspirin specifically in patients with acute myocardial infarction.

Methods

Trial Design and Oversight

TARGET-FIRST was a prospective, multicenter, open-label, randomized, controlled trial that was conducted at 40 sites across Europe.

Trial Population

Patients were eligible for enrollment if they were at least 18 years of age, were hospitalized for ST-segment elevation myocardial infarction (STEMI) or non-STEMI (NSTEMI), and had undergone complete revascularization with an abluminal biodegradable-polymer rapamycin-eluting stent (Firehawk Liberty, MicroPort) without complications. Complete revascularization was defined as treatment of all clinically significant lesions (as determined on angiography) during the index or staged (within 7 days after myocardial infarction) PCI procedure.

Randomization

After at least 30 days of dual antiplatelet therapy (aspirin plus a P2Y12 inhibitor), patients were evaluated. If they were free from ischemic or major bleeding events, they were randomly assigned in a 1:1 ratio to transition to P2Y12-inhibitor monotherapy (intervention) or to continue receiving dual antiplatelet therapy (control) for an additional 11 months.

Treatments and Follow-up

The choice of P2Y12 inhibitor (prasugrel, ticagrelor, or clopidogrel) was determined by the investigator and aligned with the guidelines of the European Society of Cardiology and local practice. Investigators were encouraged to use a potent P2Y12 inhibitor (prasugrel or ticagrelor) and to use the same P2Y12 inhibitor throughout the trial unless there was a clinical reason to switch.

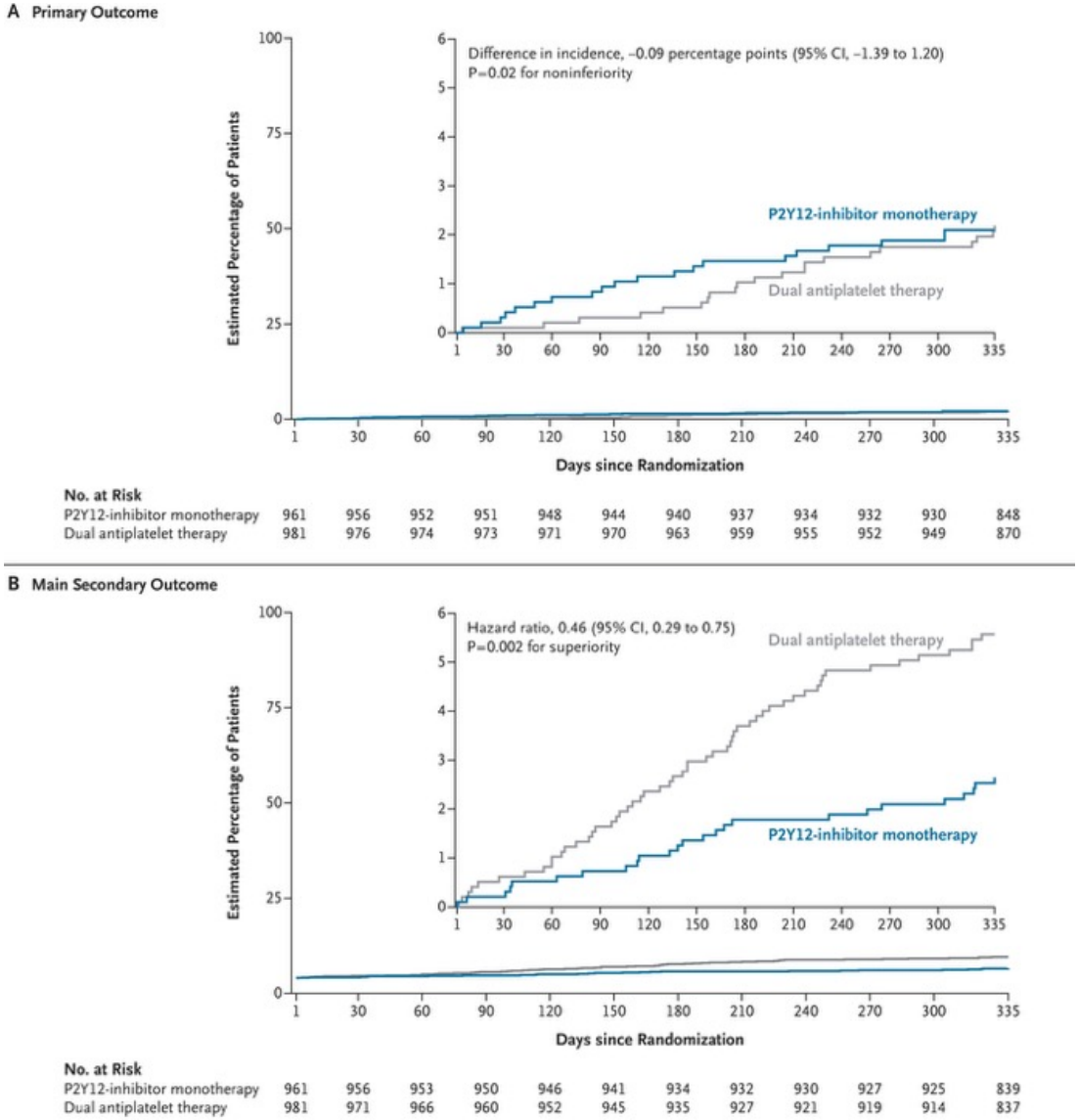
Outcomes

The primary outcome was net adverse clinical and cerebrovascular events, defined as a composite of death from any cause, myocardial infarction, stent thrombosis, stroke, or major bleeding.

Characteristic	P2Y12-Inhibitor Monotherapy (N=961)	Dual Antiplatelet Therapy (N=981)
Age — yr	61.0±10.8	61.0±10.5
Female sex — no. (%)	223 (23.2)	197 (20.1)
Body-mass index†	26.7±4.7	27.4±4.4
Current smoker — no./total no. (%)	402/959 (41.9)	410/981 (41.8)
Diabetes mellitus — no./total no (%)	135/961 (14.0)	146/981 (14.9)
Type 1, treated with insulin	10/959 (1.0)	6/981 (0.6)
Type 2, treated with insulin	26/959 (2.7)	27/981 (2.8)
Hypertension — no. (%)	367 (38.2)	384 (39.1)
Hypercholesterolemia — no. (%)	271 (28.2)	269 (27.4)
Chronic kidney disease — no. (%)	15 (1.6)	21 (2.1)
Family history of coronary disease — no./total no. (%)	260/949 (27.4)	243/970 (25.1)
Peripheral vascular disease — no. (%)	34 (3.5)	25 (2.5)
Previous myocardial infarction or previous PCI — no./total no. (%)	57/959 (5.9)	67/975 (6.9)
Previous cerebrovascular accident — no. (%)	15 (1.6)	20 (2.0)
Left ventricular ejection fraction <40% — no./total no. (%)	25/704 (3.6)	33/702 (4.7)
Indication for PCI — no. (%)		
STEMI	482 (50.2)	497 (50.7)
NSTEMI	479 (49.8)	484 (49.3)
Antiplatelet medication at randomization		
Duration of dual antiplatelet therapy after PCI — days	37.0±4.6	37.0±4.6
P2Y12 inhibitor at 1-month visit — no./total no. (%)		
Ticagrelor	706/961 (73.5)	731/980 (74.6)
Prasugrel	209/961 (21.7)	196/980 (20.0)
Clopidogrel	46/961 (4.8)	53/980 (5.4)

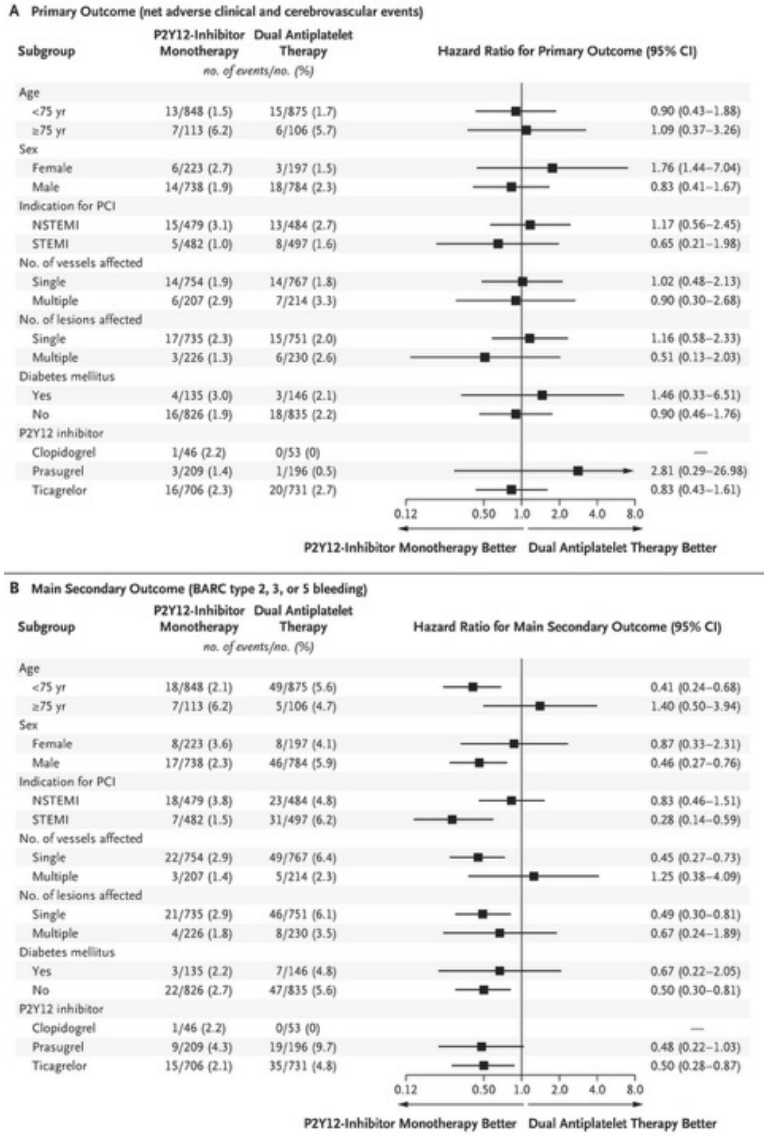
Primary and Secondary Outcomes at 11 Months after Randomization (Intention-to-Treat Population).

Outcome	P2Y12-Inhibitor Monotherapy (N=961)	Dual Antiplatelet Therapy (N=981)	Hazard Ratio (95% CI)	P Value
	no. of patients (%)			
Primary outcome: net adverse clinical and cerebrovascular events†	20 (2.1)	21 (2.2)	—	0.02
Secondary outcome: individual components of the primary outcome				
Death from any cause	4 (0.4)	2 (0.2)	2.04 (0.37–11.14)	—
Myocardial infarction	7 (0.7)	10 (1.1)	0.72 (0.27–1.88)	—
Stent thrombosis, definite or probable	1 (0.1)	0	—	—
Stroke	3 (0.3)	2 (0.2)	1.53 (0.26–9.18)	—
BARC type 3 or 5 bleeding‡	7 (0.7)	7 (0.7)	1.02 (0.36–2.91)	—
Type 3a	1 (0.1)	1 (0.1)	—	—
Type 3b	6 (0.6)	3 (0.3)	—	—
Type 3c	0	3 (0.3)	—	—
Main secondary outcome: BARC type 2, 3, or 5 bleeding§	25 (2.6)	54 (5.6)	0.46 (0.29–0.75)	0.002
Other secondary outcomes				
Death from cardiovascular causes	3 (0.3)	2 (0.2)	1.53 (0.26–9.16)	—
Patient-oriented composite outcome¶	43 (4.5)	71 (7.2)	0.61 (0.42–0.89)	—
Major adverse cardiovascular events‖	15 (1.6)	16 (1.6)	— **	—
Device-oriented composite outcome: target-lesion failure††	10 (1.1)	8 (0.8)	1.28 (0.50–3.23)	—
Ischemia-driven revascularization of target lesion	5 (0.5)	6 (0.6)	0.85 (0.26–2.79)	—
Ischemia-driven revascularization of target vessel	7 (0.7)	7 (0.7)	1.02 (0.36–2.91)	—



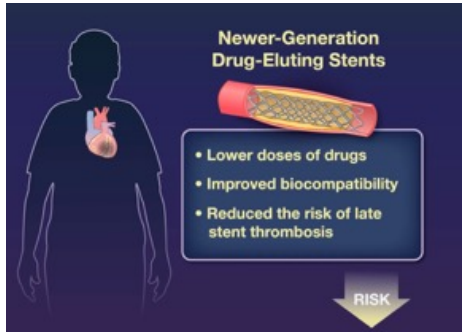
Primary and Main Secondary Outcomes.

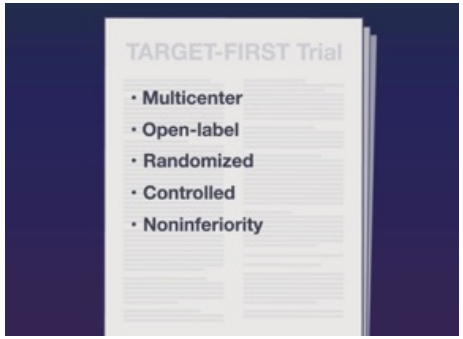
Panel A shows the incidence of net adverse clinical and cerebrovascular events, defined as a composite of death from any cause, myocardial infarction, stent thrombosis, stroke, or major bleeding (defined by the Bleeding Academic Research Consortium [BARC] as a bleeding event of type 3 or 5) (the primary outcome). Panel B shows the incidence of BARC type 2, 3, or 5 bleeding (clinically relevant bleeding) (the main secondary outcome). In each panel, the inset shows the same data on an expanded y axis.

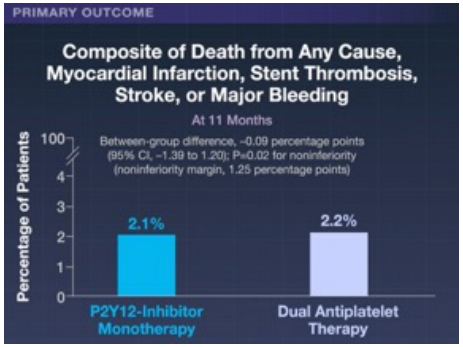


Primary and Main Secondary Outcomes in Prespecified Subgroups.

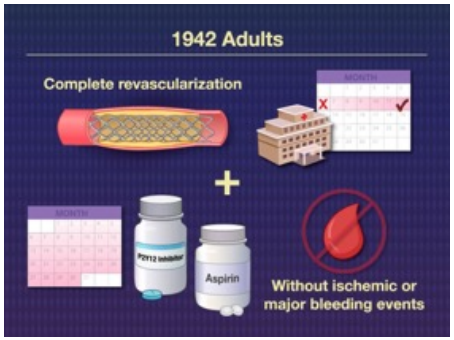
Panel A shows the subgroup analysis of net adverse clinical and cerebrovascular events, defined as a composite of death from any cause, myocardial infarction, stent thrombosis, stroke, or major bleeding (defined by the BARC as a bleeding event of type 3 or 5) (the primary outcome). The arrow on the confidence interval bar indicates that upper boundary of the confidence interval is off the scale. Panel B shows the subgroup analysis of BARC type 2, 3, or 5 bleeding (clinically relevant bleeding) (the main secondary outcome). NSTEMI denotes non–ST-segment elevation myocardial infarction, PCI percutaneous coronary intervention, and STEMI ST-segment elevation myocardial infarction.

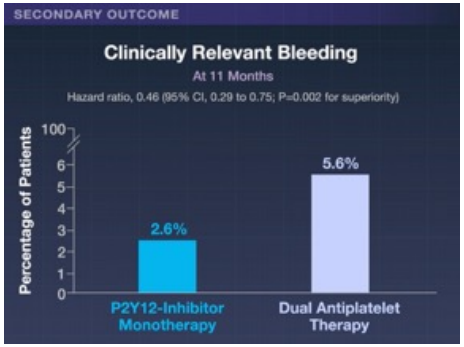

Newer-Generation
Drug-Eluting Stents
• Lower doses of drugs
• Improved biocompatibility
• Reduced the risk of late
stent thrombosis
RISK


TARGET-FIRST Trial
• Multicenter
• Open-label
• Randomized
• Controlled
• Noninferiority

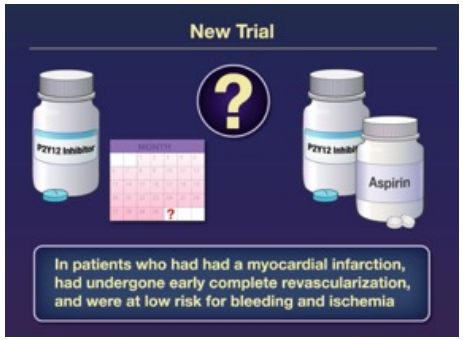

PRIMARY OUTCOME
Composite of Death from Any Cause,
Myocardial Infarction, Stent Thrombosis,
Stroke, or Major Bleeding
At 11 Months
Between-group difference, −0.09 percentage points
(95% CI, −1.39 to 1.20); P=0.02 for noninferiority
(noninferiority margin, 1.25 percentage points)
Percentage of Patients
100
4
3
2
1
0
2.1%
2.2%
P2Y12-Inhibitor
Monotherapy
Dual Antiplatelet
Therapy

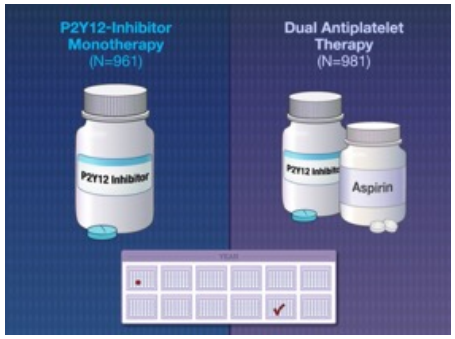

Newer-Generation
Drug-Eluting Stents
P2Y12 Inhibitor
Aspirin
?
• Lower doses of drugs
• Improved biocompatibility
• Reduced the risk of late
stent thrombosis
RISK

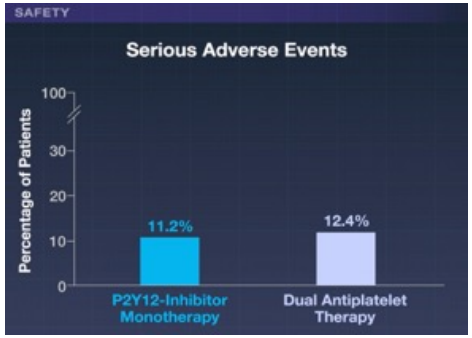

1942 Adults
Complete revascularization
MONTH
+
P2Y12 Inhibitor
Aspirin
Without ischemic or
major bleeding events


SECONDARY OUTCOME
Clinically Relevant Bleeding
At 11 Months
Hazard ratio, 0.46 (95% CI, 0.29 to 0.75; P=0.002 for superiority)
Percentage of Patients
100
6
5
4
3
2
1
0
2.6%
5.6%
P2Y12-Inhibitor
Monotherapy
Dual Antiplatelet
Therapy

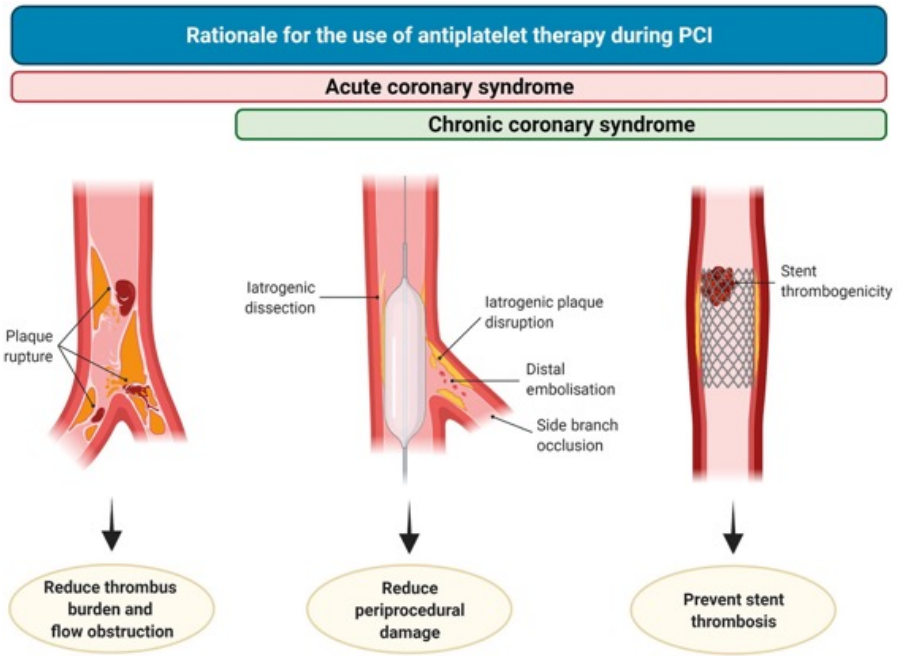

P2Y12-Inhibitor
Monotherapy
Dual Antiplatelet
Therapy
P2Y12 Inhibitor
≈
Aspirin
With regard to a composite of adverse
cardiovascular and cerebrovascular events

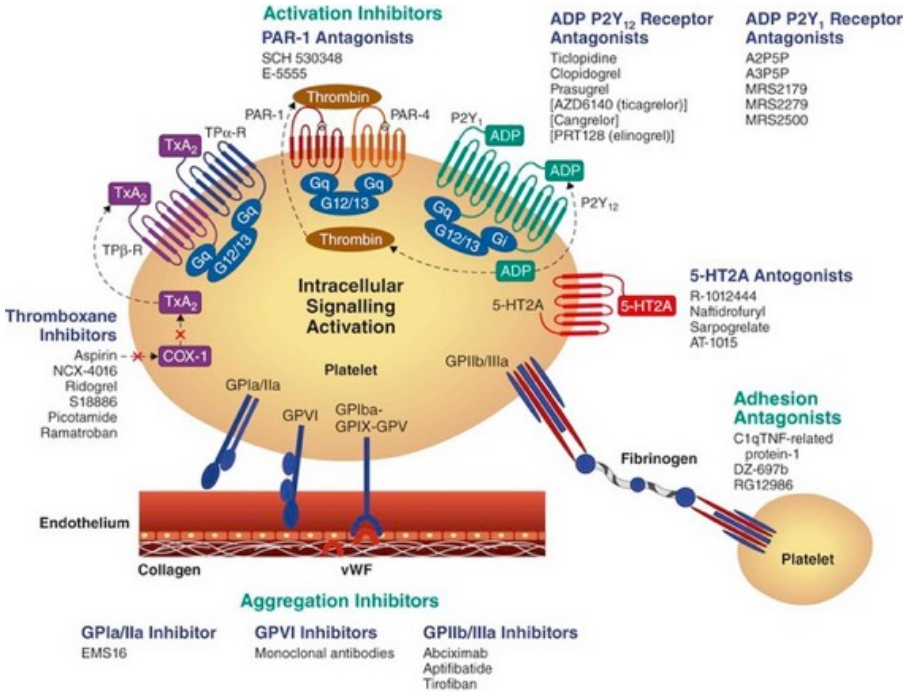

New Trial
P2Y12 Inhibitor
MONTH
?
Aspirin
In patients who had had a myocardial infarction,
had undergone early complete revascularization,
and were at low risk for bleeding and ischemia


P2Y12-Inhibitor
Monotherapy
(N=961)
Dual Antiplatelet
Therapy
(N=981)
P2Y12 Inhibitor
Aspirin
TEST


SAFETY
Serious Adverse Events
Percentage of Patients
100
30
20
10
0
11.2%
12.4%
P2Y12-Inhibitor
Monotherapy
Dual Antiplatelet
Therapy

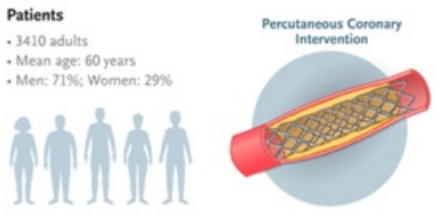
Modern stenting and antiplatelet therapy



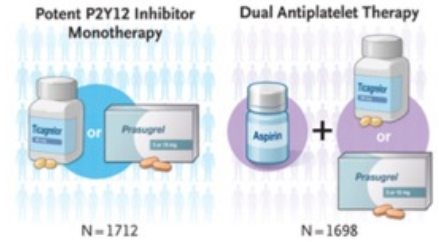


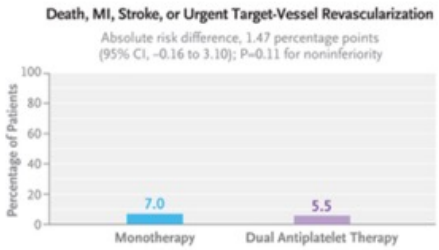
Early Withdrawal of Aspirin after PCI in Acute Coronary Syndromes

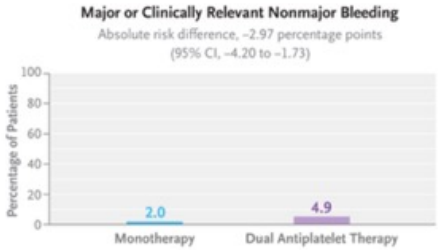
Whether potent P2Y12 inhibitor monotherapy without aspirin initiated shortly after successful percutaneous coronary intervention (PCI) is effective and safe for patients with acute coronary syndromes is unclear. The two ranked primary outcomes, assessed through 12 months, were a composite of death from any cause, myocardial infarction, stroke, or urgent target-vessel revascularization (tested for noninferiority, with a noninferiority margin of 2.5 percentage points) and major or clinically relevant nonmajor bleeding (tested for superiority).



Monotherapy versus dual therapy from day 1







We designed the NEO-MINDSET trial (Percutaneous Coronary Intervention Followed by Monotherapy Instead of Dual Antiplatelet Therapy in the Setting of Acute Coronary Syndromes) to test the hypothesis that monotherapy with a potent P2Y12 inhibitor shortly after successful PCI would be noninferior to dual antiplatelet therapy with aspirin and a potent P2Y12 inhibitor for the prevention of death or ischemic events and superior to dual antiplatelet therapy in reducing bleeding.

Trial Population

Patients were eligible for inclusion in the trial if they were at least 18 years of age, had been admitted with an acute coronary syndrome (ST-segment elevation myocardial infarction [STEMI], non–ST-segment elevation myocardial infarction, or unstable angina), and had undergone successful PCI with at least one contemporary drug-eluting stent within the first 4 days of hospitalization.

Randomization, Treatment, and Follow-up

At hospital admission, patients received antiplatelet agents according to local practices. After successful PCI with contemporary drug-eluting stents, eligible patients were randomly assigned in a 1:1 ratio in an open-label fashion to stop treatment with aspirin and receive a potent P2Y12 inhibitor alone (monotherapy) or to receive treatment with aspirin plus a potent P2Y12 inhibitor (dual antiplatelet therapy) for 12 months. Before randomization, the investigators could choose to use either prasugrel or ticagrelor as the potent P2Y12 inhibitor.

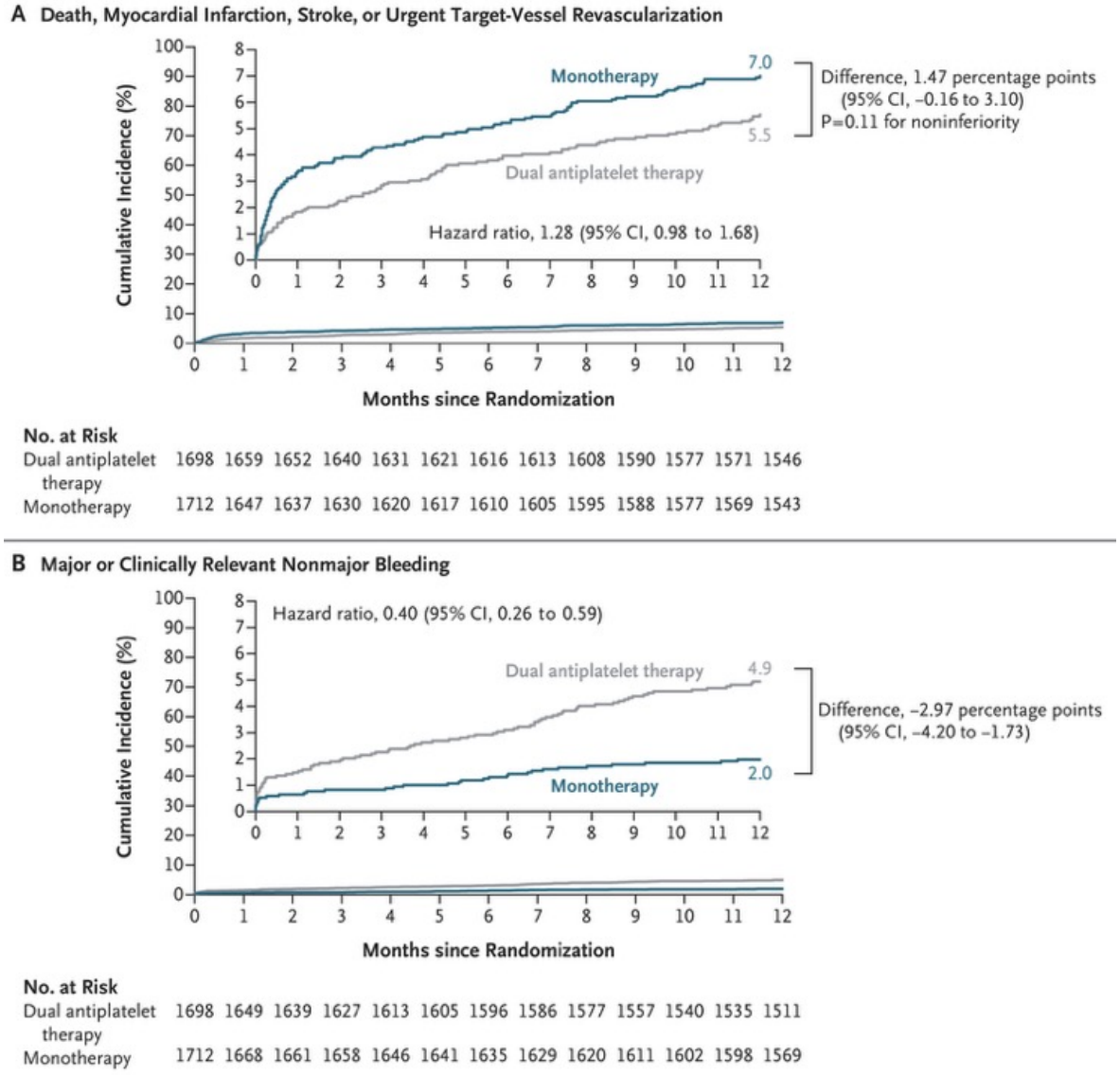
Outcomes

The two ranked primary outcomes were a composite of death from any cause, myocardial infarction, stroke, or urgent target-vessel revascularization and major or clinically relevant nonmajor bleeding.

Characteristic	Monotherapy (N=1712)	Dual Antiplatelet Therapy (N=1698)	Total (N=3410)
Age — yr	59.5±10.9	59.8±10.7	59.6±10.8
Female sex — no. (%)	502 (29.3)	497 (29.3)	999 (29.3)
Race — no. (%)†			
White	1169 (68.3)	1167 (68.7)	2336 (68.5)
Black	313 (18.3)	329 (19.4)	642 (18.8)
Mixed race	230 (13.4)	202 (11.9)	432 (12.7)
Body-mass index‡	27.6±4.5	27.5±4.4	27.5±4.5
Medical history			
Hypertension — no. (%)	1093 (63.8)	1090 (64.2)	2183 (64.0)
Diabetes — no. (%)	459 (26.8)	477 (28.1)	936 (27.4)
Dyslipidemia — no. (%)	464 (27.1)	452 (26.6)	916 (26.9)
Smoking — no./total no. (%)			
Current	597/1654 (36.1)	588/1635 (36.0)	1185/3289 (36.0)

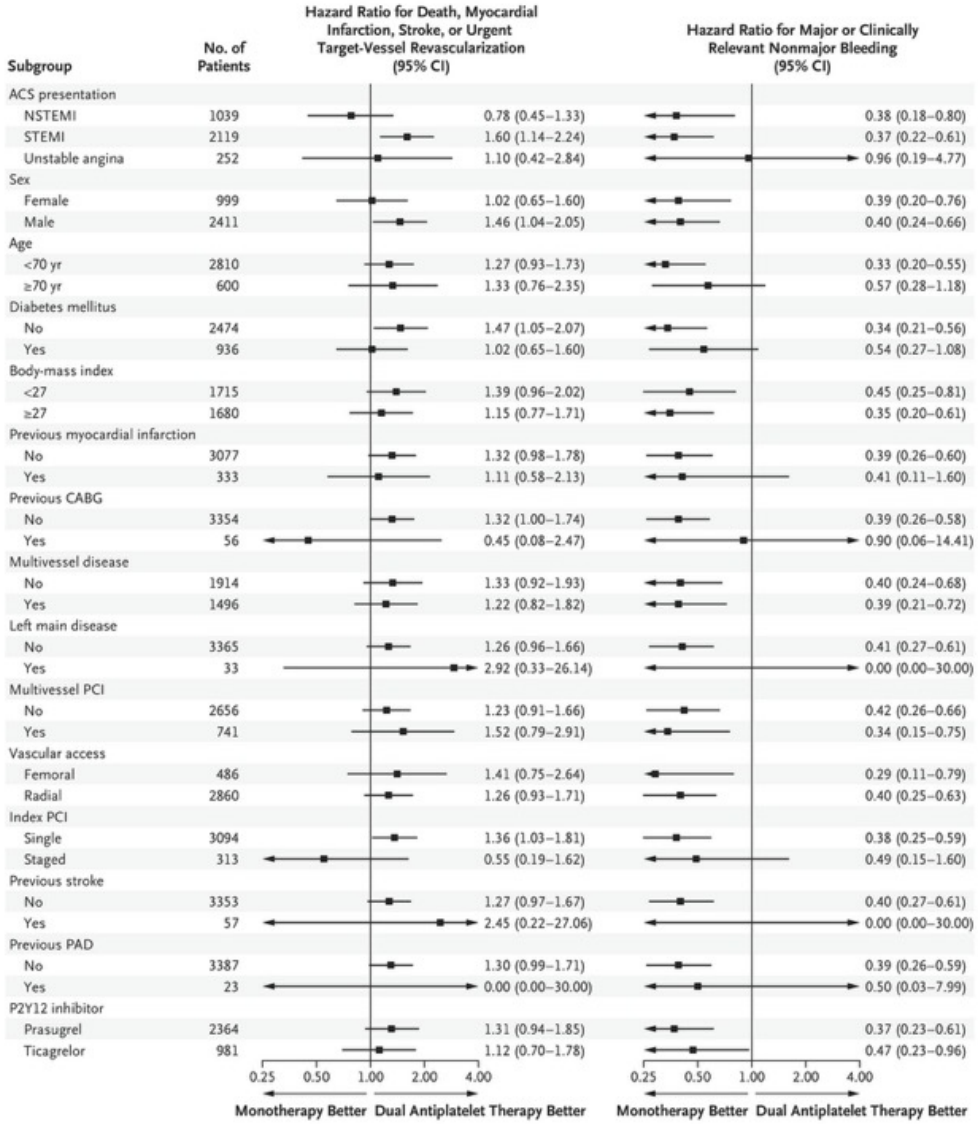
Primary and Secondary Efficacy Outcomes (Intention-to-Treat Population).

Outcome	Monotherapy (N=1712)	Dual Antiplatelet Therapy (N=1698)	Risk Difference (95% CI)	Hazard Ratio (95% CI)
	no. of patients (%)†		*percentage points*	
Primary Outcomes‡				
Death from any cause, myocardial infarction, stroke, or urgent target-vessel revascularization	119 (7.0)	93 (5.5)	1.47 (–0.16 to 3.10)	1.28 (0.98 to 1.68)
Major or clinically relevant nonmajor bleeding§	33 (2.0)	82 (4.9)	–2.97 (–4.20 to –1.73)	0.40 (0.26 to 0.59)
Secondary Outcomes				
Death from any cause	62 (3.6)	50 (3.0)		1.24 (0.85 to 1.79)
Death from cardiovascular causes	42 (2.5)	34 (2.0)		1.23 (0.78 to 1.93)
Death from noncardiovascular causes	20 (1.2)	16 (1.0)		1.25 (0.65 to 2.40)
Sudden death within 30 days	2 (0.1)	3 (0.2)		0.66 (0.11 to 3.97)
Stroke	20 (1.2)	15 (0.9)		1.33 (0.68 to 2.60)
Myocardial infarction	45 (2.7)	31 (1.9)		1.45 (0.92 to 2.30)
Invasive coronary intervention	43 (2.6)	26 (1.6)		1.65 (1.01 to 2.69)
Urgent target-vessel revascularization	22 (1.3)	12 (0.7)		1.83 (0.90 to 3.69)
Definite or probable stent thrombosis	12 (0.7)	4 (0.2)		2.99 (0.97 to 9.28)
BARC bleeding event				
Type 1 to 5	75 (4.5)	150 (9.0)		0.49 (0.37 to 0.64)
Type 1	45 (2.7)	76 (4.6)		0.58 (0.40 to 0.84)
Type 2	21 (1.3)	50 (3.0)		0.41 (0.25 to 0.69)
Type 3	11 (0.7)	33 (2.0)		0.33 (0.17 to 0.65)
Type 5	1 (0.1)	2 (0.1)		0.50 (0.05 to 5.48)
Net adverse clinical events¶	145 (8.5)	166 (9.9)		0.86 (0.69 to 1.08)



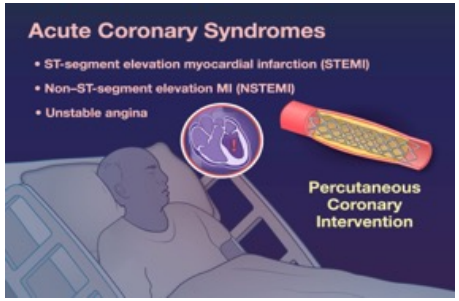
Cumulative Incidence of the Primary Outcomes According to Treatment Group.

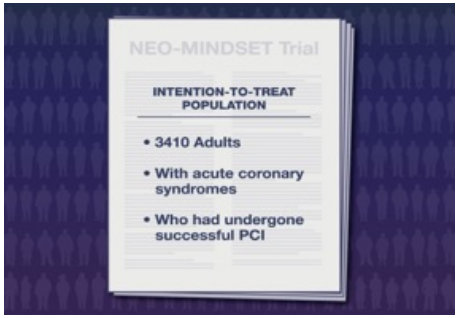
The ranked primary outcomes were a composite of death from any cause, myocardial infarction, stroke, or urgent target-vessel revascularization (Panel A) and major or clinically relevant nonmajor bleeding, defined by a Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 bleeding event (Panel B). Both primary outcomes were assessed in the intention-to-treat population. The hazard ratio is shown for monotherapy as compared with dual antiplatelet therapy. BARC bleeding types range from 0 (no bleeding) to 5 (fatal bleeding). The insets show the same data on an expanded y axis. CI denotes confidence interval.

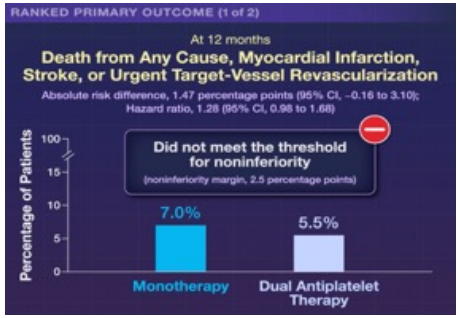


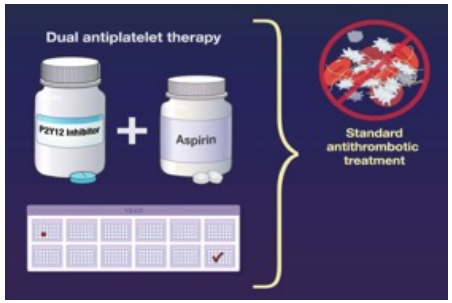
Subgroup Analyses of the Primary Outcomes.

Shown are the hazard ratios for the primary outcomes (the composite of death from any cause, myocardial infarction, stroke, or urgent target-vessel revascularization and major or clinically relevant nonmajor bleeding [BARC type 2, 3, or 5 bleeding events]) in prespecified subgroups of patients. The confidence intervals in the subgroup analyses have not been adjusted for multiplicity and therefore should not be interpreted as representing hypothesis tests of effects within the subgroups. The body-mass index is the weight in kilograms divided by the square of the height in meters. Data are missing for 15 patients for BMI, 12 for left main disease, 13 for multivessel disease, 64 for vascular access, and 3 for index PCI. ACS denotes acute coronary syndromes, NSTEMI non–ST-segment elevation myocardial infarction, PAD peripheral artery disease, and STEMI ST-segment elevation myocardial infarction.

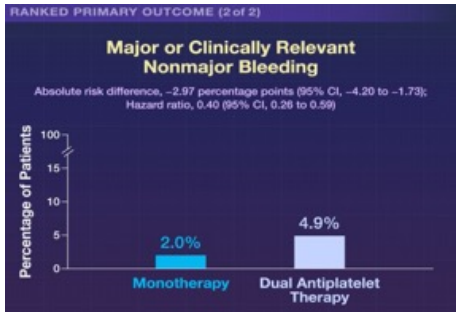

Acute Coronary Syndromes
• ST-segment elevation myocardial infarction (STEMI)
• Non–ST-segment elevation MI (NSTEMI)
• Unstable angina
Percutaneous Coronary Intervention

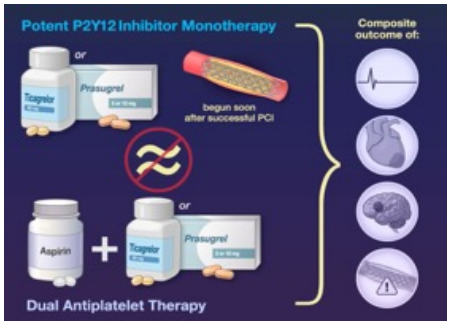

NEO-MINDSET Trial
INTENTION-TO-TREAT POPULATION
• 3410 Adults
• With acute coronary syndromes
• Who had undergone successful PCI


RANKED PRIMARY OUTCOME (1 of 2)
At 12 months
Death from Any Cause, Myocardial Infarction, Stroke, or Urgent Target-Vessel Revascularization
Absolute risk difference, 1.47 percentage points (95% CI, −0.16 to 3.10); Hazard ratio, 1.28 (95% CI, 0.98 to 1.68)
Did not meet the threshold for noninferiority
(noninferiority margin, 2.5 percentage points)
Percentage of Patients
100
15
10
5
0
7.0%
5.5%
Monotherapy
Dual Antiplatelet Therapy

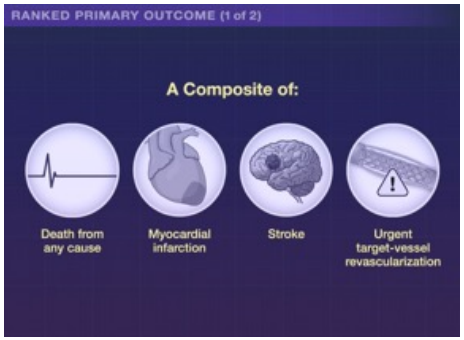

Dual antiplatelet therapy
P2Y12 Inhibitor
Aspirin
Standard antithrombotic treatment

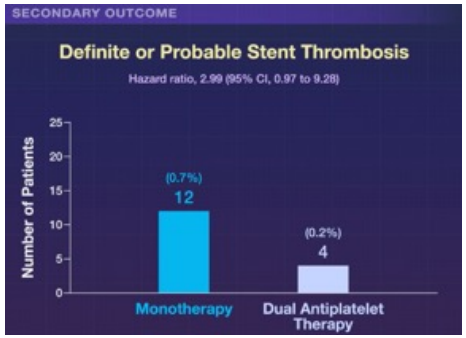

Potent P2Y12 Inhibitor Monotherapy
N=1712
or
Ticagrelor
Prasugrel
Dual Antiplatelet Therapy
N=1698
Aspirin
or
Ticagrelor
Prasugrel


RANKED PRIMARY OUTCOME (2 of 2)
Major or Clinically Relevant Nonmajor Bleeding
Absolute risk difference, −2.97 percentage points (95% CI, −4.20 to −1.73); Hazard ratio, 0.40 (95% CI, 0.26 to 0.59)
Percentage of Patients
100
15
10
5
0
2.0%
4.9%
Monotherapy
Dual Antiplatelet Therapy

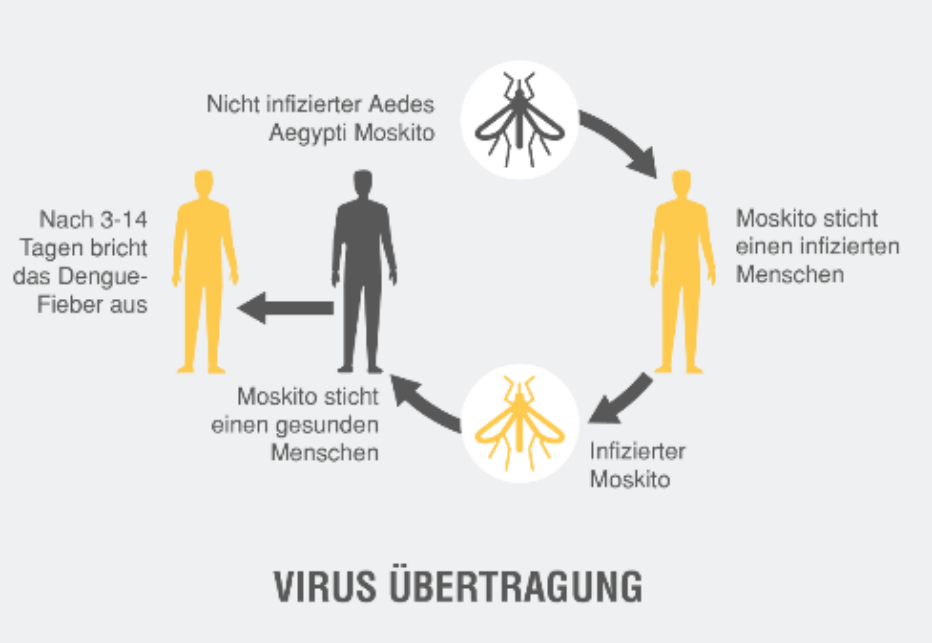

Potent P2Y12 Inhibitor Monotherapy
or
Ticagrelor
Prasugrel
begun soon after successful PCI
Aspirin
or
Ticagrelor
Prasugrel
Dual Antiplatelet Therapy
Composite outcome of:

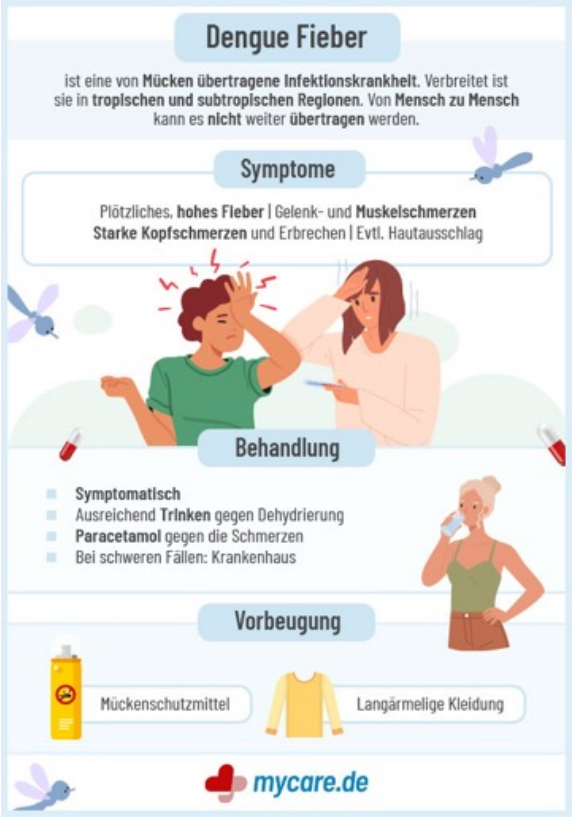

or
Ticagrelor
Prasugrel
Potent P2Y12 inhibitor monotherapy
Immediately after PCI
? Effective and Safe


RANKED PRIMARY OUTCOME (1 of 2)
A Composite of:
Death from any cause
Myocardial infarction
Stroke
Urgent target-vessel revascularization

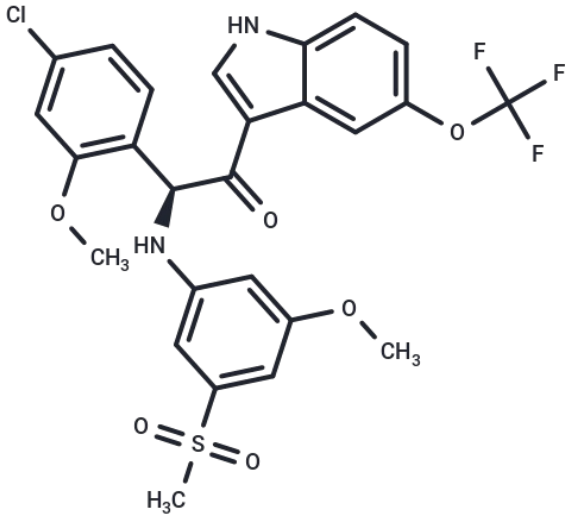

SECONDARY OUTCOME
Definite or Probable Stent Thrombosis
Hazard ratio, 2.99 (95% CI, 0.97 to 9.28)
Number of Patients
25
20
15
10
5
0
(0.7%)
12
(0.2%)
4
Monotherapy
Dual Antiplatelet Therapy

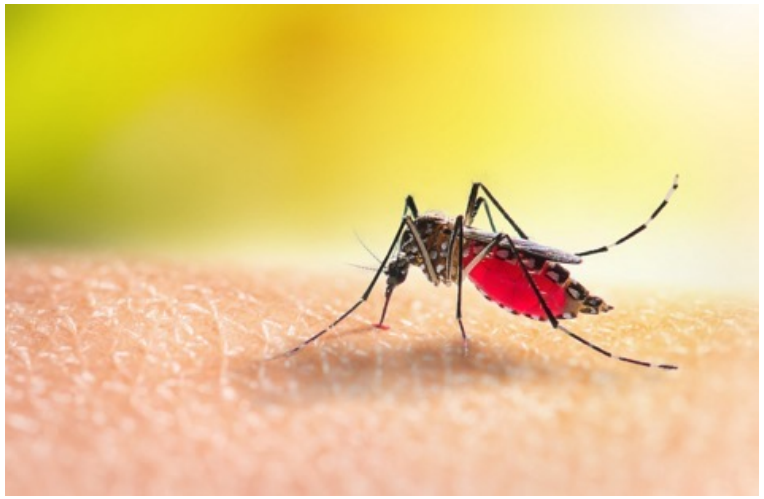
Denguefieber ist eine mückenübertragene Virusinfektion mit Symptomen wie hohem Fieber, starken Kopf- und Gliederschmerzen sowie Hautausschlag. Eine ursächliche Therapie gibt es nicht, die Behandlung konzentriert sich auf symptomatische Linderung, Schonung und viel Flüssigkeit. Schwere Formen können lebensbedrohliche Komplikationen wie Blutungen verursachen. Vorbeugung durch Mückenschutz ist wichtig, zudem gibt es eine Impfung, die jedoch nur unter bestimmten Bedingungen empfohlen wird.





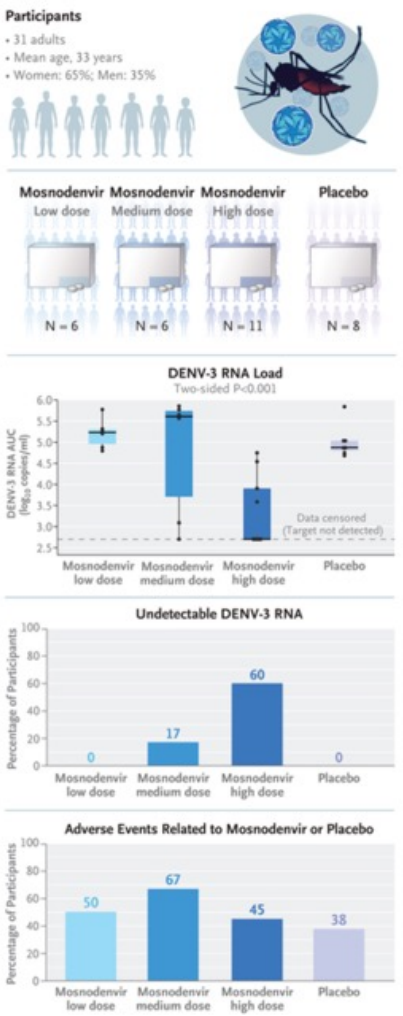
Mosnodenvir works by blocking the interaction between two key dengue viral proteins, nonstructural protein 3 (NS3) and NS4B, which effectively inhibits the virus's ability to replicate.





Daily Mosnodenvir as Dengue Prophylaxis in a Controlled Human Infection Model

Approximately half the worldwide population is at risk for dengue. No antiviral prophylaxis or treatment options are available. In a phase 2a, double-blind, randomized trial, we assigned healthy adults to receive oral mosnodenvir once daily as a low dose (40-mg loading dose followed by 10-mg maintenance dose), medium dose (200 mg followed by 50 mg), or high dose (600 mg followed by 200 mg) or matched placebo. Loading doses were given for 5 days and maintenance doses for 21 days. In a controlled human infection model, participants received subcutaneous inoculation of an underattenuated dengue virus serotype 3 (DENV-3) strain (rDEN3Δ30) on the day of the first maintenance dose (day 1). The primary efficacy end point was the DENV-3 RNA load, assessed as the $\log_{10}$ area under the concentration–time curve from day 1 (immediately before inoculation) through day 29 ($AUC_{D1–29}$). The high-dose and placebo groups were compared in the primary end-point analysis. Safety, pharmacokinetic features, and virologic and serologic features were evaluated through day 85.



Dengue is an acute disease caused by four antigenically different dengue virus serotypes (DENV-1, DENV-2, DENV-3, and DENV-4) that are transmitted to humans by aedes mosquitoes. Dengue is a growing public health threat; approximately half the worldwide population is considered by the World Health Organization to be at risk for the disease. The incidence of dengue continues to increase because of population growth and climate changes that allow expansion of the aedes vector in areas where the disease is endemic, such as the Americas and Southeast Asia; dengue is also spreading to temperate regions in the United States and Europe.

Participants

We enrolled healthy adults 18 to 55 years of age who had been confirmed to be seronegative for DENV and Zika virus before enrollment; had not traveled to any region where dengue is endemic or received any live, attenuated vaccines during the 4 weeks before enrollment; and had no plans to travel to such areas.

Trial Procedures

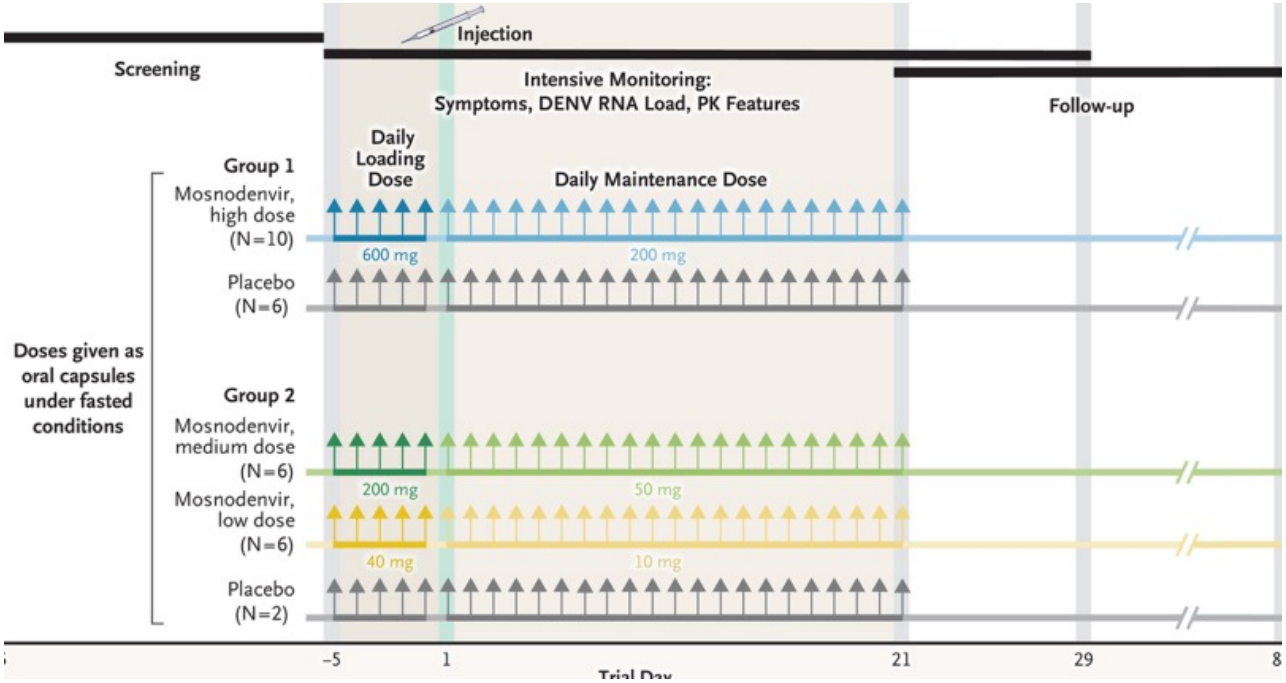
All participants attended screening visits between days −65 and −6 (i.e., 65 and 6 days, respectively, before the first maintenance dose). Cohort 1 was created to assess whether high-dose mosnodenvir was superior to placebo with regard to antiviral activity.

Mosnodenvir and placebo were supplied as 10-mg, 50-mg, and 100-mg capsules and administered orally. The participants could not have any food during the period from 8 hours before dose administration through 1 hour after administration. The loading doses were given on days −5 through −1 and the maintenance doses on days 1 through 21.

All participants were admitted to the inpatient unit from days −6 through −4 for observation after the first two loading doses; the participants were also observed for at least 30 minutes after rDEN3Δ30 challenge and after the receipt of each remaining dose. Safety was assessed throughout the trial by means of clinical laboratory testing, electrocardiography, measurement of vital signs, physical examination, and monitoring of solicited and unsolicited adverse events. Blood samples were obtained at regular intervals for virologic and pharmacokinetic assessments. Participants were followed through day 85 (64 days after the last dose).

End Points

The primary efficacy end point was the DENV-3 RNA load, assessed as the $\log_{10}$ area under the concentration–time curve from day 1 (immediately before inoculation) through day 29 ($AUC_{D1–29}$). Secondary efficacy end points included safety; the occurrence and severity of DENV infection–associated adverse events.



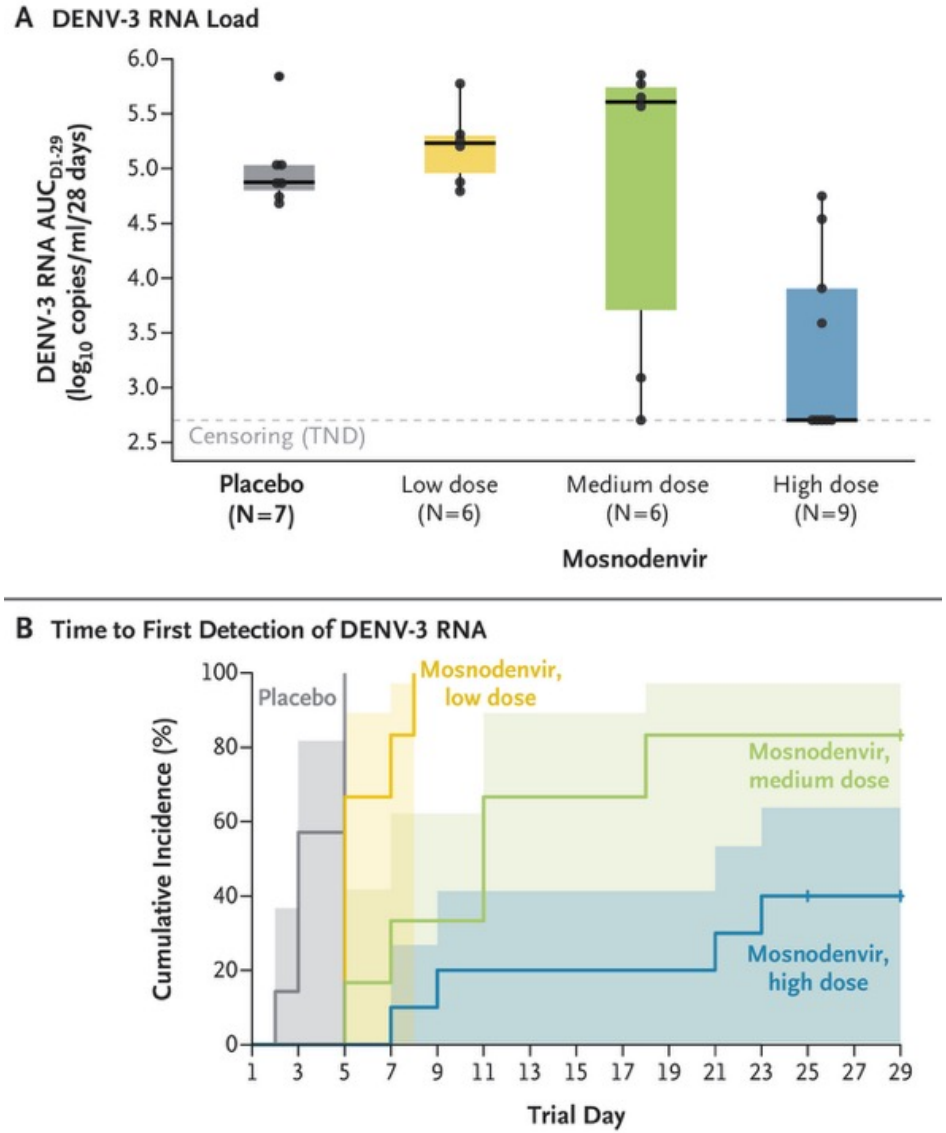
Trial Design and Enrollment.

In a sentinel subgroup, participants were randomly assigned in a 1:1 ratio to receive high-dose mosnodenvir or matched placebo (Group 1a); these participants were inoculated with a dengue virus serotype 3 (DENV-3) strain (rDEN3Δ30) in a controlled human infection model on the day of the first maintenance dose (day 1). If mosnodenvir and viral challenge had an acceptable safety profile, the remaining participants in Group 1 were randomly assigned in a 2:1 ratio to receive high-dose mosnodenvir or matched placebo (Group 1b), and the participants in Group 2 were randomly assigned in a 3:3:1 ratio to receive low-dose mosnodenvir, medium-dose mosnodenvir, or matched placebo. Participants in Groups 1b and 2 received the same inoculum on day 1 as those in Group 1a. One participant in the high-dose group withdrew consent on day –2 (i.e., before inoculation) because of moderate photosensitivity that was considered by the investigator to be related to mosnodenvir and was replaced according to protocol. PK denotes pharmacokinetic.

Variable	Mosnodenvir				Placebo (N=8)†	Overall (N=31)
	Low Dose (N=6)	Medium Dose (N=6)	High Dose (N=11)‡	Overall (N=23)		
Assigned to trial group or included as a replacement and received ≥1 oral dose — no. (%)	6 (100)	6 (100)	11 (100)	23 (100)	8 (100)	31 (100)
Inoculated with rDEN3Δ30 — no. (%)	6 (100)	6 (100)	10 (91)	22 (96)	7 (88)	29 (94)
Completed trial regimen — no. (%)§	6 (100)	6 (100)	10 (91)	22 (96)	7 (88)	29 (94)
Completed trial — no. (%)	6 (100)	6 (100)	10 (91)	22 (96)	7 (88)	29 (94)
Analysis population — no. (%)¶						
Safety	6 (100)	6 (100)	11 (100)	23 (100)	8 (100)	31 (100)
Efficacy	6 (100)	6 (100)	10 (91)	22 (96)	7 (88)	29 (94)
Pharmacokinetic	6 (100)	6 (100)	11 (100)	23 (100)	0‖	23 (74)
Age — yr	29.5±4.6	36.0±10.7	34.5±9.1	33.6±8.6	30.0±7.3	32.6±8.4
Female sex — no. (%)	4 (67)	5 (83)	7 (64)	16 (70)	4 (50)	20 (65)
Race or ethnic group — no./total no. (%)**						
American Indian or Alaska Native	0	0	0	0	1/8 (12)	1/30 (3)
Asian	0	1/6 (17)	1/11 (9)	2/22 (9)	0	2/30 (7)
Black or African American	3/5 (60)	3/6 (50)	5/11 (45)	11/22 (50)	3/8 (38)	14/30 (47)
White	2/5 (40)	2/6 (33)	3/11 (27)	7/22 (32)	3/8 (38)	10/30 (33)
Multiple	0	0	2/11 (18)	2/22 (9)	1/8 (12)	3/30 (10)
Hispanic or Latino ethnic group — no./total no. (%)**						
Yes	0	0	0	0	1/8 (12)	1/30 (3)
No	5/5 (100)	6/6 (100)	11/11 (100)	22/22 (100)	7/8 (88)	29/30 (97)
Trial site — no. (%)						
Johns Hopkins University	3 (50)	3 (50)	7 (64)	13 (57)	5 (62)	18 (58)
University of Vermont	3 (50)	3 (50)	4 (36)	10 (43)	3 (38)	13 (42)

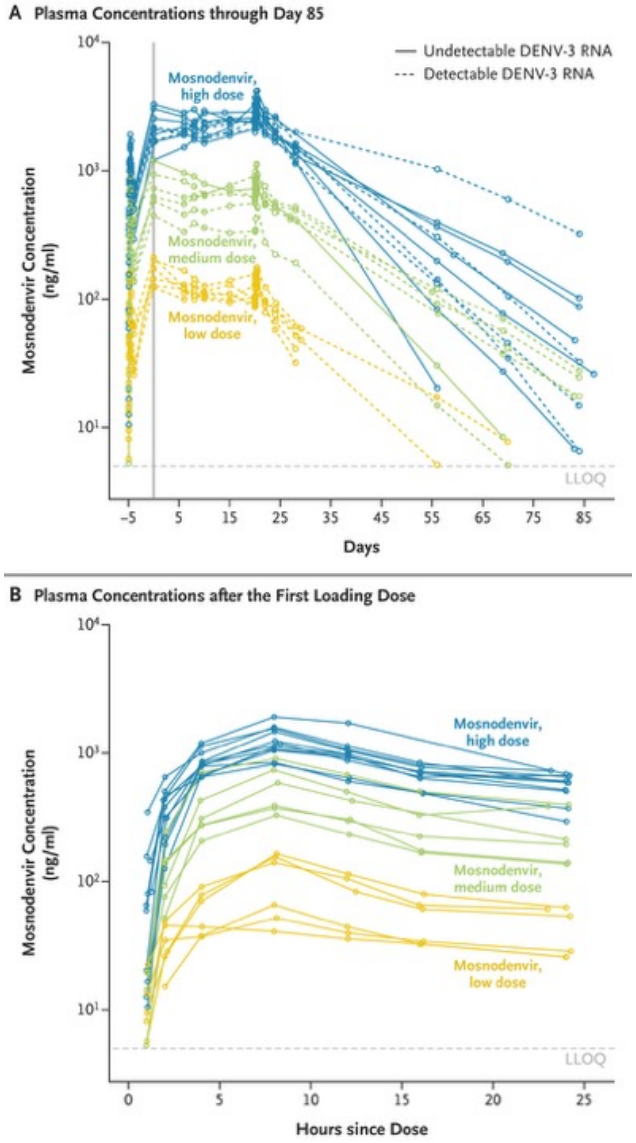
Adverse Events in the Safety Analysis Population.

	Mosnodenvir			Placebo (N=8)	Overall (N=23)
	Low Dose (N=6)	Medium Dose (N=6)	High Dose (N=11)†		
Events occurring between days −5 and 85‡					
Participants with ≥1 event — no. (%)					
Any event	6 (100)	6 (100)	11 (100)	8 (100)	23 (100)
Event related to oral dose	3 (50)	4 (67)	5 (45)	3 (38)	12 (52)
Event related to rDEN3Δ30 inoculation	5 (83)	5 (83)	3 (27)	5 (62)	13 (57)
Serious event	0	0	0	1 (12)	0
Event leading to discontinuation of oral dose	0	0	0	1 (12)	0
Event according to worst severity					
Grade 1, mild	2 (33)	2 (33)	5 (45)	3 (38)	9 (39)
Grade 2, moderate	4 (67)	3 (50)	5 (45)	4 (50)	12 (52)
Grade 3, severe	0	1 (17)	1 (9)§	1 (12)	2 (9)
Grade 4, life-threatening	0	0	0	0	0
Most common events, according to MedDRA system organ class — no. (%)¶					
Investigations					
Any MedDRA preferred term	5 (83)	4 (67)	7 (64)	3 (38)	16 (70)
Decreased hemoglobin level	1 (17)	0	3 (27)	0	4 (17)
General disorders and administration-site conditions					
Any MedDRA preferred term	4 (67)	3 (50)	5 (45)	1 (12)	12 (52)
Bruise at vessel-puncture site	4 (67)	3 (50)	4 (36)	0	11 (48)
Skin and subcutaneous tissue disorders					
Any MedDRA preferred term	2 (33)	4 (67)	6 (55)	2 (25)	12 (52)
Ecchymosis	1 (17)	1 (17)	2 (18)	0	4 (17)
Nervous system disorders					
Any MedDRA preferred term	3 (50)	2 (33)	4 (36)	3 (38)	9 (39)
Headache‖	2 (33)	1 (17)	4 (36)	3 (38)	7 (30)
Blood and lymphatic system disorders					
Any MedDRA preferred term	2 (33)	3 (50)	0	2 (25)	5 (22)
Lymphadenopathy	2 (33)	3 (50)	0	1 (12)	5 (22)
Events associated with rDEN3Δ30 infection**					
Participants with ≥1 event, according to worst severity — no. (%)					
Grade 1, mild	2 (33)	3 (50)	6 (55)	3 (38)	11 (48)
Grade 2, moderate	4 (67)	1 (17)	1 (9)	4 (50)	6 (26)
Grade 3, severe	0	0	0	0	0
Grade 4, life-threatening	0	0	0	0	0
Participants with ≥1 event, according to MedDRA preferred term — no. (%)					
Headache	6 (100)	3 (50)	4 (36)	6 (75)	13 (57)
Rash, maculopapular	5 (83)	4 (67)	3 (27)	7 (88)	12 (52)
Fatigue	4 (67)	1 (17)	3 (27)	5 (62)	8 (35)
Myalgia	5 (83)	3 (50)	0	3 (38)	8 (35)
Eye pain	3 (50)	2 (33)	0	3 (38)	5 (22)
Nausea	3 (50)	1 (17)	1 (9)	2 (25)	5 (22)
Abdominal pain	3 (50)	1 (17)	0	1 (12)	4 (17)
Arthralgia	2 (33)	1 (17)	1 (9)	2 (25)	4 (17)
Decreased appetite	1 (17)	2 (33)	0	3 (38)	3 (13)
Diarrhea	2 (33)	0	0	1 (12)	2 (9)
Pyrexia	0	1 (17)	0	1 (12)	1 (4)
Vomiting	1 (17)	0	0	2 (25)	1 (4)



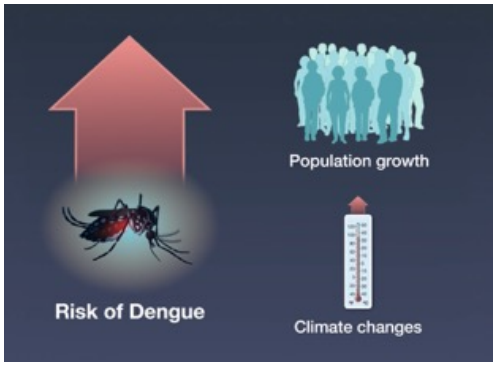
Virologic End Points in the Efficacy Analysis Population.

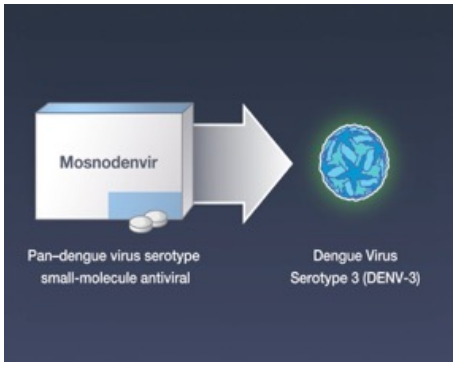
Shown is the DENV-3 RNA load, assessed as the log_{10} area under the concentration–time curve from day 1 (immediately before inoculation) through day 29 (AUC_{D1-29}) (Panel A). Black circles indicate values for individual participants; circles on the dashed line indicate undetectable DENV-3 RNA loads from days 1 through 29. In the box plots, the bottom indicates the 25th percentile, the black line the 50th percentile, and the top the 75th percentile; whiskers extend to the lowest and highest values within 1.5 times the interquartile range. One participant in the high-dose mosnodenvir group had a missing sample on day 29 and was excluded from the primary efficacy analysis because the missing value could not be imputed according to the rules of the prespecified statistical analysis plan. TND denotes target not detected. Also shown is Kaplan–Meier analysis of the time to first detection of DENV-3 RNA, according to trial group (Panel B). The time to first detection of DENV-3 RNA was defined as the interval from the day of rDEN3Δ30 inoculation to the day of the first occurrence of DENV-3 RNA detection, plus 1 day. Data for one participant in the high-dose mosnodenvir group were censored on day 25, the day of the last available DENV-3 RNA assessment with a valid result. The efficacy analysis population included all the participants in Groups 1 and 2 who received at least one dose of mosnodenvir or placebo and were inoculated with rDEN3Δ30. Shading indicates 95% confidence intervals.

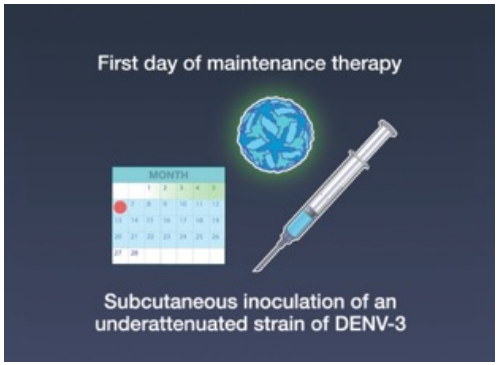


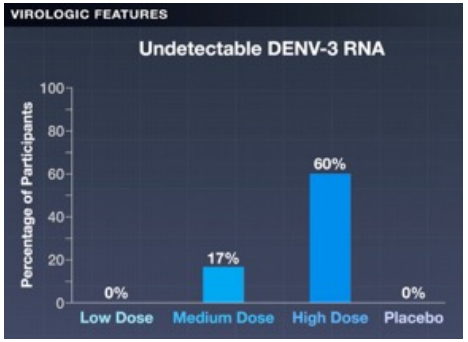
Plasma Concentrations of Mosnodenvir over Time.

Shown are plasma concentrations from day –5 (the day of the first loading dose) through day 85 (90 days after the first loading dose and 64 days after the last maintenance dose) and results of DENV-3 RNA testing in the participants according to mosnodenvir group (Panel A). Days are numbered relative to the day on which the first maintenance dose was given (day 1). The vertical line indicates the mosnodenvir concentration on day 1 immediately before inoculation with DEN3Δ30. Also shown are plasma concentrations in the trial participants during the 24-hour period after receipt of the first loading dose (Panel B). Data are for the pharmacokinetic analysis population, which included all participants in Groups 1 and 2 with at least one available pharmacokinetic result after dose administration. Open circles indicate measurement time points. Concentrations below the lower limit of quantification (LLOQ; 5 ng/ml) are not shown.

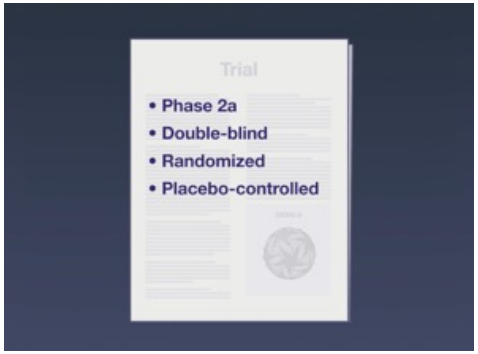

Population growth
Risk of Dengue
Climate changes

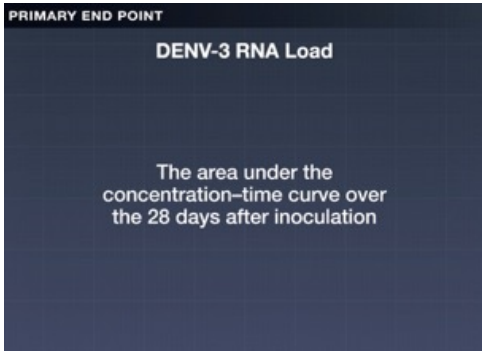

Mosnodenvir
Pan–dengue virus serotype
small-molecule antiviral
Dengue Virus
Serotype 3 (DENV-3)

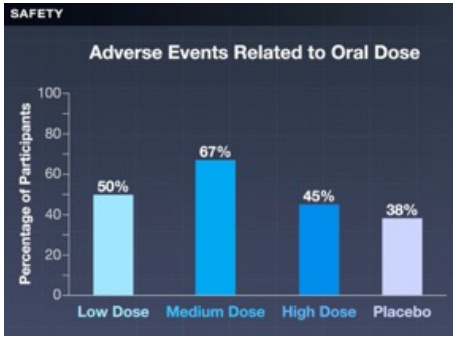

First day of maintenance therapy
Subcutaneous inoculation of an
underattenuated strain of DENV-3


VIROLOGIC FEATURES
Undetectable DENV-3 RNA
Percentage of Participants
100
80
60
40
20
0
0%
17%
60%
0%
Low Dose
Medium Dose
High Dose
Placebo

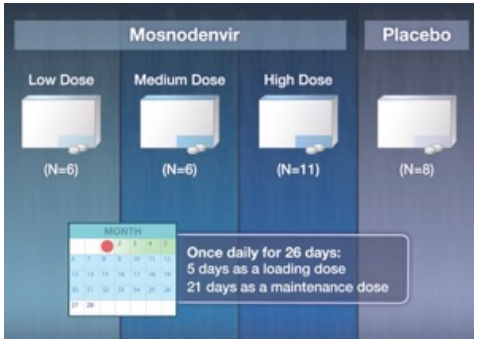

Dengue Vaccines
Take weeks to provide protection
Efficacy varies by baseline immunity to dengue virus

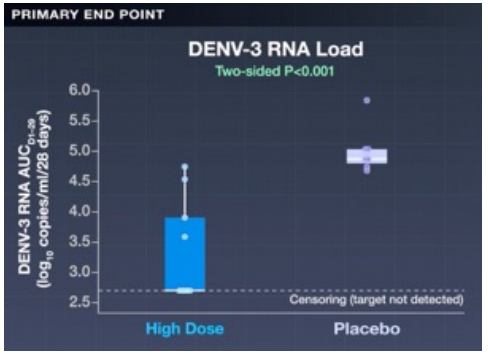

Trial
• Phase 2a
• Double-blind
• Randomized
• Placebo-controlled


PRIMARY END POINT
DENV-3 RNA Load
The area under the
concentration–time curve over
the 28 days after inoculation


SAFETY
Adverse Events Related to Oral Dose
Percentage of Participants
100
80
60
40
20
0
50%
67%
45%
38%
Low Dose
Medium Dose
High Dose
Placebo

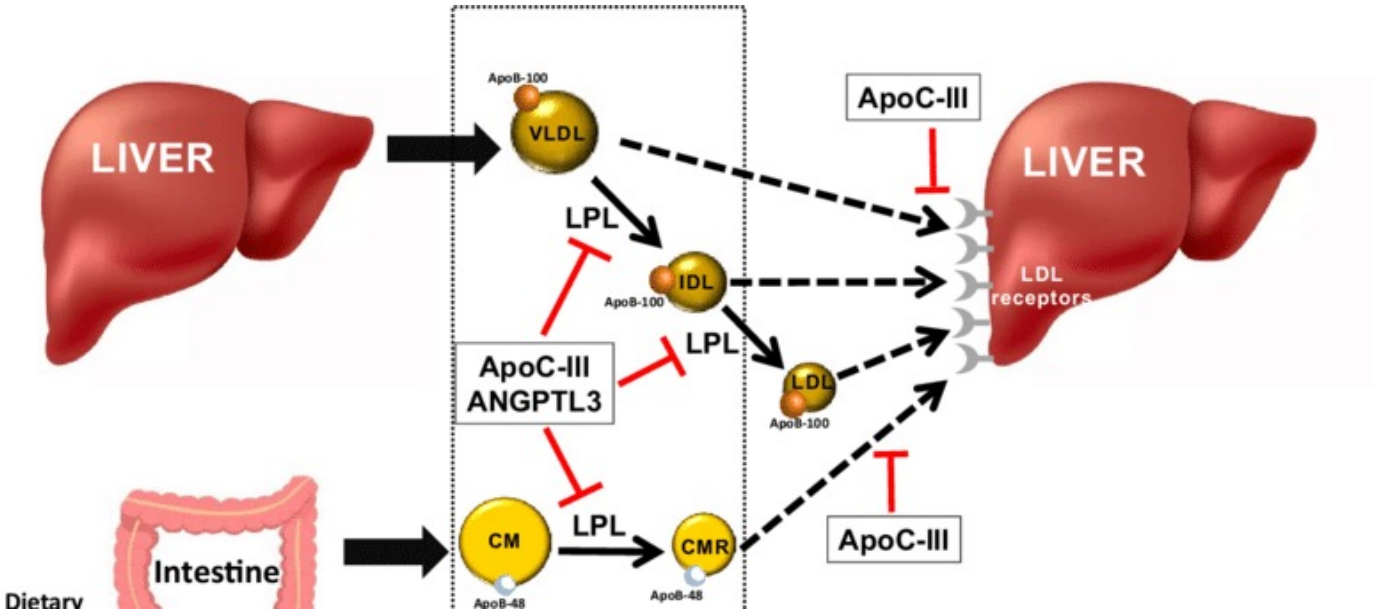

Oral Antiviral Therapy
Additional tool to prevent disease

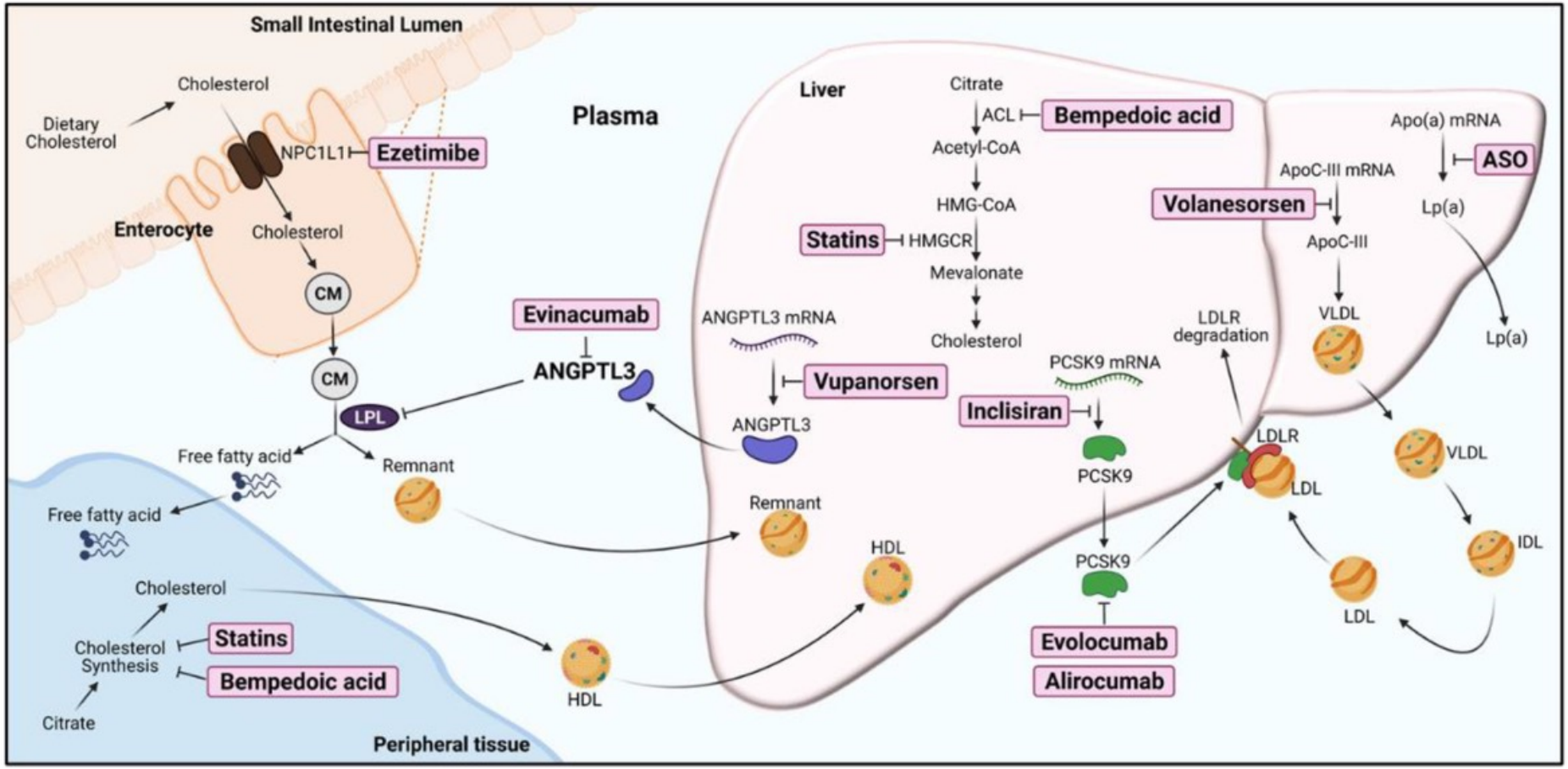

Mosnodenvir
Placebo
Low Dose
Medium Dose
High Dose
(N=6)
(N=6)
(N=11)
(N=8)
Once daily for 26 days:
5 days as a loading dose
21 days as a maintenance dose


PRIMARY END POINT
DENV-3 RNA Load
Two-sided P<0.001
DENV-3 RNA AUC0-28
(log10 copies/ml/28 days)
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
Censoring (target not detected)
High Dose
Placebo


High-Dose Mosnodenvir
Mosnodenvir
Led to a significantly lower
DENV-3 RNA load than placebo

Angiopoietin-like 3 (ANGPTL3) ist ein Protein, das hauptsächlich in der Leber produziert wird und eine wichtige Rolle im Fettstoffwechsel spielt. Es hemmt die Enzyme Lipoproteinlipase und endothelialische Lipase, was zu erhöhten Triglycerid- und LDL-Cholesterinspiegeln führt. Störungen der Funktion von ANGPTL3 können zu verschiedenen Stoffwechselerkrankungen führen, weshalb es ein vielversprechendes Ziel für Therapien zur Senkung von Blutfettwerten ist, wie z. B. mit Antikörpern oder Antisense-Oligonukleotiden.




Small Intestinal Lumen
Cholesterol
Dietary Cholesterol
NPC1L1
Ezetimibe
Enterocyte
Cholesterol
CM
CM
LPL
Free fatty acid
Remnant
Free fatty acid
Cholesterol
Cholesterol Synthesis
Statins
Bempedoic acid
Citrate
Peripheral tissue
Plasma
Evinacumab
ANGPTL3
ANGPTL3 mRNA
Vupanorsen
ANGPTL3
Remnant
HDL
HDL
Liver
Citrate
ACL
Bempedoic acid
Acetyl-CoA
HMG-CoA
Statins
HMGCR
Mevalonate
Cholesterol
PCSK9 mRNA
Inclisiran
PCSK9
PCSK9
Evolocumab
Alirocumab
LDLR degradation
LDLR
LDL
Apo(a) mRNA
ASO
ApoC-III mRNA
Volanesorsen
Lp(a)
ApoC-III
VLDL
Lp(a)
VLDL
IDL
LDL

Phase 1 Trial of CRISPR-Cas9 Gene Editing Targeting ANGPTL3

Angiopoietin-like protein 3 (ANGPTL3) inhibits lipoprotein and endothelial lipases. *ANGPTL3* loss-of-function genetic variants are associated with decreased levels of low-density lipoprotein cholesterol and triglycerides and a decreased lifetime risk of atherosclerotic cardiovascular disease.

We conducted an ascending-dose phase 1 trial to assess the safety and efficacy of CTX310, a lipid-nanoparticle–encapsulated clustered regularly interspaced short palindromic repeats–Cas9 endonuclease (CRISPR-Cas9) messenger RNA (mRNA) and guide RNA targeting hepatic *ANGPTL3* to induce a loss-of-function mutation. Adults who had uncontrolled hypercholesterolemia, hypertriglyceridemia, or mixed dyslipidemia and were receiving maximally tolerated lipid-lowering therapy received a single intravenous dose of CTX310 (0.1, 0.3, 0.6, 0.7, or 0.8 mg per kilogram of body weight). The primary end point was adverse events, including dose-limiting toxic effects.

Conclusions

Editing of *ANGPTL3* was associated with few adverse events and resulted in reductions from baseline in ANGPTL3 levels.

Editing of *ANGPTL3* with clustered regularly interspaced short palindromic repeats–Cas9 endonuclease (CRISPR-Cas9) has the potential to achieve durable genetic modification after a single treatment and to result in permanent reductions in circulating levels of atherogenic lipoproteins. CTX310 is an investigational lipid-nanoparticle–encapsulated formulation of CRISPR-Cas9 components for in vivo gene editing of the target gene, *ANGPTL3*, to induce a loss-of-function mutation in hepatocytes. In this trial, we assessed the safety, side-effect profile, and efficacy of single ascending doses of CTX310.

Drug Product

CTX310 consists of two components: messenger RNA (mRNA) encoding *Streptococcus pyogenes* Cas9 and a single guide RNA (sgRNA) targeting the gene of interest, encapsulated together in a lipid nanoparticle. The polyadenylated *S. pyogenes* Cas9 mRNA contains methylated pseudouridine to reduce inflammatory response. The sgRNA is a 100-mer single-stranded oligonucleotide. The lipid nanoparticle is composed of four components: an ionizable lipid, a polyethylene glycol lipid, 1,2-distearoyl-sn-glycero-3-phosphocholine, and cholesterol. Lipid nanoparticles undergo receptor-mediated endocytosis in hepatocytes by means of apolipoprotein E–mediated LDL receptor uptake, scavenger receptor–mediated uptake, and potentially other receptors. Endosomal escape delivers the drug product into the cytoplasm with importin-mediated delivery to the nucleus.

Trial Population and Procedures

In this phase 1A, multicenter, open-label trial of a single ascending dose, participants were enrolled at six sites in Australia, New Zealand, and the United Kingdom. Adults who were 18 to 75 years of age were eligible if they had a diagnosis of uncontrolled hypercholesterolemia (familial or nonfamilial), moderate-to-severe hypertriglyceridemia, or mixed dyslipidemia. Inclusion criteria required that the participants have disease that was refractory to maximally tolerated doses of lipid-lowering therapies.

Participants were initially enrolled into one of four ascending CTX310-dose cohorts (0.1 mg per kilogram, 0.3 mg per kilogram, 0.6 mg per kilogram, or 0.8 mg per kilogram), with doses calculated by the total amount of RNA administered and based on estimated lean body weight. CTX310 was administered as a single intravenous infusion. A cohort that received 0.7 mg per kilogram was added, and the cohort that received 0.8 mg per kilogram was expanded after the first three participants in that cohort had received the CTX310 infusion, with the goal being to better define the dose–response relationship.

End Points

The primary objective of the trial was the evaluation of the safety and side-effect profile of single ascending doses of CTX310. The primary end point was the incidence of adverse events as assessed by investigators, including dose-limiting toxic effects, which were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, of the National Cancer Institute.

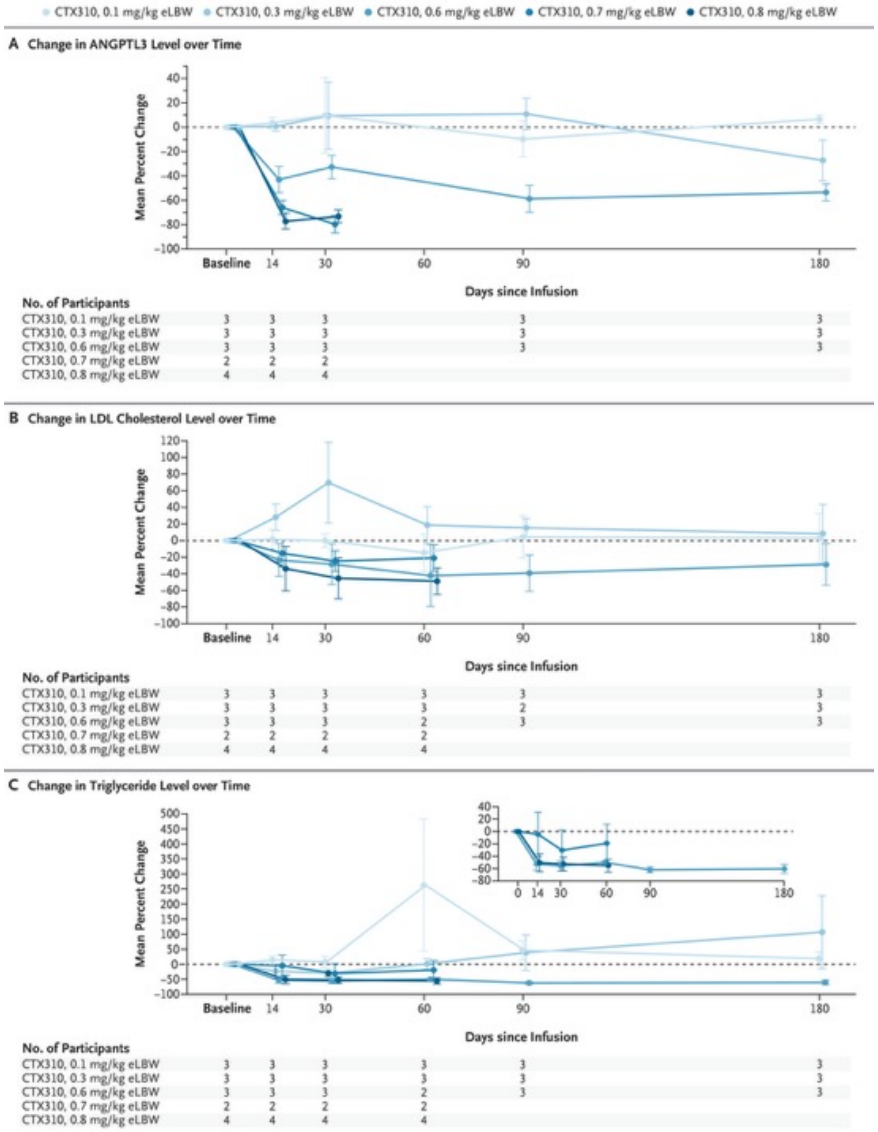
Characteristic	All Participants (N=15)
Median age (range) — yr	53 (31–68)
Male sex — no. (%)	13 (87)
Body-mass index†	31.1±4.9
White race — no. (%)‡	14 (93)
Clinical ASCVD — no. (%)	6 (40)
Familial hypercholesterolemia — no. (%)§	6 (40)
Severe hypertriglyceridemia — no. (%)	2 (13)
Mixed dyslipidemia — no. (%)¶	6 (40)
Nonfamilial hypercholesterolemia — no. (%)§	1 (7)
ANGPTL3 — ng/ml	161.8±58.0
Cholesterol level — mg/dl	
Total cholesterol	246.3±74.7
HDL cholesterol	43.0±13.7
Directly measured LDL cholesterol	154.6±79.2
Non-HDL cholesterol	203.2±73.1
Triglyceride level (IQR) — mg/dl	192.2 (108.9–252.4)
Lipoprotein(a) level (IQR) — nmol/liter	36.3 (20.0–157.6)
Apolipoprotein B — mg/dl	132.1±43.1
Type 2 diabetes mellitus — no. (%)	5 (33)
Background lipid-lowering therapy — no. (%)	
Statin	9 (60)
Ezetimibe	8 (53)
PCSK9 monoclonal antibody	6 (40)
Fibrate	4 (27)
Icosapent ethyl	1 (7)
Apheresis	1 (7)
Evinacumab	1 (7)
Statin intolerance — no. (%)‖	4 (27)

Adverse Events.

Adverse Event	All Participants (N=15)
	no. (%)
Death*	1 (7)
Any serious adverse event†	2 (13)
Serious adverse events related to CTX310	0
Any investigator-reported adverse event‡	14 (93)
Grade 1§	4 (27)
Grade 2¶	9 (60)
Grade 3	0
Grade 4	0
Grade 5*	1 (7)
Adverse event of special interest related to CTX310‡‖	4 (27)
Allergic or localized reaction	1 (7)
Infusion-related reaction**	3 (20)
Elevation in level of AST or ALT††	1 (7)

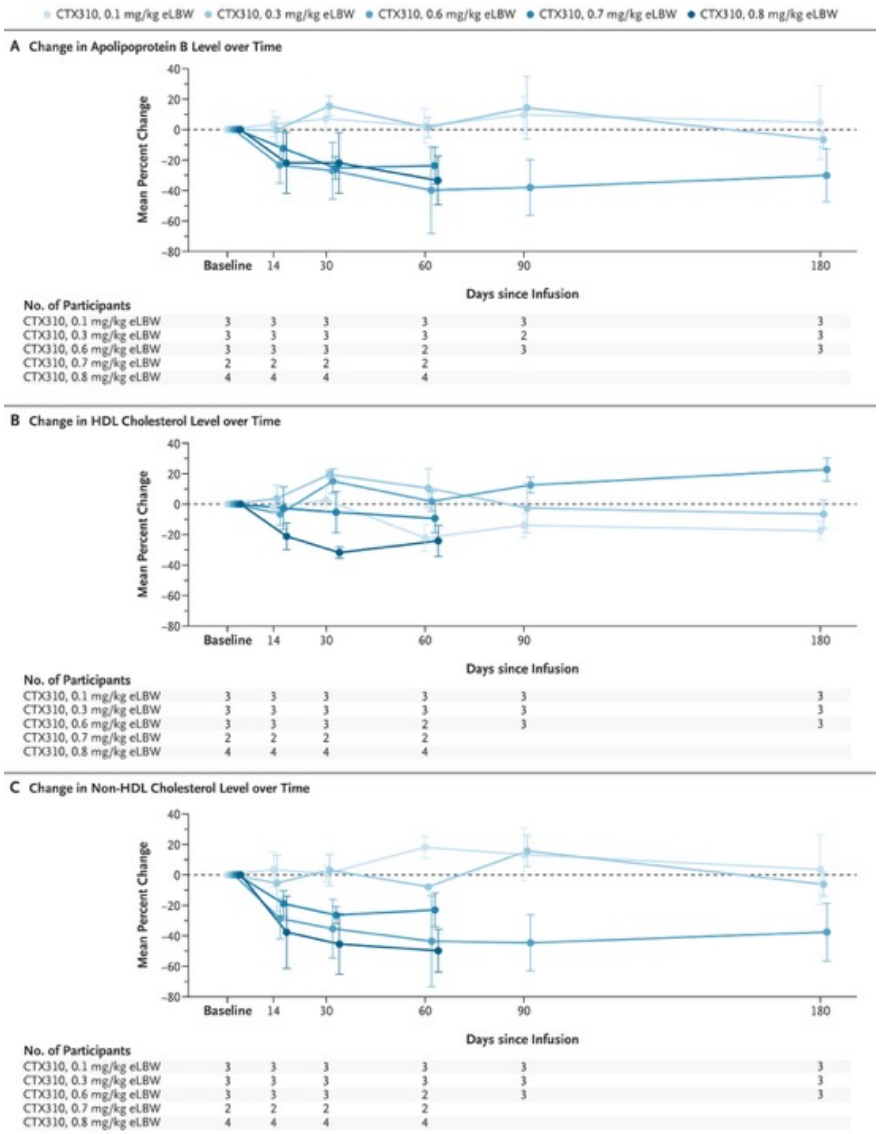
ANGPTL3 and Lipid Biomarker Levels, According to CTX310 Dose.

Variable	0.1 mg/kg (N=3)	0.3 mg/kg (N=3)	0.6 mg/kg (N=3)	0.7 mg/kg (N=2)	0.8 mg/kg (N=4)
Total administered dose (range) — mg	7.1 (5.2 to 9.5)	20.0 (18.2 to 21.8)	41.8 (35.6 to 49.1)	48.3 (45.7 to 50.9)	46.9 (35.6 to 56.4)
ANGPTL3					
Mean baseline level (range) — ng/ml	197.1 (88.3 to 348.8)	162.9 (132.1 to 202.4)	157.8 (134.1 to 190.4)	135.3 (132.7 to 137.9)	150.6 (139.0 to 164.3)
Mean level at 30-day follow-up (range) — ng/ml	262.9 (69.1 to 597.0)	168.6 (137.4 to 216.6)	107.7 (72.3 to 153.4)	27.3 (18.2 to 36.4)	39.7 (18.2 to 50.8)
Mean absolute change (range) — ng/ml	65.8 (−31.6 to 248.2)	5.7 (−50.7 to 84.5)	−50.1 (−76.6 to −36.7)	−108.0 (−119.8 to −96.2)	−110.9 (−146.1 to −96.4)
Mean percent change (range)	9.6 (−21.8 to 71.2)	9.4 (−25.0 to 63.9)	−32.7 (−51.4 to −19.4)	−79.7 (−86.8 to −72.5)	−73.2 (−89.0 to −66.9)
LDL cholesterol					
Mean baseline level (range) — mg/dl	166.5 (83.1 to 309.4)	149.9 (25.9 to 257.5)	180.2 (121.0 to 256.4)	127.6 (94.0 to 161.3)	143.5 (97.1 to 239.4)
Mean level at follow-up (range) — mg/dl†	164.6 (69.2 to 298.5)	239.4 (210.4 to 268.4)	95.0 (48.0 to 150.0)	106.1 (59.2 to 153.1)	62.4 (32.1 to 104.0)
Mean absolute change (range) — mg/dl	−1.9 (−37.9 to 42.9)	27.5 (10.8 to 44.1)	−85.2 (−208.4 to −13.1)	−21.5 (−34.8 to −8.1)	−81.1 (−207.3 to −18.9)
Mean percent change (range)	4.2 (−35.4 to 51.6)	15.4 (4.2 to 26.5)	−39.2 (−81.3 to −8.1)	−21.0 (−37.0 to −5.0)	−48.9 (−86.6 to −19.5)
Triglycerides					
Mean baseline level (range) — mg/dl	141.4 (83.3 to 184.2)	464.1 (135.5 to 1007.9)	248.0 (192.2 to 299.4)	148.8 (74.4 to 223.2)	371.6 (105.4 to 1073.5)
Mean level at follow-up (range) — mg/dl†	226.1 (76.2 to 374.7)	968.7 (101.0 to 2595.1)	95.4 (60.2 to 116.9)	97.0 (83.3 to 110.7)	101.4 (47.8 to 174.5)
Mean absolute change (range) — mg/dl	84.7 (−7.1 to 190.4)	504.6 (−39.0 to 1587.2)	−152.6 (−190.4 to −132.0)	−51.8 (−112.5 to 8.9)	−270.1 (−899.0 to −45.2)
Mean percent change (range)	46.7 (−8.5 to 103.4)	38.8 (−25.5 to 157.5)	−62.0 (−68.7 to −53.7)	−19.2 (−50.4 to 11.9)	−55.2 (−83.7 to −37.9)
Apolipoprotein B					
Mean baseline level (range) — mg/dl	132.0 (87.0 to 204.0)	139.0 (76.0 to 192.0)	153.7 (109.0 to 211.0)	121.0 (95.0 to 147.0)	116.3 (93.0 to 147.0)
Mean level at follow-up (range) — mg/dl†	144.7 (92.0 to 230.0)	190.5 (180.0 to 201.0)	85.7 (55.0 to 122.0)	95.5 (61.0 to 130.0)	72.0 (38.0 to 93.0)
Mean absolute change (range) — mg/dl	12.7 (−13.0 to 26.0)	20.0 (−12.0 to 52.0)	−68.0 (−156.0 to −19.0)	−25.5 (−34.0 to −17.0)	−44.3 (−109.0 to −4.0)
Mean percent change (range)	9.7 (−12.4 to 28.7)	14.3 (−6.3 to 34.9)	−38.0 (−73.9 to −13.5)	−23.7 (−35.8 to −11.6)	−33.4 (−74.1 to −4.3)
HDL cholesterol					
Mean baseline level (range) — mg/dl	42.4 (39.1 to 45.2)	29.8 (23.2 to 35.2)	38.7 (36.0 to 42.2)	37.5 (37.1 to 37.9)	59.3 (37.9 to 73.1)
Mean level at follow-up (range) — mg/dl†	36.3 (30.9 to 39.1)	30.0 (15.1 to 39.1)	43.7 (37.1 to 51.0)	34.0 (30.2 to 37.9)	45.5 (25.9 to 74.2)
Mean absolute change (range) — mg/dl	−6.1 (−12.0 to 0.0)	0.3 (−8.1 to 5.0)	5.0 (1.2 to 8.9)	−3.5 (−7.0 to 0.0)	−13.7 (−32.1 to 3.1)
Mean percent change (range)	−13.9 (−27.9 to 0.0)	-2.6 (−35.0 to 16.3)	12.5 (3.2 to 21.1)	−9.4 (−18.7 to 0.0)	−24.1 (−43.9 to 4.3)
Non-HDL cholesterol					
Mean baseline level (range) — mg/dl	192.7 (103.2 to 339.5)	234.6 (194.1 to 293.5)	233.3 (171.3 to 316.3)	155.6 (109.0 to 202.0)	188.7 (136.1 to 263.3)
Mean level at follow-up (range) — mg/dl†	206.0 (124.1 to 341.5)	265.4 (253.3 to 285.4)	116.9 (68.1 to 179.4)	125.1 (71.9 to 178.3)	83.4 (52.2 to 113.3)
Mean absolute change (range) — mg/dl	13.3 (−11.2 to 49.1)	30.8 (−8.1 to 63.4)	−116.4 (−248.3 to −32.9)	−30.5 (−37.1 to −24.0)	−105.3 (−211.1 to −34.0)
Mean percent change (range)	13.3 (−8.3 to 47.6)	15.7 (−2.8 to 32.7)	−44.6 (−78.5 to −15.5)	−22.9 (−34.0 to −11.9)	−49.8 (−80.2 to −25.0)



Changes in ANGPTL3, LDL Cholesterol, and Triglyceride Levels over Time with CTX310.

Panel A shows the mean percent change in angiopoietin-like protein 3 (ANGPTL3) level from baseline according to visit for each dose level. Panel B shows the mean percent change in low-density lipoprotein (LDL) cholesterol level from baseline according to visit for each dose level. Panel C shows the mean percent change in triglyceride level from baseline according to visit for each dose level. The inset in Panel C shows the results for the three highest dose groups. Day 0 in the inset indicates baseline. The highest dose administered, 0.8 mg per kilogram, produced a mean reduction of 48.9% in LDL cholesterol levels and 55.2% in triglyceride levels in four participants 60 days after treatment. I bars indicate standard errors. For each dose group, the line for percent change extends to the final time point at which data were available for all participants. The abbreviation eLBW denotes estimated lean body weight.



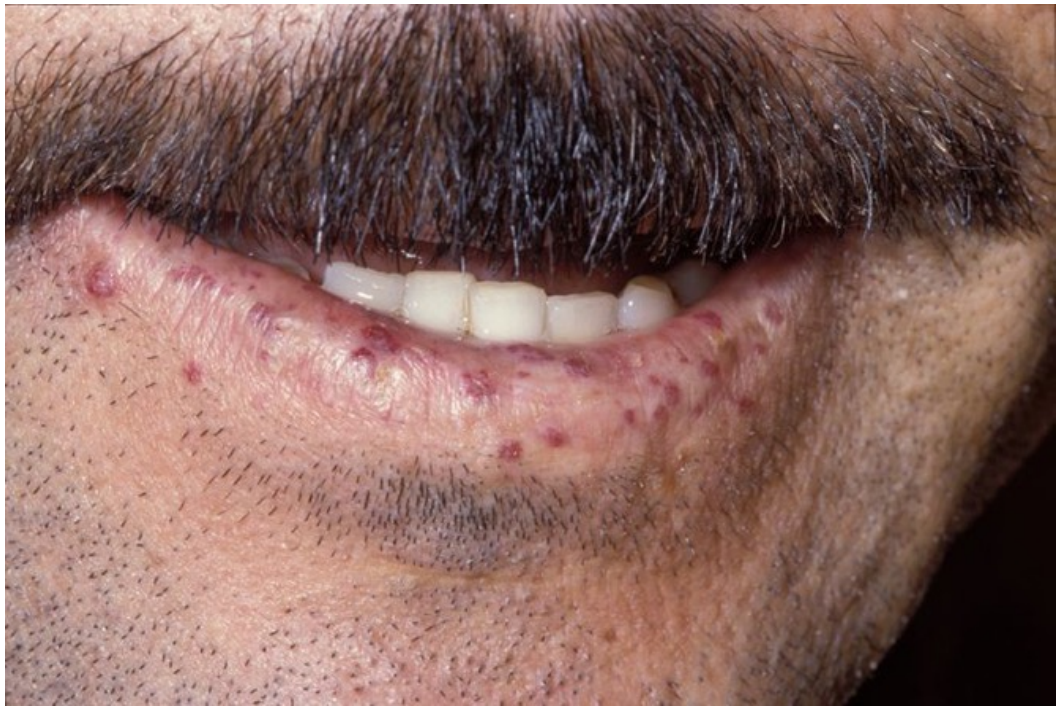
Changes in Apolipoprotein B, HDL Cholesterol, and Non-HDL Cholesterol Levels over Time with CTX310.

Panel A shows the mean percent change in apolipoprotein B level from baseline according to visit for each dose level. Panel B shows the mean percent change in high-density lipoprotein (HDL) cholesterol level from baseline according to visit for each dose level. Panel C shows the mean percent change in non-HDL cholesterol level from baseline according to visit for each dose level. I bars indicate standard errors. For each dose group, the line for percent change extends to the final time point at which data were available for all participants.

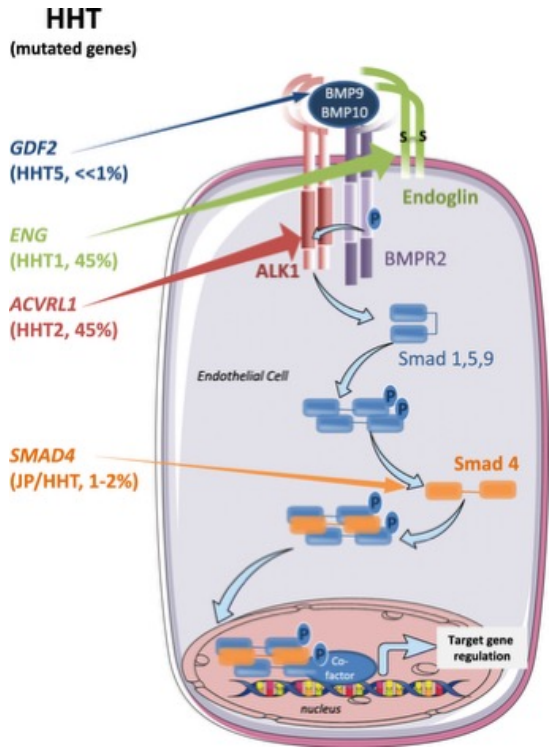
Discussion

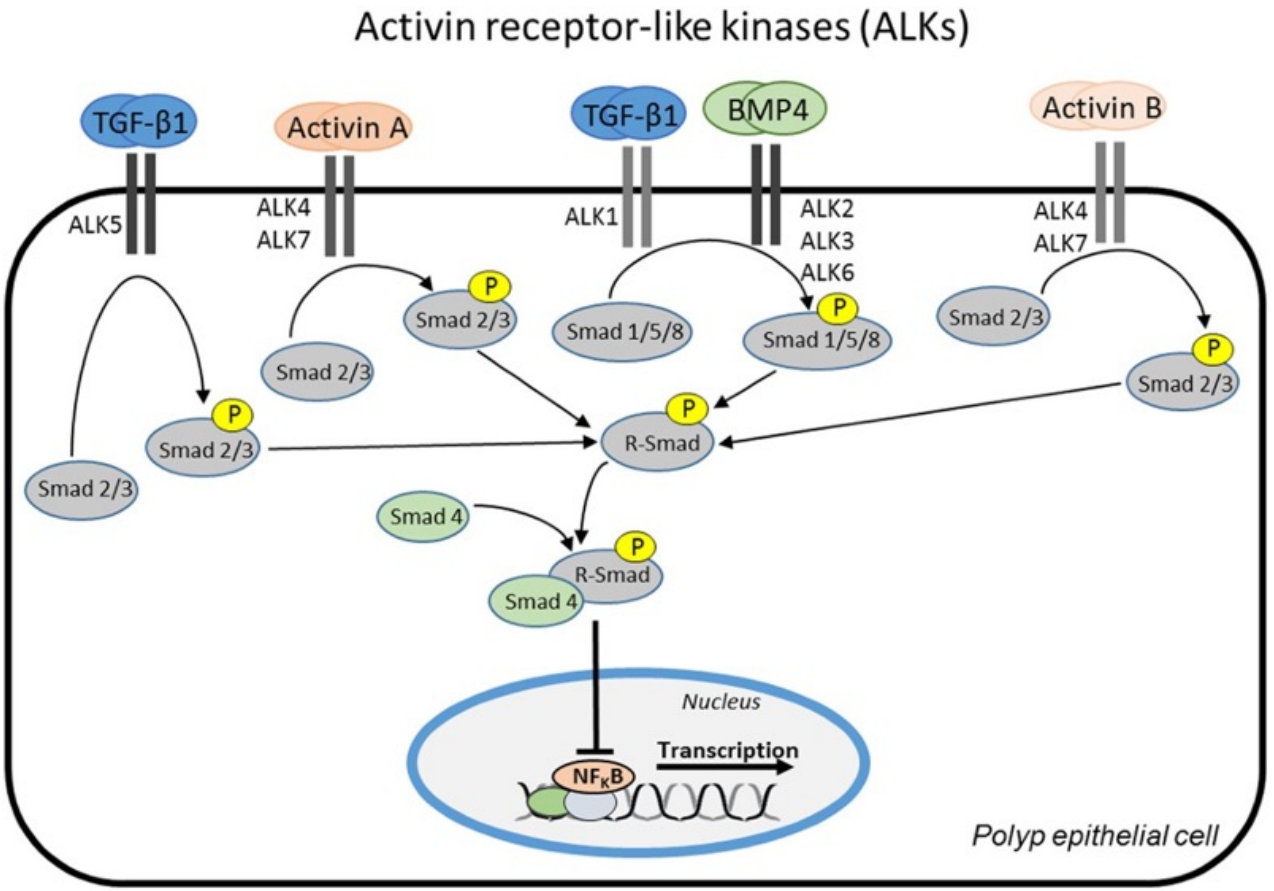
ANGPTL3 is produced almost exclusively by the liver and has broad effects on atherogenic lipoproteins, and therefore it represents an attractive target for gene editing. Lipid nanoparticles are a well-established approach for hepatic delivery of gene-editing therapies. Although many treatments for elevated LDL cholesterol levels exist, current orally administered treatments for hypertriglyceridemia have limited effectiveness, and no treatments simultaneously and substantially lower both LDL cholesterol and triglyceride levels. The observed reductions in LDL cholesterol and triglyceride levels with CTX310 are similar to those observed with evinacumab, a monoclonal antibody targeting ANGPTL3 that has been approved for use in patients with homozygous familial hypercholesterolemia. Vupanorsen, an antisense oligonucleotide, and two small interfering RNA therapies (zodasiran and solbinsiran) inhibit ANGPTL3 protein synthesis and showed lipid-lowering effects in early-phase trials. Development of vupanorsen was discontinued owing to worsening hepatic steatosis and elevations in aminotransferase levels, whereas zodasiran and solbinsiran are associated with reduced hepatic fat fraction.

Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu syndrome, is a genetic disorder causing abnormal blood vessel formation (telangiectasias and arteriovenous malformations or AVMs) that makes them fragile and prone to bleeding. Symptoms can include frequent nosebleeds and bleeding from the digestive system, while more serious complications can arise from AVMs affecting the lungs, brain, or liver, such as dizziness, stroke, or heart failure. Treatment focuses on managing bleeding and preventing complications, with options including medications, medical procedures, and lifestyle adjustments like keeping nasal passages moist.



Morbus Osler

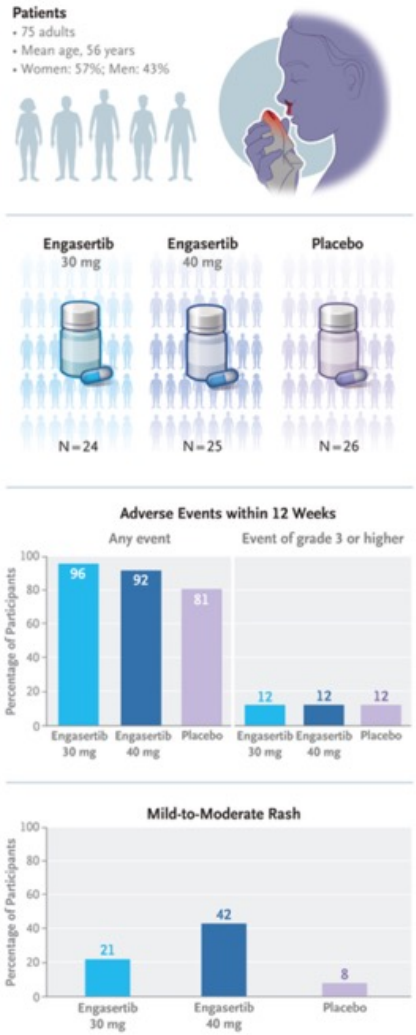




•Endoglin wirkt als Hilfsprotein für die TGF-β-Rezeptoren und reguliert die Signalwege von TGF-β und knochenmorphogenetischen Proteinen (BMPs).

Engasertib versus Placebo for Bleeding in Hereditary Hemorrhagic Telangiectasia

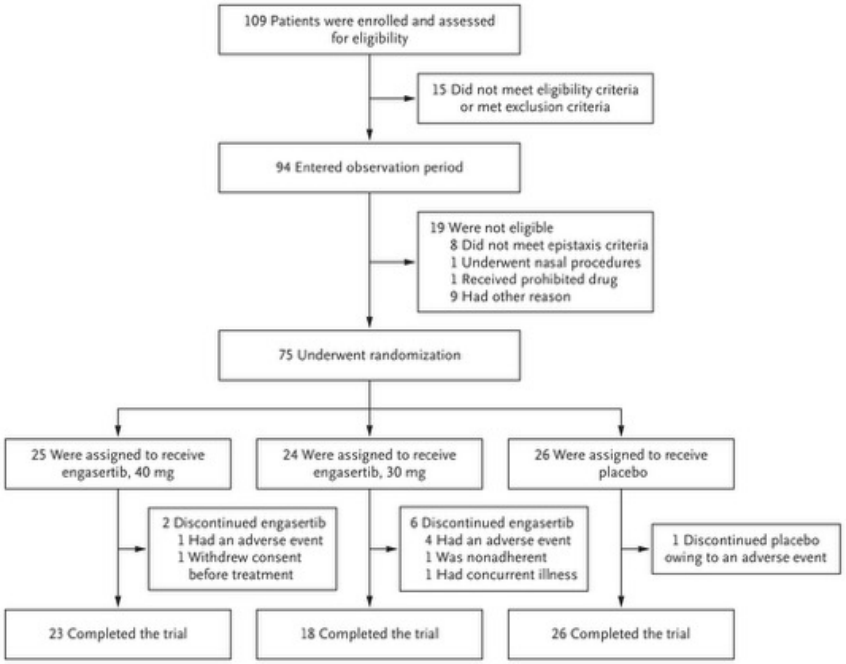
Hereditary hemorrhagic telangiectasia (HHT) can cause recurrent, severe epistaxis, as well as anemia and reduced quality of life. The disease remains without licensed therapies worldwide.
In this proof-of-concept, multicenter, double-blind, placebo-controlled trial, we evaluated the safety and efficacy of oral engasertib, a new, allosteric, selective AKT inhibitor, in patients with HHT.
Patients were randomly assigned in a 1:1:1 ratio to receive engasertib at a dose of 30 mg, engasertib at a dose of 40 mg, or placebo once daily for 12 weeks. The primary outcomes were the frequency and severity of adverse events. Key secondary outcomes included the frequency and duration of epistaxis. An open-label extension is ongoing.



Hereditary hemorrhagic telangiectasia (HHT) is an autosomal-dominant vasculopathy, with a prevalence of 1 in 3800 persons, that results from mutations in the activin receptor–like kinase 1 (ALK1) signaling pathway, which is critical in angiogenesis and vascular maintenance. HHT is the second most common inherited bleeding disorder worldwide, affects all genders and ethnic groups, and may result in reduced overall survival as compared with the general population. In addition, recent data suggest that HHT may be associated with the highest morbidity among inherited bleeding disorders in women.

Even with this considerable disease burden, no therapies to treat HHT are licensed, and no new agents have been developed specifically for HHT. Current bleeding-management strategies include the off-label use of antifibrinolytic drugs, temporizing local ablative procedures targeting nasal and gastrointestinal telangiectasias, aggressive surgery (e.g., surgical closure of the nares), and, most recently, the off-label use of antineoplastic drugs with antiangiogenic properties (e.g., bevacizumab, thalidomide, and pomalidomide). Because pathogenic variants in ALK1 signaling result in downstream overactivation of the serine–threonine kinase AKT, which drives the formation of telangiectasia and arteriovenous malformation, AKT inhibition has emerged as a promising approach for the treatment of HHT.

Characteristics	Engasertib, 30 mg (N=24)	Engasertib, 40 mg (N=24)	Placebo (N=26)	Total (N=74)
Age — yr	56.0±10.2	55.7±13.3	56.3±7.9	56.0±10.5
Female sex — no. (%)	15 (62)	15 (62)	12 (46)	42 (57)
Race — no. (%)†				
White	21 (88)	21 (88)	24 (92)	66 (89)
Other	2 (8)	1 (4)	2 (8)	5 (7)
Data missing	1 (4)	2 (8)	0	3 (4)
Genotype				
No. of patients assessed	20	19	22	61
ENG — no. (%)	6 (30)	9 (47)	7 (32)	22 (36)
ACVRL1 — no. (%)	14 (70)	9 (47)	15 (68)	38 (62)
Other — no. (%)	0	1 (5)	0	1 (2)
Epistaxis variables				
No. of patients assessed	23	23	26	72
Median frequency (IQR) — bleeding episodes per mo	42.0 (31.0–66.0)	38.0 (23.0–59.0)	38.5 (27.0–52.0)	40.0 (25.5–56.0)
Median duration (IQR) — min per mo	265 (183–609)	345 (235–643)	256 (199–500)	282 (198–554)
Median flow-intensity score (IQR)‡	35.7 (26.1–42.3)	35.4 (31.4–47.8)	38.8 (29.9–48.9)	35.9 (29.8–44.3)
Gastrointestinal bleeding — no. (%)				
Yes	9 (38)	9 (38)	6 (23)	24 (32)
Suspected	0	1 (4)	0	1 (1)
No	13 (54)	10 (42)	16 (62)	39 (53)
Unknown	2 (8)	4 (17)	4 (15)	10 (14)
HHT disease manifestations other than epistaxis — no. (%)				
Brain arteriovenous malformation	1 (4)	3 (12)	1 (4)	5 (7)
Liver arteriovenous malformation	11 (46)	7 (29)	12 (46)	30 (41)
Lung arteriovenous malformation	8 (33)	12 (50)	9 (35)	29 (39)
Hemoglobin concentration — g/dl	11.4±1.9	11.3±2.6	11.4±2.0	11.4±2.1
Anemia — no. (%)				
None or mild	15 (62)	15 (62)	16 (62)	46 (62)
Moderate or severe	9 (38)	9 (38)	10 (38)	28 (38)
Red-cell transfusions in the 10 mo before screening — no. (%)	7 (29)	4 (17)	10 (38)	21 (28)
Intravenous iron supplement in the 6 mo before screening — no. (%)	22 (92)	17 (71)	21 (81)	60 (81)
Oral iron supplement in the 6 mo before screening — no. (%)	11 (46)	6 (25)	13 (50)	30 (41)
Epistaxis Severity Score§	5.62±1.14	5.63±1.78	5.68±1.58	5.64±1.50

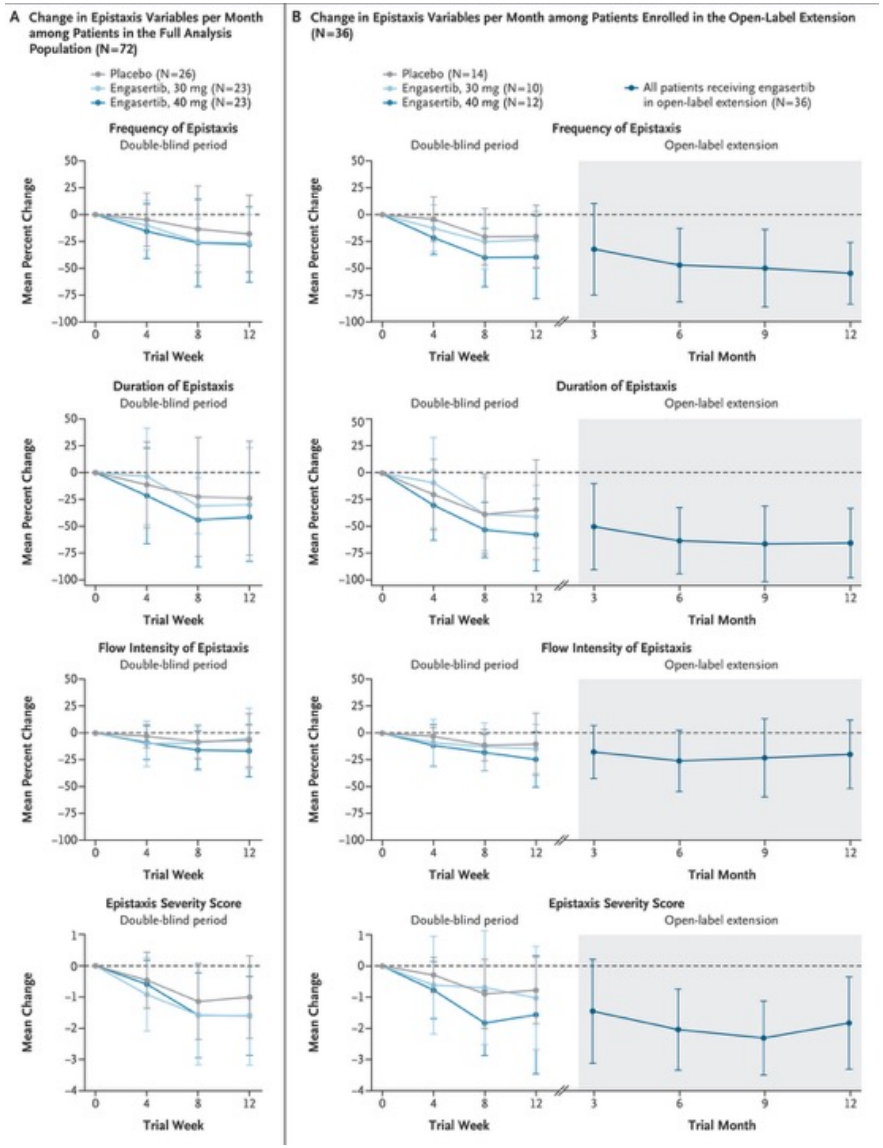


Safety Outcomes, Excluding Epistaxis as an Adverse Event

Outcome	Part 1*			Part 2†
	Engasertib, 30 mg (N=24)	Engasertib, 40 mg (N=24)	Placebo (N=26)	Engasertib, 30 mg and 40 mg (N=36)
Patients with ≥1 adverse event — no. (%)	23 (96)	22 (92)	21 (81)	35 (97)
No. of adverse events	84	66	62	202
Patients with any grade ≥3 adverse event — no. (%)	3 (12)	3 (12)	3 (12)	6 (17)
Patients with ≥1 serious adverse event — no. (%)	3 (12)	1 (4)	2 (8)	6 (17)
No. of serious adverse events	4‡	1§	4¶	9‖
Patients with ≥1 serious adverse event related to trial regimen — no. (%)	0	0	0	0
Patients with an adverse event leading to discontinuation of trial regimen — no. (%)	4 (17)	1 (4)	1 (4)	3 (8)
Patients with ≥1 adverse event of special interest — no. (%)				
Rash	6 (25)	11 (46)	2 (8)	15 (42)
Hyperglycemia	0	3 (12)	0	10 (28)
Colitis	0	0	0	0
Pneumonitis	0	0	0	0
Elevated liver-enzyme levels	1 (4)	0	0	0

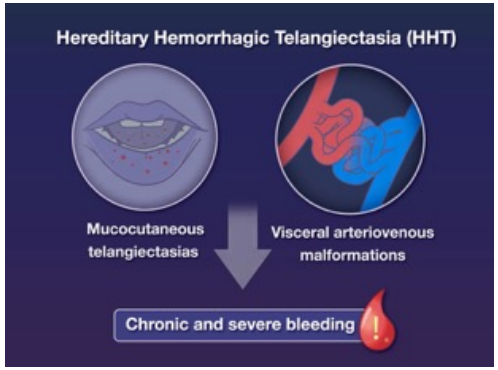
Change from Baseline in Key Secondary Efficacy Outcomes

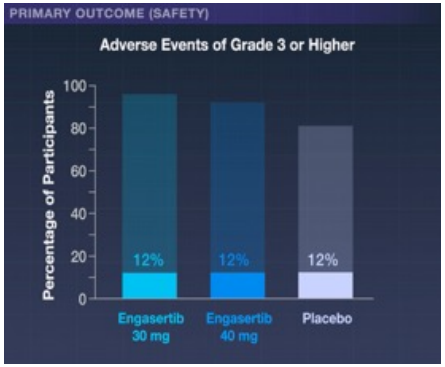
Outcome	Part 1			Part 2
	Engasertib, 30 mg (N=23)	Engasertib, 40 mg (N=23)	Placebo (N=26)	Engasertib, 30 mg and 40 mg (N=36)†
Change in epistaxis duration — %‡	−29.9±53.2	−41.4±41.0	−23.8±53.4	−65.6±32.4
Change in epistaxis frequency — %‡	−26.5±26.5	−27.8±35.1	−18.0±36.0	−54.9±28.9
Change in epistaxis flow-intensity score — %§	−5.0±28.3	−16.7±24.4	−6.8±24.7	−19.8±31.9
Change in ESS — points¶	−1.6±1.6	−1.6±1.3	−1.0±1.3	−1.8±1.5
Change in Modified ESS — points‖	−0.40±0.74	−0.33±0.82	−0.19±0.80	NA

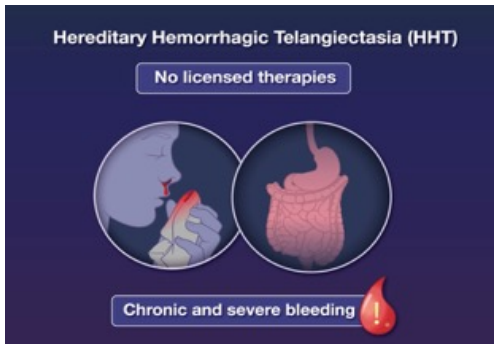


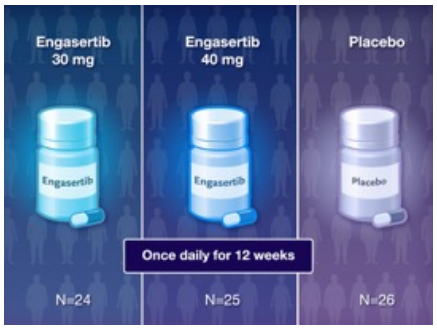
Change in Epistaxis Severity Measures over Time.

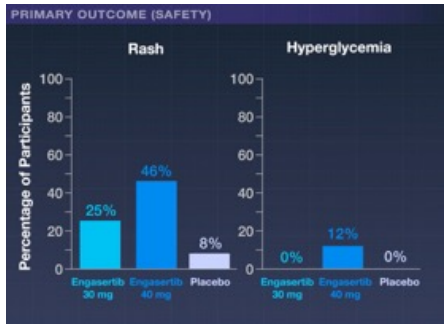
Shown is the percent change from baseline in epistaxis frequency, duration, and flow intensity and the change in Epistaxis Severity Score during the double-blind period among patients in the full analysis population (72 patients who received at least one dose of the trial regimen and underwent at least one postbaseline efficacy assessment) (Panel A) and during the double-blind period and the open-label extension among patients who were enrolled in the open-label extension (36 patients) (Panel B). The Epistaxis Severity Score ranges from 0 to 10, with higher scores indicating worse bleeding. Dots indicate the mean change, and I bars indicate the standard deviation.

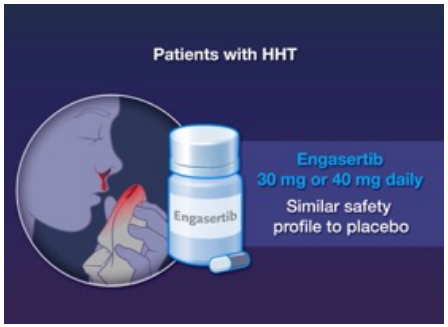


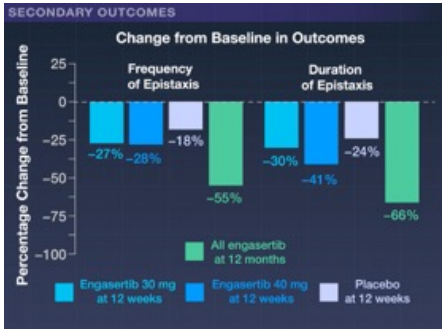












Activin receptor–like kinase 1 (ALK1)
Pathway causes HHT, TGF-b family

Strategies to Reinvigorate the Bedside Clinical Encounter

Medical trainees today spend as little as 13% of their time in direct contact with patients. As physicians spend less time with patients, fundamental bedside skills decline. This decline contributes to diagnostic error, poor clinical outcomes, and increased health care costs. More than half of outpatient diagnostic errors have been attributed to poor history taking and mistakes in the physical examination. An overreliance on technology, due in part to declining clinical skills, leads to overinvestigation and rising costs. The drift away from direct contact with patients contributes to a decrease in empathy on the part of medical students and residents and an increase in stress and burnout among practicing physicians. It also leads to a weakening of the doctor–patient relationship. Lack of time at the bedside disproportionally affects marginalized groups and propagates health care disparities. As bedside skills have declined, so too has the number of faculty members who are comfortable teaching those skills, which further contributes to their decay. To help reverse these trends, we provide practical suggestions for clinical educators to reinvigorate the teaching and practice of bedside clinical skills in the modern health care environment.

Strategies to Reinvigorate the Bedside Clinical Encounter

- Medical learners in the 21st century spend less time with patients during training than their counterparts did in the 20th century, which decreases the knowledge and practice of bedside clinical skills.
- Decreased bedside clinical skills lead to diagnostic error, poor clinical outcomes, increased health care costs, and physician burnout.
- Taking learners to the bedside facilitates clinical observation skills, creates opportunities to practice skills, and allows for evidence-based demonstrations of examination skills.
- Integration of point-of-care technology and artificial intelligence in the clinical encounter complements human observation, human clinical decision making, and human communication.
- Seeking opportunities to provide feedback on clinical skills in a context-specific way improves the technique at the bedside, as well as the interpretation of information obtained from the encounter.
- Beyond the diagnostic data obtained in the bedside clinical encounter, the physical examination helps learners navigate clinical uncertainty, helps teachers model interactions with patients, improves physician–patient communication, increases professional fulfillment, and helps address health care disparities.

Six Strategies to Reinvigorate the Bedside Encounter.

Strategy	Justification
Go to the bedside and observe (both patient and trainee)	Observation forms the basis of much of the physical examination and can provide valuable clues to the diagnosis of many diseases, as well as the prognosis. Direct observation of the trainee's clinical skills is critical for providing actionable and specific feedback. Observational skills can be improved through practice in nonmedical contexts.
Practice and teach an evidence-based approach to the physical examination	The physical examination should be used in a hypothesis-driven approach, just like any other diagnostic test. In many cases, the physical examination remains the reference-standard diagnostic test. In other cases, likelihood ratios can help in selecting the appropriate physical examination maneuver, by comparison of that maneuver with a technology-based test.
Create opportunities for intentional practice	Time at the bedside is limited, so educators need to create opportunities for intentional practice of bedside skills. Traditional morning rounds remain the best opportunity for teaching bedside clinical skills. Other teaching sessions, such as morning report, noon conference, or dedicated physical examination sessions, can provide opportunities for practice.
Use technology to teach and reinforce clinical examination skills	Point-of-care technology (e.g., use of digital stethoscopes and ultrasonography) is part of the bedside examination. It enhances diagnosis, allows learners to calibrate physical examination skills, and brings educators, learners, and patients together. Telemedicine improves access to care and allows clinicians to visit with patients in their home environment. Artificial intelligence can reduce the administrative burden, assist in the clinical reasoning process, and help in the acquisition of data. Awareness of the possibility of bias is important when existing or new technologies are used at the bedside.
Seek and provide feedback on clinical skills	Direct observation and feedback on clinical skills with real patients are rare in the United States. Assessment can drive learning. Formative assessments with real patients can inform individual learning plans.
Acknowledge the power of the bedside encounter beyond diagnosis	Approaching each encounter with curiosity can help physicians navigate uncertainty. Performing an appropriate history taking and physical examination helps patients feel cared for and can have a healing effect. Using evidence-based approaches to being fully present with patients improves the patient–physician relationship and increases professional fulfillment. Spending time at the bedside can help address health care inequities.

SCENARIO:
A 65-YEAR-OLD MALE FACTORY WORKER PRESENTS TO YOUR CLINIC WITH A CHIEF CONCERN OF SHORTNESS OF BREATH WITH EXERTION.

YOU'RE WORKING WITH A RESIDENT THAT DAY, WHO TAKES THE INITIAL HISTORY AND PRESENTS TO YOU A STORY SUGGESTIVE OF HEART FAILURE.

YOU ASK TO OBSERVE THE RESIDENT WHILE SHE PERFORMS A CARDIOVASCULAR EXAM.

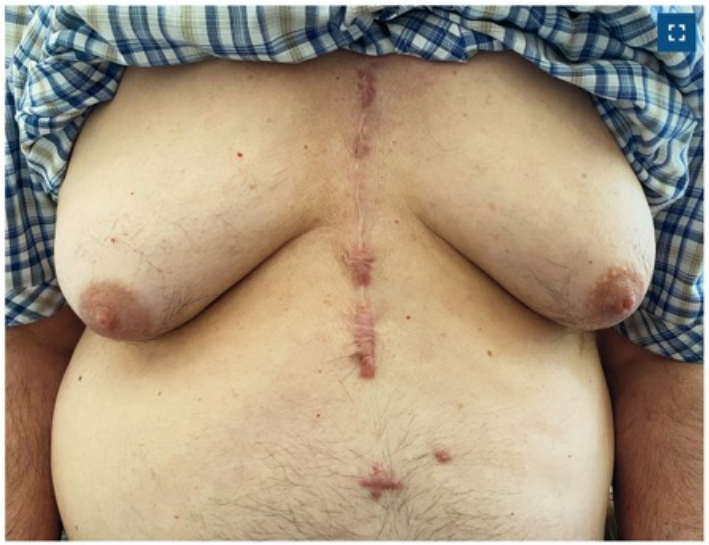

I THINK I HEAR A FAINT SYSTOLIC HEART MURMUR, BUT I'M NOT SURE.
LISTENING THROUGH THE SHIRT MAKES IT HARD TO HEAR ANYTHING AT ALL.


AGAIN, IT'S HARD TO HEAR ANYTHING THROUGH CLOTHING.
THE LUNGS SEEM REALLY QUIET, BUT I DON'T HEAR ANY OBVIOUS ABNORMALITIES.

Conclusions

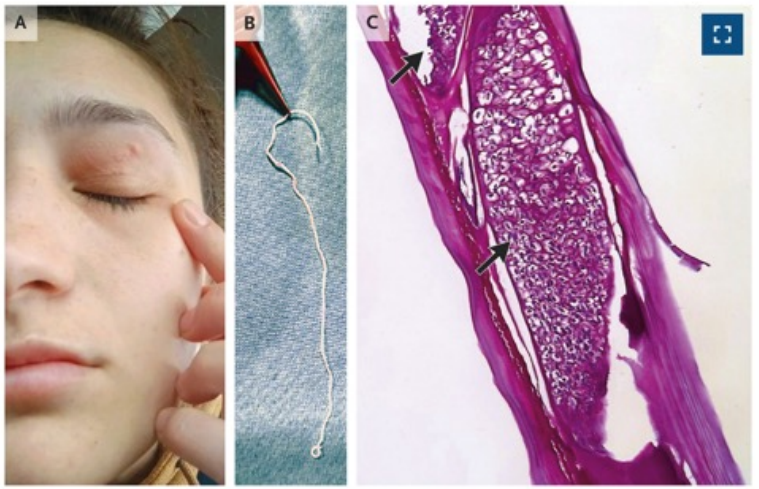
Against a backdrop of technological advances, limited time with patients, and clinical uncertainty, there is an urgent need to reinvigorate the bedside encounter in order to meet the needs of patients, trainees, and clinical educators in the 21st century. By using six strategies, clinical educators can help trainees appreciate the value of the bedside encounter in diagnostic reasoning, strengthen the patient–physician relationship, combat health care inequities, improve professional fulfillment, and avoid burnout. The words of Osler ring true more than a century later: “Medicine is learned by the bedside and not in the classroom. Let not your conceptions of the manifestations of disease come from words heard in the lecture room or read from the book. See, and then reason and compare and control. But see first.

Spironolactone-Induced Gynecomastia



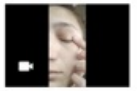
A 76-year-old man with coronary artery disease and heart failure with reduced ejection fraction presented to the cardiology clinic with an 8-month history of progressive breast enlargement and tenderness. Spironolactone had been started 4 years before presentation at a dose of 25 mg daily and was increased to 100 mg daily 1 year before presentation. Owing to hyperkalemia, the dose had been reduced to 25 mg approximately 2 months before presentation. Physical examination was notable for symmetric enlargement of glandular breast tissue on both sides. On palpation, there was tenderness but no nodules, nipple discharge, or skin retraction. There was also a sternotomy scar from previous coronary-artery bypass grafting. Laboratory studies showed normal kidney and liver function. A serum testosterone level was low-normal and serum levels of human chorionic gonadotropin, sex hormone–binding globulin, luteinizing hormone, estradiol, and thyrotropin were normal. A diagnosis of spironolactone-induced gynecomastia — an adverse drug effect seen more frequently in men taking more than 100 mg per day — was made. The mechanism is multifactorial and includes androgen-receptor blockade and increased peripheral conversion of testosterone to estradiol. Spironolactone was discontinued and eplerenone — a more selective mineralocorticoid receptor antagonist — was started. At 3 months of follow-up, the patient's breast tenderness had abated but the gynecomastia remained.

Subcutaneous Dirofilariasis



A previously healthy 26-year-old woman presented to the ophthalmology emergency department with a 1-day history of a mobile lesion in her left eyelid. She owned a dog. Physical examination was notable for a serpiginous structure within the left upper eyelid that was surrounded by mild erythema and edema (Panel A and video). Surgical excision of the lesion was subsequently performed and revealed an 11-cm roundworm (Panel B). The filiform parasite was identified as *Dirofilaria repens* on histopathological analysis, and microfilariae were seen in two uteri (Panel C, arrows). *D. repens* is a nematode whose definitive hosts are dogs, foxes, wolves, and raccoons. The species that causes heartworm in dogs is *D. immitis*. Human infection — which can result in pulmonary, subcutaneous, or ocular syndromes, depending on the infecting species — occurs when a mosquito vector transmits a larva during a blood meal. A small nodule develops at the site of inoculation and then grows into a worm over a period of months. On further history taking, the patient recalled the appearance of a nodule on her right temple 1 month before presentation that had disappeared 1 day before the lesion had appeared in her left eyelid. After extraction of the worm, the patient's symptoms abated.

VIDEO



Serpiginous Lesion in the Left Upper Eyelid 0m 6s

Case 34-2025: A 57-Year-Old Woman with Visual Disturbances and Right-Arm Shaking

Two years before the current presentation, the patient had frontotemporal and cervico-occipital headaches that lasted for several hours and were associated with photophobia. MRI showed nonspecific findings, and she received a diagnosis of migraines. The median age at the onset of migraines is 23 to 25 years of age, and the prevalence is only 5% among women older than 50 years of age. However, given the patient's family history of migraines and her clinical stability until 6 months before the current presentation, I suspect that these headaches were migraines that were unrelated to her current presentation.

Six months before the current presentation, a severe headache developed, although we are not told the location of the headache, whether it was similar to the previous migraines, or whether any features associated with increased intracranial pressure were present. At that time, the patient also had visual auras, although we are not given details about the auras. Up to one third of patients with migraines have auras. However, this patient's imaging of the head showed an abnormality in the left parietal lobe that was considered to be a more likely cause of her headache and could also be the cause of hallucinations in the lower quadrant of the right visual field.

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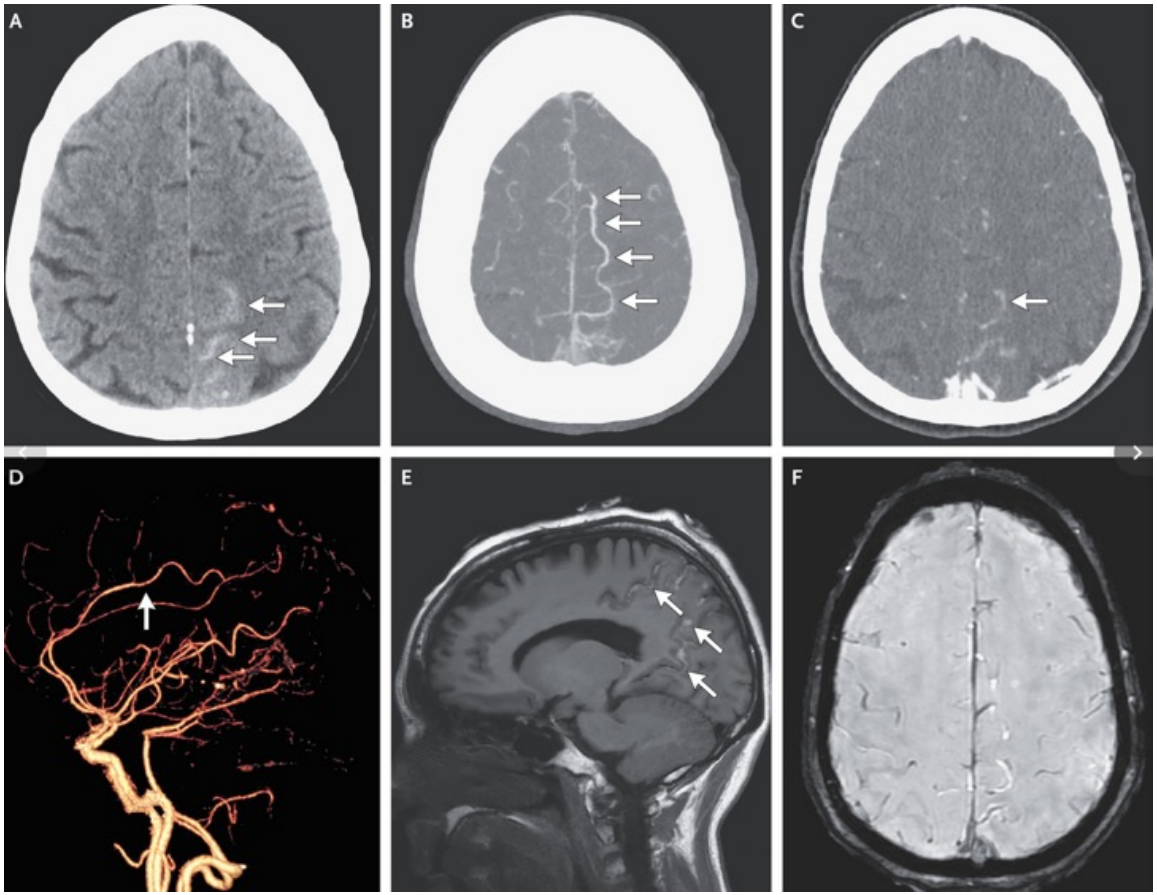


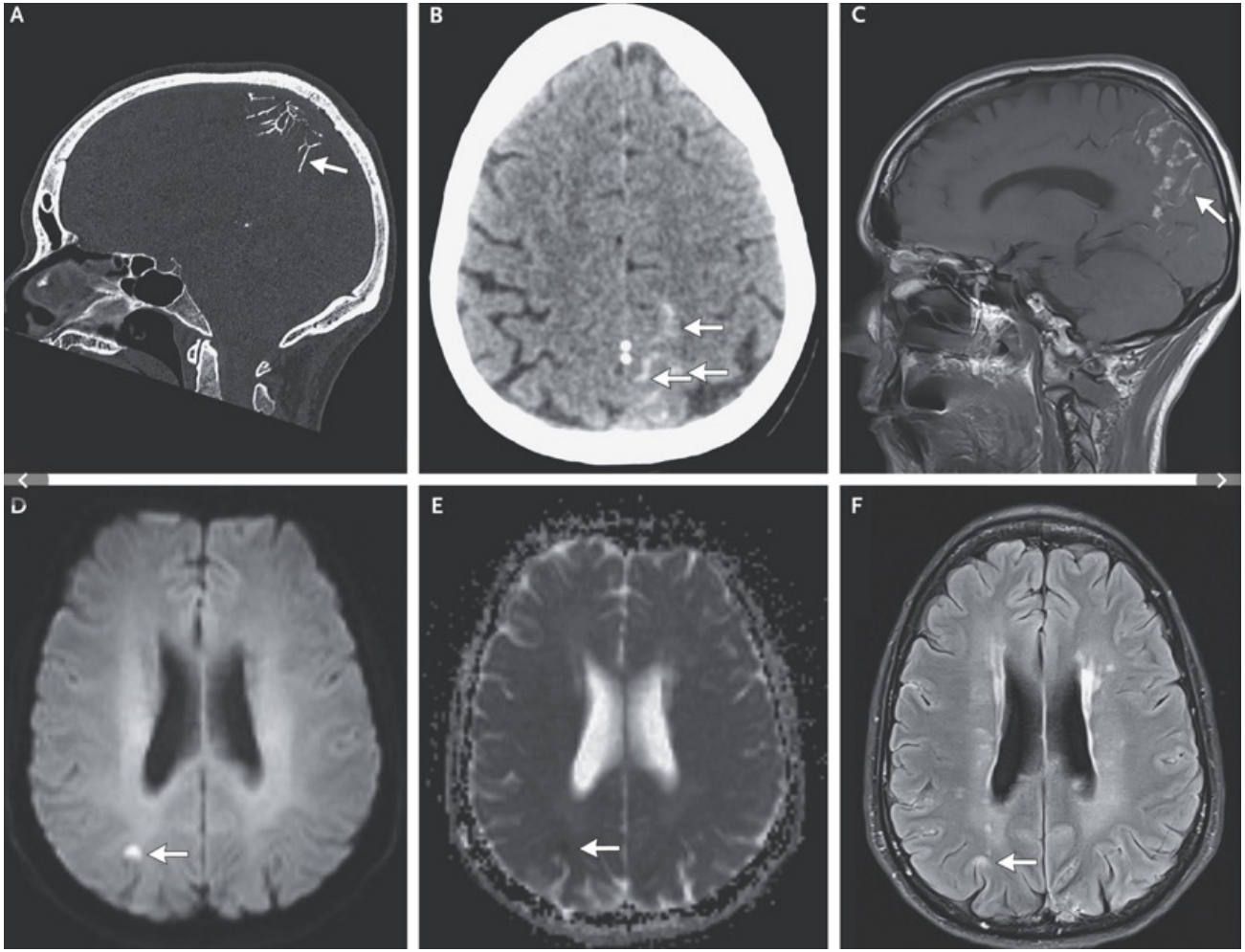
Imaging Studies of the Head, 6 Months before the Current Presentation.

An axial CT image (Panel A) shows hyperdensity concentrated in the sulci of the left parietal lobe (arrows). Axial images from CT angiography and venography (Panels B and C, respectively) show asymmetric prominence of the left distal branches of the anterior cerebral artery (Panel B, arrows) and mild prominence of the cortical veins (Panel C, arrow) in the paracentral parietal lobe. A three-dimensional reformatted image from CT angiography (Panel D) also shows asymmetric prominence of the left anterior cerebral artery (arrow). A sagittal T1-weighted MRI (Panel E) shows intrinsic hyperintensities in the sulci of the left parietal lobe (arrows). An axial susceptibility-weighted angiographic MRI (Panel F) shows no corresponding susceptibility signal in this region.

The later development of shaking in the right arm and leg was indicative of focal motor seizures, which localize to the motor cortex of the left frontal lobe. Paralysis of the right vocal cord indicates possible dysfunction of the right vagus nerve. Vertical diplopia on left lateral gaze suggests partial palsy of the right trochlear nerve. Saccadic breakdown and dysmetria that is greater on the left side are both findings indicative of cerebellar dysfunction. In the absence of other motor and sensory deficits and of systemic abnormalities on imaging, the cerebellar signs and the deficits in vagus and trochlear nerve function localize the disease process to the subarachnoid space in the posterior fossa and skull base. In summary, the progression of this patient's symptoms — from those indicating localization to the supratentorial and cortical structures to those indicating localization to the posterior fossa and skull base — suggests a diffuse process affecting the subarachnoid space and leptomeninges.

Lumbar puncture was performed, and cerebrospinal fluid (CSF) analysis showed 1 red cell per microliter, 1 nucleated cell per microliter, and normal levels of glucose and protein. Cytologic evaluation of the CSF showed no malignant cells, and flow cytometry of the CSF showed no evidence of a monoclonal B-cell population.

Ein «sakkadischer Breakdown» (oder sakkadische Störung) bezieht sich auf eine Fehlfunktion von schnellen Augenbewegungen, bei denen das Auge ein Ziel über- oder unterschießt (dysmetrische Sakkaden) oder die Zielbewegung nicht genau ausführt.

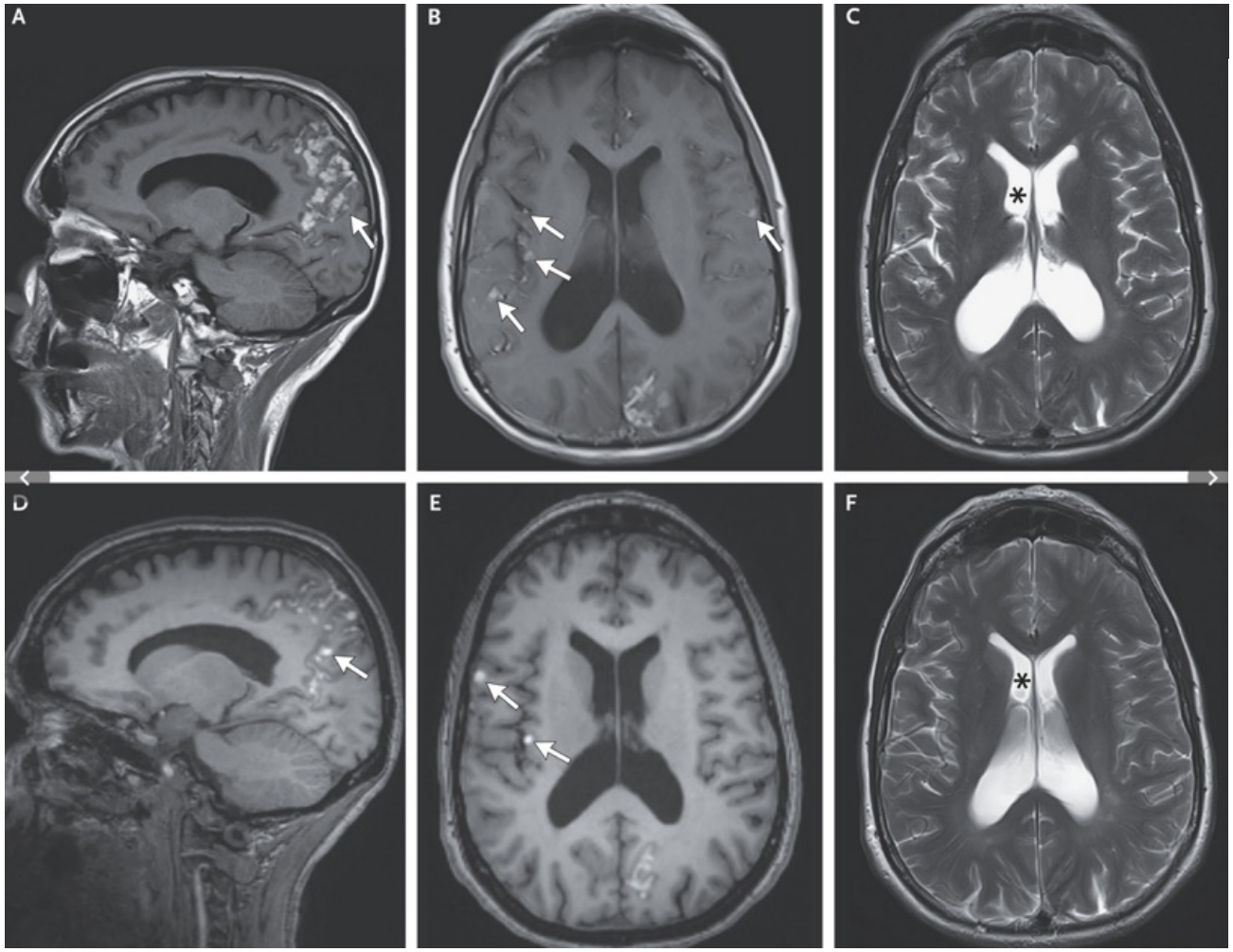


Imaging Studies of the Head, 5 Months before the Current Presentation.

A sagittal CT image (Panel A) shows hyperattenuating embolic material with a linear branching pattern along the falx cerebri (arrow). An axial CT image (Panel B) and a sagittal T1-weighted MRI (Panel C) show stability of the presumed subarachnoid hemorrhage (arrows). A punctate focus of hyperintensity in the right parietal lobe on an axial diffusion-weighted MRI (Panel D, arrow) corresponds to hypointensity on an axial apparent-diffusion-coefficient MRI (Panel E, arrow) and to hyperintensity on an axial fluid-attenuated inversion recovery MRI (Panel F, arrow).

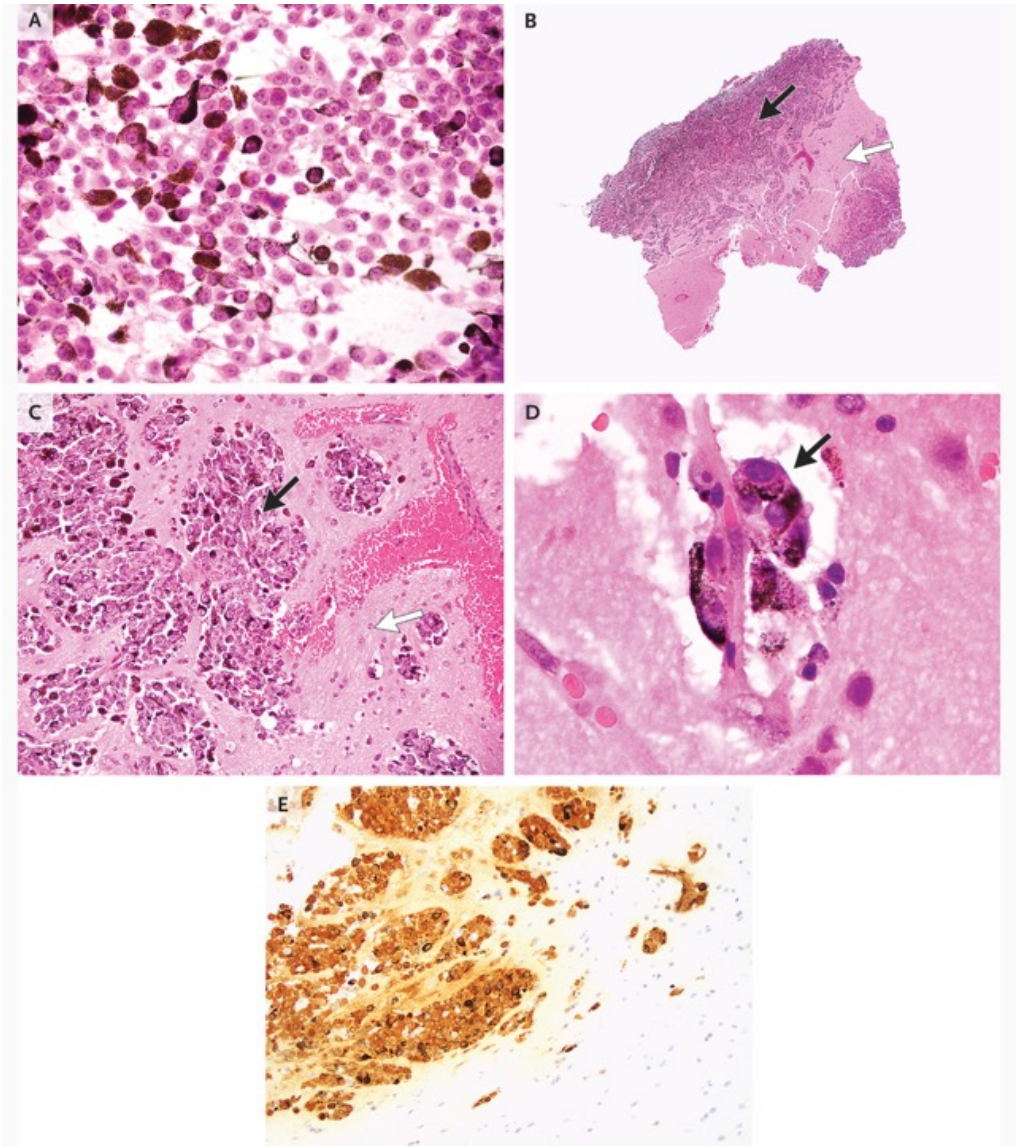
MRI of the head was performed at the time of the current presentation. T1-weighted sequences showed an increase in the intensity and distribution of the hyperintensities in the left parietal and occipital lobes and progression of the leptomeningeal thickening and sulcal nodularity throughout the cerebral hemispheres (Figure 3A and 3B) as compared with the findings seen 3 months earlier (Figure 3D and 3E). There was also enlargement of the ventricles (Figure 3C) as compared with the findings seen 3 months earlier (Figure 3F), which is suggestive of developing hydrocephalus.

Given the possibility of cancer, right frontal craniotomy with brain biopsy was performed. The dura appeared abnormal, and black tissue was noted. The pia mater was opened, and multiple samples of the abnormal tissue were obtained for evaluation.



Current Imaging Studies of the Head.

Imaging studies obtained at the time of the current presentation (Panels A, B, and C) were compared with those obtained 3 months before the current presentation (Panels D, E, and F). Sagittal and axial T1-weighted MRIs obtained on the current presentation (Panels A and B, respectively) show an increase in the intensity and distribution of the hyperintensities in the left parietal lobe and additional leptomeningeal foci in the left and right cerebral hemispheres, as compared with the findings seen on sagittal and axial T1-weighted MRIs obtained 3 months earlier (Panels D and E, respectively; arrows). An axial T2-weighted MRI obtained on the current presentation (Panel C) shows enlargement of the lateral ventricles (asterisk), as compared with the findings seen on an axial T2-weighted MRI obtained 3 months earlier (Panel F, asterisk).



Biopsy Specimens of the Brain.

Hematoxylin and eosin staining of an intraoperative-smear specimen shows neoplastic melanocytes (Panel A). Hematoxylin and eosin staining of a cortical-biopsy specimen shows a proliferation of malignant melanocytes (Panels B and C, black arrows) invading cortical gray matter (Panels B and C, white arrows) and perivascular Virchow–Robin spaces (Panel D, arrow). Immunohistochemical staining for melanocyte-inducing transcription factor is positive (Panel E).

Pathological Diagnosis

Diffuse meningeal melanomatosis.

Treatment for melanocytic tumors of the leptomeninges depends on the degree of tumor aggressiveness, which varies, and whether the tumor is localized or diffuse. These tumors rarely harbor *BRAF* mutations and are not amenable to treatment with the tyrosine kinase inhibitors that are used for cutaneous melanoma.

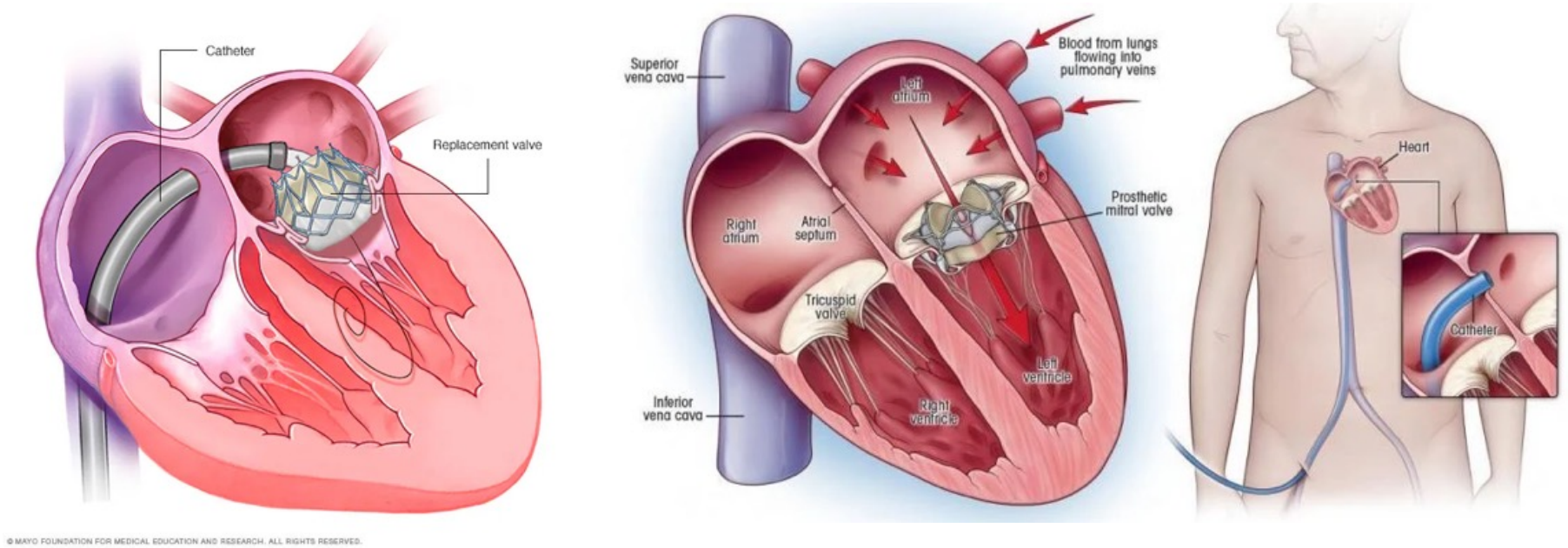
Given the lack of data on systemic therapy for meningeal melanoma, we extrapolated from data on such treatment for uveal melanoma, a disease that is also characterized by mutations in genes encoding G proteins that are not directly targetable. Both uveal and meningeal melanoma have low tumor mutational burdens, and uveal disease responds only occasionally to treatment with immune checkpoint inhibitors. We considered treatment with the bispecific fusion protein tebentafusp, which has been shown to recruit T cells and prolong survival in patients with metastatic uveal melanoma. However, the target antigen (gp100) is presented in the context of HLA-A*02:01, and the patient did not have that HLA allele.

With the understanding that the likelihood of benefit was low, the patient opted for treatment with the immune checkpoint inhibitors ipilimumab and nivolumab. After the fourth dose, her cognitive function worsened, and headaches and nausea developed. She received supportive treatment. After she was found to have progressive disease on imaging, the patient elected to receive hospice care. The patient died approximately 5 months after the initial diagnosis.

Final Diagnosis

Diffuse meningeal melanomatosis.

Der transkatheterale Mitralklappenersatz (TMVR) ist ein minimalinvasives Verfahren, um eine geschädigte Mitralklappe zu ersetzen, ohne eine offene Herzoperation durchzuführen. Dabei wird eine künstliche Klappe über einen Katheter, der durch die Leiste eingeführt wird, bis zum Herzen vorgeschoben und dort implantiert. Dieses Verfahren wird hauptsächlich bei Patienten angewendet, die ein hohes Risiko für eine Operation haben und an Mitralklappeninsuffizienz (Regurgitation) oder Mitralklappenstenose leiden.



Percutaneous transcatheter valve replacement in individuals with mitral regurgitation unsuitable for surgery or transcatheter edge-to-edge repair: a prospective, multicountry, single-arm trial

Summary

Background Patients with severe mitral regurgitation are frequently not candidates for surgery or transcatheter edge-to-edge repair (TEER). We aimed to evaluate 1-year outcomes of a novel percutaneous transseptal transcatheter mitral valve replacement (TMVR) system in patients unsuitable for surgery or TEER.

Methods In this prospective, multicentre, single-arm, pivotal trial, adult patients (aged ≥18 years) with symptomatic moderate-to-severe or severe mitral regurgitation who were not suitable for surgery or TEER were recruited at 56 centres in six countries (the USA, Canada, the UK, the Netherlands, Israel, and Australia). Eligible patients were treated with TMVR using the SAPIEN M3 system (Edwards Lifesciences, Irvine, CA, USA). The primary endpoint was a non-hierarchical composite of all-cause mortality and heart failure rehospitalisation at 1 year in the as-treated population, compared with a prespecified performance goal of 45%. This trial is registered with ClinicalTrials.gov, NCT04153292, and is ongoing.

Findings Between June 9, 2020, and Oct 10, 2023, 1171 patients were screened, of whom 299 were treated. Follow-up data were available for 283 (95%) patients at 30 days and 243 (81%) at 1 year (median follow-up 1·4 years [IQR 1·0–2·1]). The median age was 77·0 years (IQR 70·0–82·0), 152 (51%) participants self-reported as male and 147 (49%) as female, and the mean Society of Thoracic Surgeons predicted risk of 30-day mortality for mitral valve replacement was 6·6%. There were no intraprocedural deaths, no instances of left ventricular outflow tract obstruction causing haemodynamic compromise, and no conversions to surgery. The primary endpoint rate of 25·2% (95% CI 20·6–30·6) was significantly lower than the prespecified performance goal of 45% ($p<0·0001$).

Interpretation Percutaneous transseptal TMVR with the SAPIEN M3 system effectively reduced mitral regurgitation with low rates of complications and mortality. These findings support percutaneous TMVR with the SAPIEN M3 system as a therapeutic option for patients who are unsuitable for surgery or TEER.

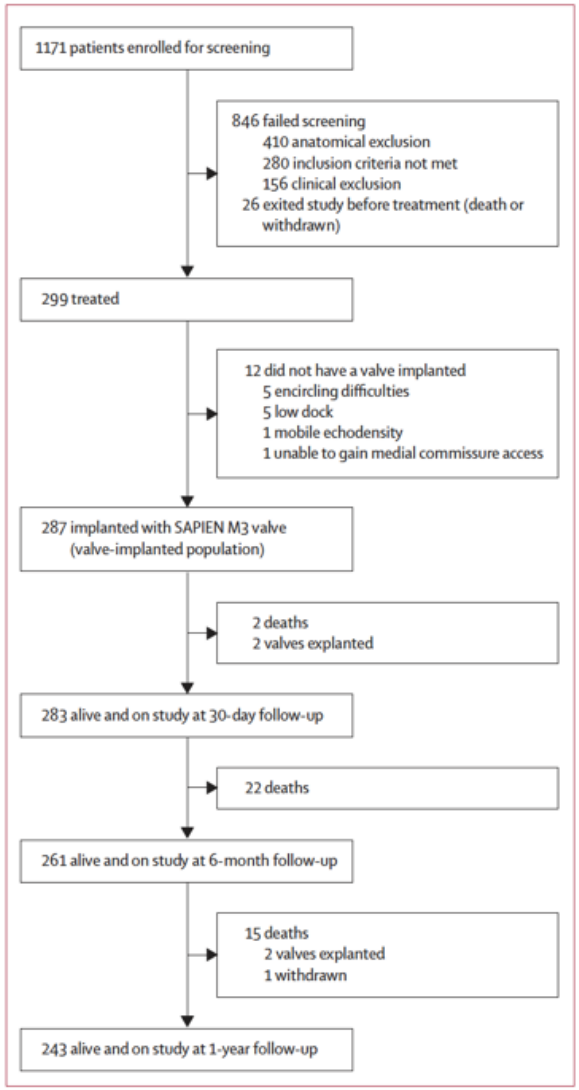


Figure 1: Trial profile

	As-treated group (n=299)
Age, years	77·0 (70·0–82·0)
Sex	
Male	152 (51%)
Female	147 (49%)
Ethnicity*	
Not Hispanic or Latino	257 (86%)
Hispanic or Latino	11 (4%)
Ethnicity unknown	31 (10%)
Race*	
White	227 (76%)
Black or African American	27 (9%)
Asian	7 (2%)
American Indian or Alaska Native	3 (1%)
Native Hawaiian or Other Pacific Islander	1 (<1%)
Other	9 (3%)
Unknown	5 (8%)
BMI, kg/m²	26·6 (23·2–31·6)
STS-PROM score for mitral valve replacement, %†	6·6% (4·1)
STS-PROM score ≥8	86 (29%)
New York Heart Association class	
I	0
II	86 (29%)
III	203 (68%)
IV	10 (3%)
Diabetes	103 (34%)
Hypertension	252 (84%)
Chronic obstructive pulmonary disease	70 (23%)
Peripheral vascular disease	45 (15%)
Congestive heart failure	225 (75%)
Rheumatic heart disease	13 (4%)
Atrial fibrillation	209 (70%)
Previous left atrial appendage occlusion	18 (6%)
Pacemaker or implantable cardioverter-defibrillator	107 (36%)
Previous myocardial infarction	90 (30%)
Previous percutaneous coronary intervention	106 (35%)
Previous coronary artery bypass grafting	91 (30%)
Previous transient ischaemic attack or stroke	56 (19%)
Previous mitral repair‡	26/298 (9%)
Previous septal modification to increase left ventricular outflow tract space§	6 (2%)
Previous aortic valve replacement	47 (16%)
Estimated glomerular filtration rate, mL/min per 1·73 m²	55·6 (43·6–69·9)
Brain natriuretic peptide, pg/mL	456·9 (560·8)

(Table 1 continues in next column)

	As-treated group (n=299)
(Continued from previous column)	
N-terminal prohormone of brain natriuretic peptide, pg/mL	1709·0 (983·0–3217·0)
Echocardiographic findings (core laboratory transthoracic echocardiography)	
Left ventricular ejection fraction, %	49·5% (38·7–58·1)
Left ventricular ejection fraction ≤40%	87 (29%)
Left ventricular end diastolic diameter, mm	54·6 (7·6)
Left ventricular end diastolic volume, mL	132·3 (106·6–170·6)
Left ventricular end systolic volume, mL	66·0 (47·1–97·8)
Mitral regurgitation aetiology	
Primary	105/297 (35%)
Secondary	173/297 (58%)
Secondary, ventricular	160/297 (54%)
Secondary, atrial	13/297 (4%)
Mixed (primary and secondary)	19/297 (6%)
Mitral regurgitation severity¶	
Moderate to severe, grade 3	156 (52%)
Severe, grade 4	143 (48%)
Mitral annular calcification‖	73 (24%)

Data are n (%), n/N (%), median (IQR), or mean (SD). STS-PROM=Society of Thoracic Surgeons Predicted Risk of Mortality. *Sex and race or ethnic group were self-reported by the patient. †STS-PROM score for mitral valve replacement is a risk-adjusted composite measure to evaluate surgical outcomes for patients undergoing mitral valve replacement. ‡Previous mitral repair included 12 previous rings, 11 previous bands, two repairs by Alfieri stitch, and one not-reported type of repair. §Septal modification included four patients who underwent pre-emptive alcohol septal ablation and two who underwent pre-emptive percutaneous septal scoring along the midline endocardium to decrease the risk of left ventricular outflow tract obstruction induced by transcatheter mitral valve replacement. All previous procedures were required to be done more than 30 days before transcatheter mitral valve replacement. ¶Mitral regurgitation severity is reported as the highest severity indicated by either transthoracic or transoesophageal echocardiography. ‖Mild to moderate mitral annular calcification detected on cardiac CT (CT mitral annular calcification score ≤4 in all cases).

Table 1: Baseline characteristics

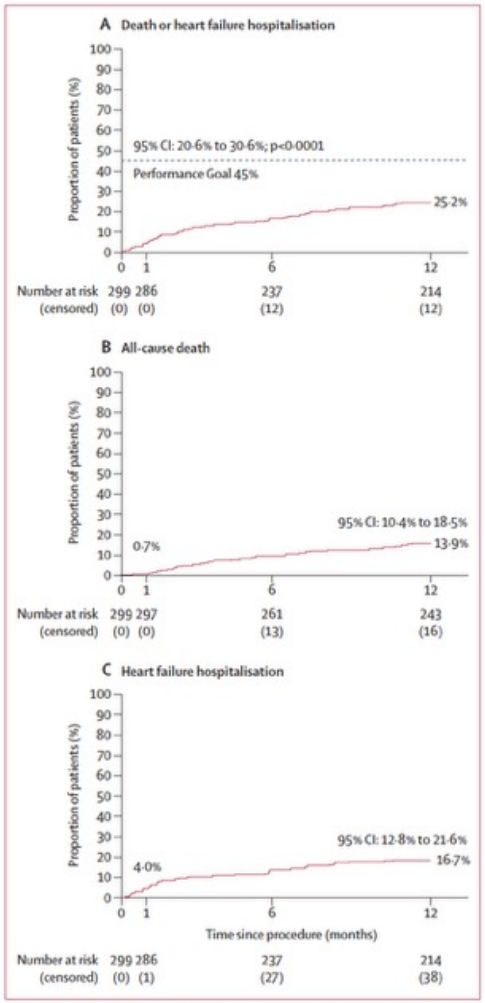


Figure 2: **Kaplan–Meier curves for the primary composite endpoint and its individual components**

Kaplan–Meier estimates of the rate of the primary composite endpoint (A) and its individual components of death from any cause (B) and heart failure rehospitalisation (C), in patients who underwent transseptal transcatheter mitral valve replacement.

	30-day visit		1-year visit	
	n	Outcome	n	Outcome
Primary endpoint				
Composite of all-cause mortality or heart failure hospitalisation at 1 year	..	..	(103, 73)/214	25·2% (20·6–30·6)
All-cause mortality	(2, 2)/297	0·7% (0·2–2·6)	(40, 40)/243	13·9% (10·4–18·5)
Cardiovascular mortality	(2, 2)/297	0·7% (0·2–2·6)	(25, 25)/243	8·9% (6·1–12·8)
Heart failure hospitalisation	(13, 12)/286	4·0% (2·3–7·0)	(63, 47)/214	16·7% (12·8–21·6)
Secondary endpoints				
Improvement in mitral regurgitation at 1 year, n/N (%)	..	..	232/232 (100%)	..
Improvement in New York Heart Association class at 1 year, n/N (%)*	..	..	171/233 (73%)	..
Improvement in Kansas City Cardiomyopathy Questionnaire overall score at 1 year, mean (SE)*	..	..	..	18·4 (1·7)
Decrease in left ventricular end diastolic volume index at 1 year, mean (SE)	..	..	..	−4·7 (1·4)
Additional outcomes				
Cardiovascular hospitalisation	(41, 36)/262	12·0% (8·8–16·3)	(173, 110)/161	38·5% (33·1–44·4)
Stroke	(8, 8)/290	2·7% (1·3–5·3)	(29, 26)/227	9·3% (6·4–13·4)
Disabling stroke	(5, 5)/293	1·7% (0·7–4·0)	(13, 11)/240	3·9% (2·2–7·0)
Non-disabling stroke	(3, 3)/294	1·0% (0·3–3·1)	(16, 15)/230	5·5% (3·3–8·9)
Clinically significant left ventricular outflow tract obstruction induced by transcatheter mitral valve replacement	(0, 0)/297	0·0% (0·0–0·0)	(0, 0)/243	0·0% (0·0–0·0)
Mitral valve reintervention	(8, 7)/291	2·3% (1·1–4·9)	(19, 18)/232	6·4% (4·1–10·1)
Paravalvular leak closure†	(6, 5)/293	1·7% (0·7–4·0)	(12, 11)/235	3·8% (2·1–6·8%)
Valve in valve‡	(0, 0)/297	0·0% (0·0–0·0)	(3, 3)/240	1·2% (0·4–3·6)
Surgical mitral valve replacement§	(2, 2)/295	0·7% (0·2–2·7)	(4, 4)/243	1·5% (0·5–3·9)
Bleeding, MVARC¶	(80, 66)/231	22·1% (17·8–27·2)	(160, 113)/157	39·4% (33·9–45·3)
Major bleeding or above, MVARC¶	(29, 26)/271	8·7% (6·0–12·5)	(62, 52)/207	18·5% (14·4–23·6)
Myocardial infarction requiring revascularisation	(0, 0)/297	0·0% (0·0–0·0)	(1, 1)/242	0·3% (0·0–2·4)
Major cardiac structural complications	(7, 7)/291	2·3% (1·1–4·8)	(8, 8)/241	2·7% (1·4–5·3)
Major access site vascular complications	(9, 9)/288	3·0% (1·6–5·7)	(16, 16)/233	5·6% (3·5–9·0)
Major iatrogenic atrial septal defects‖	(7, 7)/290	2·3% (1·1–4·8)	(14, 14)/235	4·9% (2·9–8·2)
Femoral access complication	(2, 2)/295	0·7% (0·2–2·6)	(2, 2)/241	0·7% (0·2–2·6)
Clinically significant valve thrombosis**	(7, 7)/290	2·3% (1·1–4·9)	(19, 19)/227	6·7% (4·3–10·3)
Haemolysis requiring intervention††	(13, 13)/285	4·3% (2·5–7·4)	(21, 21)/230	7·1% (4·7–10·8)
Atrial fibrillation, new onset	(7, 7)/81	7·9% (3·8–15·8)	(10, 10)/60	11·5% (6·4–20·4)
New permanent pacemaker	(5, 5)/187	2·6% (1·1–6·1)	(10, 10)/146	5·5% (3·0–10·1)
Endocarditis	(0, 0)/297	0·0% (0·0–0·0)	(4, 4)/241	1·5% (0·6–4·0)
Acute kidney injury requiring renal replacement therapy‡‡	(5, 5)/293	1·7% (0·7–4·0)	..	..
Improvement in 6-min walk test at 1 year, mean (SE)	..	..	..	14·4 (6·2)
Days alive and out of hospital at 1 year, median (IQR)	..	..	..	358·0 (342·0–363·0)

Data are (n events, n patients with the event)/n at risk, or Kaplan–Meier estimate % (95% CI), unless otherwise stated. MVARC=Mitral Valve Academic Research Consortium. *Kansas City Cardiomyopathy Questionnaire overall score and New York Heart Association class were site reported. †One surgical paravalvular leak closure. ‡Valve in valve occurred in three patients, two due to device thrombosis and one due to mitral stenosis. §Surgical mitral valve replacement occurred in four patients due to severe paravalvular leak (low dock that caused prolapse on the lateral side with moderate-to-severe lateral paravalvular leak, severe paravalvular leak in the setting of two small linear hypermobile echodensities suspicious for endocarditis, haemolysis in the setting of paravalvular leak, and increased asymmetrical movement of the valve prosthesis resulting in paravalvular leak). ¶Major bleeding or above includes bleeding with the MVARC primary bleeding scale of major, extensive, life-threatening, or fatal. ‖Five major iatrogenic atrial septal defects occurred through discharge; data were site reported. **Clinically significant valve thrombosis includes leaflet thickening with impaired leaflet motion with mitral valve stenosis (increase in mean mitral valve gradient ≥5 mm Hg) and clinical signs or symptoms of mitral valve stenosis. ††Haemolysis requiring blood transfusion or mitral valve reintervention. ‡‡Acute kidney injury was adjudicated up to 30 days, so no value for 1 year is reported.

Table 2: **Key clinical outcomes**

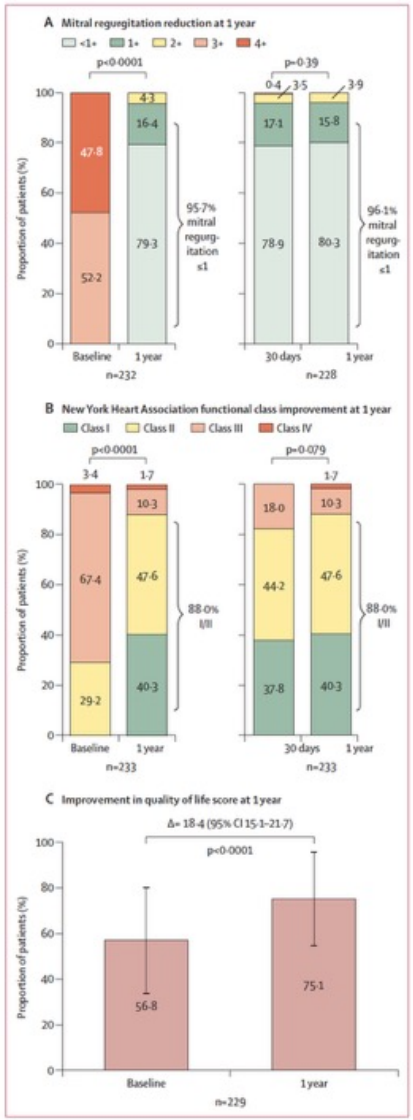


***Figure 3*: Reduction in mitral regurgitation, improvement in functional status, and quality of life at 1 year**

(A) Relative frequency of mitral regurgitation severity grades. Grade <1+ indicates no or trace mitral regurgitation, grade 1+ mild mitral regurgitation, grade 2+ moderate mitral regurgitation, grade 3+ moderate-to-severe mitral regurgitation, and grade 4+ severe mitral regurgitation. (B) New York Heart Association class is a measure of functional status, with a higher class indicating more severe symptoms. Paired comparisons between baseline and 1 year and between 30 days and 1 year are shown. (C) Paired comparisons between baseline and 1 year for the Kansas City Cardiomyopathy Questionnaire overall score, with higher scores indicating better quality of life.

Research in context

Evidence before this study

Before the ENCIRCLE trial, available evidence for transcatheter mitral valve replacement was restricted to early feasibility and early-phase studies, largely involving transapical access, which is associated with higher procedural morbidity and mortality. Specifically, there were no published studies evaluating transseptal transcatheter mitral valve replacement in non-calcified native mitral valves. We searched MEDLINE (via PubMed) for publications between database inception and Sept 9, 2025, using terms "transseptal transcatheter mitral valve replacement in native mitral valve", "transseptal TMVR", and "TMVR in native mitral valve", with no language restrictions. The published studies included registries and early feasibility studies evaluating aortic transcatheter heart valves in mitral annular calcification and failed surgical bioprostheses or annuloplasty rings, as well as early feasibility studies evaluating dedicated mitral transcatheter valves (SAPIEN M3 [Edwards Lifesciences, Irvine, CA, USA], EVOQUE [Edwards Lifesciences], Intrepid [Medtronic, Minneapolis, MN, USA], AltaValve [4C Medical, Maple Grove, MN, USA], and HighLife [HighLife Medical, Irvine, CA, USA]). No pivotal trial had been published for a fully percutaneous, transseptal transcatheter mitral valve replacement (TMVR) system.

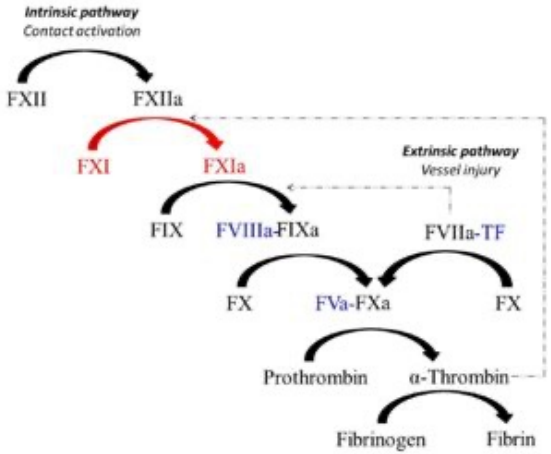
Added value of this study

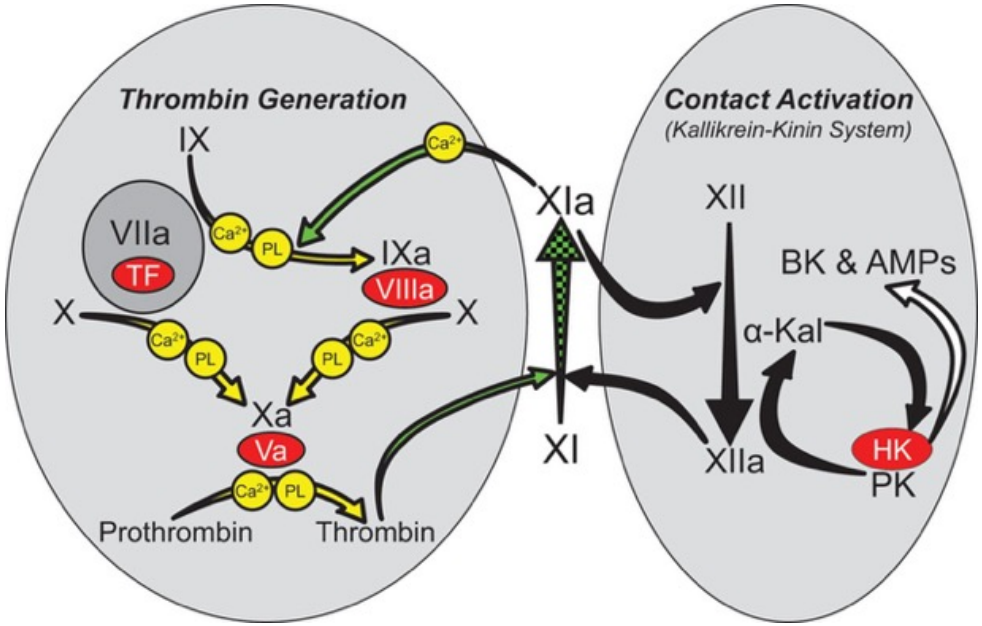
This study reports the primary endpoint results of the ENCIRCLE (sapiEN M3 system transCatheter mItral valve ReplaCement via transseptaL accEss) trial, the first pivotal clinical trial of a fully percutaneous, transseptal TMVR system. The SAPIEN M3 system was evaluated in patients unsuitable for surgery or transcatheter edge-to-edge repair (TEER). The procedure was associated with a low 30-day mortality (0·7% *vs* Society of Thoracic Surgeons predicted risk of mortality of 6·6%; observed-to-expected ratio 0·1), sustained mitral regurgitation reduction (≥95% of patients with grade ≤1 mitral regurgitation at 30 days and 1 year), and a procedural safety profile similar to TEER. Patients had clinically meaningful and durable improvements in symptoms and quality of life.

Implications of all the available evidence

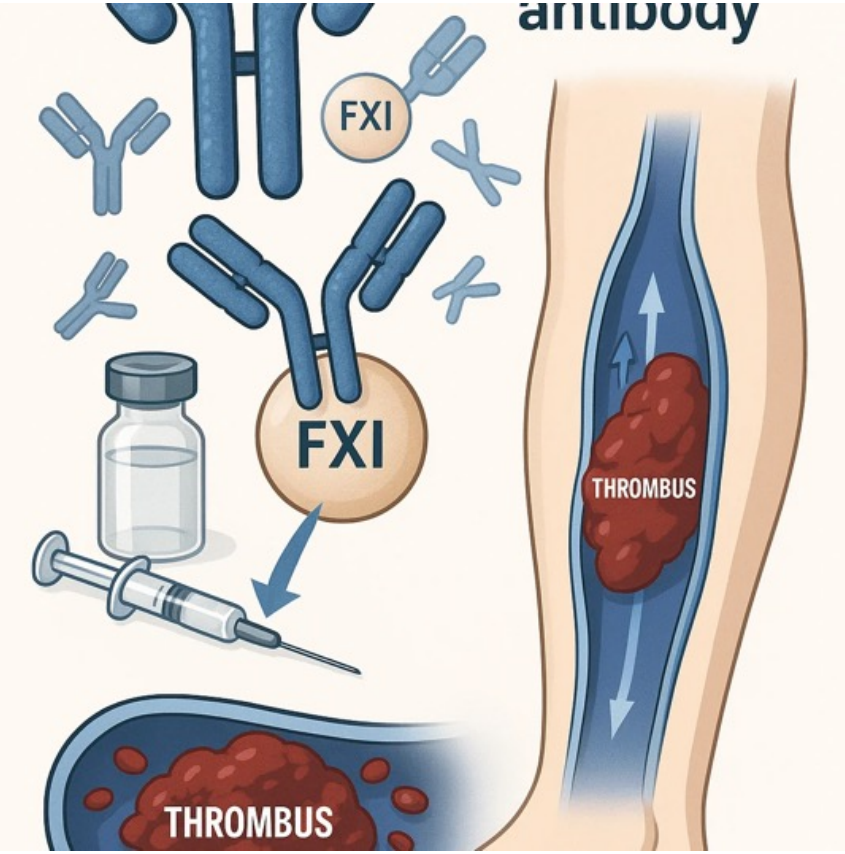
This novel percutaneous TMVR device is the first to show durable mitral regurgitation reduction with procedural safety comparable to TEER. This therapy expands treatment options for patients unsuitable for surgery or TEER and also allows for future reintervention with percutaneous transseptal mitral valve-in-valve implantation in the event of structural valve deterioration. By contrast, reintervention after failed TEER remains a major limitation, as it often renders subsequent transcatheter procedures technically challenging or unfeasible. The capacity for reintervention is therefore a crucial consideration in the lifetime management of mitral regurgitation.

Faktor XI, auch bekannt als **Plasma-Thromboplastin-Antecedent (PTA)** oder **Rosenthal-Faktor**, ist ein Protein, das eine wichtige Rolle bei der Blutgerinnung spielt. Ein Mangel daran kann zu einer angeborenen Blutgerinnungsstörung, der **Hämophilie C**, führen. Diese Störung ist seltener als Hämophilie A und B und äußert sich oft durch verstärkte Blutungen nach Verletzungen oder Operationen, mit geringerer Häufigkeit spontaner Blutungen.





Regeneron Factor XI Antibodies Show Superior Efficacy for VTE Prevention in Phase 2 Trials



Regeneron Pharmaceuticals recently presented Phase 2 clinical trial data on two novel Factor XI antibodies, REGN7508 and REGN9933, demonstrating their antithrombotic effects in patients undergoing unilateral total knee arthroplasty. These data were simultaneously published in The Lancet and presented at the 2025 American Heart Association Scientific Sessions, highlighting the potential of these antibodies to provide effective venous thromboembolism (VTE) prevention with a favorable bleeding safety profile.

Efficacy and safety of REGN9933^{A2} and REGN7508^{Cat} for preventing postoperative venous thromboembolism (ROXI-VTE-I and ROXI-VTE-II): two randomised, open-label, phase 2 trials

Summary

Background Coagulation factor XI (FXI) inhibitors can reduce the incidence of thrombosis without increasing bleeding risk. FXI is activated by factor XIIa (FXIIa) or thrombin. REGN7508^{Cat} is an antibody that binds to the FXI catalytic domain, blocking both its activity and activation by FXIIa and thrombin. REGN9933^{A2} binds to the FXI apple 2 domain and blocks FXI activation by FXIIa. We aimed to compare the efficacy and safety of REGN9933^{A2} and enoxaparin, with apixaban as an exploratory comparator, and REGN7508^{Cat} and enoxaparin for venous thromboembolism prevention.

Methods ROXI-VTE-I and ROXI-VTE-II are randomised, open-label, phase 2 studies in patients (aged ≥50 years) undergoing knee arthroplasty across 15 centres in seven countries and 12 centres in five countries, respectively. In ROXI-VTE-I, patients were randomised (1:1:1) to receive REGN9933^{A2} (300 mg intravenously once), enoxaparin (40 mg subcutaneously once daily), or apixaban (2·5 mg orally twice a day; an exploratory comparator) after surgery. In ROXI-VTE-II, patients were randomised (2:1) to receive REGN7508^{Cat} (250 mg intravenously once) or enoxaparin (40 mg subcutaneously once daily) after surgery. Enoxaparin and apixaban were continued through the day of venography or day 12, whichever was earlier. The primary endpoint in both studies was objectively confirmed venous thromboembolism (a composite of asymptomatic deep-vein thrombosis of the operated leg, objectively confirmed symptomatic deep-vein thrombosis of either leg, or confirmed non-fatal or fatal pulmonary embolism) through day 12 after the first dose of study drug (administered 12–24 h after the end of surgery). In the modified intention-to-treat population (randomly allocated patients who received at least one dose of study treatment and had either an evaluable venogram or confirmed symptomatic venous thromboembolism) for the primary analyses, REGN9933^{A2} or REGN7508^{Cat} was considered superior to enoxaparin if the posterior probability that the log odds ratio (OR) <0 was greater than 95%. For ROXI-VTE-II, the OR was estimated for REGN7508^{Cat} versus the combined enoxaparin groups of ROXI-VTE-I (discounted by half) and ROXI-VTE-II. The main safety outcome was the composite of major and clinically relevant non-major bleeding. ROXI-VTE-I and ROXI-VTE-II are registered with ClinicalTrials.gov (NCT05618808 and NCT06454630).

Findings Patients were enrolled from May 24, 2023, to May 27, 2024, in ROXI-VTE-I (n=373) and from June 27, 2024, to Jan 21, 2025, in ROXI-VTE-II (n=179). The median follow-up time was 74 days (IQR 72–76) for both studies. In ROXI-VTE-I, venous thromboembolism occurred in 20 (17%) of 116 patients in the REGN9933^{A2} group, 26 (22%) of 117 in the enoxaparin group, and 14 (12%) of 113 in the apixaban group through day 12. For REGN9933^{A2} versus enoxaparin, the mean adjusted OR (aOR) was 0·78 (90% credible interval 0·47–1·32); the posterior probability was 78·5%. In ROXI-VTE-II, venous thromboembolism occurred in eight (7%) of 113 in the REGN7508^{Cat} group and ten (17%) of 58 patients in the enoxaparin group through day 12. For REGN7508^{Cat} versus the combined enoxaparin groups, the mean aOR was 0·37 (0·20–0·68); the posterior probability was 99·8%. There were no major or clinically relevant non-major bleeds in any group. The most common treatment-emergent adverse event was postoperative anaemia (nine [7%] of 123 patients in the REGN9933^{A2} group, 11 [9%] of 125 in the enoxaparin group, and 16 [13%] of 125 in the apixaban group in ROXI-VTE-I; and six [5%] of 120 in the REGN7508^{Cat} group in ROXI-VTE-II). Serious adverse events occurred in four (3%), one (1%), and two (2%) patients given REGN9933^{A2}, enoxaparin, and apixaban in ROXI-VTE-I; and in two (2%) patients who received REGN7508^{Cat} and none who received enoxaparin in ROXI-VTE-II. No treatment-related deaths occurred.

Interpretation REGN7508^{Cat} was superior to enoxaparin for venous thromboembolism prevention; REGN9933^{A2} was not superior to enoxaparin. The findings with REGN7508^{Cat} confirm the role of FXI in postoperative venous thromboembolism, and the findings with REGN9933^{A2} suggest that FXIIa-driven FXI activation contributes to this process.

Introduction

Coagulation factor XI (FXI) has emerged as a target for effective anticoagulation without a concomitant increase in the risk of bleeding, because it drives thrombus expansion but is not essential for haemostasis.[1] Thus, individuals with low FXI levels are at a lower risk of venous thromboembolism and ischaemic stroke than those with normal FXI levels,[2,3] but rarely have spontaneous bleeding.[4] Additionally, in phase 2 proof-of-concept studies in patients undergoing total knee arthroplasty, FXI inhibitors significantly reduced the risk of postoperative venous thromboembolism without increasing the risk of bleeding compared with enoxaparin.[5–9]

FXI is positioned in the intrinsic pathway of coagulation, where it can be activated by the active form of factor XII (FXIIa) or thrombin. Activation of FXI appears to be an important step in the pathogenesis of postoperative venous thromboembolism; milvexian, an oral inhibitor of the active form of FXI (FXIa), and abelacimab, an antibody that binds to FXI and blocks its activity and its activation by both FXIIa and thrombin, were associated with a lower risk of postoperative venous thromboembolism than enoxaparin in phase 2 clinical trials.[7,8] Postoperative venous thromboembolism is likely to be triggered by tissue factor exposed at the operative site, which activates coagulation via the extrinsic pathway.[10,11] However, the contribution of FXI activation by FXIIa to the onset of postoperative venous thromboembolism is uncertain.

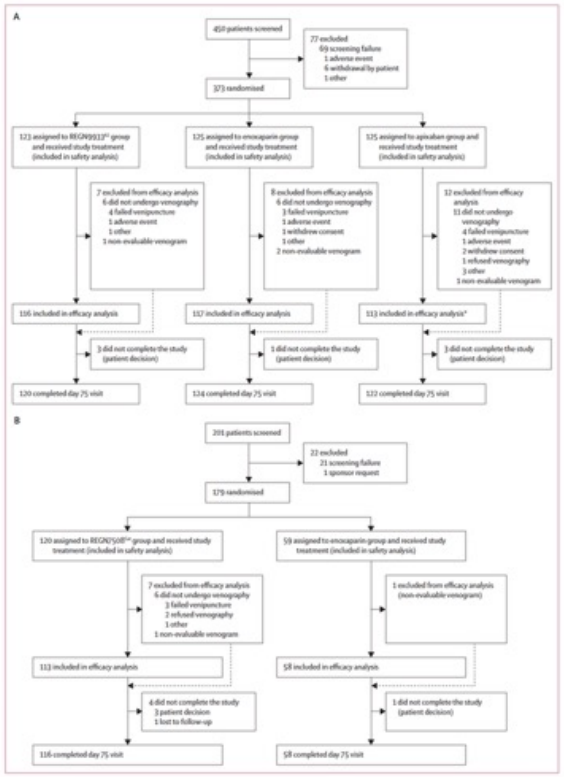


Figure 1: Trial profiles for ROXI-VTE-I (A) and ROXI-VTE-II (B)
*One patient had confirmed symptomatic non-fatal pulmonary embolism in the apixaban group and did not undergo venography; this patient was included in the efficacy analysis.

	ROXI-VTE-I			ROXI-VTE-II	
	REGN9933[A2] group (n=123)	Enoxaparin group (n=125)	Apixaban group (n=125)	REGN7508[Cat] group (n=120)	Enoxaparin group (n=59)
Age, years	66 (60–73)	66 (61–72)	66 (61–72)	67 (61–72)	66 (61–72)
Sex					
Male	28 (23%)	21 (17%)	36 (29%)	28 (23%)	15 (25%)
Female	95 (77%)	104 (83%)	89 (71%)	92 (77%)	44 (75%)
Ethnicity					
Hispanic or Latino	3 (2%)	2 (2%)	4 (3%)	4 (3%)	1 (2%)
Not Hispanic or Latino	120 (98%)	121 (97%)	121 (97%)	115 (96%)	58 (98%)
Not reported	0	2 (2%)	0	1 (1%)	0
Weight, kg	92 (80–103)	90 (80–102)	93 (81–102)	91 (80–101)	85 (77–95)
Estimated glomerular filtration rate, mL/min per 1·73 m²	77 (65–91)	78 (68–92)	79 (67–89)	80 (68–93)	80 (69–90)
Type of anaesthesia					
General	4 (3%)	1 (1%)	3 (2%)	1 (1%)	2 (3%)
Regional	97 (79%)	105 (84%)	96 (77%)	83 (69%)	43 (73%)
More than one type reported	22 (18%)	19 (15%)	26 (21%)	36 (30%)	14 (24%)
Duration of surgery, h	1·4 (1·2–1·8)	1·4 (1·3–1·6)	1·3 (1·2–1·7)	1·5 (1·2–2·0)	1·4 (1·3–2·0)
Tourniquet use	38 (31%)	39 (31%)	42 (34%)	51 (43%)	25 (42%)
Duration of tourniquet use*, min	82 (60–90)	70 (60–90)	75 (62–95)	65 (55–90)	68 (57–91)
Time from surgery to ambulation, days	2 (2–2)	2 (2–2)	2 (2–2)	2 (1–2)	2 (1–2)
Length of hospital stay, days	10 (9–12)	10 (9–12)	11 (10–12)	10 (9–12)	10 (9–12)
Baseline factor XI activity, %	114 (97–138)	113 (91–135)	116 (100–135)	118 (99–135)	121 (105–138)
Baseline activated partial-thromboplastin time, s	28 (25–31)	28 (26–31)	28 (25–29)	28 (26–31)	27 (26–30)

Data are median (IQR) or n (%). *Medians calculated among those with tourniquet use only.

Table 1: **Baseline demographic and clinical characteristics of randomly assigned patients in ROXI-VTE-I and ROXI-VTE-II**

	Patients with event, n (%)			Mean aOR (90% CrI or 90% CI) for REGN9933^{A2} *vs* enoxaparin
	REGN9933^{A2} group	Enoxaparin group	Apixaban group	
Efficacy*	n=116	n=117	n=113	
Venous thromboembolism (primary efficacy outcome)†	20 (17%)	26 (22%)	14 (12%)	0·78 (0·47–1·32)†, posterior probability 78·5%‡
Supportive analysis: frequentist estimates	..	..	..	0·72 (0·41–1·25)§, nominal p=0·32
Components of the primary efficacy outcome				
Asymptomatic deep-vein thrombosis	20 (17%)	26 (22%)	13 (12%)	..
Proximal	0	3 (3%)¶	1 (1%)¶	..
Distal	20 (17%)	26 (22%)	13 (12%)	..
Symptomatic deep-vein thrombosis	0	0	0	..
Non-fatal pulmonary embolism	0	0	1 (1%)	..
Fatal pulmonary embolism	0	0	0	..
Major venous thromboembolism	0	3 (3%)	2 (2%)	0·44 (0·16–1·61)†
Safety	n=123	n=125	n=125	
Major or clinically relevant non-major bleeding‖				
Major bleeding	0	0	0	..
Clinically relevant non-major bleeding	0	0	0	..
Minor bleeding	0	1 (1%)	0	..
Blood transfusion**	1 (1%)	4 (3%)	3 (2%)	..
Adverse events				
≥1 adverse event	27 (22%)	26 (21%)	31 (25%)	..
Serious adverse event	4 (3%)	1 (1%)	2 (2%)	..

aOR=adjusted odds ratio. CI=confidence interval. CrI=credible interval. *Protocol deviations of "procedure (venography) performed outside window" were reported in two patients from the REGN9933^{A2} group and one patient from the enoxaparin group. †Analyses are based on a Bayesian logistic regression model adjusted by country, age group, and treatment group; values in parentheses are 90% CrIs. ‡Posterior probability for the superiority of REGN9933^{A2} *vs* enoxaparin. §The overall aOR is based on the Cochran–Mantel–Haenszel method stratified by country and age group; values in parentheses are 90% CIs. ¶Patients in the enoxaparin and apixaban groups who had proximal deep-vein thrombosis also had distal deep-vein thrombosis. ‖From randomisation through time of venography (or day 12, whichever was earlier). **Blood transfusions were given either as a part of standard of care for total knee arthroplasty or due to an adverse event (postoperative anaemia not related to bleeding events); no blood transfusions due to major bleeding were required.

Table 2: **Efficacy and safety outcomes in ROXI-VTE-I**

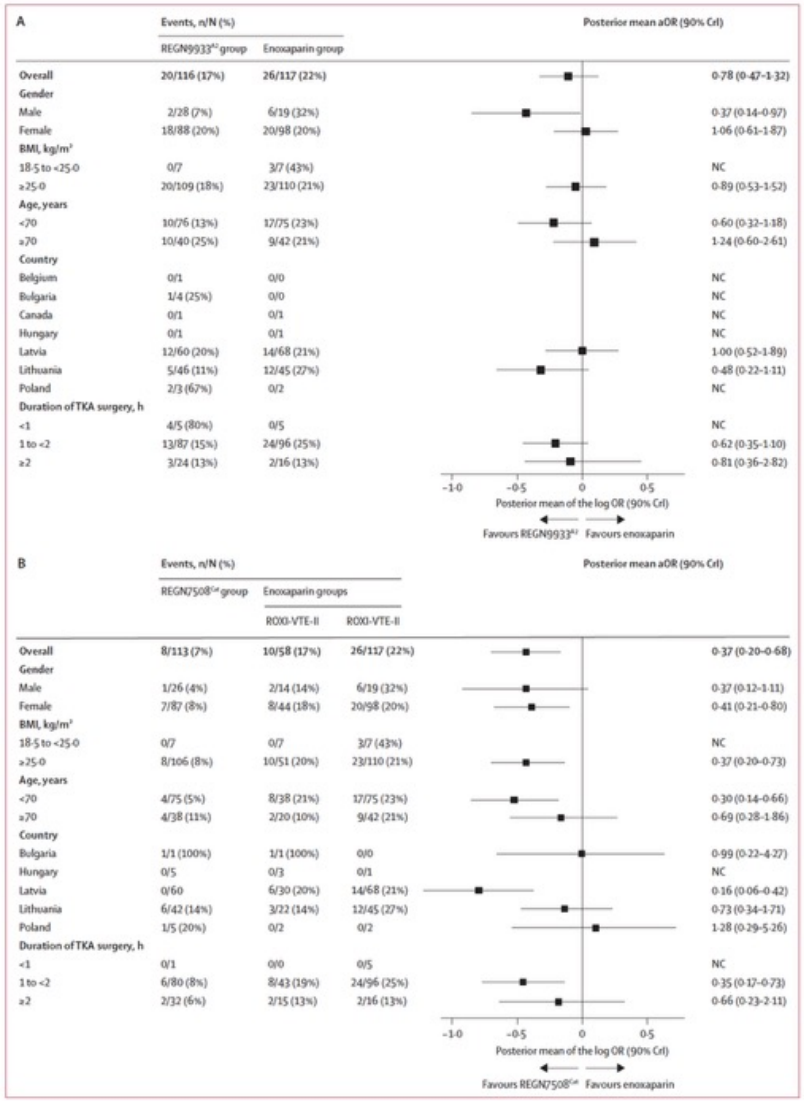


Figure 2: Prespecified subgroup analyses in ROXI-VTE-I and ROXI-VTE-II
(A) Incidence of adjudicated, confirmed venous thromboembolism through day 12 for the comparison of REGN9933[42] versus enoxaparin in ROXI-VTE-I. (B) Incidence of adjudicated, confirmed venous thromboembolism through day 12 for the comparison of REGN7508[1–4] versus enoxaparin in ROXI-VTE-II. Analyses were based on a Bayesian logistic regression model adjusted by country, age group, and treatment group. In ROXI-VTE-I, the aOR is for REGN9933[42] versus enoxaparin. In ROXI-VTE-II, the aOR is for REGN7508[1–4] versus combined enoxaparin (enoxaparin group data from the ROXI-VTE-I was discounted by half). aOR=adjusted odds ratio. CrI=credible interval. NC=not calculated due to absence of responses or insufficient sample size within the subgroup. TKA=total knee arthroplasty.

	Patients with event, n (%)		Mean aOR (90% CrI or 90% CI) for REGN7508^{Cat} *vs* enoxaparin
	REGN7508^{Cat} group	Enoxaparin group	
Efficacy	n=113	n=58	
Venous thromboembolism (primary efficacy outcome)*	8 (7%)	10 (17%)	0·37 (0·20–0·68)*, posterior probability 99·8%†
Supportive analysis: frequentist estimates	..	..	0·38 (0·17–0·88)‡, nominal p=0·04
Components of the primary efficacy outcome			
Asymptomatic deep-vein thrombosis	8 (7%)	10 (17%)	..
Proximal	0	1 (2%)§	..
Distal	8 (7%)	10 (17%)	..
Symptomatic deep-vein thrombosis	0	0	..
Non-fatal pulmonary embolism	0	0	..
Fatal pulmonary embolism	0	0	..
Major venous thromboembolism	0	1 (2%)	0·50 (0·15–1·97)*
Safety	n=120	n=59	
Major or clinically relevant non-major bleeding¶			
Major bleeding	0	0	..
Clinically relevant non-major bleeding	0	0	..
Minor bleeding	0	0	..
Blood transfusion‖	0	0	..
Adverse events			
≥1 adverse event	26 (22%)	17 (29%)	..
Serious adverse event	2 (2%)	0	..

aOR=adjusted odds ratio. CI=confidence interval. CrI=credible interval. *Analyses are based on a Bayesian logistic regression model adjusted by country, age group, and treatment group; enoxaparin treatment groups from ROXI-VTE-I (discounted by half) and ROXI-VTE-II were combined for the data; values in parentheses are 90% CrIs. †Posterior probability for the superiority of REGN7508^{Cat} vs enoxaparin. ‡The overall aOR is based on the Cochran–Mantel–Haenszel method stratified by country and age group; values in parentheses are 90% CIs; the enoxaparin group only includes participants from ROXI-VTE-II. §One patient in the enoxaparin group had both proximal and distal deep-vein thrombosis. ¶From randomisation through time of venography (or day 12, whichever was earlier). ‖Blood transfusions were given either as a part of standard of care for total knee arthroplasty or due to an adverse event (postoperative anaemia not related to bleeding events); no blood transfusions due to major bleeding were required.

Table 3: **Efficacy and safety outcomes in ROXI-VTE-II**

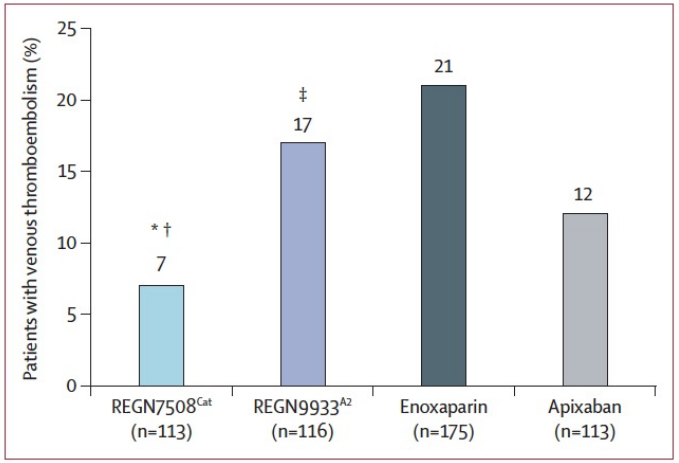


Figure 3: **Supplemental cross-study analyses of the primary endpoint in ROXI-VTE-I and ROXI-VTE-II**

The 95% CI of the risk difference was estimated using the bootstrap approach with 2500 replications. *Risk difference –13·6% (95% CI –21·1 to –6·0) for the REGN7508^{Cat} group versus the pooled enoxaparin group. †Risk difference –5·3% (–13·2 to 2·4) for the REGN7508^{Cat} group versus the apixaban group. ‡Risk difference –3·5% (–12·7 to 5·7) for the REGN9933^{A2} group versus the pooled enoxaparin group. CI=confidence interval.

Research in context

Evidence before this study

We searched PubMed for articles published until June, 2025, using various combinations of search terms "thrombosis", "venous thromboembolism", "anticoagulation", "anticoagulants", "factor XI", "FXI", "FXIa", "prevention", and "treatment". No language or year restrictions were applied. Thrombosis is a significant cause of morbidity and mortality worldwide. The current standard-of-care anticoagulants for the prevention and treatment of thrombosis include vitamin K antagonists, heparins, and direct oral anticoagulants, all of which directly or indirectly target the common pathway of coagulation, although bleeding risk remains a considerable concern. Coagulation factor XI (FXI), a component of the intrinsic coagulation pathway, amplifies thrombus growth but is not essential for haemostasis. Thus, FXI inhibitors could reduce the risk of thrombosis without commensurate effects on haemostasis. This concept is supported by the observations that patients with congenital FXI deficiency are protected from thrombosis but rarely have spontaneous bleeding. New anticoagulants are often assessed in patients undergoing elective total knee arthroplasty as part of initial evaluation, as these patients are at risk for postoperative venous thromboembolism, and efficacy can be evaluated using routine venography after surgery. Previously reported phase 2 trials in such patients compared abelacimab (an antibody that binds FXI and blocks its activity and activation), osocimab (an inhibitory antibody against the active form of FXI [FXIa]), and milvexian (a small molecule FXIa inhibitor) with enoxaparin. Overall, the FXI inhibitors significantly reduced the incidence of venous thromboembolism compared with enoxaparin, confirming the importance of FXI in the pathogenesis of postoperative venous thromboembolism. FXI can be activated by the active form of factor XII (FXIIa) or thrombin; however, attenuation of arterial thromboembolism with FXI inhibitors has not yet been shown, and the contribution of FXIIa-driven FXI activation to postoperative venous thromboembolism is unknown. REGN9933^{A2} and REGN7508^{Cat} are fully human monoclonal antibodies that bind to distinct domains on FXI (REGN9933^{A2} to the apple 2 domain of FXI, blocking its activation only by FXIIa; and REGN7508^{Cat} to the catalytic domain of FXI, blocking its activity and activation by both FXIIa and thrombin). Therefore, these antibodies can be used to assess the relative contributions of FXIIa and thrombin to postoperative venous thromboembolism.

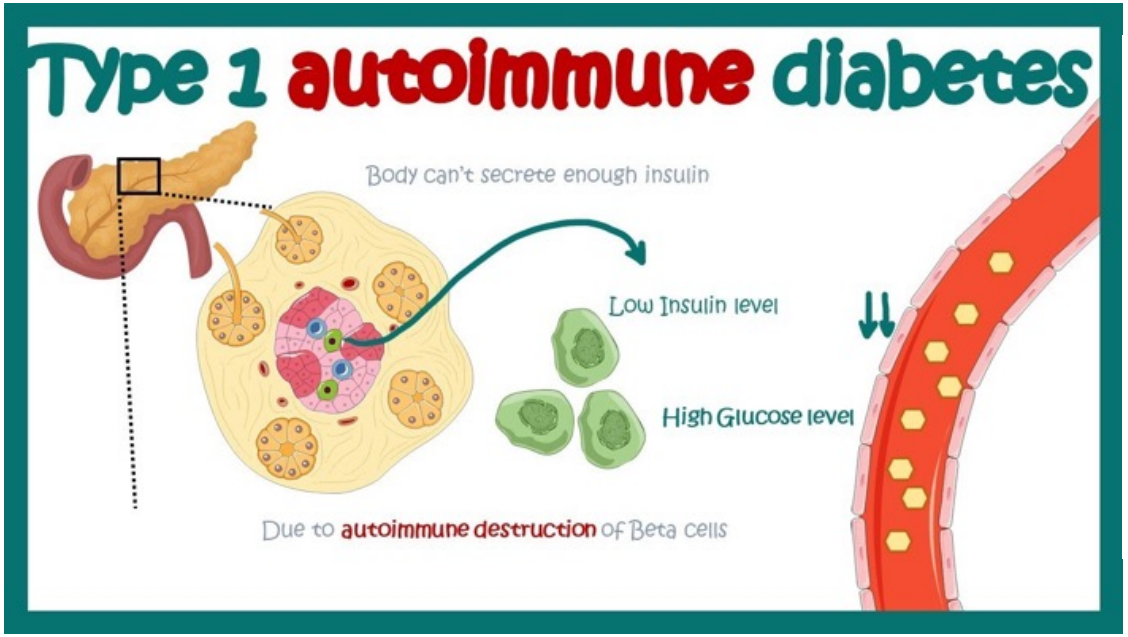
Added value of this study

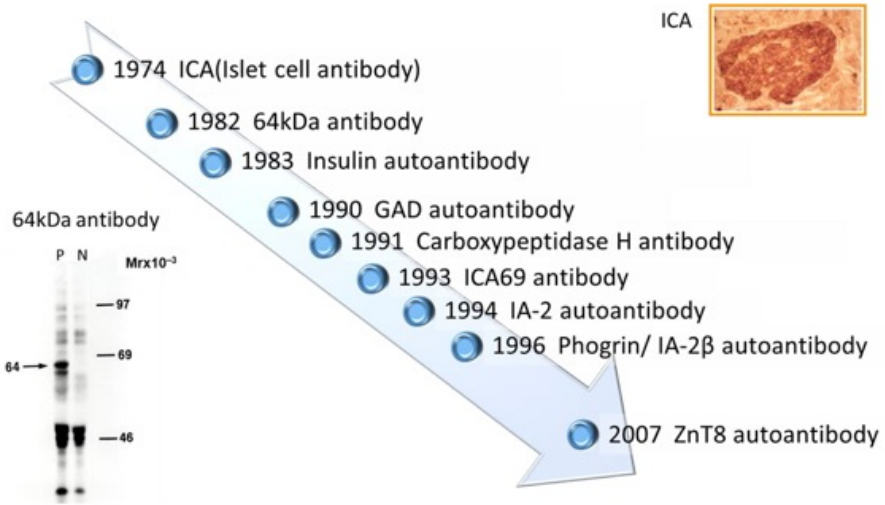
The ROXI-VTE-I and ROXI-VTE-II are two proof-of-concept, phase 2 studies that evaluated the efficacy and safety of REGN9933^{A2} and REGN7508^{Cat}, respectively, compared with enoxaparin in patients undergoing total knee arthroplasty. The results of the studies confirm the role of FXI in the development of postoperative venous thromboembolism. The finding that REGN7508^{Cat} is superior to enoxaparin provides additional evidence that FXI is essential in the pathogenesis of postoperative venous thromboembolism. Although REGN9933^{A2} did not show superiority over enoxaparin, the findings suggest that activation of FXI by FXIIa contributes to the pathogenesis of postoperative venous thromboembolism.

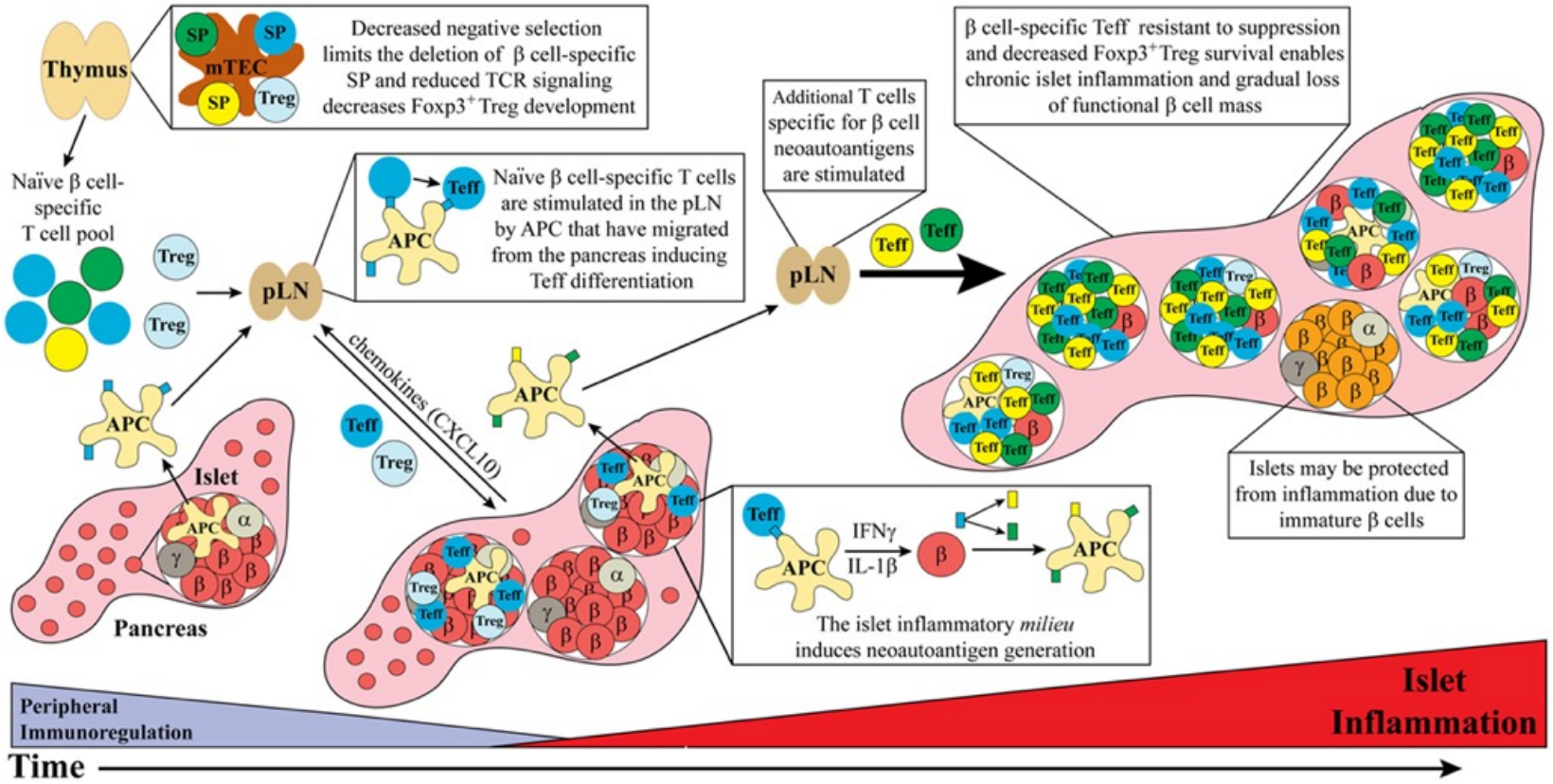
Implications of all the available evidence

The ROXI-VTE-I and ROXI-VTE-II studies provide additional support for the concept that FXI inhibition attenuates thrombosis without increasing the risk of bleeding. Further trials are needed to confirm the safety of REGN9933^{A2} and REGN7508^{Cat}, and to ascertain whether their distinct mechanisms of action enable tailored therapy depending on the driver of FXI activation.

In diabetes, **GAD** refers to **Glutamic Acid Decarboxylase**, an enzyme found in the insulin-producing beta cells of the pancreas. The immune system in people with type 1 diabetes mistakenly produces **autoantibodies** that target and destroy these GAD-containing cells, leading to insulin deficiency.







A peripheral lymph node (pLN) a general term for any lymph node outside of the central lymphatic system, crucial for immune memory against skin and other peripheral infections.

Oral insulin administration is being studied for its **immune-modulating effects** in the context of type 1 diabetes (T1D) prevention and treatment, primarily through a process called **oral tolerance**. The goal is to induce the immune system to tolerate insulin as a self-antigen, thereby slowing or preventing the autoimmune destruction of insulin-producing beta cells.

Immune Modulation Mechanisms

- **Antigen-Specific Immunotherapy:** T1D is caused by self-reactive T cells attacking beta cells. Oral insulin acts as an autoantigen delivered via the digestive system to engage the adaptive immune system in a specific way.
- **Induction of Immune Tolerance:** The gastrointestinal tract is a major site for inducing immune tolerance. When a high dose of insulin is administered orally, it is believed to promote the generation of regulatory T cells (Tregs) that can suppress the activation of the harmful autoreactive T cells.
- **Cytokine Profile Shifts:** This modulation can lead to a shift in the immune response from a pro-inflammatory T-helper 1 (Th1) type to a more anti-inflammatory T-helper 2 (Th2) type, which involves the secretion of regulatory cytokines like IL-10 and TGF-β.

Efficacy of once-daily, high-dose, oral insulin immunotherapy in children genetically at risk for type 1 diabetes (POInT): a European, randomised, placebo-controlled, primary prevention trial

Summary

Background Type 1 diabetes begins with autoimmunity against pancreatic islet antigens, including insulin. The aim of the Primary Oral Insulin Trial (POInT) was to evaluate the efficacy and safety of daily high-dose oral insulin to prevent the development of islet autoantibodies and diabetes.

Methods In this randomised, controlled, primary prevention trial, genetic screening in seven obstetric and paediatric clinics in Germany, Poland, Sweden, Belgium, and the UK identified newborns with a greater than 10% risk of developing islet autoimmunity. Eligible infants aged 4–7 months were randomly assigned in a 1:1 ratio to receive insulin manufactured from human zinc–insulin crystals administered orally at a once-daily dose of 7·5 mg for 2 months, increasing to 22·5 mg for 2 months and 67·5 mg until age 3 years, or placebo. Participants were randomly assigned via a web-based application and were stratified by site. The primary outcome was the development of two or more islet autoantibodies or diabetes assessed throughout follow-up until a maximum age of 6·5 years. A secondary outcome was the development of dysglycaemia or diabetes. Islet autoantibodies were measured in samples collected at baseline and during study visits conducted at outpatient clinics at 2, 4, and 8 months after randomisation, at age 18 months, and every 6 months thereafter. All participants and their family members, investigators of the study, and laboratory personnel remained masked to treatment allocation during the whole study. All randomly assigned participants who correctly fulfilled eligibility criteria and had not reached the primary outcome at the baseline visit (modified intention-to-treat) were included in the primary analysis. All participants who received at least one dose of study drug were included in the safety analysis. POInT is registered with ClinicalTrials.gov (NCT03364868) and is complete.

Findings Of 241 977 screened newborns, 2750 (1·14%) had an elevated genetic risk of developing islet autoimmunity and 1050 (38·2%) of the eligible infants (531 males [51%], 519 females [49%]), were assigned to oral insulin or placebo between Feb 7, 2018, and March 24, 2021. Two participants in the oral insulin group and none in the placebo group were excluded from the modified intention-to-treat analysis. The primary outcome developed in 52 (10%) participants in the insulin group and 46 (9%) in the placebo group (hazard ratio 1·12 [95% CI 0·76–1·67], p=0·57). An interaction between treatment and the *INS* rs1004446 genotype was observed, with an increase in the primary outcome in participants in the insulin group carrying non-susceptible *INS* genotypes compared with the placebo group (2·10 [1·08–4·09]) and protection against diabetes or dysglycaemia in participants in the insulin group carrying susceptible *INS* genotypes compared with the placebo group (0·38 [0·17–0·86]). Blood glucose values less than 50 mg/dL were observed in two (0·03%) of 7210 measurements in the insulin group and six (0·08%) of 7070 measurements in the placebo group. Of 10 252 reported adverse events, 5076 (49·5%) occurred in 507 (96·0%) of 528 participants in the oral insulin group and 5176 (50·5%) occurred in 500 (95·8%) of 522 participants in the placebo group. One death occurred in the oral insulin group and was unrelated to the study drug following independent review.

Interpretation There was no evidence that high-dose, daily oral insulin prevents the development of islet autoantibodies. Further studies are needed to assess the benefit of primary oral insulin therapy for preventing diabetes in *INS* genotype-selected infants.

Orale Toleranz ist ein immunologischer Prozess, der eine Unterdrückung der Immunreaktion auf oral aufgenommene Antigene wie Nahrungsmittel bewirkt. Sie verhindert eine Überreaktion des Immunsystems auf harmlose Substanzen und ist entscheidend für die Aufrechterhaltung der immunologischen Homöostase im Darm. Bei diesem Prozess wird eine systemische Unempfindlichkeit gegenüber Antigenen induziert, die über den Verdauungstrakt aufgenommen werden.

Introduction

Preventing disease through early intervention is a compelling alternative to chronic disease management. Primary prevention of food allergy can be achieved by oral immunotherapy during infancy.[1,2] However, this approach has not been tested for autoimmune diseases.

Type 1 diabetes is an autoimmune disease with an incidence that has increased globally over recent decades.[3] Over 9 million people are living with type 1 diabetes, including 2·7 million in Europe and 1·8 million children and adolescents worldwide.[4] Insulin is a key early autoantigen in childhood type 1 diabetes. Autoantibodies against insulin often appear in genetically susceptible children in the first years of life.[5] This loss of immune tolerance to insulin frequently leads to more generalised islet autoimmunity and clinical diabetes.[6] The autoimmunity against insulin is strongly associated with the HLA DRB1*04-DQB1*0302 haplotype and genotypes of the *INS* gene, which encodes insulin.[7,8]

Attempts have been made to prevent type 1 diabetes in individuals with established islet autoimmunity by administering the insulin autoantigen orally,[9,10] intranasally,[11,12] intravenously, or subcutaneously.[13] Treatment-associated changes in the immune response to insulin were observed in some of the studies, suggesting that the treatment might be immunomodulatory.[12,13] None of these trials achieved their primary outcome of diabetes prevention. However, beneficial treatment effects were observed in subgroup analyses of the oral insulin immunotherapy trials.[9,10,14]

We reasoned that the efficacy of autoantigen-specific therapy would improve if the autoantigen is administered before the development of autoantibodies. Key challenges included the optimal antigen dose and identification of at-risk infants. We previously showed that daily oral administration of high doses (67·5 mg) of insulin was well tolerated, without inducing hypoglycaemia. Treatment was associated with immune responses to insulin with features of immune regulation, primarily in children with a susceptible *INS* genotype.[15,16] We also established a polygenic risk score for islet autoantibodies and diabetes, and assembled a European network to screen newborns for type 1 diabetes genetic risk.[17,18]

The Primary Oral Insulin Trial (POInT) was conducted to establish whether daily oral administration of insulin from infancy is safe and reduces the incidence of autoantibodies and diabetes in children with elevated genetic risk for type 1 diabetes.[19] This is the first trial to assess the efficacy of active oral exposure to an autoantigen before the onset of autoimmunity.

The term "insulin INS genotype" does not refer to a single, simple genotype, but rather to variations within the human **INS gene**, which provides instructions for producing insulin. A key type of variation is the **variable number tandem repeat (VNTR) polymorphism**, where individuals are classified as having Class I or Class III VNTR alleles based on the number of repeat units. The specific VNTR genotype (e.g., I/I, I/III, or III/III) can influence glucose levels and is a factor in diabetes susceptibility.

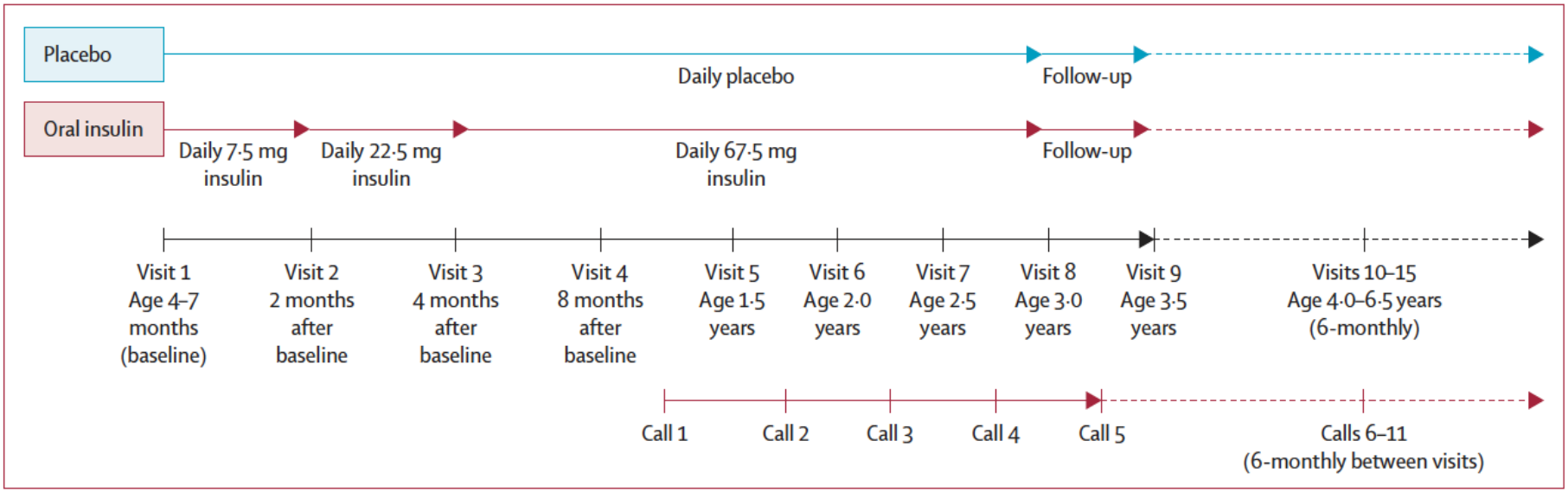


Figure 1: **Trial design**

Each study participant was treated with the study drug until visit 8 (age 3 years) and followed up for at least another 6 months until visit 9 (age 3·5 years, indicated by solid lines). Thereafter, each study participant continued to be followed up until the last study participant completed the minimum follow-up of 6 months, with a maximal follow-up until visit 15 (age 6·5 years, indicated by dashed lines).

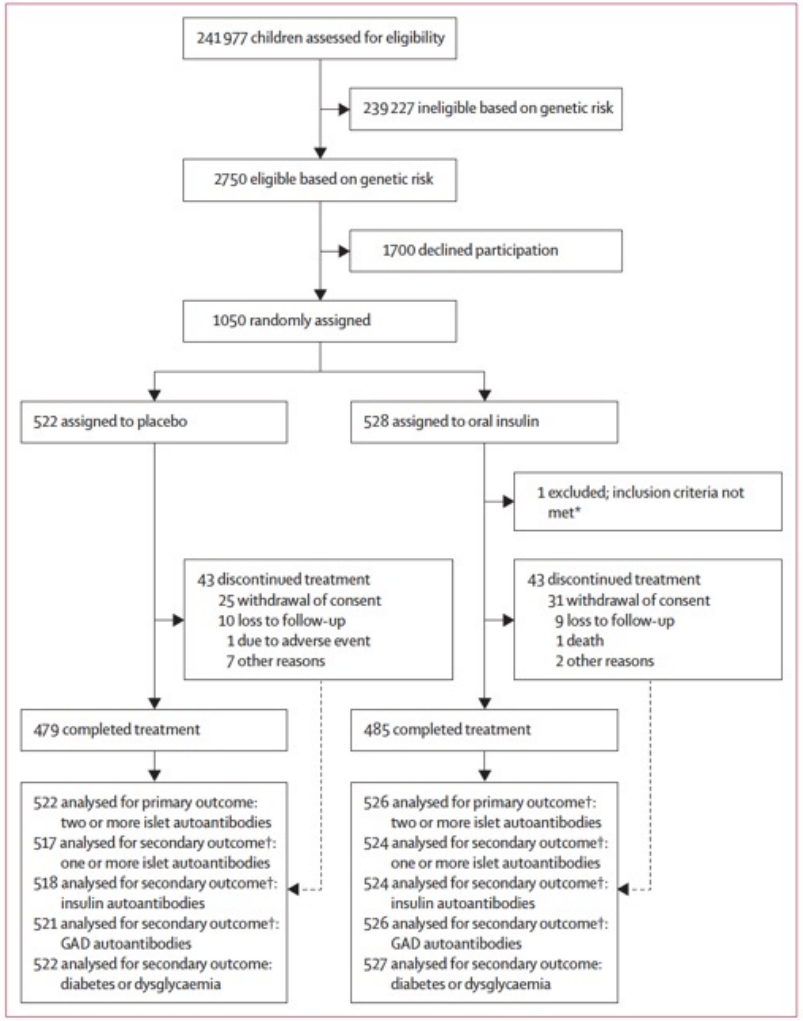


Figure 2: **Distribution of participants in the treatment groups of the trial**
*After randomisation, it was found that the genetic inclusion criteria were not met, as there was no first-degree family history of type 1 diabetes, but only a half-sibling with type 1 diabetes, and the genetic risk score was <14·4. †Outcomes already present at baseline were excluded from the respective analyses.

	Placebo (n=522)	Oral insulin (n=528)	Oral insulin (mITT population*, n=526)
Sex			
Female	260 (50%)	259 (49%)	257 (49%)
Male	262 (50%)	269 (51%)	269 (51%)
First-degree family history of type 1 diabetes	283 (54%)	272 (52%)	270 (51%)
Mother	118 (23%)	105 (20%)	105 (20%)
Father	121 (23%)	127 (24%)	127 (24%)
Sibling	33 (6%)	28 (5%)	27 (5%)
Multiple	11 (2%)	12 (2%)	11 (2%)
HLA genotype			
DR3/DR4-DQ8	280 (54%)	285 (54%)	284 (54%)
DR4-DQ8/DR4-DQ8	44 (8%)	51 (10%)	51 (10%)
DR4-DQ8/other	198 (38%)	192 (36%)	191 (36%)
Study site (country)			
Munich (Germany)	122 (23%)	120 (23%)	120 (23%)
Dresden (Germany)	74 (14%)	77 (15%)	77 (15%)
Hanover (Germany)	55 (11%)	56 (11%)	55 (10%)
Warsaw (Poland)	121 (23%)	121 (23%)	120 (23%)
Malmö (Sweden)	85 (16%)	88 (17%)	88 (17%)
Leuven (Belgium)	40 (8%)	40 (8%)	40 (8%)
Oxford (UK)	25 (5%)	26 (5%)	26 (5%)
INS SNP rs1004446			
CC (T1D risk genotype)	290 (56%)	296 (56%)	295 (56%)
Other	228 (44%)	228 (43%)	227 (43%)
Missing	4 (1%)	4 (1%)	4 (1%)
Age, months	6·1 (5·4–6·5)	6·0 (5·4–6·5)	6·0 (5·4–6·5)
Weight, kg	7·7 (7·2–8·4)	7·8 (7·1–8·5)	7·8 (7·1–8·5)
BMI, kg/m²	17·1 (15·9–18·2)	16·9 (16·0–18·1)	16·9 (16·0–18·1)
Vitamin D3, ng/mL	40·1 (33·0–47·8)	39·2 (32·7–47·0)	39·2 (32·6–46·9)

Data are n (%) or median (IQR). *INS* SNP=insulin gene single nucleotide polymorphism. mITT=modified intention-to-treat. T1D=type 1 diabetes. *For the placebo group, both the modified and initial intent-to-treat populations of the primary outcome were identical.

Table: **Baseline characteristics of participants enrolled in the trial**

Primary outcome: 2 or more antibodies

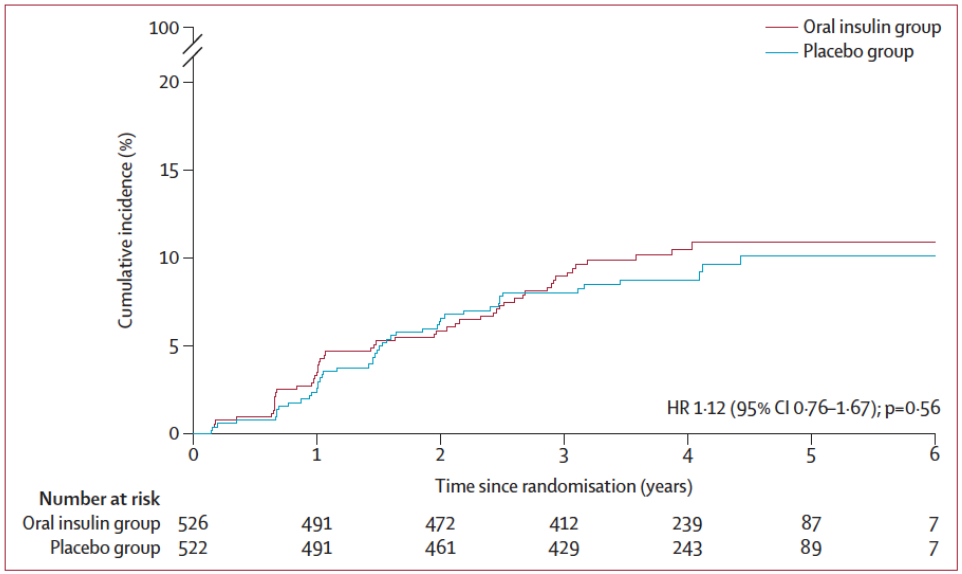


***Figure 3*: Kaplan–Meier curves for the effects of treatment with oral insulin on the development of the primary outcome (two or more islet autoantibodies)**

The red line shows the estimate of the proportions of participants who received oral insulin who developed the primary outcome after randomisation; the blue line shows participants who received placebo and developed the primary outcome. Five participants (two in the insulin group, three in the placebo group) developed diabetes with one preceding islet autoantibody without developing a second islet autoantibody and, therefore, reached the primary outcome at diabetes onset. There is no evidence of a difference in the cumulative risk of developing the primary outcome between the treatment groups. HR=hazard ratio.

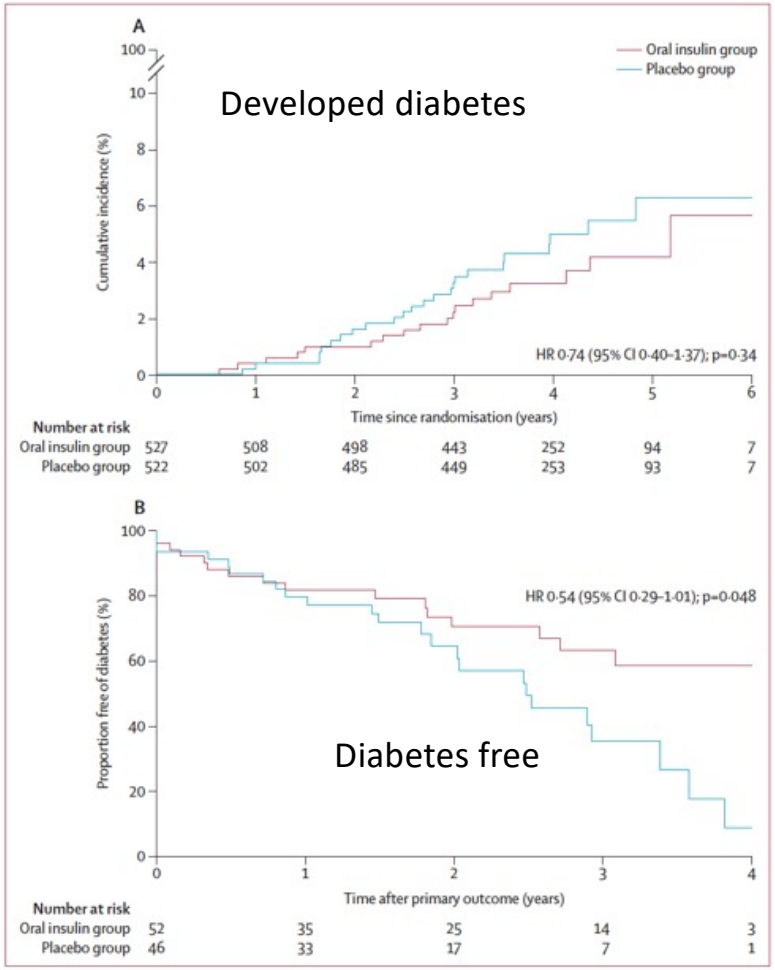


***Figure 4*: Kaplan–Meier curves or the effects of treatment with oral insulin on the development of secondary and exploratory outcomes**

(A) Estimates of the proportions of participants who developed diabetes or dysglycaemia after randomisation among those who received oral insulin or placebo. No evidence of a difference in the cumulative risks was observed between the treatment groups. (B) Proportion of participants with the primary outcome who remained diabetes-free among those who received oral insulin or placebo. HR=hazard ratio.

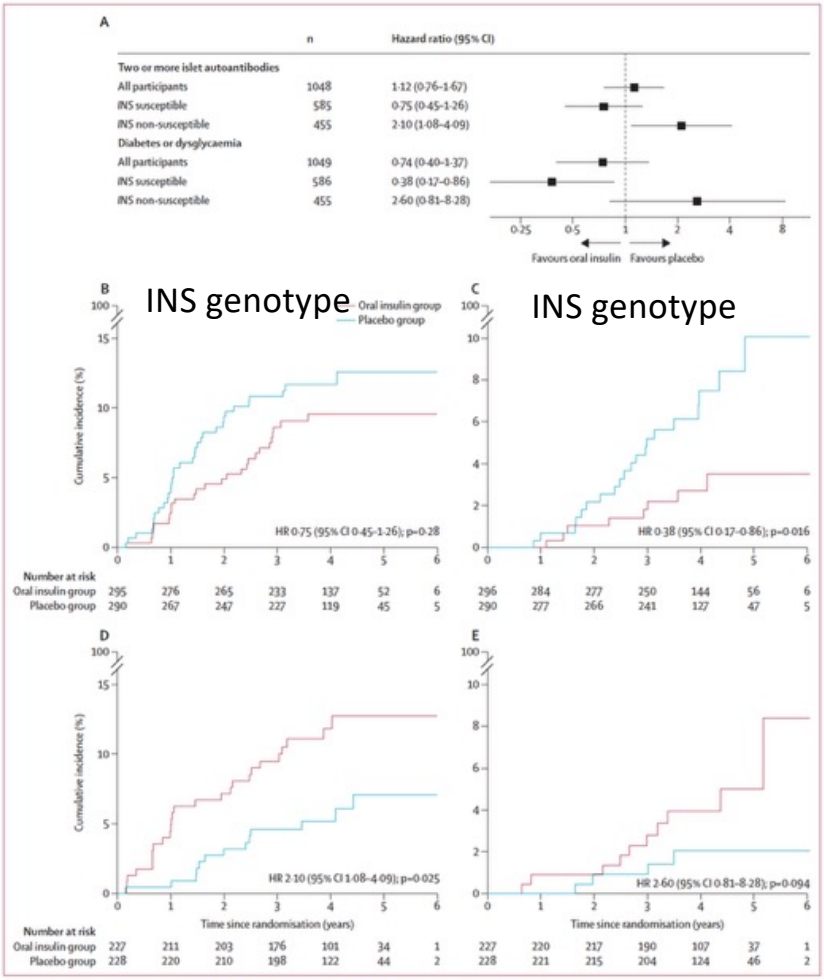


Figure 5: **Subgroup analyses of the effects of treatment with oral insulin, stratified by *INS* genotype (rs1004446)**
(A) Forest plots of the hazard ratios and their 95% CIs for the development of two or more islet autoantibodies (primary outcome) and for the development of diabetes or dysglycaemia (secondary outcome) in the oral insulin group compared with the placebo group, calculated in univariate Cox models. Hazard ratios are reported for all participants and separately for participants with the diabetes-susceptible (CC) or non-susceptible (CT and TT) *INS* rs1004446 genotypes. Kaplan–Meier estimates of the proportions of participants developing the primary outcome (B) and the secondary outcome of diabetes or dysglycaemia after randomisation among participants carrying the type 1 diabetes-susceptible *INS* genotype (C) who received oral insulin or placebo. Kaplan–Meier estimates of the proportions of participants developing the primary outcome (D) and the secondary outcome of diabetes or dysglycaemia since randomisation among participants carrying the type 1 diabetes non-susceptible *INS* genotypes (E) who received oral insulin or placebo. HR=hazard ratio.

Research in context

Evidence before this study

For the background in preparing the protocol (submitted to regulators on July 6, 2017) we searched MEDLINE, PubMed, ClinicalTrials.gov, EudraCT, Embase, the Cochrane Central Register of Clinical Trials, and WHO Clinical Trials Registry Platform from Jan 1, 1990, to March 31, 2017, using the keywords "T1D", "type 1 diabetes", "oral insulin", "oral immunotherapy", "randomised clinical trials", AND "islet autoantibodies" without language restrictions. We also hand-searched reviews with these search terms published between Jan 1, 1990, and March 31, 2017. The search revealed one phase 2b, randomised, double-blind, placebo-controlled secondary prevention trial evaluating the efficacy of once-daily 7·5 mg oral insulin to delay the onset of type 1 diabetes in individuals who were islet autoantibody positive. No treatment effect was observed in the trial, although a post-hoc analysis showed a significant delay in type 1 diabetes in a subgroup with high-titre insulin autoantibodies who received oral insulin. A small, dose-finding, double-blind, randomised controlled study in islet autoantibody-negative children with high genetic risk for type 1 diabetes (Pre-POInT) identified an immune response to insulin in participants who received a once-daily dose of 67·5 mg oral insulin. Searches were updated to March 31, 2025, revealing one phase 2a, randomised, double-blind, placebo-controlled trial of oral insulin at the doses used in POInT (Pre-POInT early), which showed no safety concerns down to an age of 6 months and an association of an immune response to insulin with type 1 diabetes-susceptible *INS* genotypes, but was not designed to assess efficacy. A second phase 2b, randomised, double-blind, placebo-controlled trial done in individuals after the onset of islet autoantibodies (TN07) reported no overall effect of once-daily 7·5 mg oral insulin to delay the onset of type 1 diabetes, but a treatment effect in prespecified strata and in post-hoc analyses in participants with HLA DR4 alleles and IA-2 autoantibodies. No randomised controlled trial assessing the efficacy of treatment with a type 1 diabetes autoantigen administered before the appearance of islet autoantibodies was found. Additional searches were done using the keywords "autoimmune disease", "autoantigen", "oral immunotherapy", "randomised clinical trials", AND "autoantibodies", revealing no additional trials evaluating the efficacy of oral autoantigen immunotherapy for the prevention of autoimmunity before the development of autoantibodies or disease symptoms.

Added value of this study

POInT is the first randomised, double-blind, placebo-controlled trial to test the efficacy of autoantigen-based therapy (oral insulin) for preventing islet autoimmunity and the first to examine the effect of high-dose oral insulin on the development of type 1 diabetes. It is also the first trial to use newborn genetic screening to enrol infants from the general population who are at risk for type 1 diabetes. The study showed the feasibility of newborn screening and recruitment into primary prevention trials, randomly assigning 1050 infants in 3·1 years, and confirmation of the predicted risk of greater than 10% for early stage type 1 diabetes in eligible infants. The primary outcome was the development of early stage 1, 2, or 3 type 1 diabetes (two or more islet autoantibodies or diabetes). The study found that daily oral insulin treatment did not reduce the incidence of islet autoantibodies. A prespecified analysis showed that treatment was associated with a slower progression to clinical (stage 3) type 1 diabetes in participants who developed islet autoantibodies, suggesting that high-dose oral insulin therapy commenced before the onset of autoimmunity delays the onset of diabetes. A key susceptibility gene for type 1 diabetes is the *INS* gene, which encodes the treatment antigen—a major autoantigen target of childhood type 1 diabetes. The study found a pharmacogenetic interaction between the treatment and genotypes of this gene. The treatment protected against developing stage 2 or 3 type 1 diabetes in participants with a susceptible genotype. In contrast, treatment was associated with an increased incidence of islet autoantibodies in participants with a non-susceptible genotype. High-dose oral insulin immunotherapy was safe and well tolerated, suggesting that it is suitable for further trials assessing its therapeutic value in preventing type 1 diabetes.

Implications of all the available evidence

At present, teplizumab is the only drug approved in some countries, including the USA, for delaying the onset of clinical type 1 diabetes in individuals with stage 2 type 1 diabetes. No drug is approved or has shown efficacy in earlier stages or given as a primary prevention treatment. Despite no evidence of an effect on the development of islet autoantibodies, our prespecified analyses suggest that daily oral insulin given as a primary prevention therapy can safely modify disease progression. This provides a premise for suitably powered future trials that test this hypothesis. Furthermore, the novel pharmacogenetic interaction supports the concept of personalised antigen-specific therapy based on a priori genetic selection for susceptibility to insulin autoimmunity (HLA DR4 and susceptible *INS* genotypes) and is supported by the post-hoc observation of oral insulin treatment efficacy in HLA DR4-positive individuals in the TN07 trial. All available evidence, therefore, indicates that autoantigen-specific therapy should be considered as a worthwhile strategy to prevent or delay clinical type 1 diabetes and that the success of this strategy will likely depend on appropriate genetic selection for treatment and timing of the intervention. Genetic selection for trial participation is feasible and successful through newborn screening. Further trials are required to support our observations and to explore different treatment schedules.

Contemporary, non-invasive imaging diagnosis of chronic coronary artery disease

Coronary artery disease is one of the leading causes of morbidity and mortality worldwide. Although it can present with an acute coronary syndrome, it is often characterised by long periods of stability, known as chronic coronary artery disease. This Review presents a comprehensive overview of the diagnosis of the disease, with a focus on cardiac imaging. We discuss various cardiac imaging modalities, including CT coronary angiography, stress echocardiogram, stress single-photon emission CT, PET, and stress cardiac magnetic resonance. We also compare the roles of anatomical (eg, CT coronary angiography) versus functional (eg, stress echocardiogram) tests and examine the potential utility of artificial intelligence in more detail.

CT coronary angiography is the best bet.

Pre-test likelihood of CAD					
	Low	No testing necessary		Option for CAC for ASCVD risk stratification	
	Intermediate–high	Younger patient (<65 years of age)	Or	Less obstructive CAD suspected	CCTA favoured
	Intermediate–high	Older patient (≥65 years of age)	Or	More obstructive CAD suspected	Stress testing favoured

	Favours use of CCTA	Favours use of stress imaging
Goal	• Rule out obstructive CAD • Detect non-obstructive CAD	• Ischaemia-guided management
Availability and expertise	• High-quality imaging and expert interpretation routinely available	• High-quality imaging and expert interpretation routinely available
Likelihood of obstructive CAD	• Age <65 years	• Age ≥65 years
Previous test results	• Previous functional study inconclusive	• Previous CCTA inconclusive
Other compelling indications	• Anomalous coronary arteries • Require evaluation of aorta or pulmonary arteries	• Suspect scar (especially if PET or stress CMR available) • Suspect coronary microvascular dysfunction (when PET or CMR available)

Stress testing information					
	ETT	Stress echocardiography	SPECT MPI	PET MPI	Stress CMR MPI
Patient capable of exercise	●	●	●		
Pharmacological stress indicated		●	●	●	●
Quantitative flow				●	●
Left ventricular dysfunction or scar		●	●	●	●

Figure 1: **Guide to choosing the most appropriate diagnostic test**
Adapted from Gulati et al,[8] by permission of the American Heart Association. Based on the pre-test likelihood—from the American Heart Association and American College of Cardiology's chest pain guideline.
ASCVD=atherosclerotic cardiovascular disease. CAC=coronary artery calcium. CAD=coronary artery disease. CCTA=coronary CT angiography. CMR=cardiovascular magnetic resonance. ETT=exercise tolerance test. MPI=myocardial perfusion imaging. SPECT=single-photon emission CT.

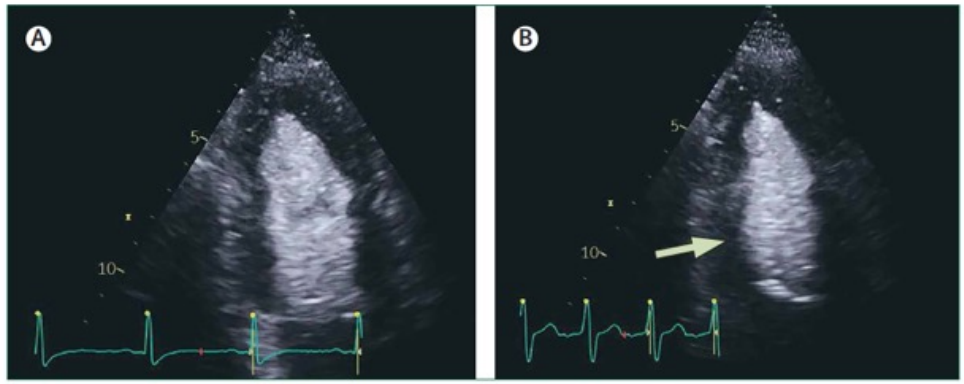


Figure 2: **Pharmacological (dobutamine) contrast stress echocardiography**
An apical, two-chamber view of the left ventricle is shown at baseline (A) and at peak dose (B) in systole. Dyskinesia develops in the right coronary artery territory (indicated by the yellow arrow) at the peak dose (infusion rate) of dobutamine, signifying inducible ischaemia in the right coronary artery territory.

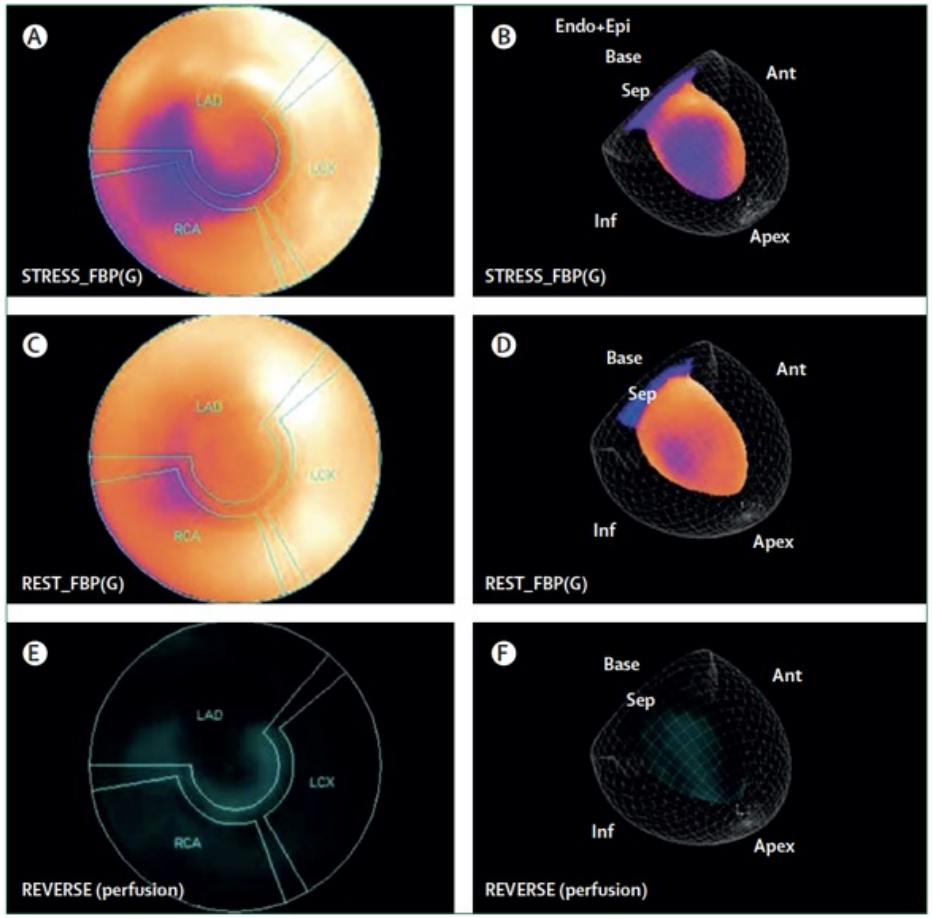


Figure 3: **Pharmacological (dipyridamole) single-photon emission CT myocardial perfusion**
A parametric map (A) and a three-dimensional, surface-rendered model of the left ventricle (B) are shown during maximal hyperaemia and during rest (C, D). Hypoperfusion occurs in the inferior septum or right coronary artery territory after dipyridamole-induced coronary vasodilatation and hyperaemia. Subtraction of the rest and stress images generate a parametric map (E) and a surface-rendered model (F) of the area of hypoperfusion. Ant=anterior. Endo=endocardial. Epi=epicardial. FBP=filtered backprojection. Inf=inferior. LAD=left anterior descending coronary artery. LCX=left circumflex coronary artery. RCA=right coronary artery. Sep=septal.

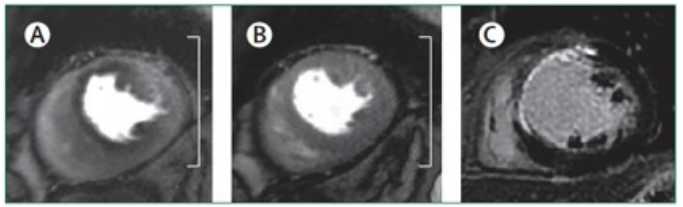


Figure 4: **Stress cardiac magnetic resonance**
(A) An extensive, subendocardial perfusion defect is seen during regadenoson-induced vasodilator stress—ie, a reversible defect. (B) No such perfusion defect is seen at rest, indicating inducible ischaemia in the left anterior descending coronary artery territory. (C) A left anterior descending coronary artery territory infarct on delayed enhancement imaging, which might cause a fixed defect on stress cardiac magnetic resonance.

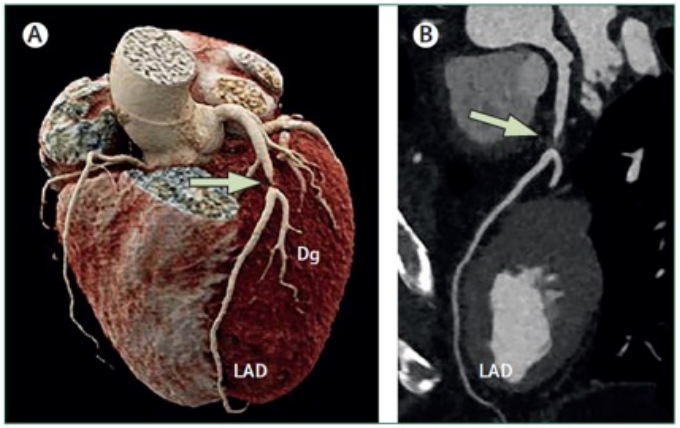


Figure 5: **CT coronary angiography**
A severe, non-calcified lesion can be seen in the left anterior descending coronary artery, just proximal to a large diagonal branch (arrow). (A) Volume-rendered, three-dimensional angiographic reconstruction. (B) Curved multiplanar reformatted image. Dg=diagonal branch. LAD=left anterior descending coronary artery.

Conclusion

Multimodality cardiac imaging, including anatomical (eg, CT coronary angiography) and functional tests (eg, stress echocardiography, SPECT, PET, and stress CMR), allows comprehensive characterisation of patients with chronic coronary artery disease. However, most acute coronary syndromes occur in arterial segments with non-obstructive disease, which can be appreciated on CT coronary angiography but not on functional tests only detecting ischaemia. Based on outcome data from long-term trials showing improved prognostication compared with functional tests and earlier institution of preventive therapies, including lifestyle modification and prescription of aspirin and statins, CT coronary angiography is gaining traction as the initial choice for imaging diagnosis of chronic coronary artery disease, especially in individuals at low risk.

Health care in the USA: money has become the mission

Despite extraordinary scientific and medical resources, the US health-care system underperforms. In this Review we consider the damage wrought by decades of market-based policies that have stimulated profit-seeking by insurers and health-care providers. Policy makers have subcontracted coverage under the public Medicaid and Medicare programmes for people with low incomes and those older than 64 years to private insurance firms—which now derive most of their revenues from those programmes—raising taxpayers' costs and constricting patients' care. Despite worrisome evidence of misbehaviour, firms obligated to prioritise shareholders' interests—and, more recently, private equity firms with a single-minded focus on short-term profit—have gained control of vital clinical resources. President Biden rescinded some of Donald Trump's most egregious first-term policies, expanded coverage for lower-income Americans, and initiated modest drug price controls. Since regaining office, President Trump has laid siege to science and public health, cut US$990 billion from Medicaid to offset tax reductions for the wealthy, and is accelerating Medicare's privatisation. State governments can tighten regulation of profit-driven abuses, and the medical community should resist Trump's health-harming agenda. But neither restoring the pre-Trump status quo, nor further attempts to reconcile the human rights of patients with the property claims of investors will suffice. Reforms must, instead, decommercialise insurance and care provision.

Doctors have doubled; health-care „managers“ have increased 20-fold

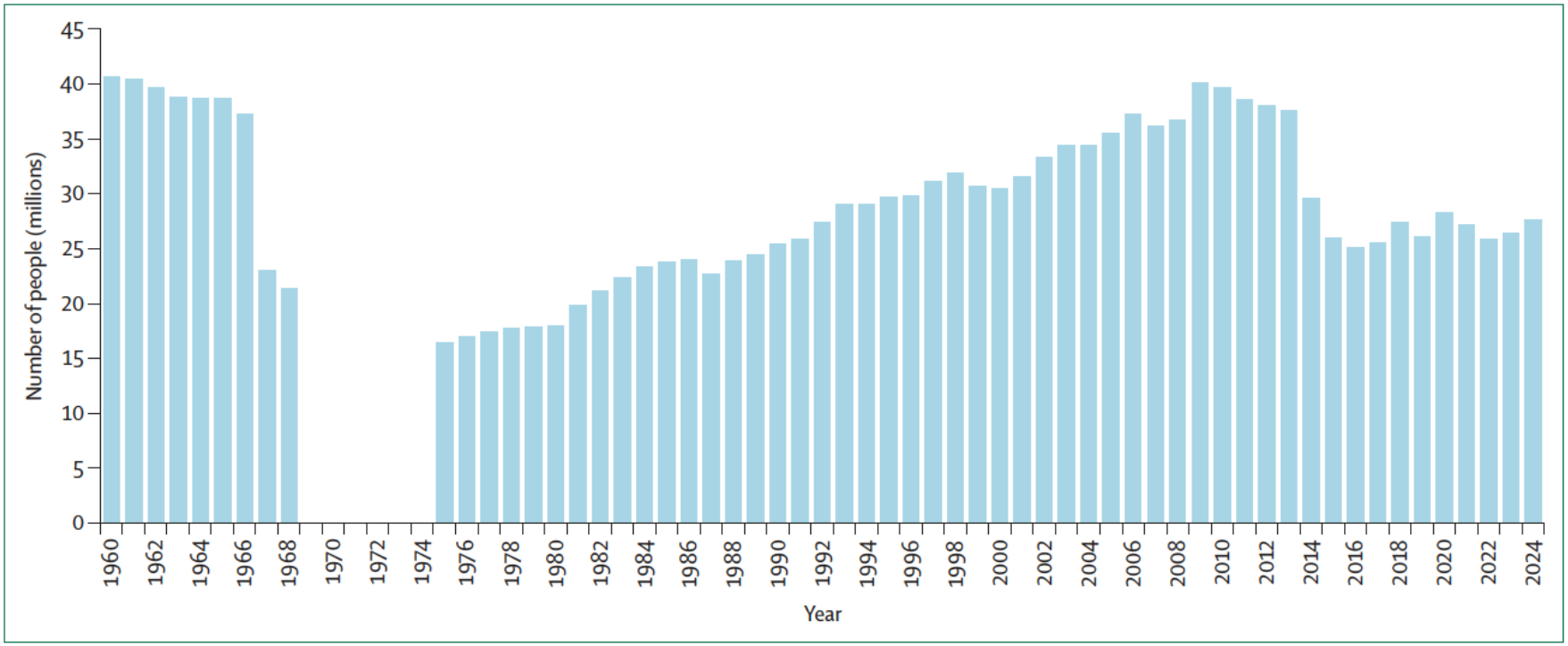


Figure 1: **Number of uninsured people, USA, 1960–2024**

No nationwide survey data available for 1969–74. Data from analysis of data from the Current Population Survey, American Community Survey, National Health Interview Survey, Health Insurance Association of America, and the Social Security Bulletin (Himmelstein DU, Woolhandler S, unpublished).

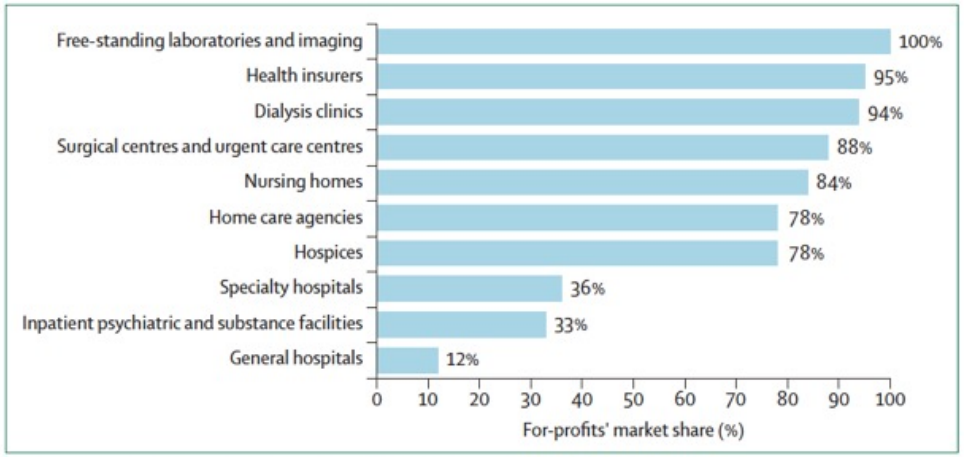


Figure 2: **For-profits' market share of health insurers and facilities, 2022**
Data from the Medicare Payment Advisory Commission data on hospices, and Woolhandler S, Himmelstein DU.[30] Analysis of data from 2022 Service Annual Survey.[16]

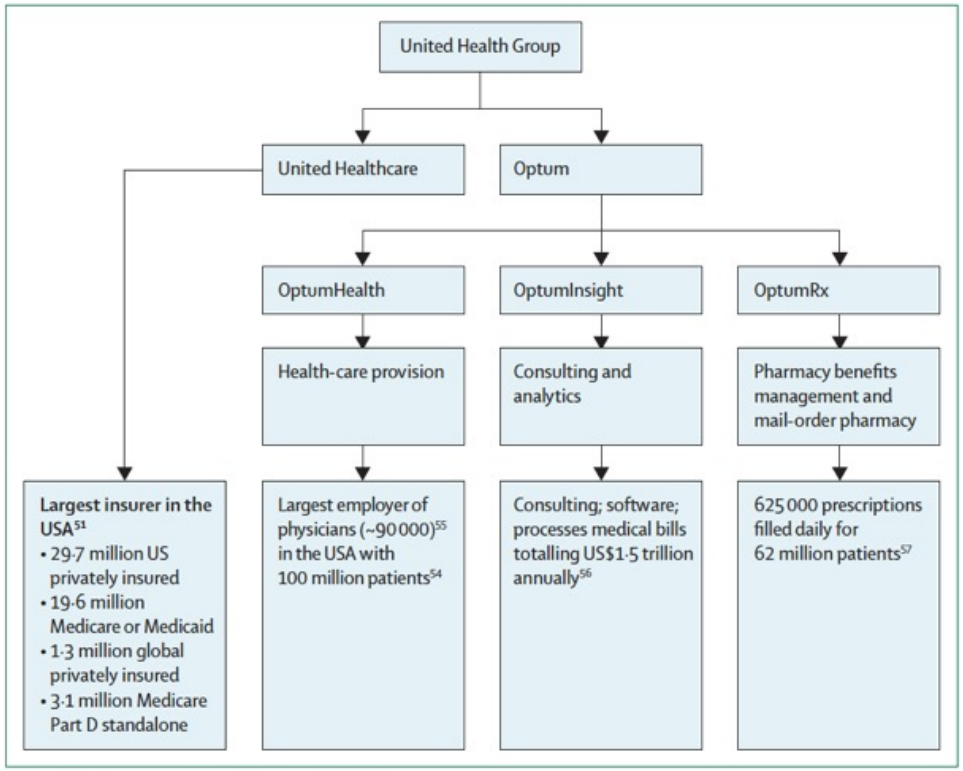


Figure 3: **Health operations of UnitedHealth**

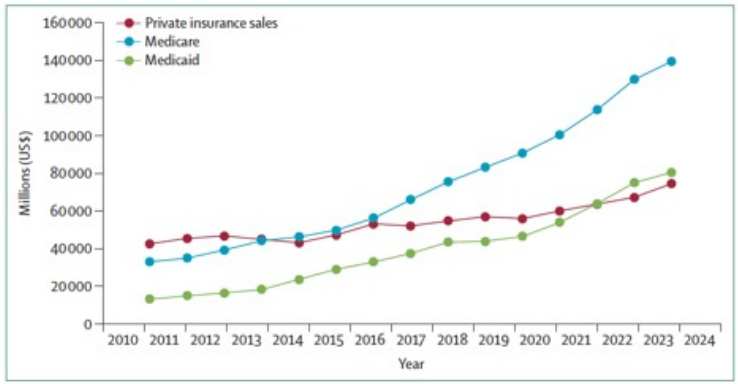


Figure 4: **UnitedHealthcare's health insurance revenues from private and public sources, USA, 2010–24**
Data from UnitedHealthcare Securities and Exchange Commission filings, multiple years: 2023–24 from 2024 annual report;[54] 2020–22 from 2022 annual report;[70] 2017–19 from 2019 annual report;[71] 2014–16 from 2016 annual report;[72] 2011–13 from 2013 annual report;[73] 2010 from 2012 annual report.[74] Private insurance sales represents UnitedHealthcare Employer and Individual—Domestic revenue (global private revenue is excluded from this figure). Medicare represents UnitedHealthcare Medicare and retirement revenue. Medicaid includes health plans and care programmes to beneficiaries of acute and long-term care Medicaid plans, the Children's Health Insurance Program, special needs plans, and Medicare–Medicaid eligible beneficiaries eligible for both Medicare and Medicaid and other federal, state, and community health-care programmes.

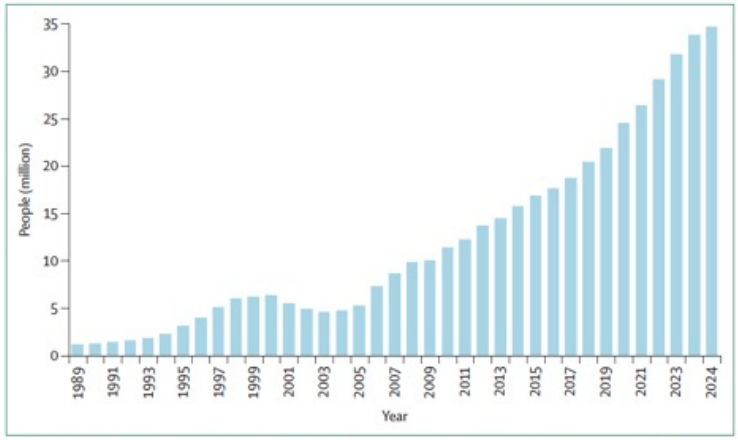


Figure 5: **Number of Medicare beneficiaries enrolled in private Medicare advantage plans, 1989–2025**
Analysis of data from KFF and Centers for Medicare and Medicaid Services (Himmelstein DU, Woolhandler S, unpublished).

***Panel:* How private Medicare Advantage plans have obtained US$612 billion in overpayments from the public Medicare programme since 2007**

At its inception in 1965, Medicare directly paid hospitals, physicians, and other providers on a fee-for-service basis. A 1972 law allowed Medicare beneficiaries to opt for coverage by a private, managed-care plan (now called Medicare Advantage) with the government paying the premiums. A 1982 law expanded the Medicare Advantage programme.

Policy makers advocated such subcontracting of Medicare coverage to private insurers as a cost-saving strategy. However, as detailed in this panel, insurers have raised taxpayers' costs by exploiting loopholes in the formula used to calculate premiums. As a result, Congress' official Medicare Payment Advisory Commission estimates that between 2007 and 2024 the federal government paid private Medicare Advantage plans US$612 billion more than it would have spent to cover Medicare Advantage enrolees in traditional, fully public Medicare.[82]

Medicare Advantage premiums are determined from each enrolee's risk score, an overall measure of severity of illness (and expected costs of care) calculated from a list of the enrolee's diagnoses. Because Medicare Advantage insurers provide the list of diagnoses, they can inflate their premium revenues by listing more (or more severe) diagnoses—so-called upcoding. Plans that enrol 83% of all Medicare Advantage beneficiaries appear to engage in upcoding.[83]

Most Medicare Advantage upcoding is legal, for example tweaking diagnostic labels or padding patients' medical records with inactive problems or irrelevant diagnoses that cost the plan little but boost the risk scores. For instance, labelling a patient's pressure ulcer as stage 3 rather than of unspecified severity can increase the premium by $10 000.[84] Similarly, adding a diagnosis of secondary hyperaldosteronism (even without a confirmatory blood test) for patients with congestive heart failure increased United Healthcare's government-paid premiums by $451 million over 3 years.[85]

Medicare Advantage plans' control of clinicians facilitates such upcoding. Some Medicare Advantage plans manipulate nominally independent physicians by offering them bonuses for recording more diagnoses in patients' medical records.[86] However, purchasing physicians' practices, as UnitedHealth and CVS Health have done, confers more direct leverage than the offering of bonuses.

In many cases, diagnoses are recorded by insurance company administrative staff who comb through patients' charts for laboratory results or old problem lists, or by nurses who make in-home visits to ferret out risk-score-boosting conditions but provide no treatment.[87] Insurance industry lobbying blocked federal regulators' 2014 proposal to outlaw that practice.[88] But outright fraud also occurs; auditors and investigative journalists have found that many plans boost enrolees' risk scores by claiming diagnoses that no doctor ever treated.[89,90]

Upcoding increased UnitedHealths' Medicare Advantage premiums by an estimated $13.9 billion in 2021 (an average of $1,863 per enrolee)[91] and raised taxpayers' payments to all Medicare Advantage plans combined by $38 billion in 2024.[30]

Medicare Advantage insurers garner additional overpayments by cherry-picking—ie, selectively enrolling Medicare beneficiaries who are less ill (and less expensive) than the average patient with a given diagnosis. Patients with the same diagnosis often differ dramatically in the amount (and expense) of care they need. For instance, among Medicare enrolees diagnosed with congestive heart failure, the costliest (presumably sickest) 5% incurred costs 322-fold higher than the least costly 5%.[92]

Cherry-picking is facilitated by severely ill patients' reluctance to switch doctors and hospitals, often required if they choose Medicare Advantage since, unlike traditional Medicare which covers care at virtually any doctor and hospital, Medicare Advantage plans contract with a specific network of providers, often excluding expensive specialised providers such as cancer centres. Additionally, severely ill Medicare Advantage enrolees often encounter managed-care restrictions (eg, requirements to obtain prior approval for expensive care) that might prod them to switch to traditional Medicare, which has few such restrictions. The Medicare Payment Advisory Commission estimates that in 2024, Medicare Advantage plans' cherry picking resulted in $41 billion in overpayments—payments that add to the $38 billion overpayment generated by upcoding. Finally, the US Department of Justice recently ruled that two of the largest Medicare Advantage insurers have paid kickbacks to insurance brokers for steering disabled (and hence unprofitably ill) Medicare beneficiaries away from Medicare Advantage.[93]

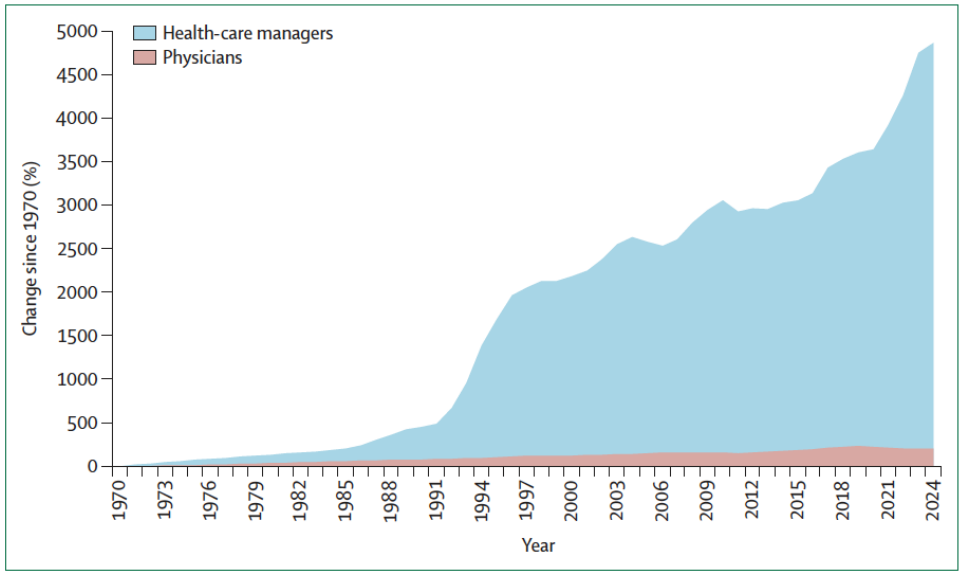


Figure 6: **Growth in the numbers of physicians and health-care managers, 1970–2024**
Analysis of data from the Current Population Survey, Bureau of Labor Statistics and National Center for Health Statistics (Himmelstein DU, Woolhandler S, unpublished).

Although advance at the federal level is unlikely while President Trump is in office, states can implement restrictions and regulations on private equity acquisitions and for-profit ownership of health facilities,[172] mirroring New York's long-standing ban on for-profit hospitals. States can also enforce the spirit, not just the letter, of the many existing laws proscribing non-physician ownership of medical practices, and, like Connecticut, end their subcontracting of Medicaid coverage to for-profit managed care insurers. States where abortion remains legal should (as eight states have already done)[173] pass laws shielding practitioners who tele-prescribe abortion pills to out-of-state residents from extradition demands by abortion-banning states.

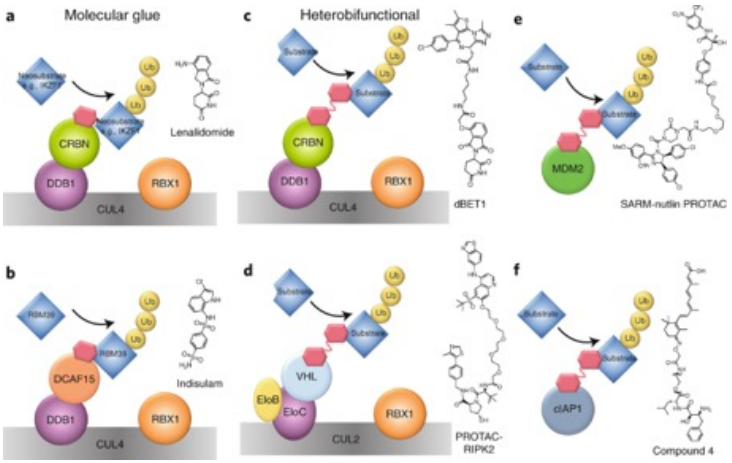
Health professionals should be vocal in opposing the Government's many-faceted assaults on health and human rights, and countering disinformation regarding the benefits of global health cooperation and vaccines, and the health threats posed by war and climate change. However, the severity of the problems of the health-care system calls for reimagining America's health policies, not a return to the failed previous state of affairs.

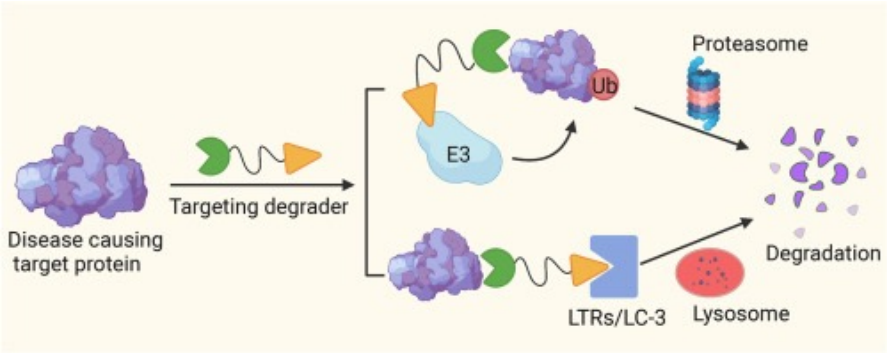
Decommercialised national health insurance, so-called Medicare-for-all, would minimise financial barriers to care,[174] saving many lives.[175] Numerous studies (including by the official Congressional Budget Office) support the fiscal viability of such reform; the hundreds of billions saved annually on insurance-related bureaucracy would fully offset the costs of expanding and improving coverage.[170,176,177]

However, the surge in investor ownership, and the consolidation and profit-seeking among non-profits now necessitate reforming delivery-system ownership, not just payment policies.[178] Communities, not the profit motive, should direct the goals and governance of hospitals and other essential health-care institutions. In some regions, more stringent regulation of non-profits could accomplish this. Where a single health system now dominates and exercises monopoly power, direct public ownership might be more appropriate (but would require compensating current owners for the value of their assets). Public ownership is already the norm in many American communities, where government or hospital districts own and operate local hospitals,[179] as well as in the National Institute of Health Clinical Center, and the Veterans Administration. Such reforms seem improbable today. But political winds have shifted in the past: Hoover's aversion to social spending gave way to Roosevelt's New Deal; after McCarthyism came the Civil Rights and Great Society advances. The health-care destabilisation unleashed by Trump, and the likely backlash as his betrayal of promises (eg, to protect Medicare and Medicaid) become apparent, could open unforeseen options for reform. Public policies created the USA's profligate and brutish health-care system. Repairing it will require radically different policies, not further attempts to reconcile the human rights of patients with the property claims of investors.

Targeted protein degradation (TPD) is a therapeutic strategy that uses the cell's natural waste disposal system to destroy specific disease-causing proteins. Unlike traditional drugs that only inhibit a protein's function, TPD molecules like PROTACs and molecular glues recruit the body's own ubiquitin–proteasome system (UPS) to tag the protein for degradation and elimination. This approach is promising for targeting previously "undruggable" proteins and can be used for diseases like cancer, as well as in other therapeutic areas.

Proteolysis targeting chimeras are PROTACS

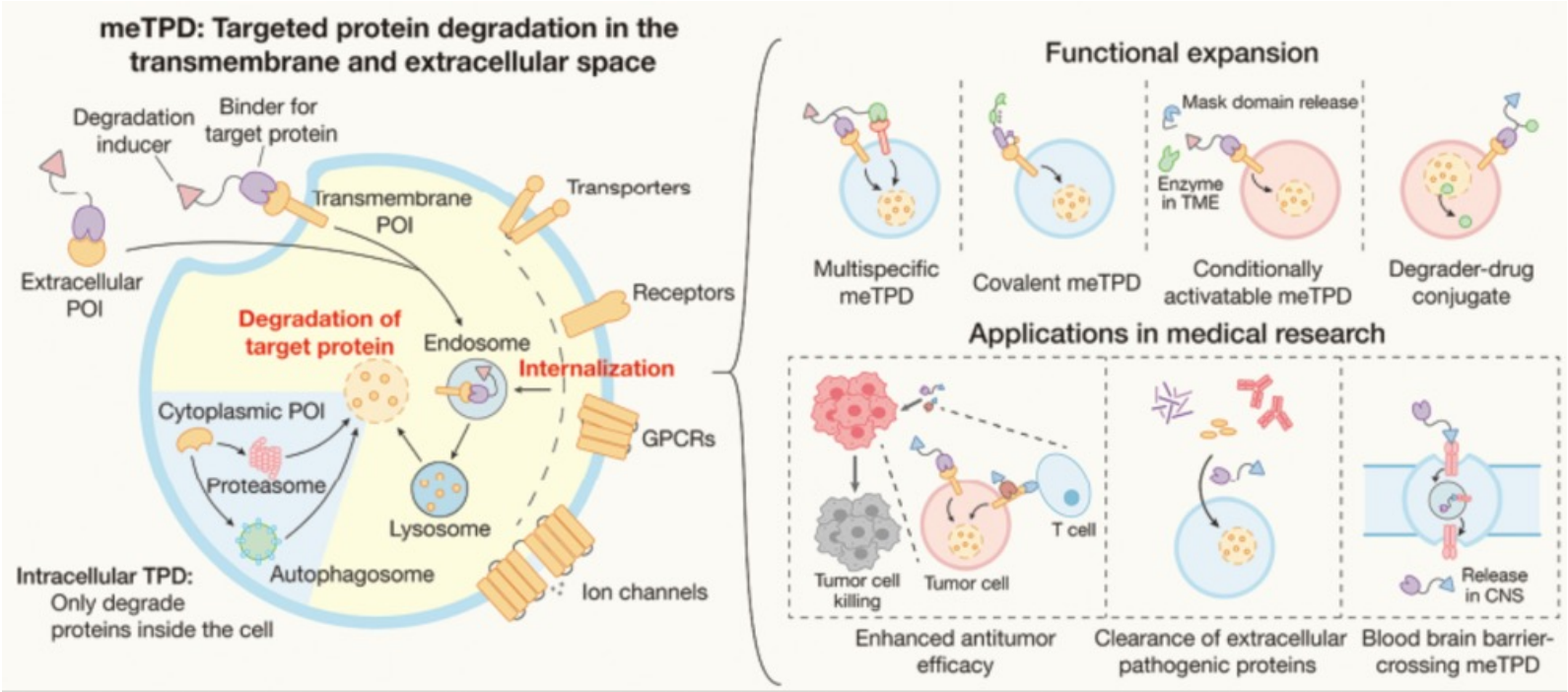




Lenalidomid ist ein Medikament zur Behandlung von Krebserkrankungen wie dem Multiplen Myelom und follikulärem Lymphom. Es gehört zur Gruppe der Immunmodulatoren und wirkt, indem es das Immunsystem gegen Tumorzellen stärkt, das Tumorwachstum hemmt und die Bildung neuer Blutgefäße für den Tumor unterbindet.

Targeted protein degradation in the transmembrane and extracellular space

BACKGROUND: Transmembrane and extracellular proteins play critical roles in maintaining cellular functions and communication, tissue integrity, and overall homeostasis of the body, and their dysfunction is known to cause cancer, neurodegeneration, inflammation, autoimmune diseases, and metabolic disorders. Direct manipulation of membrane proteins often requires the binding of a drug to the target's functional site to modulate its activity. Although targeted protein degradation (TPD) strategies have rapidly emerged as paradigm-shifting technologies to selectively degrade the target protein without necessarily targeting the functional site, classic TPD strategies such as proteolysis-targeting chimeras (PROTACs) and molecular glues are predominantly confined to targeting intracellular proteins owing to the localization of the cellular protein quality-control machinery. Recently, several approaches have emerged as a general strategy for TPD in the transmembrane and extracellular space (meTPD). We review advances in meTPD, including their distinctive features, challenges, and opportunities, as well as their applications in biology, ranging from basic advances to the development of cellular and molecular therapeutics.

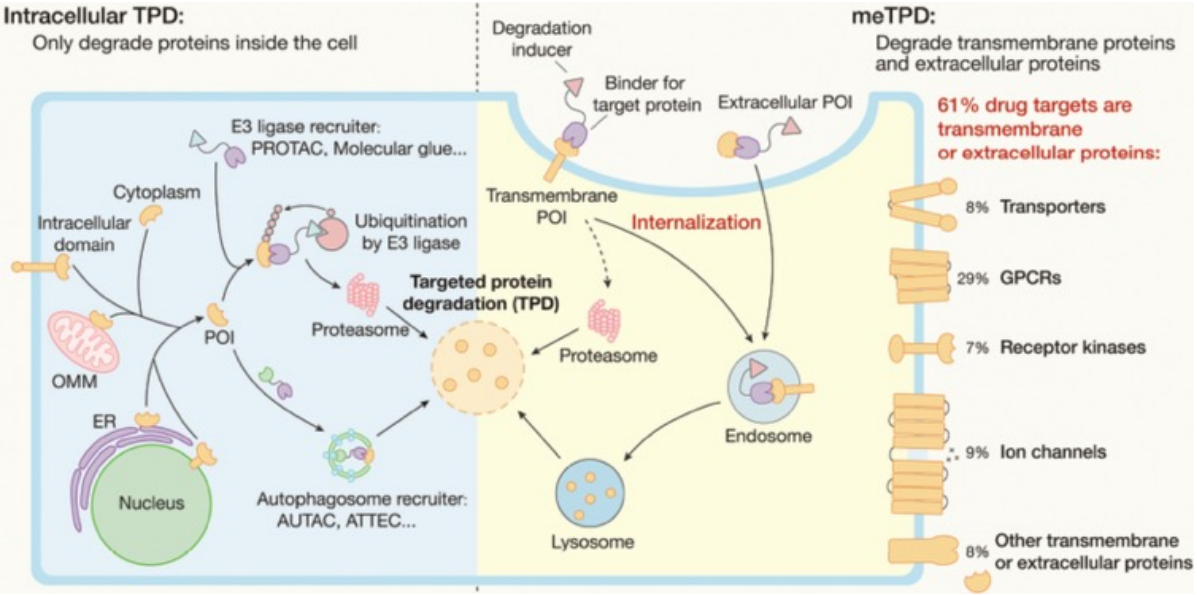


meTPD strategies. meTPD triggers target internalization and subsequent degradation, representing the integration of TPD with intracellular delivery. Beyond the degradation of a single target, emerging concepts in meTPD hold promise for expansion of the meTPD functional repertoire. Development of meTPD also offers broad applications in medical research. CNS, central nervous system; GPCRs, G protein–coupled receptors; POI, protein of interest; TME, tumor microenvironment.

ADVANCES: Since the emergence of the first meTPD strategy in late 2020, more than 30 distinct meTPD concepts have been developed, with large variance in their modalities and mechanisms. meTPD demonstrates notable efficacy, exceeding 70% in many cases and beyond 95% after optimization. The fundamental mechanistic distinction between meTPD and classic intracellular TPD is that the former needs to direct the target protein to enter the cell from the cell surface or extracellular space. Rather than a simple or natural extension of intracellular TPD, meTPD represents the integration of TPD and intracellular protein delivery. We highlight key concepts and developments, including the development of meTPD degraders that undergo rapid endocytosis, as well as unmet needs and several emerging directions that hold promise for advancing the meTPD field, including covalent, multispecific, and conditionally activatable meTPD strategies.

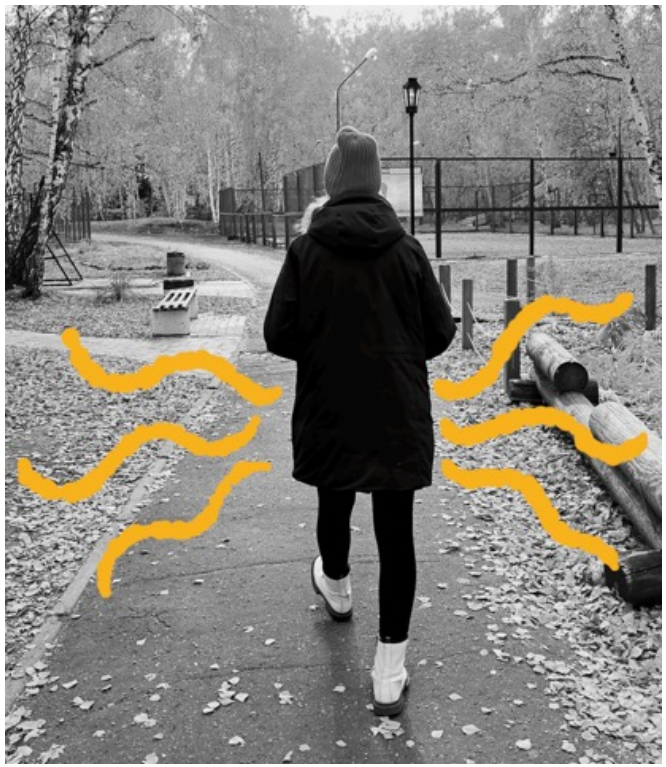
OUTLOOK: meTPD holds great potential for biological research through rapid, convenient, and reversible membrane protein degradation, avoiding the issue of compensation and variation in genetic backgrounds. Furthermore, although meTPD development is in the early stages, several strategies have led to the founding of biotech companies, highlighting the rapidly growing interest in the pharmaceutical industry as well as the therapeutic potential of meTPD. For example, the meTPD chimera BHV-1300 has entered a phase 1 clinical trial; in preclinical studies as a treatment for myasthenia gravis, it exhibited faster immunoglobulin G (IgG) reduction with intermittent dosing than the mainstream FcRn inhibitors. Because meTPD degraders undergo internalization and endocytosis to achieve target degradation, they also offer a platform for intracellular delivery of various cargoes, such as toxins, signaling modulators, and antigen peptides. As an example, the combination of meTPD and small interfering RNA has facilitated simultaneous target degradation and gene silencing. We anticipate that meTPD-based drug and tracer delivery and vaccine generation will have far-reaching clinical impact.

Proteolysis targeting chimeras PROTACS



meTPD expands the landscape of TPD to the transmembrane and extracellular space. By circumventing the need for functional blockage, TPD enables the induced degradation of diverse proteins, including many undruggable targets. Classic TPD strategies, such as PROTACs and molecular glues, primarily degrade intracellular proteins; however, nearly 61% of drug targets are transmembrane or extracellular proteins, including transporters, receptor kinases, G protein–coupled receptors (GPCRs), ion channels, and others. Emerging meTPD strategies address this gap through the targeted degradation of transmembrane and extracellular proteins and potentially offer broad therapeutic applications in degrading these proteins, many of which remain as challenging or undruggable targets for conventional occupancy-driven pharmacology. AUTAC, autophagy-targeting chimera, ATTEC, autophagy-tethering compounds; ER, endoplasmic reticulum; OMM, outer mitochondrial membrane.

Try a ‘fart walk’ to ease the pressure after that big Thanksgiving meal



Is there an easy way to relieve gas without medication?

The warm fuzzy feeling you get from a delicious holiday meal can be quickly eclipsed by the gassy one that follows. Fortunately, gastroenterologists have an old trick for this: Take a fart walk.

I recommend trying a leisurely walk until you start to feel better. But, in theory, any mild physical activity works. Controlled experiments have found that even gentle cycling is more than sufficient to relieve trapped gas.

If the siren call of the couch beckons nonetheless, resist the urge to lie down. Intestinal gas passes about 33 percent more efficiently when you’re sitting upright than when you’re horizontal.