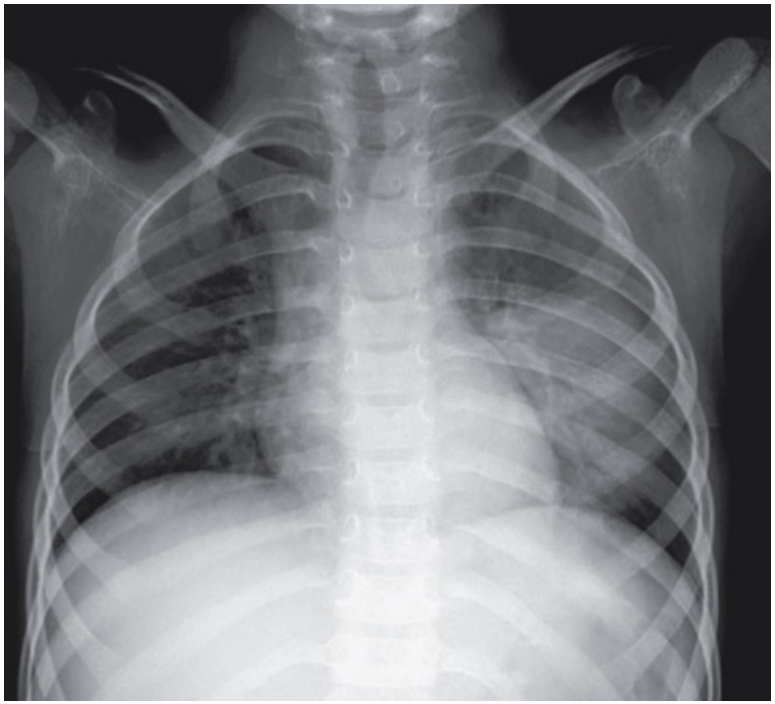
https://www.mdc-berlin.de/de/veroeffentlichungstypen/clinical-journal-club

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 previously healthy 4-year-old girl presented to the emergency department with a 3-day history of dry cough and fever. On physical examination, intercostal retractions and decreased breath sounds over the left lung were observed. A chest radiograph is shown. What is the most likely diagnosis?

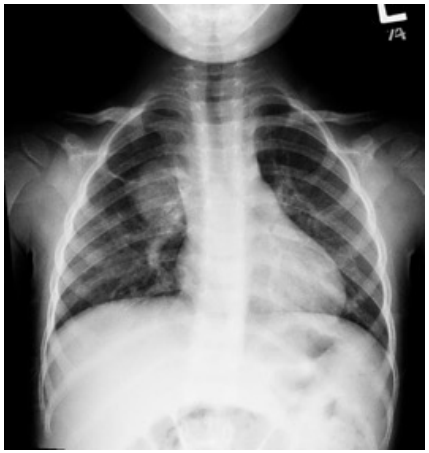
Bronchogenic cyst
Pulmonary abcess
Pulmonary infarct
Pulmonary metastasis
Round pneumonia

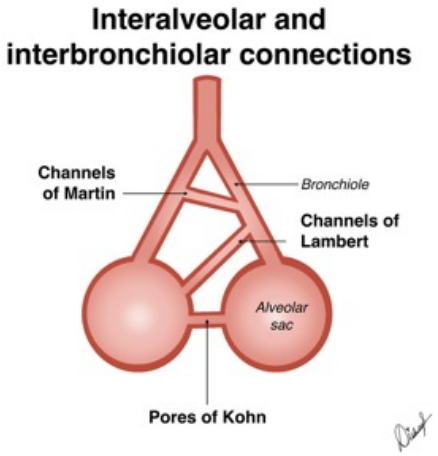
A diagnosis of round pneumonia was made. Round pneumonia refers to the presence of a spherical or rounded lesion on chest imaging in young children with pneumonia. In early childhood, pathways of collateral ventilation — particularly the small openings between adjacent alveoli and between bronchioles and alveoli — are poorly developed, so pulmonary consolidation may be more delineated and compact than in adults. Air bronchograms may not be visible in all cases of round pneumonia, but are in this case (frontal view, arrows).

Round pneumonia is a type of pneumonia usually only seen in pediatric patients. They are well defined, rounded opacities that represent regions of infected consolidation.

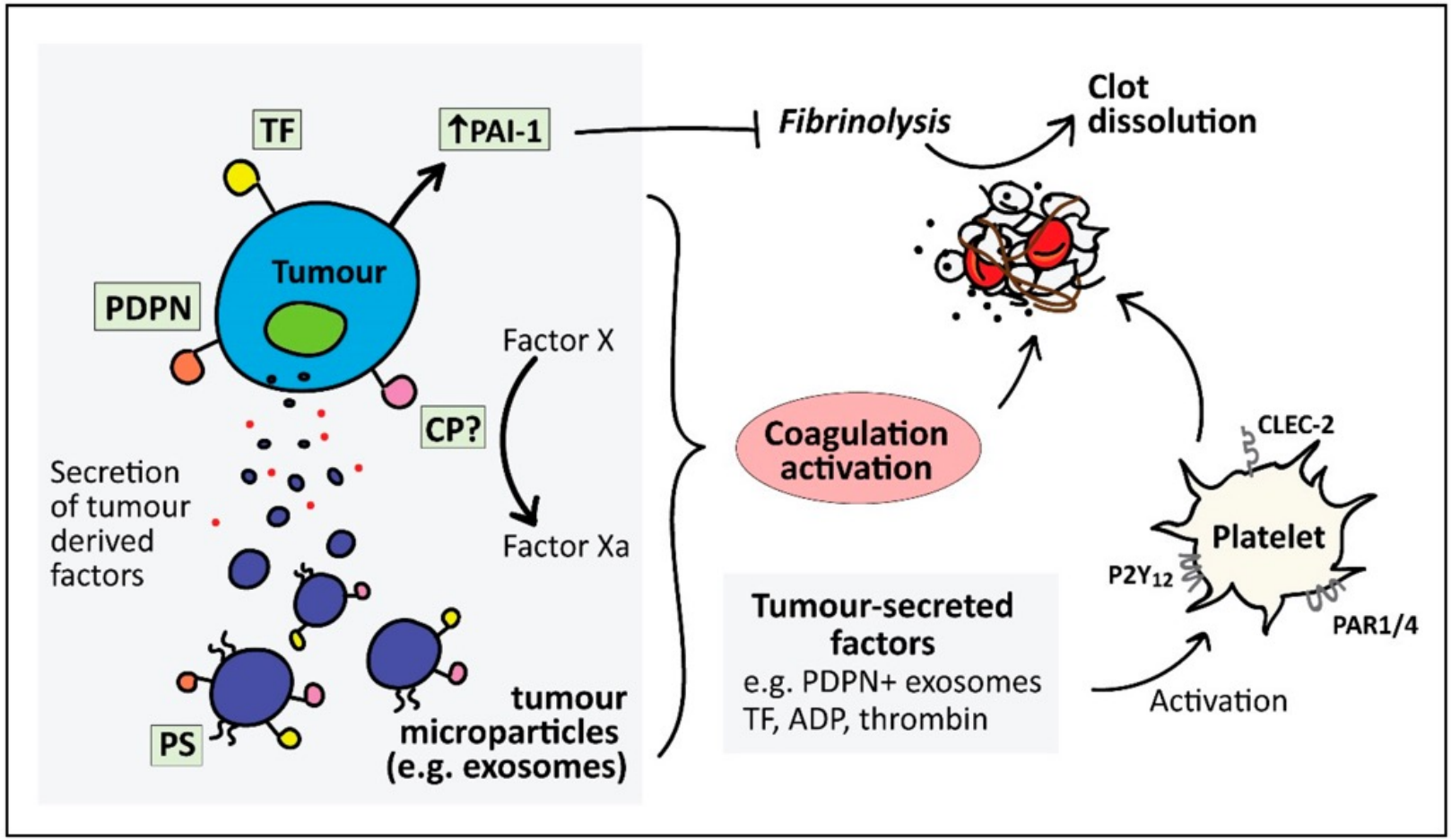
The mean age of patients with round pneumonia is 5 years and 90% of patients who present with round pneumonia are younger than 12 years 5. Round pneumonia is uncommon after the age of 8 years because collateral airways tend to be well developed by this age.

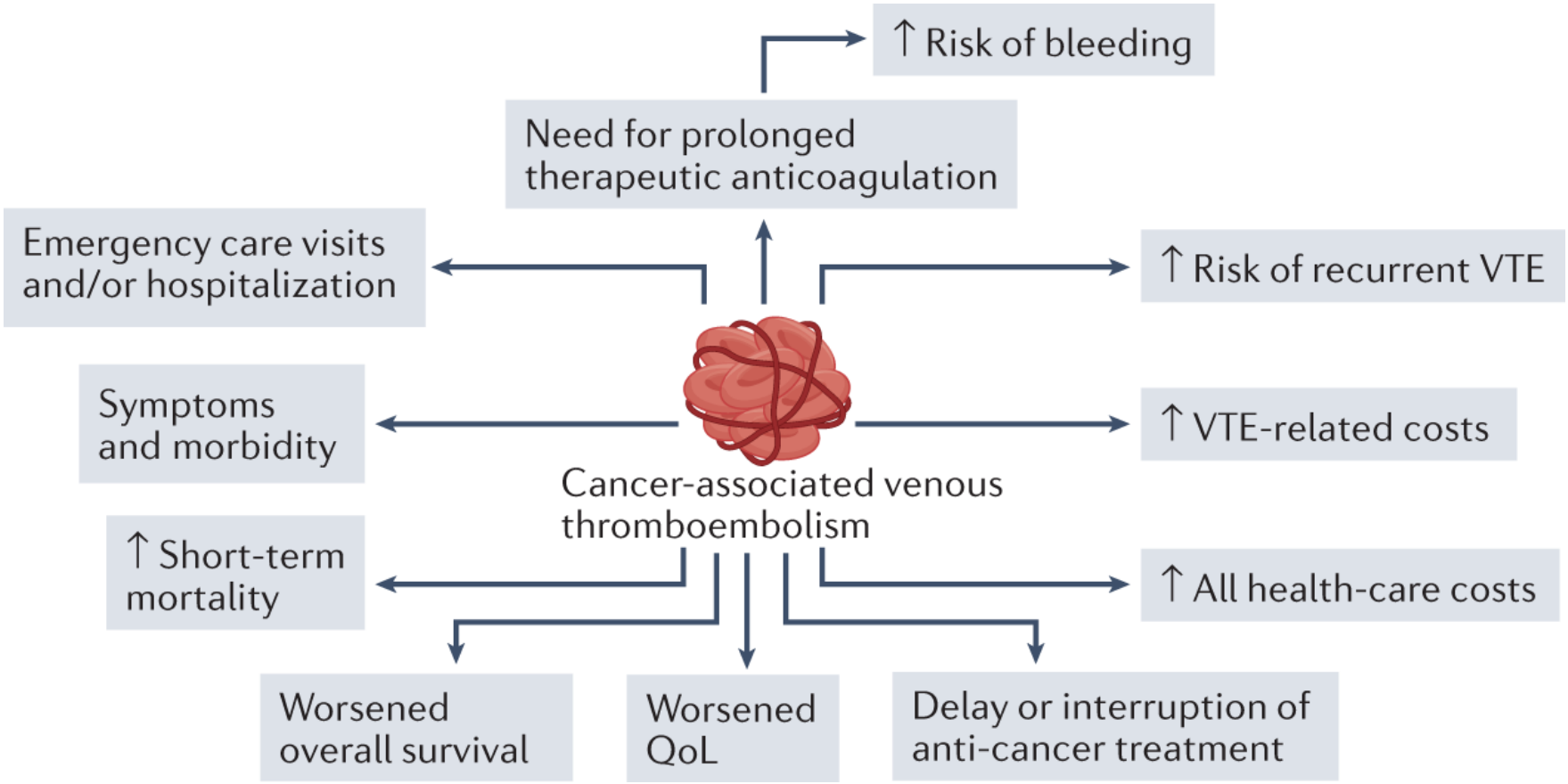
The proposed theory as to why children develop round pneumonia and adults do not, relates to the development of inter-alveolar communications and collateral airways. These are called pores of Kohn and canals of Lambert, and when they develop, they allow air-drift between the parenchymal subsegments. In adults, these allow lateral dissemination of infection throughout a lobe, leading to lobar pneumonia. In children, where these have not developed, the limited spread of infection results in round pneumonia.





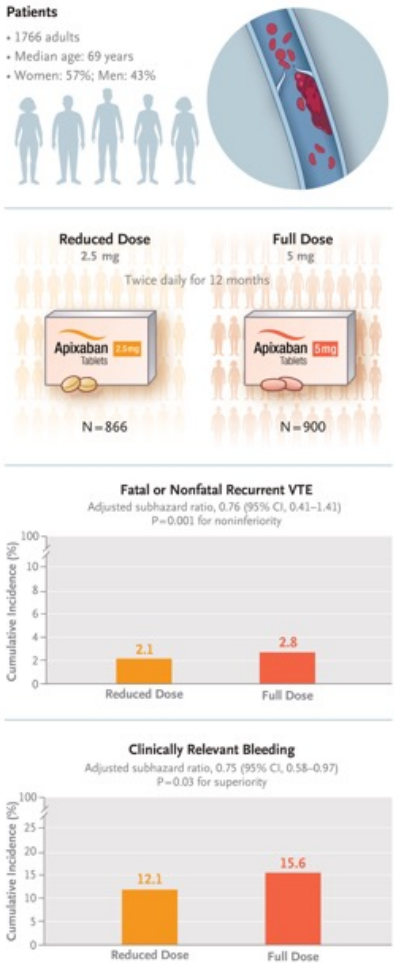
Krebspatienten haben ein erhöhtes Risiko für Thrombosen. Das Risiko kann bis zu siebenfach höher sein. Thrombosen können auch auf das Vorliegen eines Tumors hindeuten.




↑ Risk of bleeding
Need for prolonged therapeutic anticoagulation
Emergency care visits and/or hospitalization
↑ Risk of recurrent VTE
Symptoms and morbidity
↑ VTE-related costs
Cancer-associated venous thromboembolism
↑ Short-term mortality
↑ All health-care costs
Worsened overall survival
Worsened QoL
Delay or interruption of anti-cancer treatment

Extended Reduced-Dose Apixaban for Cancer-Associated Venous Thromboembolism

In patients with active cancer and venous thromboembolism, whether extended treatment with a reduced dose of an oral anticoagulant is effective in preventing recurrent thromboembolic events and decreasing bleeding is unclear. We conducted a randomized, double-blind, noninferiority trial with blinded central outcome adjudication. Consecutive patients with active cancer and proximal deep-vein thrombosis or pulmonary embolism who had completed at least 6 months of anticoagulant therapy were randomly assigned in a 1:1 ratio to receive oral apixaban at a reduced (2.5 mg) or full (5.0 mg) dose twice daily for 12 months. The primary outcome was centrally adjudicated fatal or nonfatal recurrent venous thromboembolism, assessed in a noninferiority analysis (margin of 2.00 for the upper boundary of the 95% confidence interval of the subhazard ratio). The key secondary outcome was clinically relevant bleeding, assessed in a superiority analysis.



Patients with cancer are at higher risk for venous thromboembolism than the general population. Patients with cancer-associated venous thromboembolism are at greater risk for recurrent events despite anticoagulant therapy and for bleeding complications than patients with venous thromboembolism who do not have cancer. Anticoagulation with a direct oral anticoagulant or low-molecular-weight heparin is recommended for an initial period of 6 months.

Randomization and Trial Intervention

Patients with active cancer and venous thromboembolism (defined as proximal deep-vein thrombosis of the lower limb [popliteal or more proximal vein of the lower limb or inferior vena cava] or symptomatic or incidental pulmonary embolism in a segmental or larger pulmonary artery) who had completed at least 6 months of treatment with a low-molecular-weight heparin, direct oral anticoagulant, or vitamin K antagonist and were without objectively documented symptomatic recurrent events during this treatment period were eligible. Patients were randomly assigned in a 1:1 ratio to a reduced-dose regimen of apixaban (2.5 mg twice daily) or a full-dose regimen (5.0 mg twice daily), with treatment administered for 12 months.

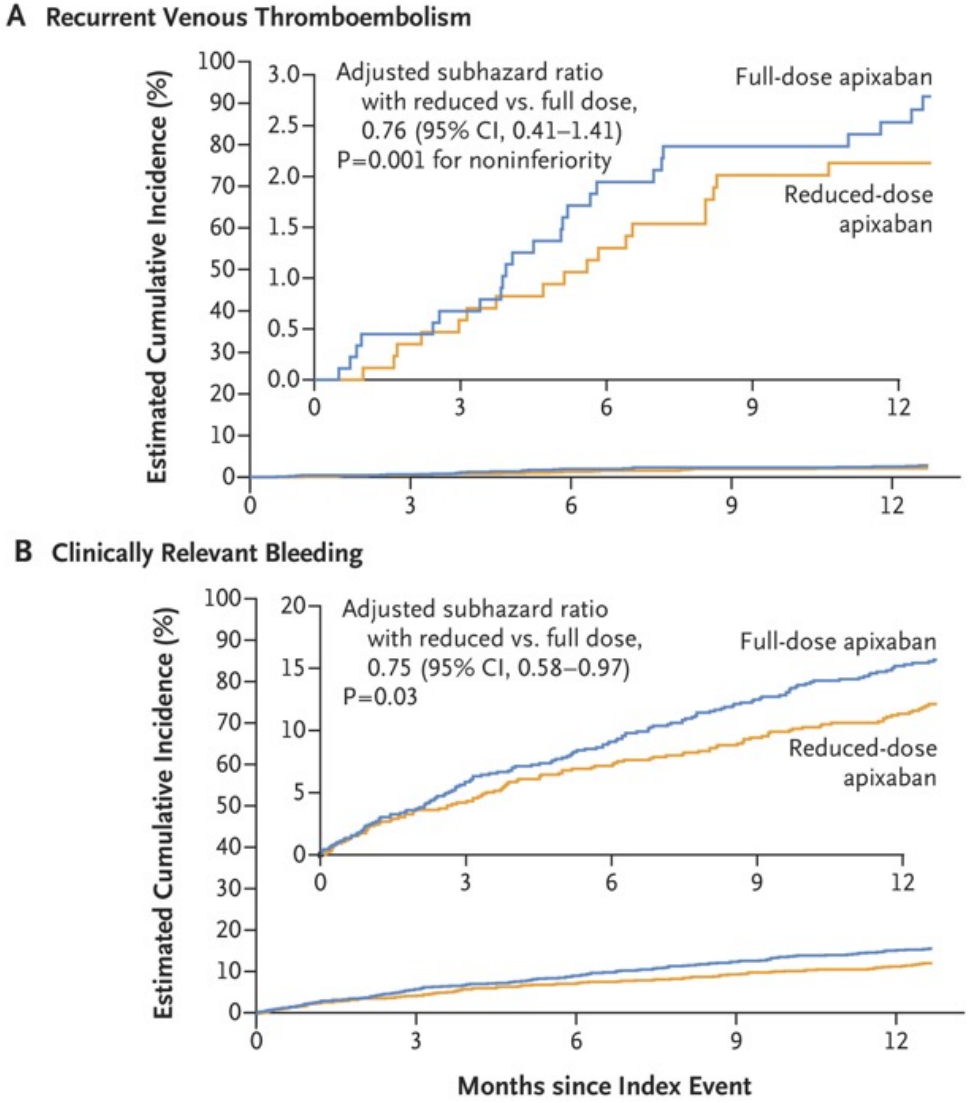
Outcome Measures

The primary efficacy outcome was centrally adjudicated fatal or nonfatal recurrent venous thromboembolism over the 12-month follow-up period. Recurrent venous thromboembolism was defined, according to the International Society on Thrombosis and Haemostasis guidance criteria,

Characteristic	Reduced-Dose Apixaban (N=866)	Full-Dose Apixaban (N=900)
Age — yr	67.2±11.0	67.7±11.4
Male sex — no. (%)	375 (43.3)	391 (43.4)
Body weight — kg	75.7±16.3	75.7±16.4
Body-mass index†	27.0±5.3	27.0±5.4
Platelet count <100,000/mm³ — no./total no. (%)	18/863 (2.1)	15/899 (1.7)
Creatinine clearance <50 ml/min — no./total no. (%)	115/864 (13.3)	127/900 (14.1)
Qualifying diagnosis of venous thromboembolism — no. (%)		
Pulmonary embolism with or without lower-limb proximal deep-vein thrombosis	669 (77.3)	665 (73.9)
Lower-limb proximal deep-vein thrombosis only	197 (22.7)	235 (26.1)
Clinical manifestation of index venous thromboembolism — no./total no. (%)		
Symptomatic deep-vein thrombosis or pulmonary embolism	528/856 (61.7)	580/888 (65.3)
Incidental pulmonary embolism	290/856 (33.9)	275/888 (31.0)
Incidental deep-vein thrombosis only	38/856 (4.4)	33/888 (3.7)
History of venous thromboembolism — no. (%)	157 (18.1)	170 (18.9)
Active cancer — no. (%)‡	864 (99.8)	897 (99.7)
Stage of cancer — no. (%)		
Localized	111 (12.8)	117 (13.0)
Locally advanced	115 (13.3)	113 (12.6)
Metastatic	574 (66.3)	584 (64.9)
Other	64 (7.4)	83 (9.2)
Unknown	2 (0.2)	3 (0.3)
Site of cancer — no. (%)		
Breast	199 (23.0)	202 (22.4)
Prostate	77 (8.9)	87 (9.7)
Colon or rectum	123 (14.2)	148 (16.4)
Lung	99 (11.4)	100 (11.1)
Other	368 (42.5)	363 (40.3)
ECOG performance-status score — no. (%)§		
0	456 (52.7)	504 (56.0)
1	342 (39.5)	329 (36.6)
2	67 (7.7)	63 (7.0)
Unknown	1 (0.1)	4 (0.4)

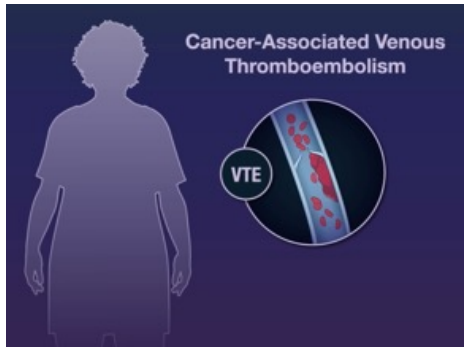
Clinical Outcomes during the Trial Period.

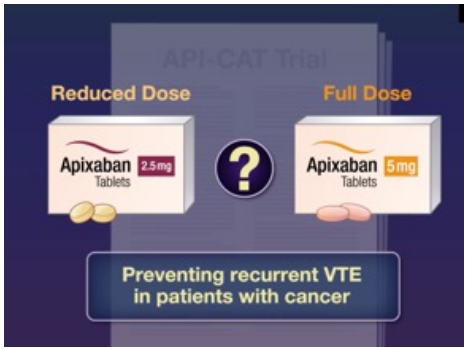
Outcome	Reduced-Dose Apixaban (N=866)	Full-Dose Apixaban (N=900)	Treatment Effect (95% CI)	P Value
	number (percent)			
Primary efficacy outcome: recurrent venous thromboembolism†	18 (2.1)	24 (2.8)	0.76 (0.41–1.41)	0.001
Recurrent symptomatic venous thromboembolism	17 (2.0)	18 (2.1)	0.97 (0.50–1.88)	—
Lower-limb deep-vein thrombosis‡	8 (0.9)	6 (0.7)	—	
Pulmonary embolism	9 (1.1)	10 (1.2)	—	
Fatal pulmonary embolism	0	0	—	
Unexplained sudden death§	3 (0.4)	2 (0.3)	—	
Upper-limb deep-vein thrombosis	1 (0.1)	3 (0.4)	—	
Central venous catheter–related thrombosis	1 (0.1)	2 (0.2)	—	
Incidental venous thromboembolism¶	1 (0.1)	6 (0.7)	—	
Recurrent major venous thromboembolism‖	17 (2.0)	21 (2.4)	0.83 (0.44–1.57)	—
Key secondary safety outcome: major or clinically relevant nonmajor bleeding**	102 (12.1)	136 (15.6)	0.75 (0.58–0.97)	0.03
Major bleeding	24 (2.9)	37 (4.3)	0.66 (0.40–1.10)	—
Fatal bleeding	2 (0.2)	2 (0.2)	—	
Major gastrointestinal bleeding	12 (1.4)	25 (2.9)	—	
Upper gastrointestinal bleeding	6 (0.7)	13 (1.5)	—	
Lower gastrointestinal bleeding	7 (0.8)	13 (1.5)	—	
Clinically relevant nonmajor bleeding	84 (10.0)	107 (12.3)	0.79 (0.59–1.05)	
Other secondary outcomes				
Death from any cause	148 (17.7)	168 (19.6)	0.96 (0.86–1.06)	—
Recurrent symptomatic venous thromboembolism, major bleeding, or death from any cause††	167 (19.9)	191 (22.1)	0.96 (0.87–1.07)	—
Major venous thromboembolism or major bleeding‡‡	41 (5.2)	55 (6.8)	0.96 (0.87–1.06)	—

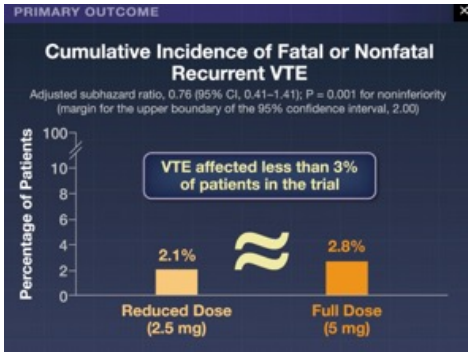


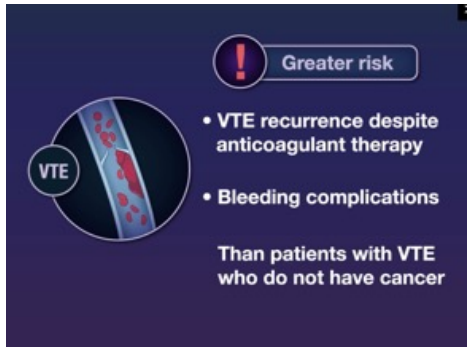
Recurrent Venous Thromboembolism and Clinically Relevant Bleeding (Intention-to-Treat Population).

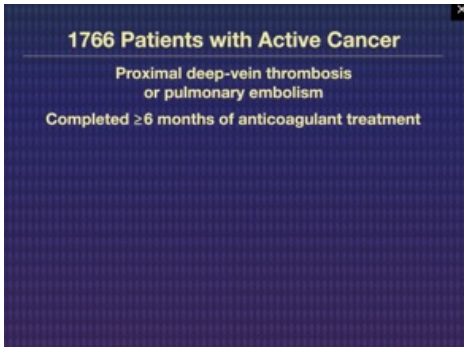
Shown is the cumulative incidence of recurrent venous thromboembolism (primary efficacy outcome) (Panel A) and of clinically relevant bleeding (key secondary safety outcome) (Panel B) among patients who received apixaban at a reduced (2.5 mg) or full (5.0 mg) dose twice daily for 12 months. The P value for the primary efficacy outcome was for noninferiority (margin for the upper boundary of the 95% confidence interval of the subdistribution hazard ratio [subhazard ratio], 2.00), and the P value for the key secondary safety outcome was for superiority. In both panels, the inset shows the same data on an expanded y axis.

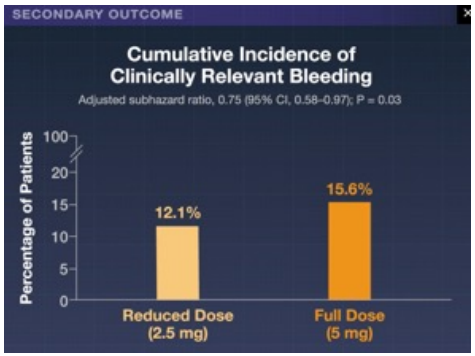

Cancer-Associated Venous Thromboembolism
VTE

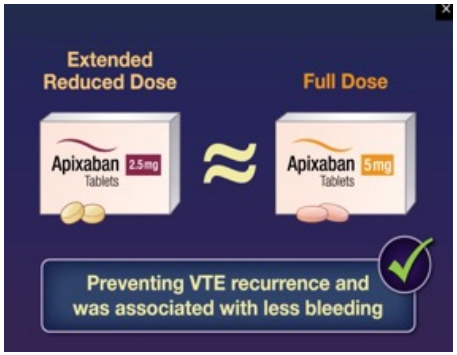

Reduced Dose
Full Dose
Apixaban 2.5mg Tablets
?
Apixaban 5mg Tablets
Preventing recurrent VTE in patients with cancer

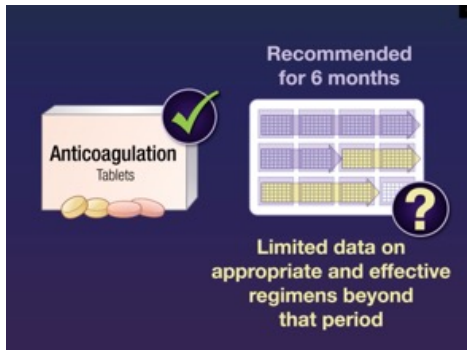

PRIMARY OUTCOME
Cumulative Incidence of Fatal or Nonfatal Recurrent VTE
Adjusted subhazard ratio, 0.76 (95% CI, 0.41–1.41); P = 0.001 for noninferiority (margin for the upper boundary of the 95% confidence interval, 2.00)
Percentage of Patients
VTE affected less than 3% of patients in the trial
2.1%
2.8%
Reduced Dose (2.5 mg)
Full Dose (5 mg)

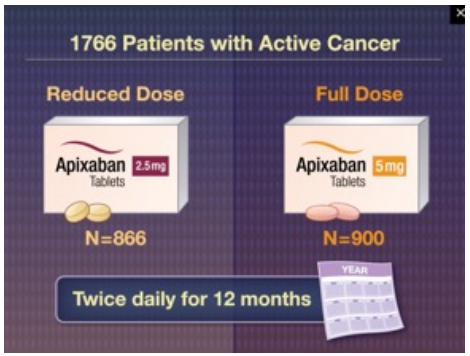

Greater risk
VTE
• VTE recurrence despite anticoagulant therapy
• Bleeding complications
Than patients with VTE who do not have cancer


1766 Patients with Active Cancer
Proximal deep-vein thrombosis or pulmonary embolism
Completed ≥6 months of anticoagulant treatment


SECONDARY OUTCOME
Cumulative Incidence of Clinically Relevant Bleeding
Adjusted subhazard ratio, 0.75 (95% CI, 0.58–0.97); P = 0.03
Percentage of Patients
12.1%
15.6%
Reduced Dose (2.5 mg)
Full Dose (5 mg)

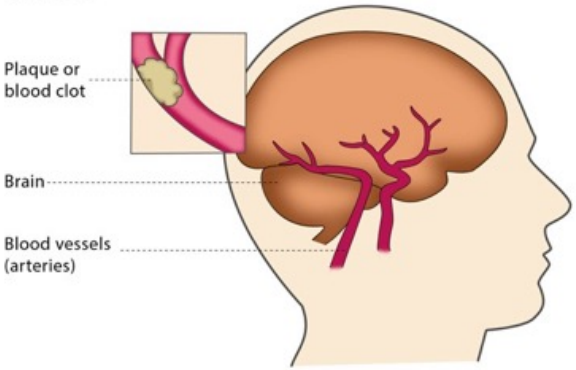

Extended Reduced Dose
Full Dose
Apixaban 2.5mg Tablets
Apixaban 5mg Tablets
Preventing VTE recurrence and was associated with less bleeding

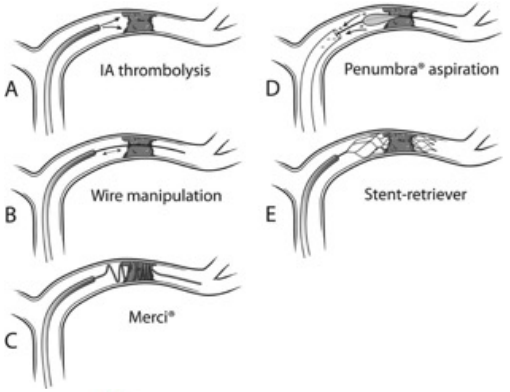

Recommended for 6 months
Anticoagulation Tablets
?
Limited data on appropriate and effective regimens beyond that period

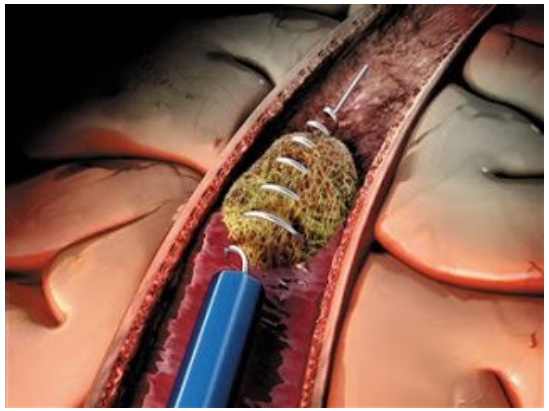

1766 Patients with Active Cancer
Reduced Dose
Full Dose
Apixaban 2.5mg Tablets
Apixaban 5mg Tablets
N=866
N=900
Twice daily for 12 months
YEAR

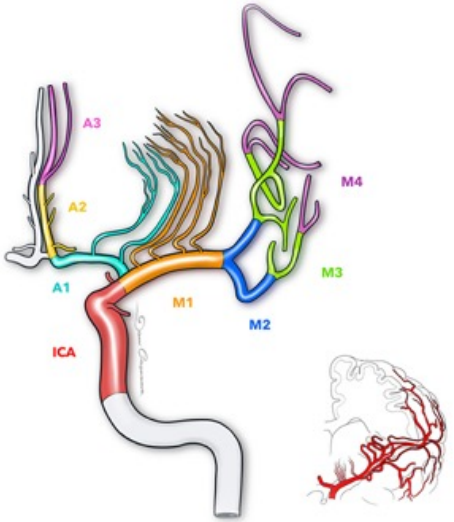

SECONDARY OUTCOME
Death from Any Cause
Adjusted hazard ratio, 0.96 (95% CI, 0.86–1.06)
Percentage of Patients
17.7%
19.6%
Reduced Dose (2.5 mg)
Full Dose (5 mg)

Endovascular treatment of stroke

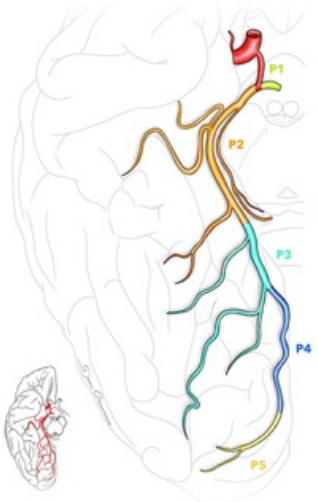








	M2	M3	M4	A1	A2	A3
DISTAL	x	x	x	x	x	x
DISCOUNT	x*	x		x	x	x
ESCAPE-MeVO	x	x			x	x
DISTALS	x	x		x	x	x



	P1	P2	P3
DISTAL	x	x	x
DISCOUNT	x	x	x
ESCAPE-MeVO		x	x
DISTALS	x	x	x

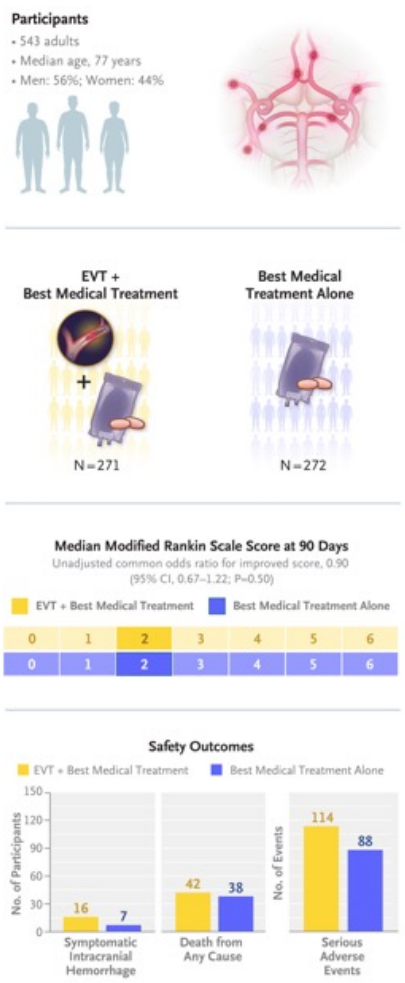
The National Institutes of Health Stroke Scale (NIHSS) is a tool that assesses the severity of a stroke. It's a widely used tool that helps healthcare providers diagnose and treat stroke patients.

1a. Level of consciousness	0 = Alert; keenly responsive 1 = Not alert, but arousable by minor stimulation 2 = Not alert; requires repeated stimulation 3 = Unresponsive or responds only with reflex
1b. Level of consciousness questions: What is the month? What is your age?	0 = Both answers correct 1 = Answers 1 question correctly 2 = Answers 2 questions correctly
1c. Level of consciousness commands: Open and close your eyes Grip and release your hand	0 = Performs both tasks correctly 1 = Performs 1 task correctly 2 = Performs neither task correctly
2. Best gaze	0 = Normal 1 = Partial gaze palsy 2 = Forced deviation
3. Visual	0 = No visual loss 1 = Partial hemianopia 2 = Complete hemianopia 3 = Bilateral hemianopia
4. Facial palsy	0 = Normal symmetric movements 1 = Minor paralysis 2 = Partial paralysis 3 = Complete paralysis of 1 or both sides
5. Motor arm 5a. Left arm 5b. Right arm	0 = No drift 1 = Drift 2 = Some effort against gravity 3 = No effort against gravity; limb falls 4 = No movement
6. Motor leg 6a. Left leg 6b. Right leg	0 = No drift 1 = Drift 2 = Some effort against gravity 3 = No effort against gravity 4 = No movement
7. Limb ataxia	0 = Absent 1 = Present in 1 limb 2 = Present in 2 limbs
8. Sensory	0 = Normal; no sensory loss 1 = Mild-to-moderate sensory loss 2 = Severe to total sensory loss
9. Best language	0 = No aphasia; normal 1 = Mild to moderate aphasia 2 = Severe aphasia 3 = Mute, global aphasia
10. Dysarthria	0 = Normal 1 = Mild to moderate dysarthria 2 = Severe dysarthria
11. Extinction and inattention	0 = No abnormality 1 = Visual, tactile, auditory, spatial, or personal inattention 2 = Profound hemi-inattention or extinction
Total score = 0–42	

Endovascular Treatment for Stroke Due to Occlusion of Medium or Distal Vessels

Endovascular treatment (EVT) of stroke with large-vessel occlusion is known to be safe and effective. The effect of EVT for occlusion of medium or distal vessels is unclear.

We randomly assigned participants with an isolated occlusion of medium or distal vessels (occlusion of the nondominant or codominant M2 segment of the middle cerebral artery [MCA]; the M3 or M4 segment of the MCA; the A1, A2, or A3 segment of the anterior cerebral artery; or the P1, P2, or P3 segment of the posterior cerebral artery) to receive EVT plus best medical treatment or best medical treatment alone within 24 hours after the participant was last seen to be well. The primary outcome was the level of disability at 90 days, as assessed with the modified Rankin scale score.



Endovascular treatment (EVT) is beneficial in persons with an acute ischemic stroke caused by a large-vessel occlusion of the internal carotid artery, the M1 segment of the middle cerebral artery (MCA), or the basilar artery. Evidence from randomized trials also suggests that EVT is beneficial in persons with acute occlusions of the dominant M2 segment of the MCA. However, data from randomized, controlled trials are lacking on whether EVT is also beneficial in persons with occlusion of medium or distal vessels. Current American and European guidelines neither recommend nor discourage EVT in persons with occlusion of medium or distal vessels. We therefore performed a randomized, controlled trial to assess whether EVT in addition to best medical treatment is more effective in reducing disability and death than best medical treatment alone in persons with an isolated occlusion of medium or distal vessels treated within 24 hours after the person was last seen to be well.

Participants

Participants were eligible for inclusion if they were 18 years of age or older, lived at home before the stroke, had an acute ischemic stroke caused by an isolated occlusion of medium or distal vessels confirmed by means of computed tomographic (CT) angiography or magnetic resonance imaging (MRI) angiography, and had a National Institutes of Health Stroke Scale (NIHSS) score (range, 0 to 42, with higher scores indicating more severe symptoms) of at least 4.

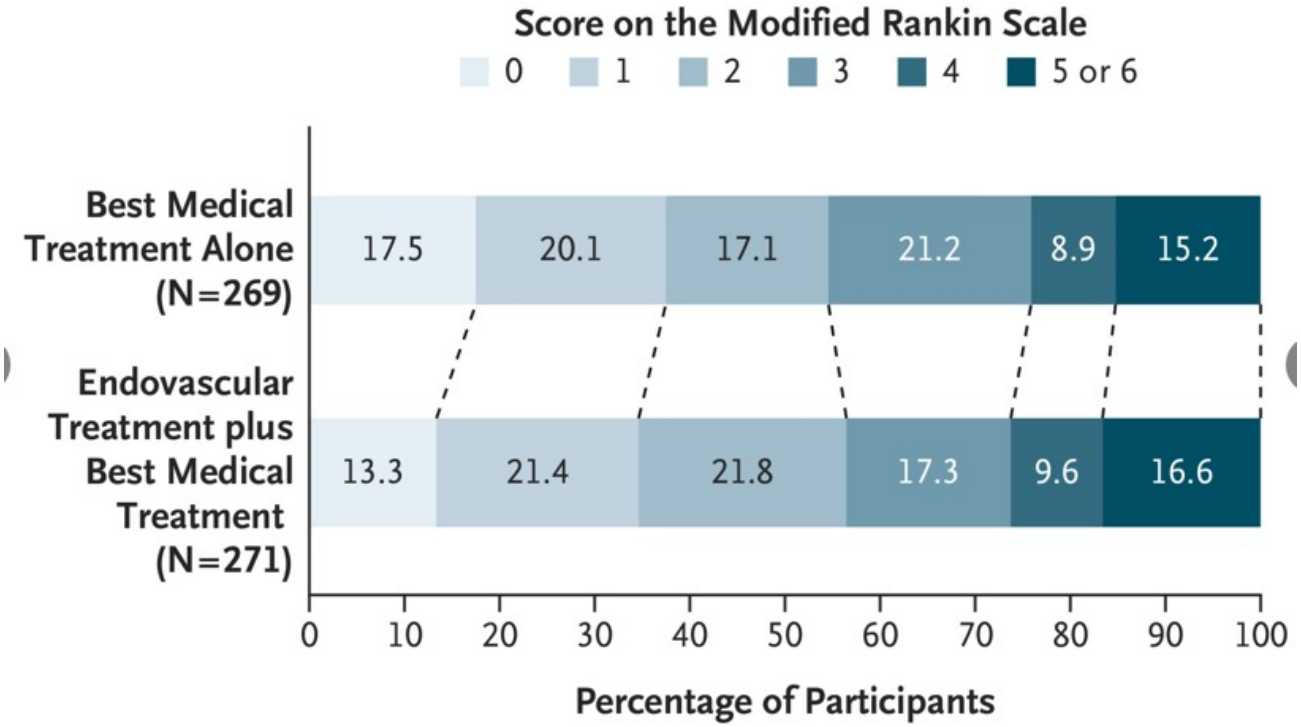
Outcomes

The primary outcome was the level of disability in performing daily activities at 90 days after the stroke as assessed with the modified Rankin scale; scores range from 0 to 6, with higher scores indicating more severe disability.

Characteristic	EVT plus Best Medical Treatment (N=271)	Best Medical Treatment Alone (N=272)
Age		
Median (IQR) — yr	77 (68–83)	77.5 (68–84)
>80 yr — no. (%)	102 (37.6)	111 (40.8)
Female sex — no. (%)	116 (42.8)	123 (45.2)
Modified Rankin scale score before stroke — no./total no. (%)†		
0 or 1	223/271 (82.3)	213/270 (78.9)
2	28/271 (10.3)	32/270 (11.9)
3 or 4	20/271 (7.4)	25/270 (9.3)
Median NIHSS score at admission (IQR)‡	6 (5–9)	6 (5–9)
Occlusion location — no. (%)§		
M2 segment	129 (47.6)	110 (40.4)
M3 segment	62 (22.9)	84 (30.9)
M4 segment	3 (1.1)	0
A1 segment	0	1 (0.4)
A2 segment	11 (4.1)	5 (1.8)
A3 segment	9 (3.3)	5 (1.8)
P1 segment	17 (6.3)	13 (4.8)
P2 segment	32 (11.8)	41 (15.1)
P3 segment	6 (2.2)	11 (4.0)
No occlusion	1 (0.4)	2 (0.7)
M1 segment	1 (0.4)	0
Intravenous thrombolysis therapy — no. (%)	168 (62.0)	187 (68.8)
Interval between time that participant was last seen to be well and randomization (IQR) — hr	3.8 (2.3–9.0)	4.0 (2.3–9.9)
Interval between time that participant was last seen to be well and imaging (IQR) — hr	3.3 (1.6–8.8)	3.5 (1.6–9.5)
Interval between imaging and arterial puncture (IQR) — min	70.0 (54.0–95.0)	—
Interval between time that participant was last seen to be well and arterial puncture (IQR) — hr	4.9 (2.9–10.7)	—
Tandem occlusion — no. (%)¶	14 (5.2)	19 (7.0)

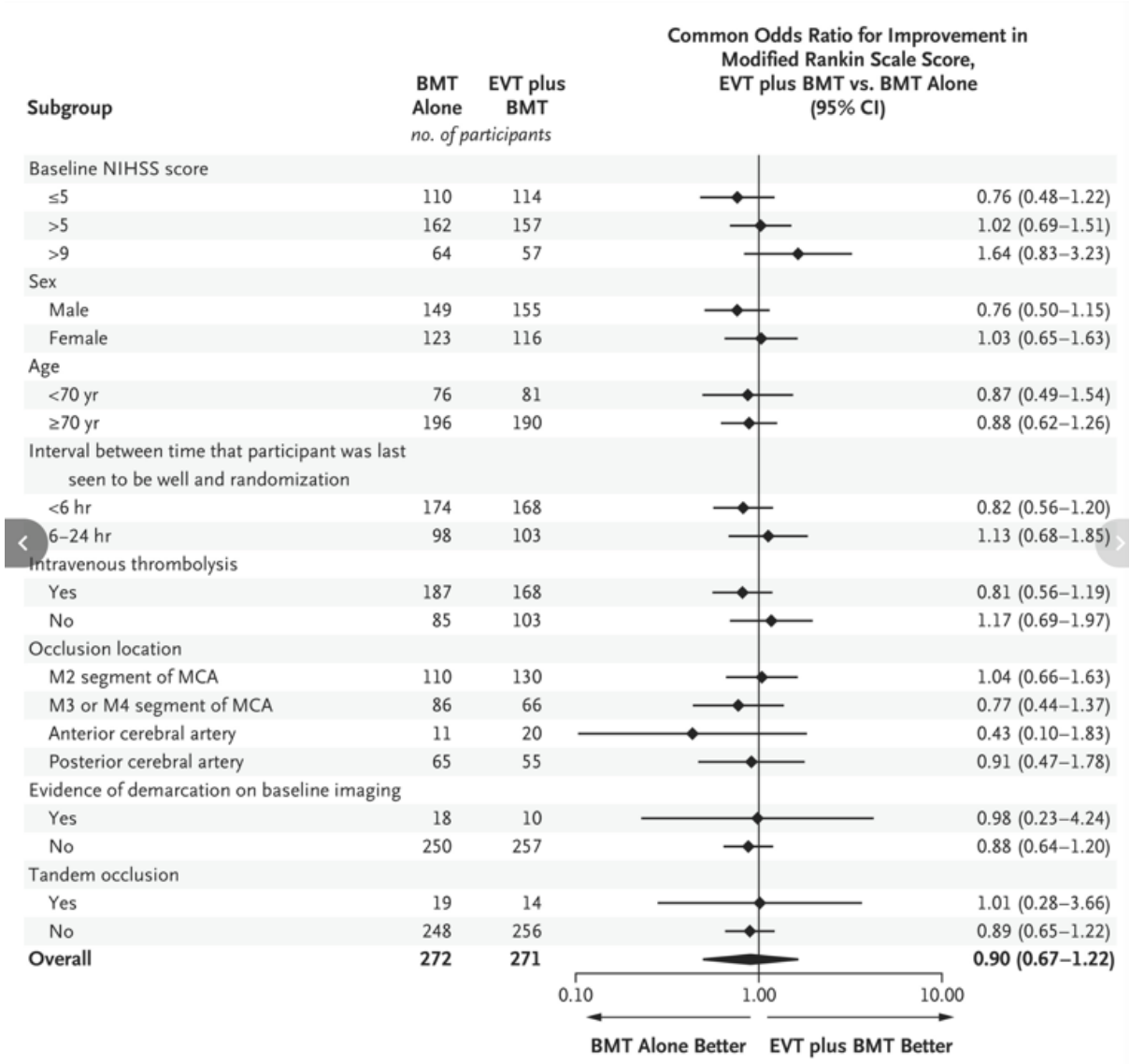
Outcomes According to Assigned Treatment.

Outcome	EVT plus Best Medical Treatment (N=271)	Best Medical Treatment Alone (N=272)	Treatment Effect (95% CI)*
Primary outcome			
Median modified Rankin scale score at 90 days (IQR)	2.0 (1.0–4.0)	2.0 (1.0–3.0)	0.90 (0.67 to 1.22)†‡
Secondary clinical outcomes			
Excellent functional outcome at 90 days — no./total no. (%)§	94/271 (34.7)	101/269 (37.5)	0.88 (0.61 to 1.25)¶
Change in severity of neurologic deficit at 24 hr (IQR)‖	0.4 (–0.2 to 0.8)	0.3 (0.0 to 0.8)	0.02 (–0.10 to 0.14)**
Median quality-of-life scores (IQR)††			
Mobility	2.0 (1.0 to 3.0)	2.0 (1.0 to –3.0)	1.05 (0.74 to 1.49)†
Self-care	1.0 (1.0 to 2.0)	1.0 (1.0 to 2.0)	1.25 (0.86 to 1.80)†
Everyday activities	2.0 (1.0 to 3.0)	2.0 (1.0 to 3.0)	1.09 (0.76 to 1.55)†
Pain or physical discomfort	1.0 (1.0 to 2.0)	1.0 (1.0 to 3.0)	0.96 (0.66 to 1.40)†
Fear or depression	1.0 (1.0 to 2.0)	1.0 (1.0 to 2.0)	1.13 (0.77 to 1.65)†
Visual analogue scale	70.0 (50.0 to 81.2)	70.0 (50.0 to 80.0)	0.94 (–3.59 to 5.74)**
Cognitive function‡‡	23.0 (18.2 to 26.0)	23.0 (18.0 to 27.0)	0.13 (–1.22 to 1.48) §§
Safety outcomes			
Death from any cause at 90 days — no. (%)	42 (15.5)	38 (14.0)	1.17 (0.71 to 1.90)¶¶
Symptomatic intracranial hemorrhage within 24 hr — no. (%)	16 (5.9)	7 (2.6)	2.38 (0.44 to 6.14)¶¶
Serious adverse events within 90 days — no.	114	88	1.27 (0.84 to 1.97)¶¶
Adverse event related to procedure or device — no. (%)			
Embolization in previously unaffected territory	17 (6.3)	—	
Arterial perforation	8 (3.0)	—	
Access hematoma	10 (3.7)	—	



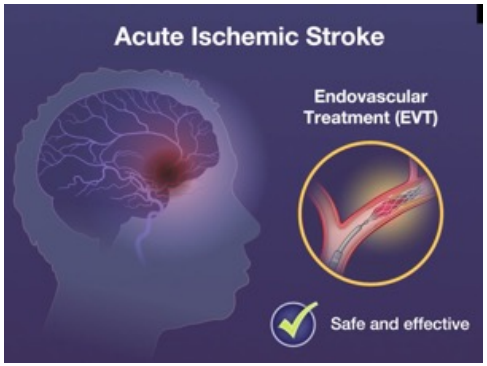
Modified Rankin Scale Scores at 90 Days.

Scores on the modified Rankin scale range from 0 to 6, with higher scores indicating more severe disability.

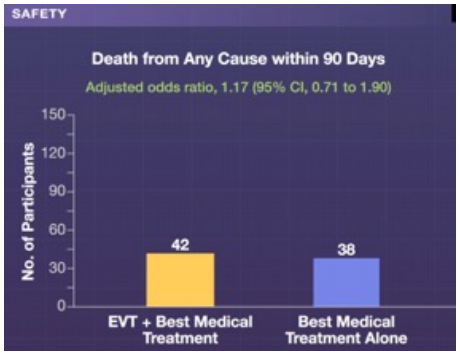


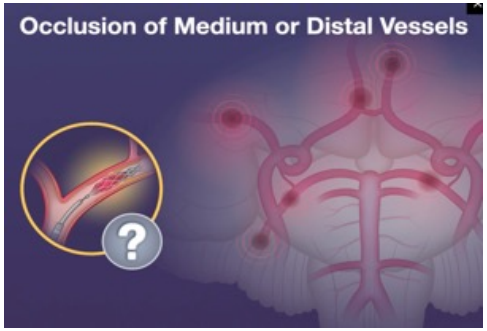
Subgroup Analyses.

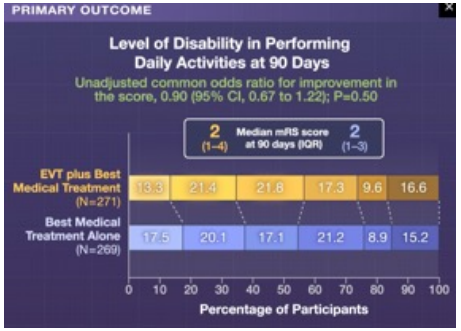
The widths of the confidence intervals have not been adjusted for multiplicity and cannot be used to infer treatment effects. Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating more severe symptoms. BMT denotes best medical treatment, EVT endovascular treatment, and MCA middle cerebral artery.

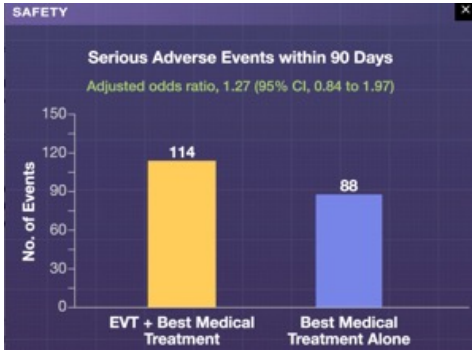

Acute Ischemic Stroke
Endovascular Treatment (EVT)
Safe and effective

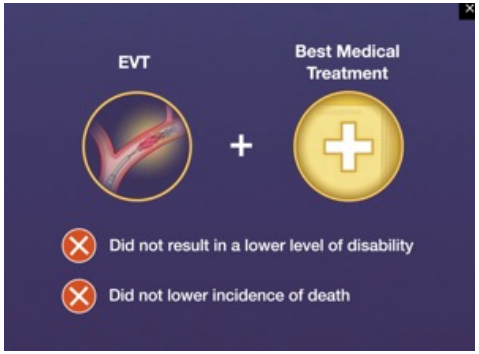

EVT + Best Medical Treatment (N=277)
Best Medical Treatment Alone (N=276)
Within 24 hours after the patient was last seen to be well

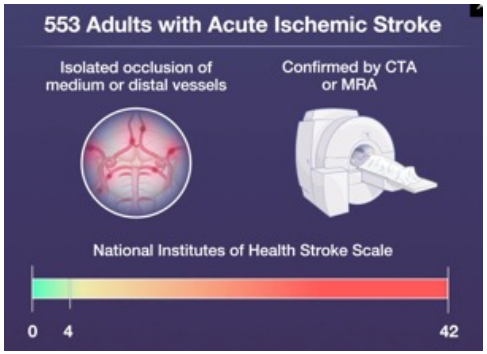

SAFETY
Death from Any Cause within 90 Days
Adjusted odds ratio, 1.17 (95% CI, 0.71 to 1.90)
No. of Participants
150
120
90
60
30
0
42
38
EVT + Best Medical Treatment
Best Medical Treatment Alone

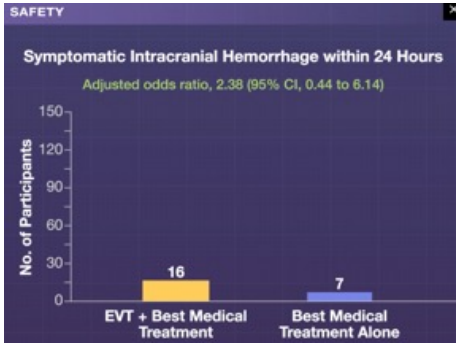

Occlusion of Medium or Distal Vessels
?

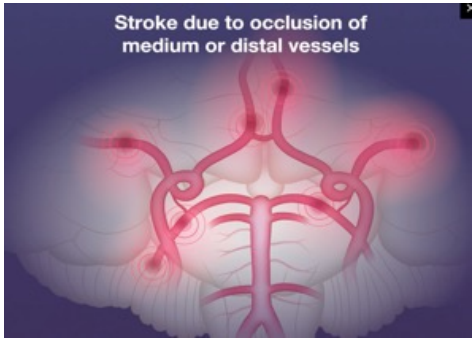

PRIMARY OUTCOME
Level of Disability in Performing Daily Activities at 90 Days
Unadjusted common odds ratio for improvement in the score, 0.90 (95% CI, 0.67 to 1.22); P=0.50
2 (1–4) Median mRS score at 90 days (IQR) 2 (1–3)
EVT plus Best Medical Treatment (N=271)
18.3 21.4 21.8 17.3 9.6 16.6
Best Medical Treatment Alone (N=269)
17.5 20.1 17.1 21.2 8.9 15.2
0 10 20 30 40 50 60 70 80 90 100
Percentage of Participants

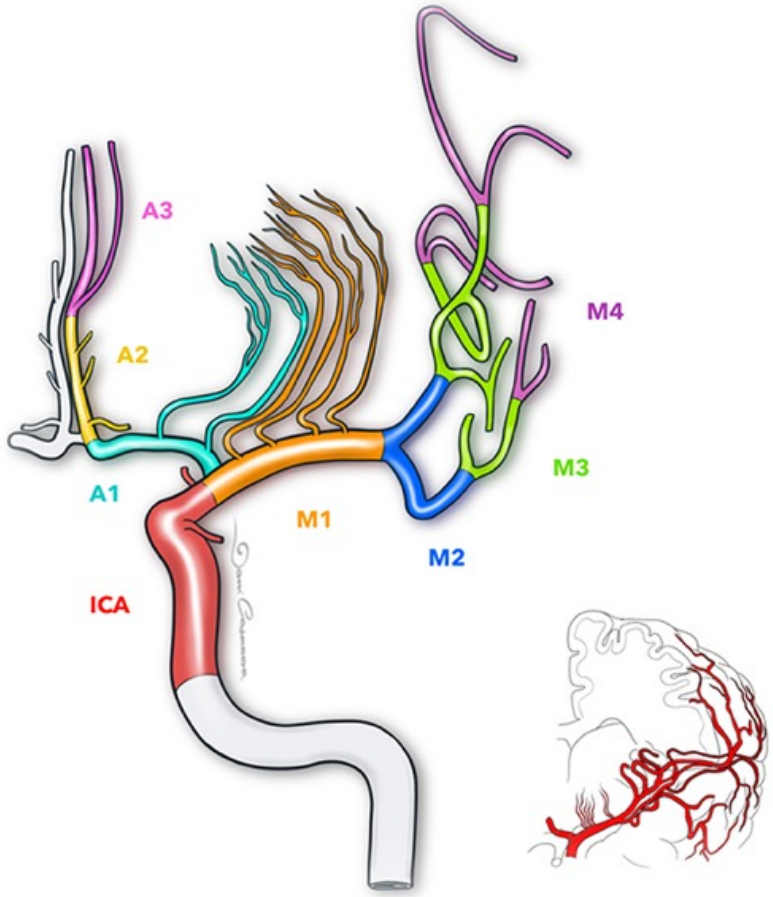

SAFETY
Serious Adverse Events within 90 Days
Adjusted odds ratio, 1.27 (95% CI, 0.84 to 1.97)
No. of Events
150
120
90
60
30
0
114
88
EVT + Best Medical Treatment
Best Medical Treatment Alone


EVT
Best Medical Treatment
+
Did not result in a lower level of disability
Did not lower incidence of death

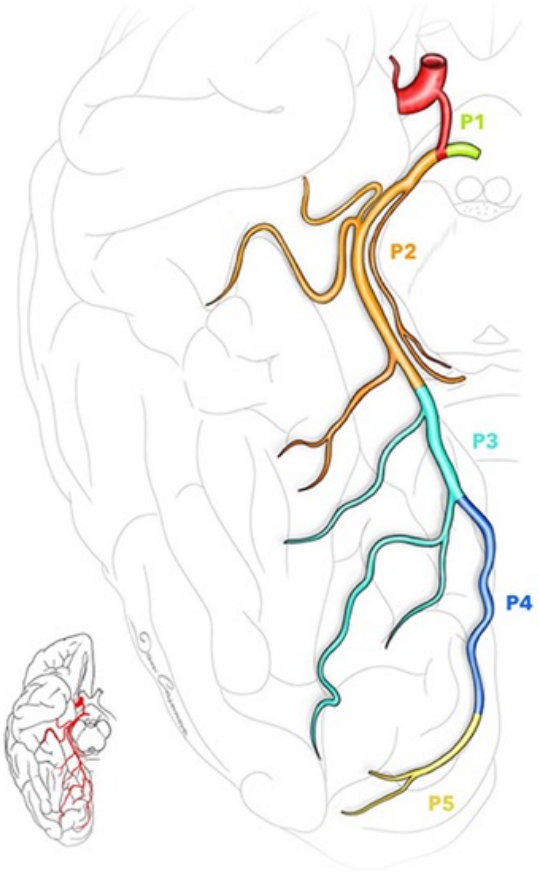

553 Adults with Acute Ischemic Stroke
Isolated occlusion of medium or distal vessels
Confirmed by CTA or MRA
National Institutes of Health Stroke Scale
0
4
42


SAFETY
Symptomatic Intracranial Hemorrhage within 24 Hours
Adjusted odds ratio, 2.38 (95% CI, 0.44 to 6.14)
No. of Participants
150
120
90
60
30
0
16
7
EVT + Best Medical Treatment
Best Medical Treatment Alone


Stroke due to occlusion of medium or distal vessels



	M2	M3	M4	A1	A2	A3
DISTAL	x	x	x	x	x	x
DISCOUNT	x*	x		x	x	x
ESCAPE-MeVO	x	x			x	x
DISTALS	x	x		x	x	x

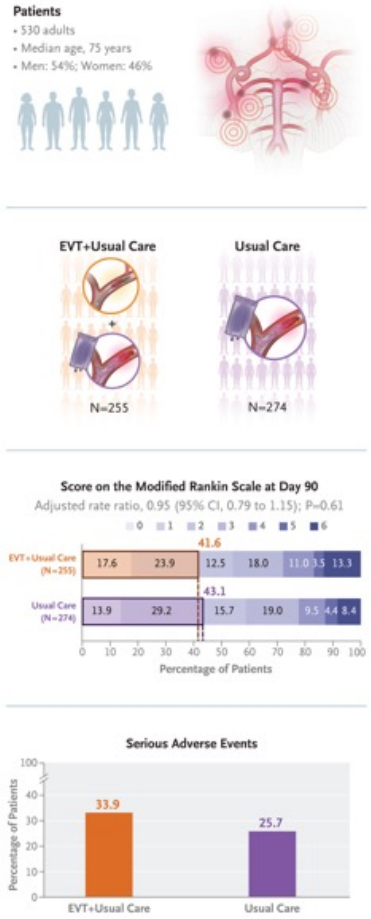


	P1	P2	P3
DISTAL	x	x	x
DISCOUNT	x	x	x
ESCAPE-MeVO		x	x
DISTALS	x	x	x

Endovascular Treatment of Stroke Due to Medium-Vessel Occlusion

Whether the large effect size of endovascular thrombectomy (EVT) for stroke due to large-vessel occlusion applies to stroke due to medium-vessel occlusion is unclear.

In a multicenter, prospective, randomized, open-label trial with blinded outcome evaluation, we assigned patients with acute ischemic stroke due to medium-vessel occlusion who presented within 12 hours from the time that they were last known to be well and who had favorable baseline noninvasive brain imaging to receive EVT plus usual care or usual care alone. The primary outcome was the modified Rankin scale score (range, 0 [no symptoms] to 6 [death]) at 90 days, reported as the percentage of patients with a score of 0 or 1.



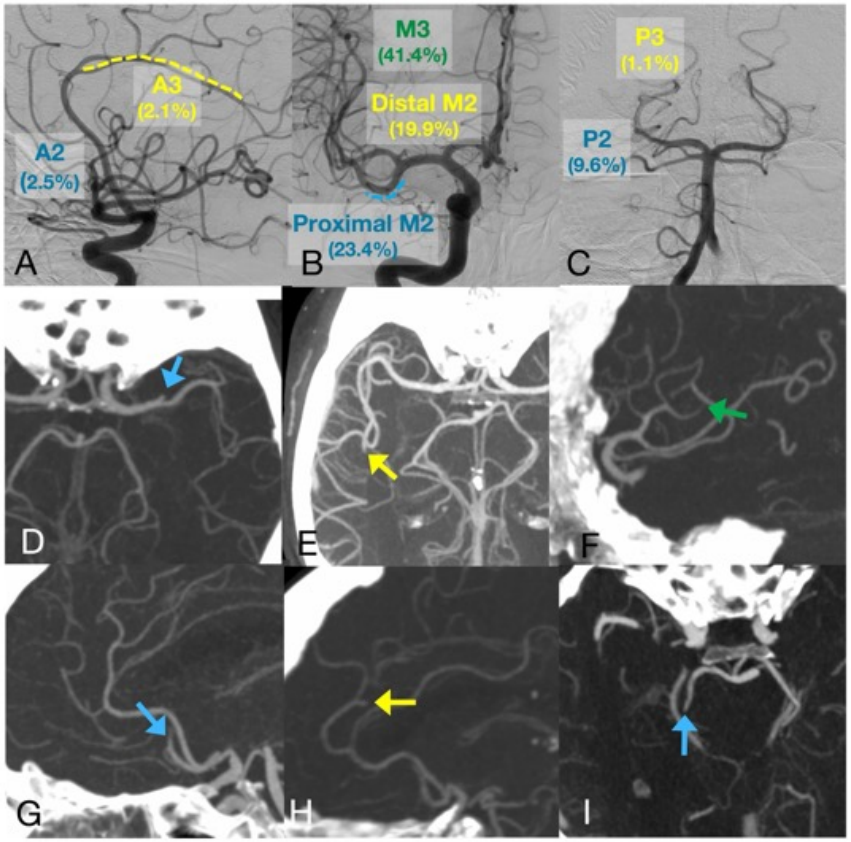
Acute ischemic stroke caused by an occlusion of the intracranial internal carotid artery or M1 segment (main trunk) of the middle cerebral artery (a large-vessel occlusion) causes high mortality, and outcomes without treatment are poor. In contrast, acute ischemic stroke due to medium-vessel occlusion has a better prognosis because the point of occlusion in the vascular tree is located more distally and the volume of ischemic brain tissue downstream from the occlusion is smaller. Nevertheless, half the patients with acute ischemic stroke due to a medium-vessel occlusion do not have an excellent outcome with currently available best medical care, and one third are not functionally independent 90 days after the index stroke.

Patient Population

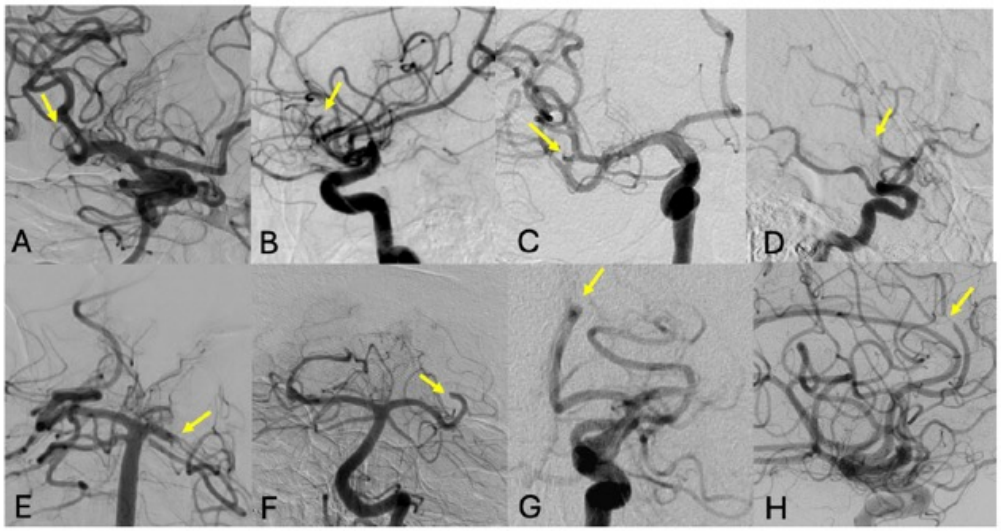
Eligible patients were adults recruited from hospital emergency departments at the time of presentation with an acute ischemic stroke caused by a medium-vessel occlusion. A medium-vessel occlusion was defined as an occlusion of the M2 or M3 segment of the middle cerebral artery, occlusion of the A2 or A3 segment of the anterior cerebral artery, or occlusion of the P2 or P3 segment of the posterior cerebral artery.

Clinical Assessments and Outcomes

Patients' demographic characteristics, medical history, laboratory variables, and stroke symptoms and severity were assessed at presentation (see the protocol). The primary outcome was measured at 90 days on the modified Rankin scale, a 7-point ordered categorical scale with scores ranging from 0 (no disability) to 6 (death).



Anatomical definitions of Medium Vessel Occlusion (MeVO) locations. (A) - (C) Catheter angiogram images. Percentages below vessel segments in (A) - (C) indicate observed frequencies of the respective occlusion locations in the trial. (A) lateral internal carotid artery angiographic run illustrating the A2 (blue) and A3 (yellow) segments of the anterior cerebral artery. (B) antero-posterior internal carotid artery angiographic run illustrating the proximal M2 (blue), distal M2 (yellow) and M3 (green) segments of the middle cerebral artery. The transition from proximal to distal M2 segment was hereby defined as the point that was 1 cm distal to the middle cerebral artery bi-/trifurcation. (C) Antero-posterior right vertebral artery angiographic run illustrating the P2 (blue) and P3 (yellow) segments of the posterior cerebral artery. (D) - (I) exemplary MeVOs from trial patients on CT angiograms. (D) Left proximal M2 occlusion on an axial CTA reformation (blue arrow). (E) Right distal M2 occlusion on an axial CTA reformation (yellow arrow). (F) M3 occlusion on a sagittal CTA reformation (green arrow). (G) A2 occlusion on a sagittal CTA reformation (blue arrow). (H) A3 occlusion on a sagittal CTA reformation (yellow arrow). (I) P2 occlusion on an axial CTA reformation (blue arrow).

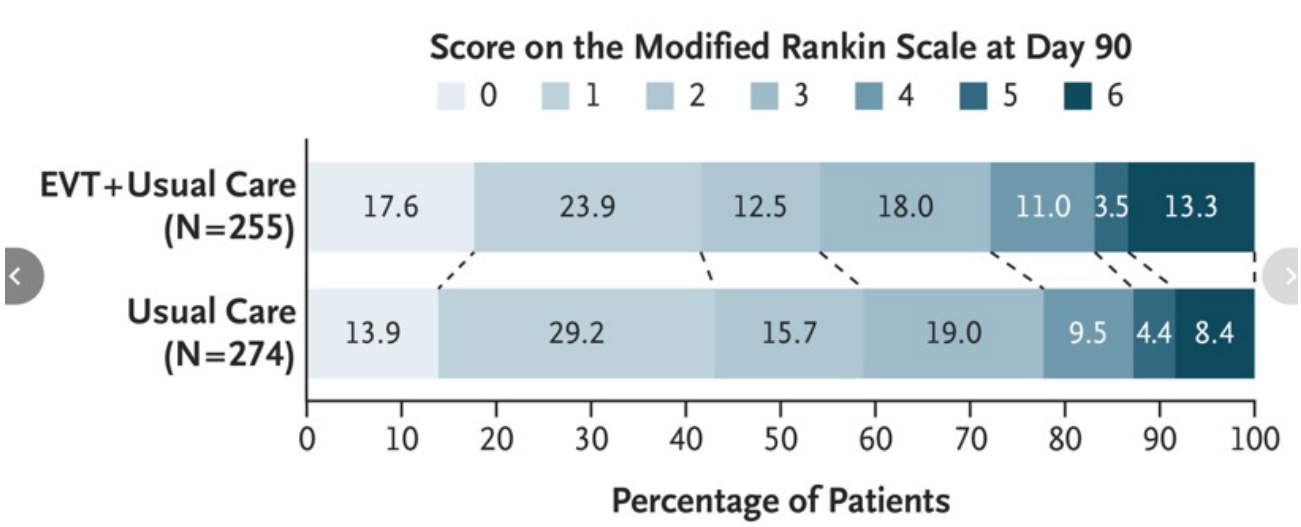


Angiographic examples of medium vessel occlusions. Occlusion locations are indicated with yellow arrows. (A) Right proximal posterior branch M2 segment middle cerebral artery occlusion on antero-posterior angiographic run. (B) Left distal anterior branch M2 segment middle cerebral artery occlusion on lateral angiographic run. (C) Right M3 segment middle cerebral artery occlusion on antero-posterior angiographic run. Note that in ESCAPE-MeVO, middle cerebral artery branch occlusions that were located in non-dominant middle cerebral artery branches proximal to the circular sulcus of the insula, were classified as M3 segment occlusions. Hence, this occlusion, albeit located proximal to the circular sulcus of the insula, was classified as an M3 segment occlusion. (D) Another example of a left distal posterior M2 segment occlusion on a lateral angiographic run. (E) Left P2 segment posterior cerebral artery occlusion on an antero-posterior angiographic run. Note that from this image, it is not evident whether this is a P1 segment or P2 segment posterior cerebral artery occlusion. However, the CT angiogram showed that there was a hypoplastic posterior cerebral artery that joined the posterior cerebral artery just proximal to the occlusion, and hence, this occlusion is located in the P2 segment. (F) Left P3 segment posterior cerebral artery occlusion on an antero-posterior angiographic run. (G) Left distal A2 segment anterior cerebral artery occlusion on an antero-posterior angiographic run. (H) Right A3 segment anterior cerebral artery occlusion on a lateral angiographic run.

Characteristic	EVT + Usual Care (N=255)	Usual Care (N=274)
Age — yr		
Median	74	76
Interquartile range	63–82	65–83
Female sex — no. (%)	118 (46.3)	127 (46.4)
White race — no. (%)†	216 (84.7)	224 (81.8)
Medical history — no. (%)		
Hypertension	184 (72.2)	212 (77.4)
Hyperlipidemia	114 (44.7)	128 (46.7)
Ischemic heart disease	62 (24.3)	81 (29.6)
Diabetes mellitus	59 (23.1)	74 (27.0)
Previous stroke or transient ischemic attack	61 (23.9)	56 (20.4)
Smoking status — no. (%)		
Current smoker	31 (12.2)	49 (17.9)
Former smoker	66 (25.9)	73 (26.6)
Clinical presentation		
Atrial fibrillation or flutter on baseline electrocardiogram — no. (%)	81 (31.8)	76 (27.7)
NIHSS score‡		
Median	8	7
Interquartile range	6–11	5–11
Location of occlusion on CTA — no./total no. (%)§		
M2 segment of MCA, proximal	64/253 (25.3)	58/269 (21.6)
M2 segment of MCA, distal	63/253 (24.9)	41/269 (15.2)
M3 segment of MCA	90/253 (35.6)	126/269 (46.8)
ASPECTS¶		
Median	9	10
Interquartile range	8–10	9–10
Intravenous thrombolysis treatment — no. (%)	144 (56.5)	165 (60.2)
Time from onset to randomization — min‖		
Median	270	253
Interquartile range	160–438	148–396
Final MeVO-eTICI score of 2b, 2c, or 3 — no./total no. (%)**	190/253 (75.1)	—

Efficacy Results.

Outcome	EVT + Usual Care (N=255)	Usual Care (N=274)	Unadjusted Effect Size	Adjusted Effect Size
Primary outcome				
Modified Rankin scale score at 90 days†				
Median	2	2	—	—
Interquartile range	1–4	1–3		
Modified Rankin scale score of 0 or 1 at 90 days — no. (%)	106 (41.6)	118 (43.1)	Rate ratio, 0.97 (0.79 to 1.18)	Rate ratio, 0.95 (0.79 to 1.15)
Secondary outcomes				
Modified Rankin scale score of 0–2 at 90 days — no. (%)	138 (54.1)	161 (58.8)	Rate ratio, 0.92 (0.79 to 1.07)	Rate ratio, 0.92 (0.80 to 1.05)
Death at 90 days — no. (%)	34 (13.3)	23 (8.4)	Hazard ratio, 1.62 (0.95 to 2.75)	Hazard ratio, 1.82 (1.06 to 3.12)
Barthel Index ≥95 at 90 days — no./total no. (%)‡	130/243 (53.5)	167/258 (64.7)	Rate ratio, 0.83 (0.71 to 0.96)	Rate ratio, 0.81 (0.71 to 0.93)
EQ-5D-5L Index§	0.64±0.02	0.69±0.02	Difference, −0.04 (−0.11 to 0.02)	Beta coefficient, −0.05 (−0.11 to 0.01)
Mean EQ VAS score¶	61.8	63.4	Difference, −1.6 (−7.2 to 4.0)	Beta coefficient, −2.2 (−7.6 to 3.1)
Infarct volume — ml‖				
Mean volume at 18–54 hr	31.9	29.1	—	—
Volume with square-root transformation	4.35±0.23	4.30±0.20	Difference, −0.05 (−0.64 to 0.54)	Beta coefficient, 0.03 (−0.53 to 0.58)

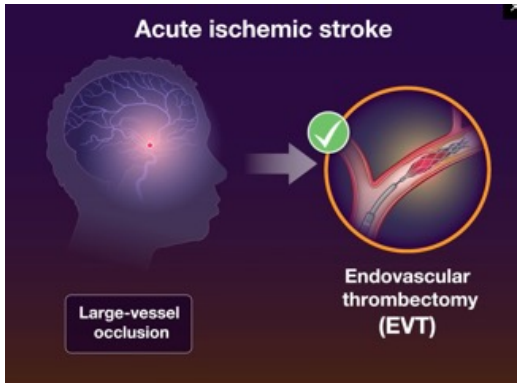


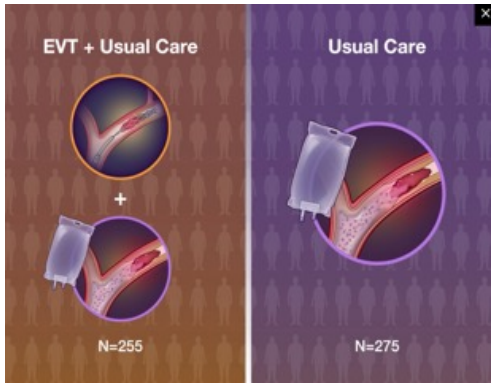
Distribution of Scores on the Modified Rankin Scale at 90 Days (Intention-to-Treat Population).

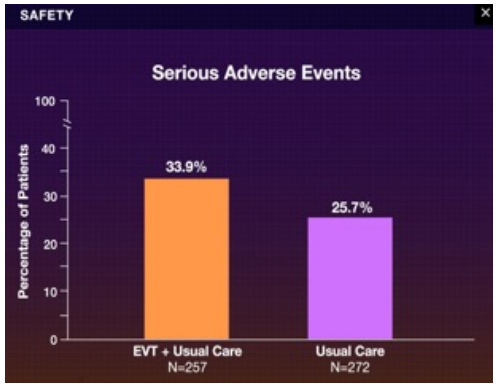
Scores on the modified Rankin scale range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death. The graph shows the distribution of scores at 90 days in the group that received endovascular thrombectomy (EVT) plus usual care and in the group that received usual care alone. The intention-to-treat population included all the patients who had undergone randomization, except for one patient who withdrew immediately after randomization. Percentages may not total 100 because of rounding.

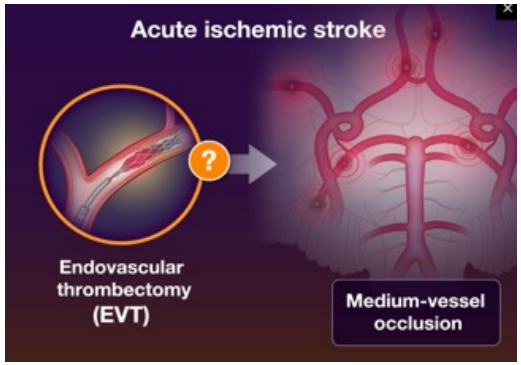
Serious Adverse Events and Intracranial Hemorrhage Classification (As-Treated Population).

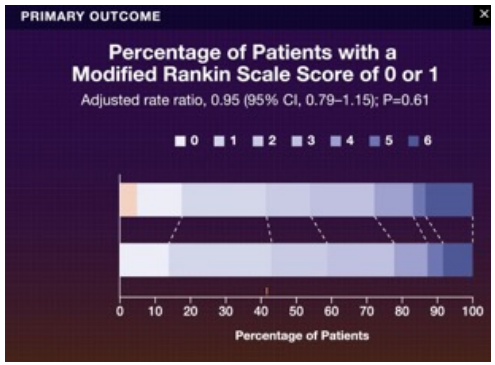
Variable	EVT + Usual Care (N=257)	Usual Care (N=272)
Any serious adverse event	87 (33.9)	70 (25.7)
Pneumonia	18 (7.0)	9 (3.3)
Recurrent stroke	14 (5.4)	10 (3.7)
Stroke progression	14 (5.4)	5 (1.8)
Symptomatic intracranial hemorrhage	14 (5.4)	6 (2.2)
Urinary tract infection	3 (1.2)	5 (1.8)
Covid-19	1 (0.4)	0
Other infection	7 (2.7)	4 (1.5)
New or worsening cancer	3 (1.2)	3 (1.1)
Seizure	3 (1.2)	5 (1.8)
Congestive heart failure	2 (0.8)	5 (1.8)
Endocarditis	2 (0.8)	1 (0.4)
Pulmonary embolus or deep venous thrombosis	2 (0.8)	3 (1.1)
Atrial fibrillation	1 (0.4)	5 (1.8)
Arterial-access complication	2 (0.8)	0
Procedural arterial injury	1 (0.4)	0
Heidelberg intracranial hemorrhage classification — no./total no. (%)†		
None	143/256 (55.9)	196/269 (72.9)
1a, Hemorrhagic infarction type 1	48/256 (18.8)	41/269 (15.2)
1b, Hemorrhagic infarction type 2	28/256 (10.9)	14/269 (5.2)
1c, Parenchymal hematoma type 1	13/256 (5.1)	11/269 (4.1)
2, Parenchymal hematoma type 2	4/256 (1.6)	4/269 (1.5)
3b, Intraventricular hemorrhage	1/256 (0.4)	1/269 (0.4)
3c, Subarachnoid hemorrhage	19/256 (7.4)	2/269 (0.7)

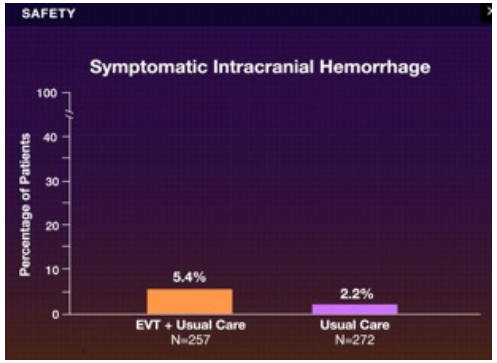

Acute ischemic stroke
Large-vessel occlusion
Endovascular thrombectomy (EVT)

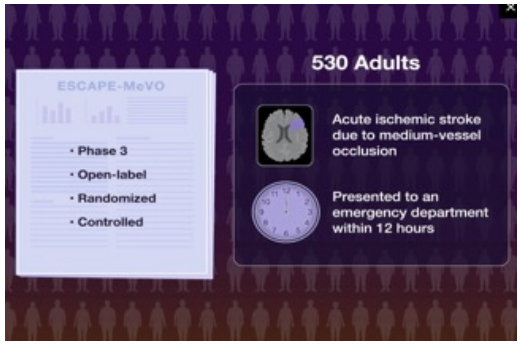

EVT + Usual Care
Usual Care
+
N=255
N=275

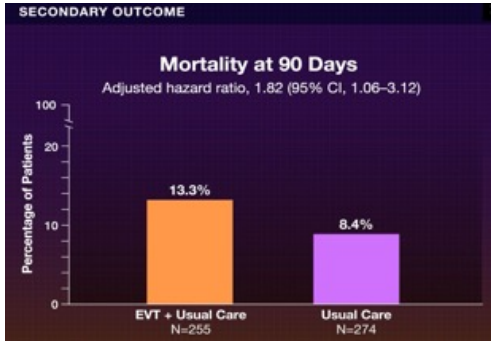

SAFETY
Serious Adverse Events
Percentage of Patients
100
40
30
20
10
0
33.9%
25.7%
EVT + Usual Care
N=257
Usual Care
N=272


Acute ischemic stroke
?
Endovascular thrombectomy (EVT)
Medium-vessel occlusion


PRIMARY OUTCOME
Percentage of Patients with a Modified Rankin Scale Score of 0 or 1
Adjusted rate ratio, 0.95 (95% CI, 0.79–1.15); P=0.61
0
1
2
3
4
5
6
0
10
20
30
40
50
60
70
80
90
100
Percentage of Patients

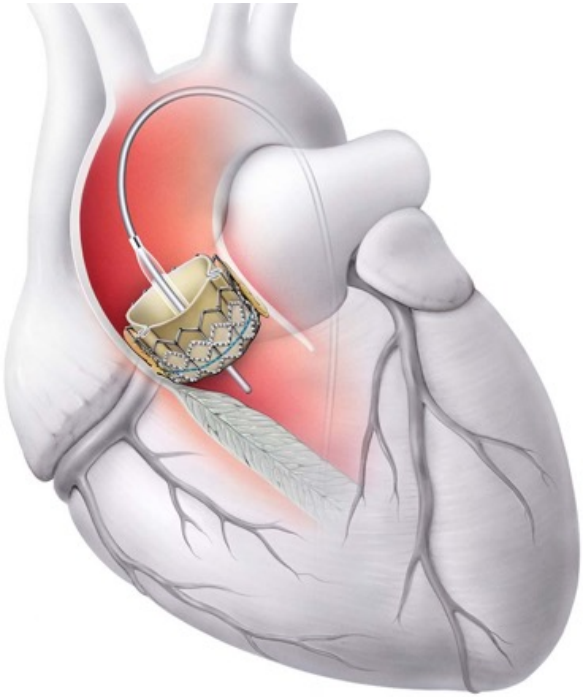

SAFETY
Symptomatic Intracranial Hemorrhage
Percentage of Patients
100
40
30
20
10
0
5.4%
2.2%
EVT + Usual Care
N=257
Usual Care
N=272


530 Adults
ESCAPE-MeVO
• Phase 3
• Open-label
• Randomized
• Controlled
Acute ischemic stroke due to medium-vessel occlusion
Presented to an emergency department within 12 hours

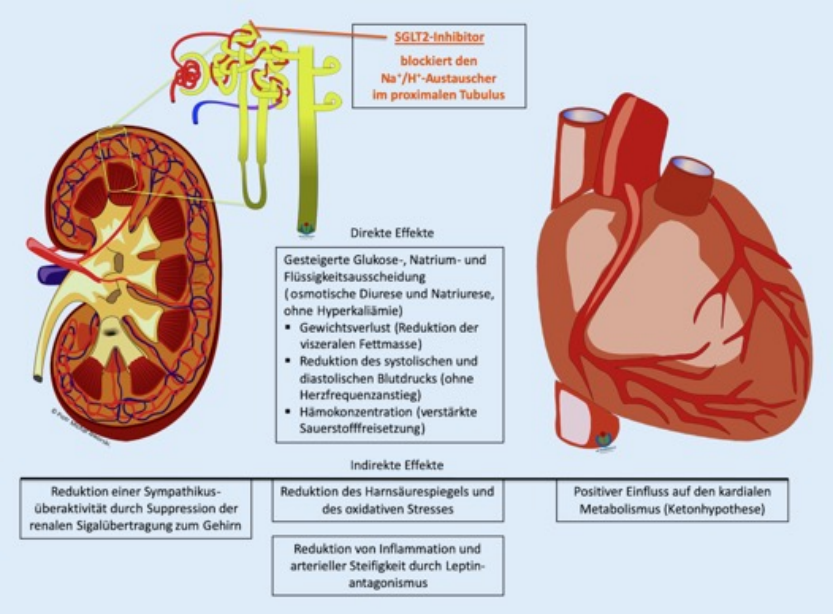

SECONDARY OUTCOME
Mortality at 90 Days
Adjusted hazard ratio, 1.82 (95% CI, 1.06–3.12)
Percentage of Patients
100
20
10
0
13.3%
8.4%
EVT + Usual Care
N=255
Usual Care
N=274


Endovascular thrombectomy within 12 hours did not lead to better outcomes at 90 days than usual care

TAVI, kurz für Transkatheter-Aortenklappenimplantation, ist ein minimal-invasives Verfahren zur Behandlung der Aortenklappenstenose, bei dem eine neue Aortenklappe über einen Katheter eingesetzt wird, ohne den Brustkorb zu öffnen

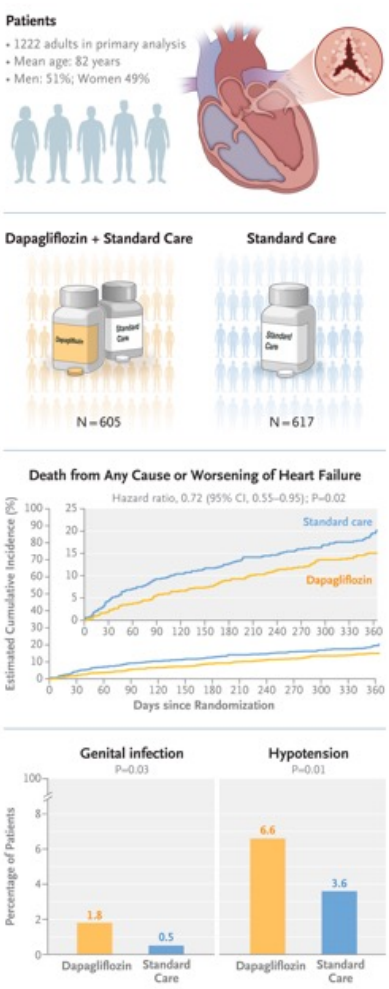


SGLT2-Inhibitoren (Natrium-Glucose-Cotransporter-2-Hemmer) sind Medikamente, die bei Diabetes mellitus Typ 2, chronischer Herzinsuffizienz und chronischer Niereninsuffizienz eingesetzt werden. Sie werden auch Gliflozine genannt.



Dapagliflozin in Patients Undergoing Transcatheter Aortic-Valve Implantation

Sodium–glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of heart-failure admission among high-risk patients. However, most patients with valvular heart disease, including those undergoing transcatheter aortic-valve implantation (TAVI), have been excluded from randomized trials. We conducted this randomized, controlled trial in Spain to evaluate the efficacy of dapagliflozin (at a dose of 10 mg once daily) as compared with standard care alone in patients with aortic stenosis who were undergoing TAVI. All the patients had a history of heart failure plus at least one of the following: renal insufficiency, diabetes, or left ventricular systolic dysfunction. The primary outcome was a composite of death from any cause or worsening of heart failure, defined as hospitalization or an urgent visit, at 1 year of follow-up.



Aortic stenosis is the most common valvular heart disease in Western countries, and its prevalence is increasing because of aging of the population. The advent of transcatheter aortic-valve implantation (TAVI) has changed how aortic stenosis is managed, with TAVI becoming the standard of care, especially for older patients. Many patients with aortic stenosis who are treated with TAVI still face a high risk of hospitalization for heart failure, which is associated with high mortality among these patients.

Sodium–glucose cotransporter 2 (SGLT2) inhibitors have been shown to be effective in reducing heart-failure–related admissions across a wide spectrum of high-risk patients. Both U.S. and European clinical practice guidelines recommend the use of SGLT2 inhibitors in patients with heart failure regardless of their left ventricular ejection fraction or diabetes status. However, the supporting evidence for this recommendation is less robust when it comes to patients with heart failure attributable to reversible conditions, such as aortic stenosis.

Patients

Patients with severe aortic stenosis undergoing TAVI were eligible for enrollment if they had had a previous episode of aortic stenosis–related heart failure, including any hospitalization for heart failure or urgent heart-failure visit that led to the administration of an intravenous diuretic before TAVI and any of the following conditions: moderate renal insufficiency (estimated glomerular filtrate rate [eGFR], 25 to 75 ml per minute per 1.73 m^2 of body-surface area), diabetes mellitus, or a left ventricular ejection fraction of 40% or less.

Outcomes

The primary outcome was a composite of death from any cause or worsening of heart failure, with the latter defined as either hospitalization for heart failure or an urgent heart-failure visit leading to the administration of intravenous diuretics.

Characteristic	Dapagliflozin (N=605)	Standard Care (N=618)†
Age — yr	82.4±5.6	82.4±5.5
Female sex — no. (%)	299 (49.4)	305 (49.4)
Cardiovascular disease history and risk factors — no. (%)		
Diabetes mellitus type 2	264 (43.6)	273 (44.2)
Hypertension	518 (85.6)	519 (84.0)
Coronary artery disease	237 (39.2)	197 (31.9)
Previous myocardial infarction	51 (8.4)	52 (8.4)
Previous stroke	61 (10.1)	69 (11.2)
Peripheral-artery disease	51 (8.4)	43 (7.0)
Atrial fibrillation	250 (41.3)	274 (44.3)
Echocardiographic data		
Mean gradient — mm Hg‡	47.8±13.7	46.6±13.5
Left ventricular ejection fraction		
Percentage	54.9±12.3	54.8±12.1
Value ≤40% — no. (%)	109 (18.0)	103 (16.7)
Moderate or severe left ventricular hypertrophy — no. (%)	368 (60.8)	367 (59.4)
Mitral regurgitation of grade ≥3 — no. (%)	99 (16.4)	99 (16.0)
Laboratory data		
Hemoglobin — g/dl§	11.9±1.7	12.0±1.7
Estimated glomerular filtration rate		
Mean — ml/min/1.73 m^2 of body-surface area¶	56.0±16.4	56.4±16.3
Value of 25 to 75 ml/min/1.73 m^2 — no. (%)	529 (87.4)	555 (89.8)
NT-proBNP — pg/ml‖	6324.0±19,948.9	5301.1±6622.0
In-hospital complications after TAVI — no./total no. (%)		
Myocardial infarction	2/605 (0.3)	1/618 (0.2)
Stroke	10/605 (1.7)	15/618 (2.4)
New-onset bundle-branch block**	151/471 (32.1)	146/448 (32.6)
Pacemaker implantation††	105/544 (19.3)	103/543 (19.0)
Post-TAVI aortic regurgitation grade ≥3	27/605 (4.5)	37/618 (6.0)
Baseline therapy — no. (%)		
Acetylsalicylic acid	318 (52.6)	298 (48.2)
P2Y12 inhibitor	125 (20.7)	118 (19.1)
Oral anticoagulation	280 (46.3)	300 (48.5)
Beta-blocker	219 (36.2)	230 (37.2)
Renin–angiotensin system inhibitor	380 (62.8)	364 (58.9)
Aldosterone-receptor blocker	84 (13.9)	97 (15.7)
Diuretic	441 (72.9)	473 (76.5)
Insulin therapy	53 (8.8)	60 (9.7)

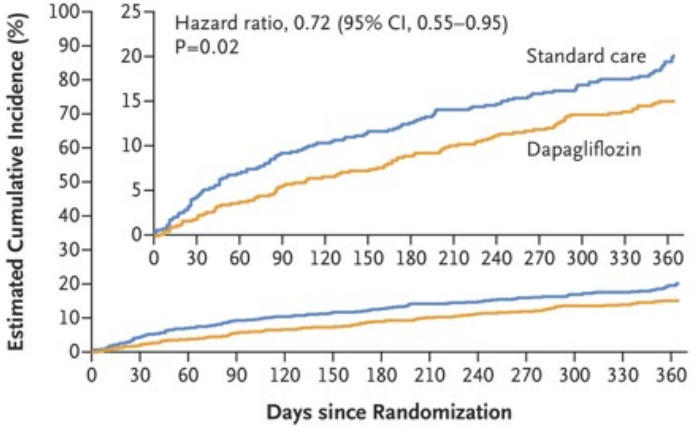
Primary, Secondary, and Other Outcomes.

Outcome	Dapagliflozin (N=605)	Standard Care (N=617)	Treatment Effect (95% CI)*
Primary composite outcome — no. (%)	91 (15.0)	124 (20.1)	0.72 (0.55–0.95)†‡
Components of the primary outcome — no. (%)			
Death from any cause	47 (7.8)	55 (8.9)	0.87 (0.59–1.28)‡
Worsening of heart failure	57 (9.4)	89 (14.4)	0.63 (0.45–0.88)§
Hospitalization for heart failure	45 (7.4)	66 (10.7)	0.68 (0.46–0.99)§
Urgent heart-failure visit	17 (2.8)	37 (6.0)	0.46 (0.26–0.82)§
Key secondary outcomes			
Death from cardiovascular causes — no. (%)	27 (4.5)	33 (5.3)	0.81 (0.49–1.35)§
Hospitalization for heart failure or death from cardiovascular causes — no. (%)	61 (10.1)	85 (13.8)	0.71 (0.51–0.98)§
Total no. of hospitalizations for heart failure or deaths from cardiovascular causes	79	121	0.67 (0.47–0.95)¶

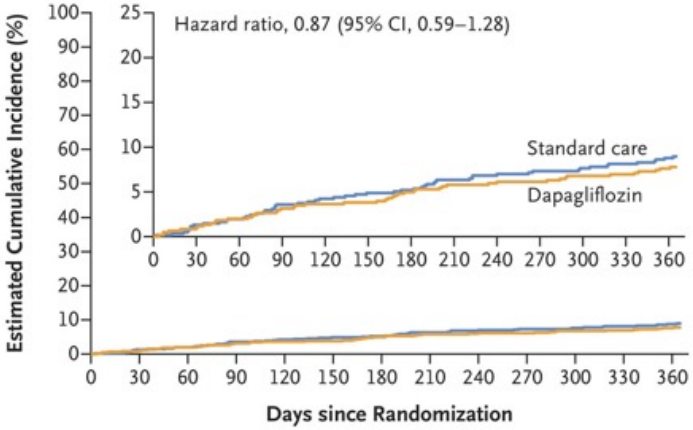
Safety End Points.

End Point	Dapagliflozin (N=605)	Standard Care (N=617)	P Value
	number (percent)		
Genitourinary infection	94 (15.5)	71 (11.5)	0.04
Genital infection	11 (1.8)	3 (0.5)	0.03
Urinary tract infection	83 (13.7)	68 (11.0)	0.15
Relevant urinary tract infection*	17 (2.8)	11 (1.8)	0.23
Bacteremia	31 (5.1)	32 (5.2)	0.96
Hypotension	40 (6.6)	22 (3.6)	0.01
Syncope	22 (3.6)	13 (2.1)	0.11
Ketoacidosis	0	0	—
Major hypoglycemia	4 (0.7)	8 (1.3)	0.26
Necrotizing fasciitis	0	0	—
Nontraumatic amputation	5 (0.8)	4 (0.6)	0.72
Cancer	30 (5.0)	22 (3.6)	0.23

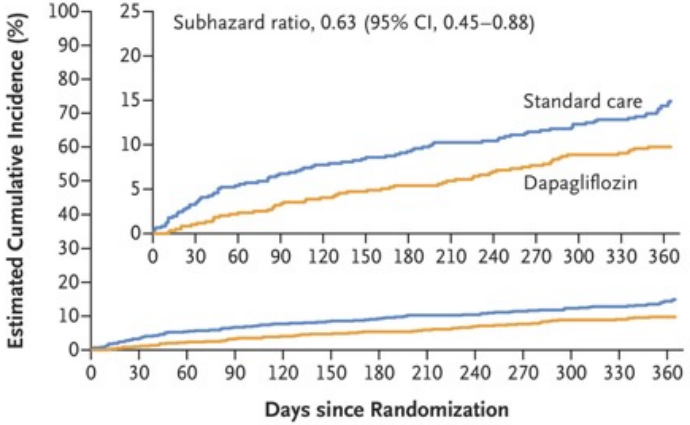
A Death from Any Cause or Worsening of Heart Failure



B Death from Any Cause

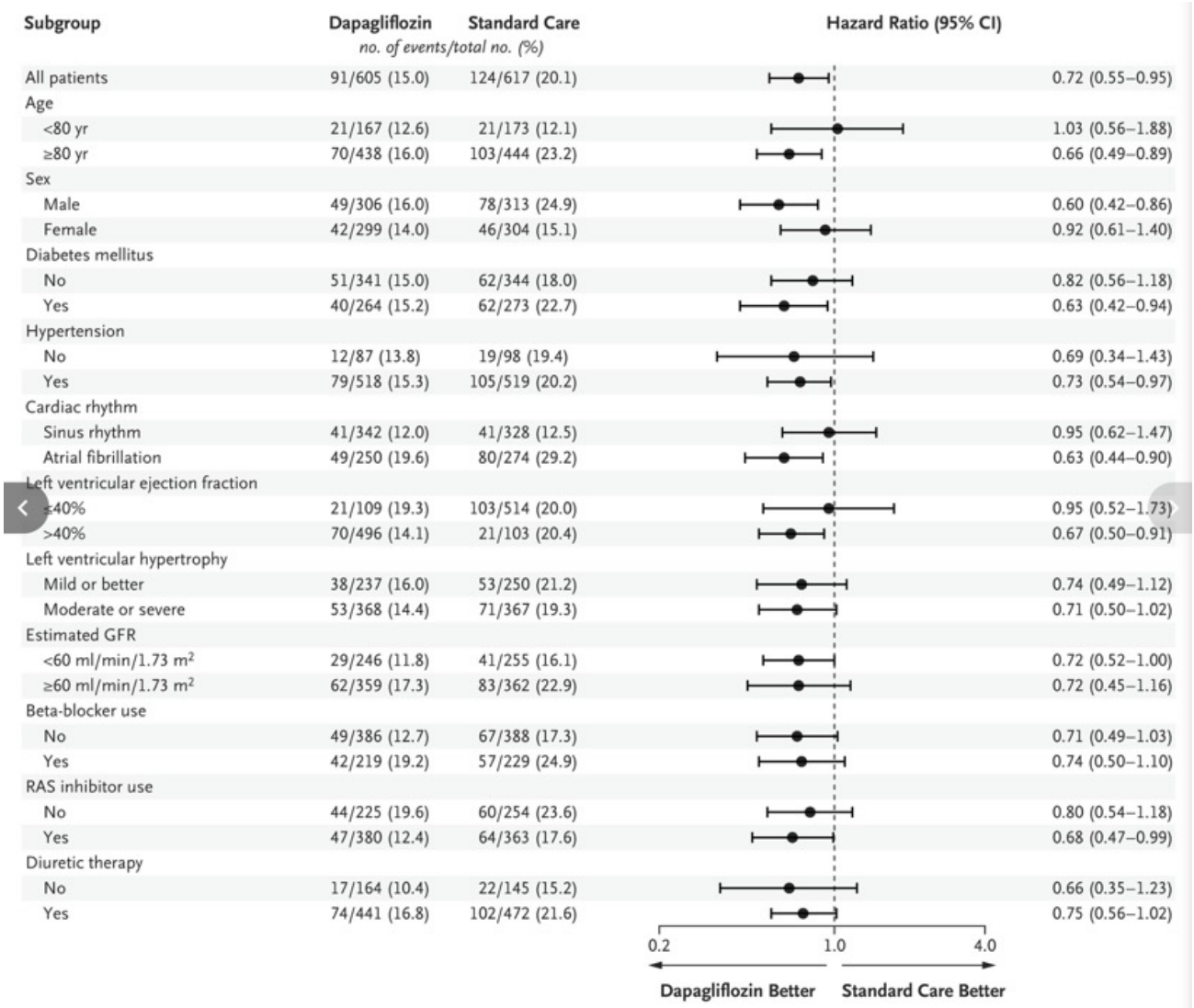


C Worsening of Heart Failure



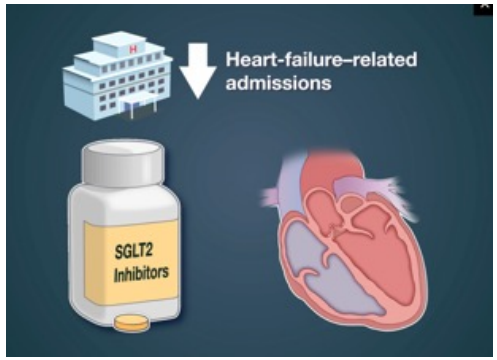
Kaplan–Meier Estimates and Cumulative Incidence of the Primary Outcome and Its Components.

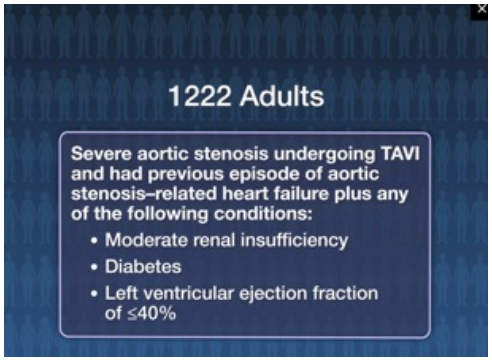
Panel A shows the time until the composite primary outcome of death from any cause or worsening of heart failure; the latter was defined as either an unplanned hospitalization or an urgent medical visit. Panels B and C show the time until death from any cause and first worsening of heart failure, respectively. The insets show the same data on an expanded y axis. Hazard ratios and 95% confidence intervals were estimated with the use of Cox regression models. The widths of the confidence intervals have not been adjusted for multiple comparisons and should not be used in place of hypothesis testing.

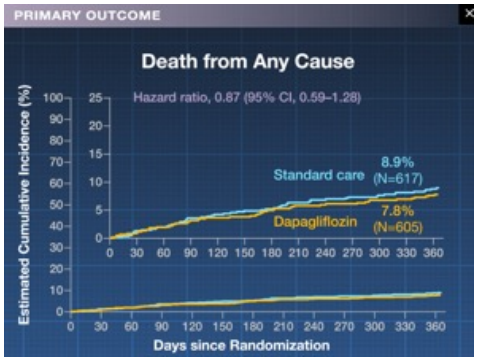


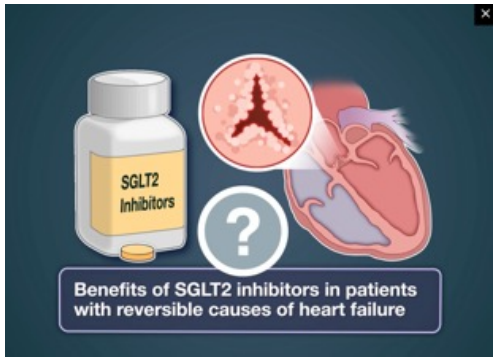
Primary Outcome in Prespecified Subgroups.

The forest plot shows the primary outcome (a composite of death from any cause or worsening of heart failure) in prespecified subgroups of patients. In the cardiac rhythm category, a rhythm other than sinus rhythm or atrial fibrillation was identified in 13 patients in the dapagliflozin group and in 15 patients in the standard-care group. The abbreviation eGFR denotes estimated glomerular filtration rate, and RAS renin–angiotensin system.

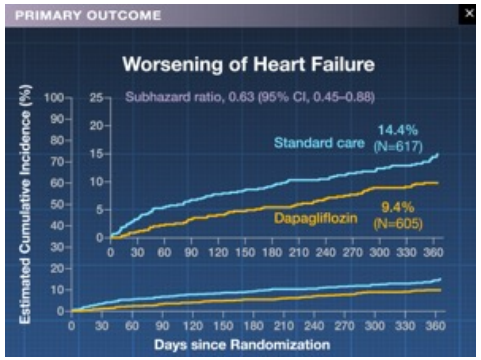

Heart-failure–related admissions
SGLT2 Inhibitors


1222 Adults
Severe aortic stenosis undergoing TAVI and had previous episode of aortic stenosis–related heart failure plus any of the following conditions:
• Moderate renal insufficiency
• Diabetes
• Left ventricular ejection fraction of ≤40%

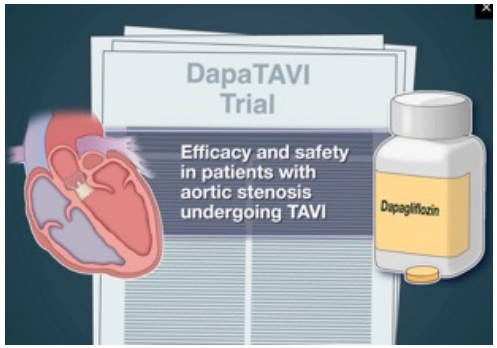

PRIMARY OUTCOME
Death from Any Cause
Hazard ratio, 0.87 (95% CI, 0.59–1.28)
Standard care 8.9% (N=617)
Dapagliflozin 7.8% (N=605)
Estimated Cumulative Incidence (%)
Days since Randomization

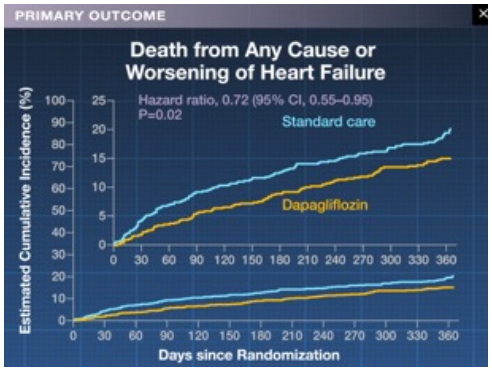

SGLT2 Inhibitors
?
Benefits of SGLT2 inhibitors in patients with reversible causes of heart failure

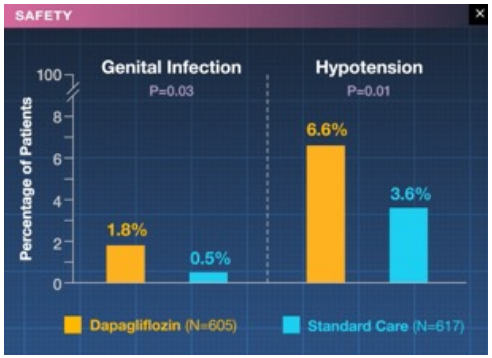

1222 Adults
Dapagliflozin
Standard Care
• 10 mg Dapagliflozin once daily
• Plus standard care
• Standard care alone


PRIMARY OUTCOME
Worsening of Heart Failure
Subhazard ratio, 0.63 (95% CI, 0.45–0.88)
Standard care 14.4% (N=617)
Dapagliflozin 9.4% (N=605)
Estimated Cumulative Incidence (%)
Days since Randomization

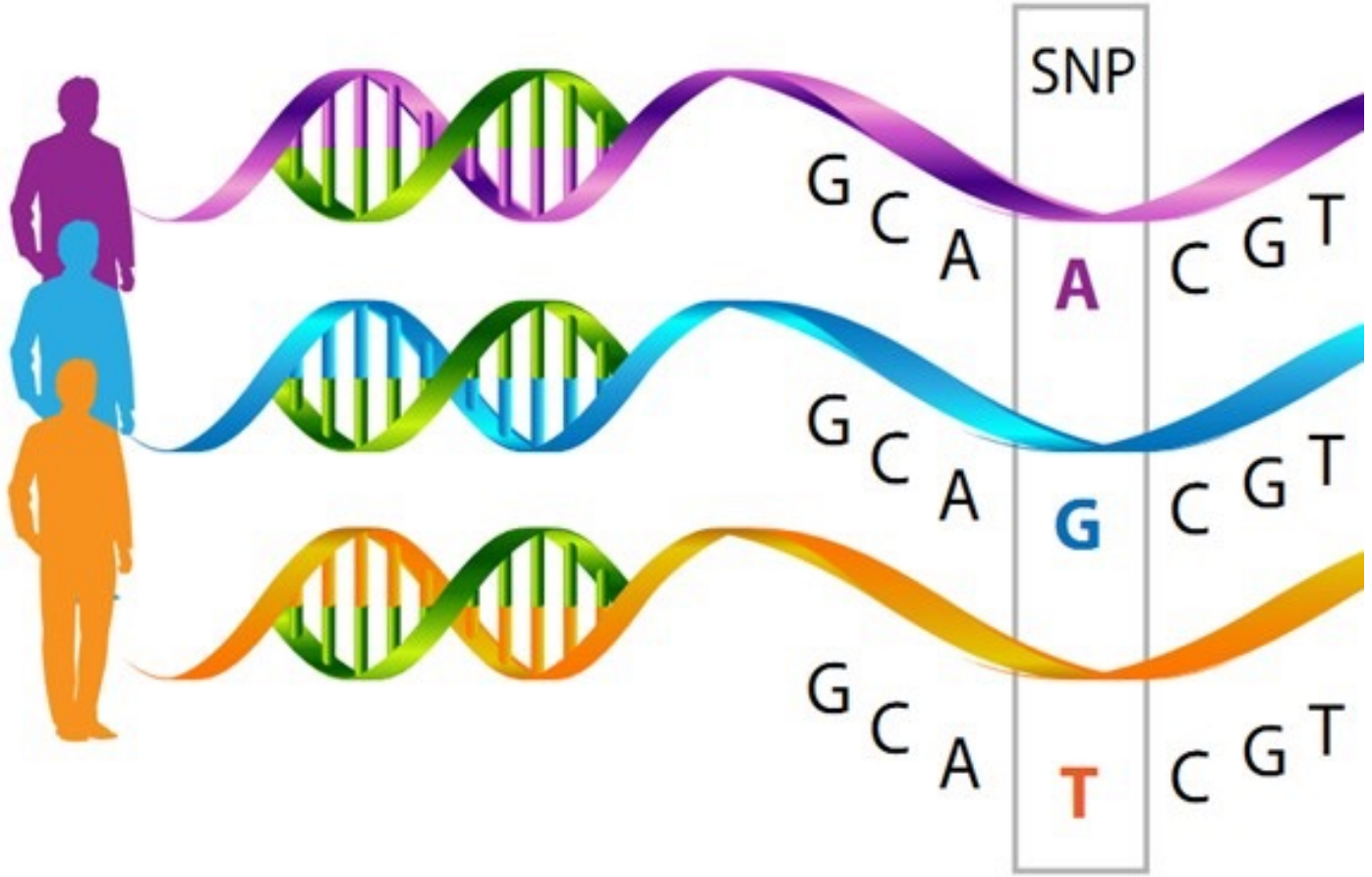

Addition of dapagliflozin to standard care lowered the incidence of death or worsening of heart failure at 1 year, as compared with standard care alone
Dapagliflozin
Standard Care


DapaTAVI Trial
Efficacy and safety in patients with aortic stenosis undergoing TAVI
Dapagliflozin


PRIMARY OUTCOME
Death from Any Cause or Worsening of Heart Failure
Hazard ratio, 0.72 (95% CI, 0.55–0.95)
P=0.02
Standard care
Dapagliflozin
Estimated Cumulative Incidence (%)
Days since Randomization

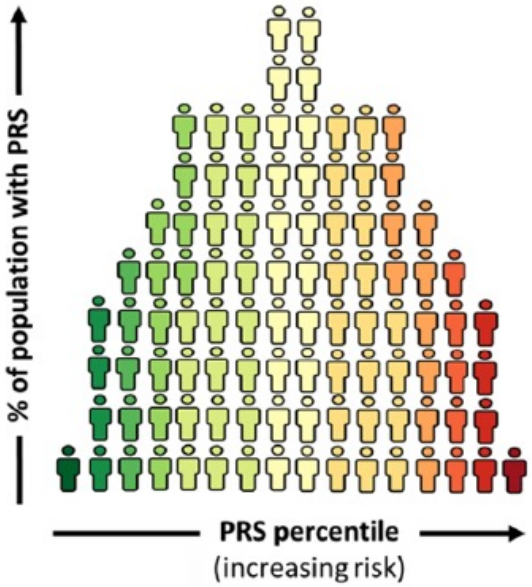

SAFETY
Genital Infection
P=0.03
Hypotension
P=0.01
Percentage of Patients
1.8%
0.5%
6.6%
3.6%
Dapagliflozin (N=605)
Standard Care (N=617)

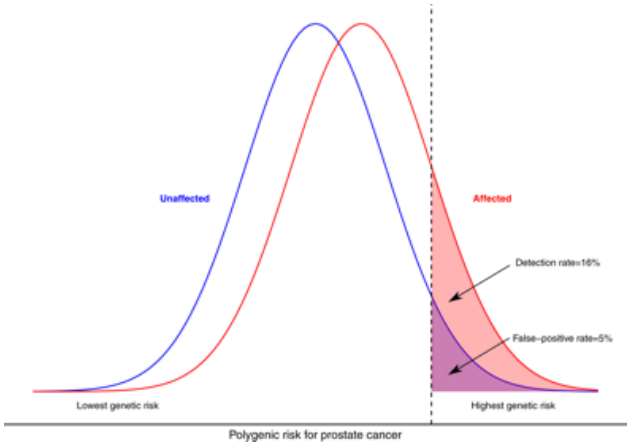
Etwa zehn Millionen solcher SNPs sind schätzungsweise im Genom vorhanden.



A polygenic risk score (PRS) is a genetic screening tool that estimates a person's risk of developing a disease. It's also known as a polygenic score (PGS), genetic risk score (GRS), or genome-wide score.

PRS percentile	Risk of disease vs. reference group
0-1	Lowest
1-5	
5-10	
10-20	
20-40	
40-60 (reference)	1
60-80	
80-90	
90-95	
95-99	
99-100	Highest





Source: RGA

Effect of polygenic risk score for clinically significant prostate cancer in a screening program: The BARCODE 1 study results.

Assessment of a Polygenic Risk Score in Screening for Prostate Cancer

The incidence of prostate cancer is increasing. Screening with an assay of prostate-specific antigen (PSA) has a high rate for false positive results. Genomewide association studies have identified common germline variants in persons with prostate cancer, which can be used to calculate a polygenic risk score associated with risk of prostate cancer.

We recruited persons 55 to 69 years of age from primary care centers in the United Kingdom. Using germline DNA extracted from saliva, we derived polygenic risk scores from 130 variants known to be associated with an increased risk of prostate cancer. Participants with a polygenic risk score in the 90th percentile or higher were invited to undergo prostate cancer screening with multiparametric magnetic resonance imaging (MRI) and transperineal biopsy, irrespective of PSA level.

Among 40,292 persons invited to participate, 8953 (22.2%) expressed interest in participating and 6393 had their polygenic risk score calculated; 745 (11.7%) had a polygenic risk score in the 90th percentile or higher and were invited to undergo screening. Of these 745 participants, 468 (62.8%) underwent MRI and prostate biopsy; prostate cancer was detected in 187 participants (40.0%).

Conclusions

In a prostate cancer screening program involving participants in the top decile of risk as determined by a polygenic risk score, the percentage found to have clinically significant disease was higher than the percentage that would have been identified with the use of PSA or MRI.

Methods

Study Design and Participants

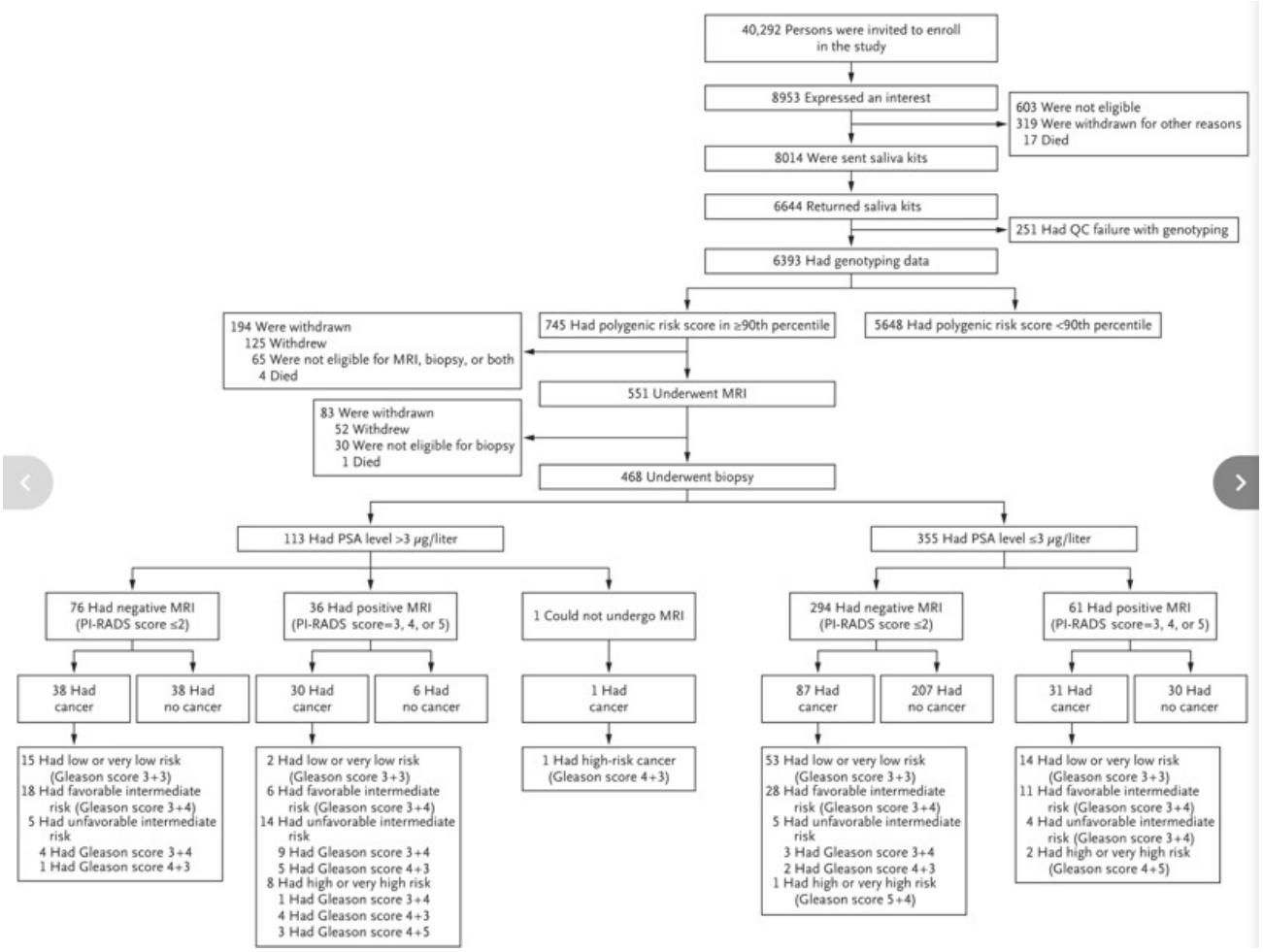
BARCODE1 is an ongoing, prospectively designed, single-group study that received approval from the London–Chelsea Research Ethics Committee and the Health Research Authority. The Institute of Cancer Research provides regulatory oversight of the BARCODE1 study. Recruitment was coordinated at 69 primary care centers across three clinical research networks (Kent, Surrey, and Sussex; South London; and the Thames Valley and South Midlands). Patient databases were screened, and eligible persons were invited by letter. Patients were eligible if they had been assigned male sex at birth, were 55 to 69 years of age, reported European ancestry, had no personal history of prostate cancer, were not currently undergoing testing for suspected prostate cancer, had not undergone prostate biopsy within the previous 12 months, and had no known contraindications to MRI or biopsy.

The panel consisted of 130 European-ancestry SNPs known to be associated with an increased risk of prostate cancer (Table S2) and has been validated for use only in persons of European ancestry. The polygenic risk score for each participant was calculated with the use of the sum of weighted alleles for the 130 SNPs. Study participants with a polygenic risk score in at least the 90th percentile (on the basis of a reference population from the ProtecT [Prostate Testing for Cancer and Treatment] study) were referred to a cancer center for genetic-risk counseling. This counseling involved a discussion with experienced clinicians about the meaning of the polygenic risk score results.

Wang A, Shen J, Rodriguez AA, et al. Characterizing prostate cancer risk through multi-ancestry genome-wide discovery of 187 novel risk variants. *Nat Genet* 2023;55:2065-2074.

Schumacher FR, Al Olama AA, Berndt SI, et al. Association analyses of more than 140,000 men identify 63 new prostate cancer susceptibility loci. *Nat Genet* 2018;50:928-936.

Benafif S, Ni Raghallaigh H, McGrowder E, et al. The BARCODE1 pilot: a feasibility study of using germline single nucleotide polymorphisms to target prostate cancer screening. *BJU Int* 2022;129:325-336.



Participant Pathway through the BARCODE1 Study.

Shown is the participant pathway through the study, from initial invitation to biopsy outcome. Cancers were classified in accordance with the National Comprehensive Cancer Network 2024 criteria for risk of metastasis (very low, low, favorable intermediate, unfavorable intermediate, high, or very high risk) and Gleason score (scores range from 6 to 10 [sum of the primary grade plus the secondary grade], with higher scores indicating a more aggressive form of prostate cancer). Prostate Imaging Reporting and Data System (PI-RADS) scores range from 1 to 5, with higher scores indicating a higher cancer risk. PSA denotes prostate-specific antigen, and QC quality control.

Table S1: Eligibility Criteria

Inclusion Criteria:
• Men aged 55 to 69 years.
• Caucasian ethnicity.
• WHO performance status 0-2
• Absence of any psychological, familial, sociological or geographical situation potentially hampering compliance with the study protocol and follow-up schedule.
Exclusion criteria
• Non-Caucasian ethnicity (including mixed race or Ashkenazi Jewish (excluded as these groups have different genetic risk profiles from those being studied).
• Previous diagnosis of cancer with a life-expectancy of less than five years.
• Negative prostate biopsy within one year before recruitment.
• Previous diagnosis of prostate cancer.
• Co-morbidities making prostate biopsy risk unacceptable (anticoagulants or antiplatelet medication including Warfarin, Clopidogrel, Apixaban, Dabigatran or other NOAC medications (Novel Oral Anti-Coagulant); poorly controlled diabetes, cardiovascular/respiratory disease, immunosuppressive medication or splenectomy)
• Men with body mass index (BMI) 40 and above.
• Men with BMI 35 and above plus other co-morbidities.
• Contraindications to having an MRI (pacemakers, aneurysm clips, metallic cardiac valve/stent, Ventriculo-Peritoneal (VP) shunt, cochlear implant, neurotransmitter, metallic foreign bodies in eye(s), other metalwork, claustrophobia).
• Any significant psychological conditions that may be worsened or exacerbated by participation in the study.

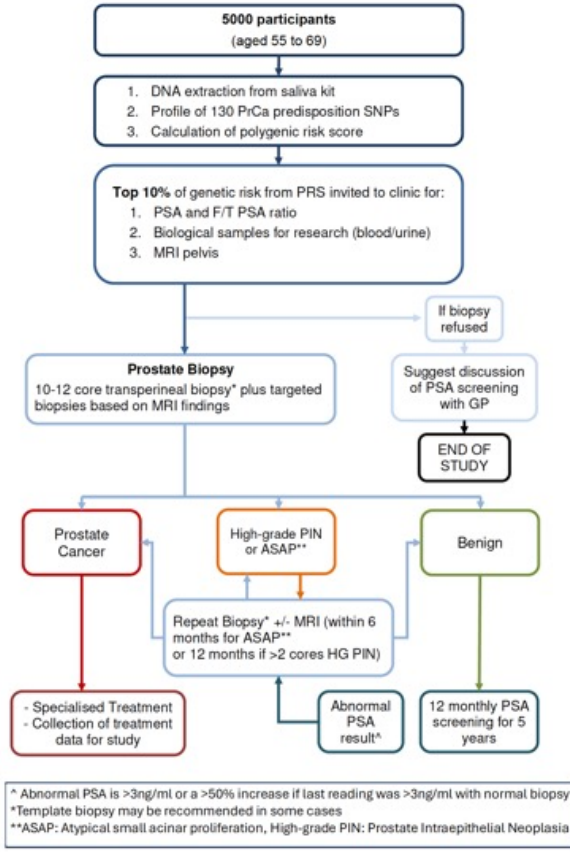


Table S2: List of 130 Risk SNPs used to calculate PRS

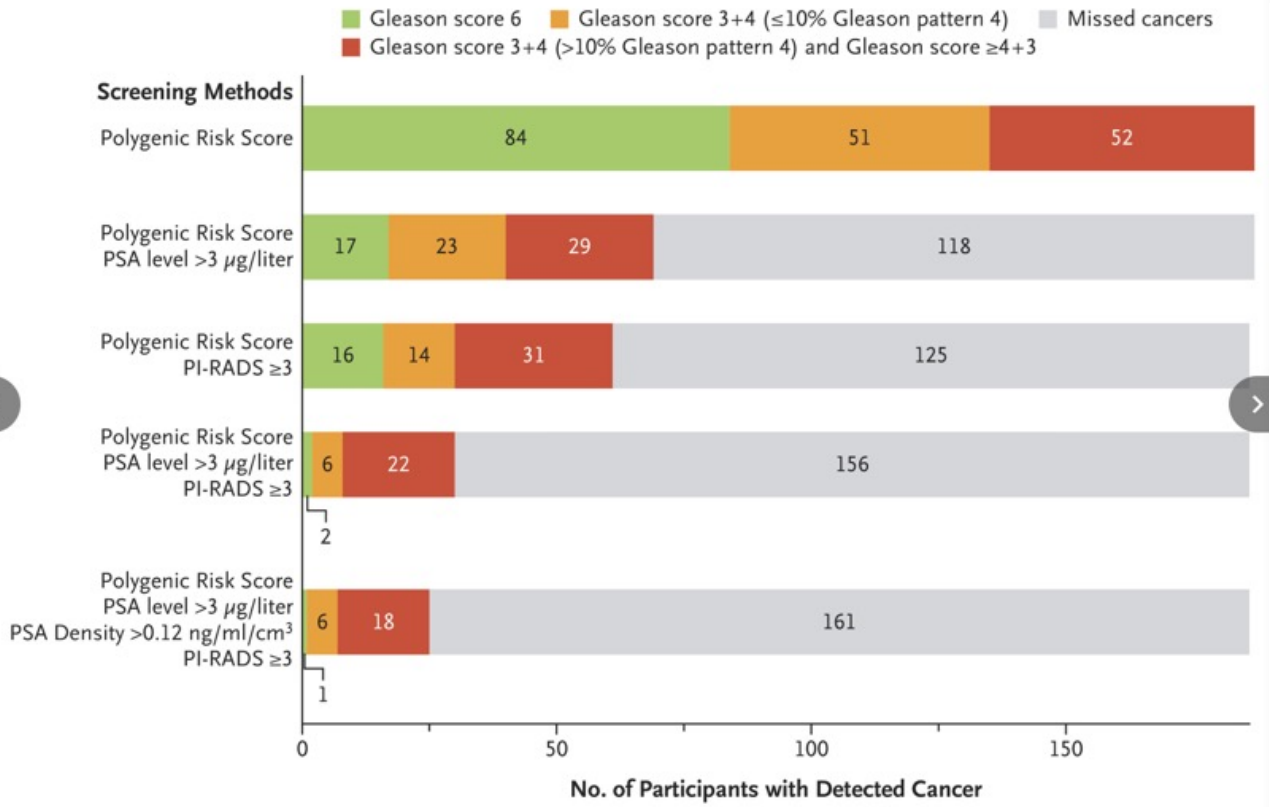
rsID	Chromosome	hg19 position
rs17599629	1	150658287
rs1218582	1	154834183
rs1043608	1	153909069
rs56391074	1	88210715
rs4245739	1	204518842
rs721048	2	63131731
rs10187424	2	85794297
rs12621278	2	173311553
rs7584330	2	238387228
rs3771570	2	242382864
rs62106670	2	8597123
rs74702681	2	66652885
rs11691517	2	111893096
rs34925593	2	174234547
rs59308963	2	202123479
rs9287719	2	10710730
rs13385191	2	20888265
rs1465618	2	43553949
rs2660753	3	87110674
rs7611694	3	113275624
rs10934853	3	128038373
rs6763931	3	141102833
rs10936632	3	170130102
rs1283104	3	106962521
rs142436749	3	169093100
rs10009409	4	73855253
rs1894292	4	74349158
rs17021918	4	95562877
rs7679673	4	106061534
rs76551843	5	169172133
rs4976790	5	177968915
rs2242652	5	1280028
rs12653946	5	1895829
rs2121875	5	44365545
rs12665339	6	30601232
rs9296068	6	32988695
rs4713266	6	11219030
rs7767188	6	30073776
rs3096702	6	32192331
rs3129859	6	32400939
rs1983891	6	41536427
rs2273669	6	109285189
rs339331	6	117210052
rs1933488	6	153441079
rs9364554	6	160833664
rs17621345	7	40875192
rs11452686	7	20414110
rs12155172	7	20994491
rs10486567	7	27976563
rs56232506	7	47437244
rs6465657	7	97816327
rs183373024	8	128104117
rs2928679	8	23438975
rs11135910	8	25892142
rs12543663	8	127924659
rs10086908	8	128011937
rs16901979	8	128124916
rs620861	8	128335673
rs6983267	8	128413305
rs1447295	8	128485038
rs1048169	9	19055965
rs1182	9	132576060
rs17694493	9	22041998
rs61830900	10	871481
rs1935581	10	90195149
rs76934034	10	46082985
rs10993994	10	51549496
rs3850699	10	104414221
rs4962416	10	126696872
rs61890184	11	7547587
rs2277283	11	61908440
rs11290954	11	76260543
rs1800057	11	108143456
rs138466039	11	125054793
rs878987	11	134266372
rs1881502	11	1507512
rs7127900	11	2233574
rs7931342	11	68994497
rs11568818	11	102401661
rs11214775	11	113807181
rs2066827	12	12871099
rs10845938	12	14416918
rs7968403	12	65012824
rs7295014	12	133067989
rs5799921	12	90160530
rs80130819	12	48419618
rs10875943	12	49676010
rs902774	12	53273904
rs1270884	12	114685571
rs1004030	14	23305649
rs11629412	14	37138294
rs8008270	14	53372330
rs7141529	14	69126744
rs8014671	14	71092256
rs4924487	15	40922915
rs33984059	15	56385868
rs201158093	16	82178893
rs28441558	17	7803118
rs2680708	17	56456120
rs684232	17	618965
rs11649743	17	36074979
rs4430796	17	36098040
rs138213197	17	46805705
rs11650494	17	47345186
rs1859962	17	69108753
rs8093601	18	51772473
rs28607662	18	53230859
rs12956892	18	56746315
rs10460109	18	73036165
rs7241993	18	76773973
rs11666569	19	17214073
rs118005503	19	32167803
rs61088131	19	42700947
rs8102476	19	38735613
rs11672691	19	41985587
rs2735839	19	51364623
rs11480453	20	31347512
rs6126982	20	52456445
rs12480328	20	49527922
rs2427345	20	61015611
rs6062509	20	62362563
rs1041449	21	42901421
rs9625483	22	28888939
rs9623117	22	40452119
rs5759167	22	43500212
rs5945619	X	51241672
rs2807031	X	52896949
rs5919432	X	67021550
rs17321482	X	11482634
rs2405942	X	9814135

Characteristics of the Participants According to Cancer Diagnosis.

Characteristic	No Cancer (N=281)	Any Prostate Cancer (N=187)	Clinically Significant Prostate Cancer (N=103)
Median age at diagnosis (IQR) — yr	63 (60–67)	64 (60–68)	65 (60–69)
Median PSA (IQR) — μg/liter	1.4 (0.9–2.3)	2.1 (1.3–4.2)	3.1 (1.8–6.3)
Median polygenic risk score percentile (IQR)	95 (92–98)	95 (93–99)	96 (93–99)
PI-RADS score — no. (%)†			
1	7 (2.5)	1 (0.5)	1 (1.0)
2	238 (84.7)	124 (66.7)	56 (54.9)
3	24 (8.5)	19 (10.2)	9 (8.8)
4	10 (3.6)	22 (11.8)	17 (16.7)
5	2 (0.7)	20 (10.8)	19 (18.6)
Family history of prostate cancer — no. (%)‡			
No	232 (82.6)	147 (78.6)	74 (71.8)
Yes	49 (17.4)	40 (21.4)	29 (28.2)

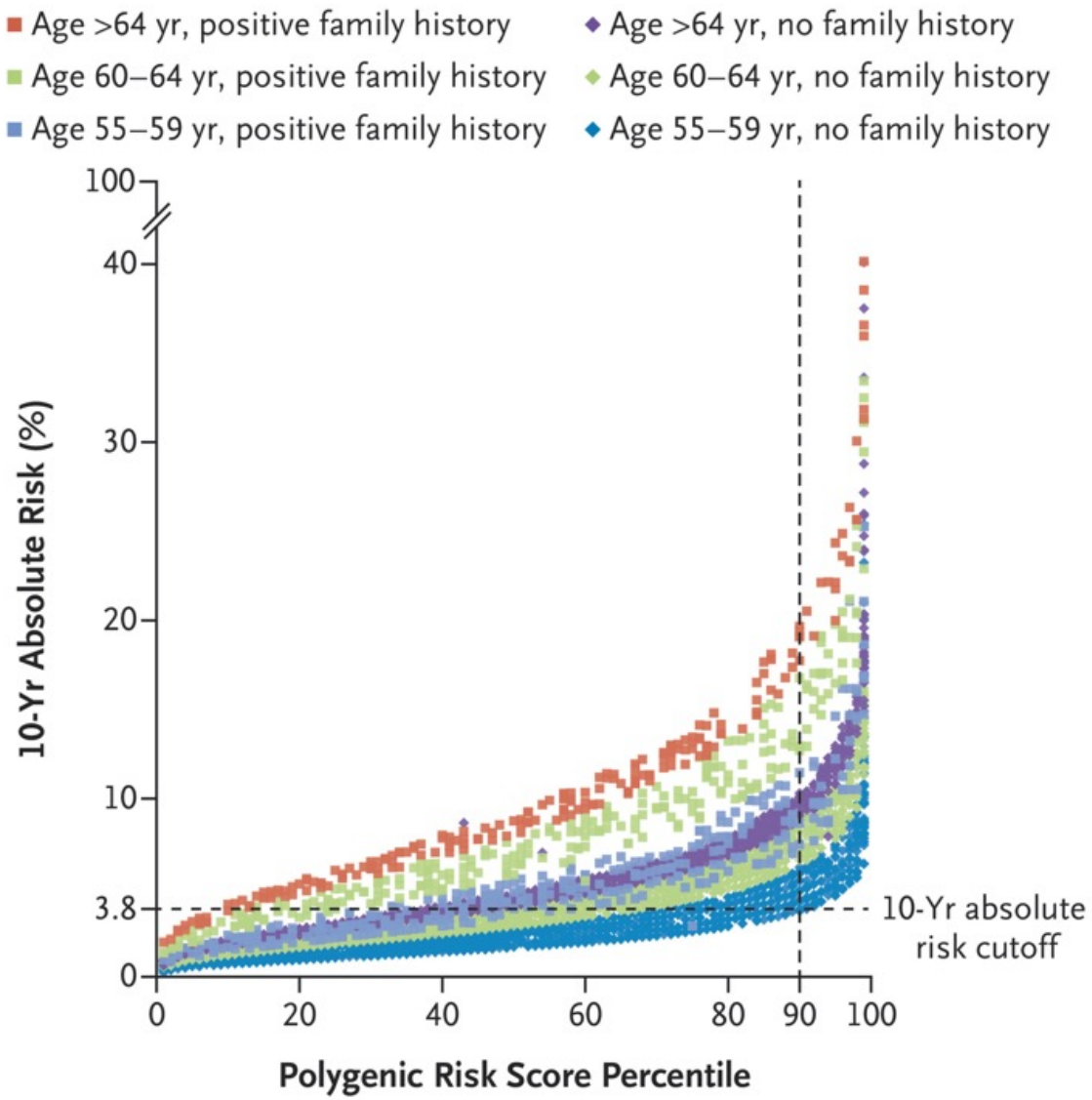
Characteristics of the Cancers Detected and Those That Would Have Been Missed, with Stratification According to Polygenic Risk Score, PSA Level, and MRI Results.

NCCN Cancer Classification	Polygenic Risk Score ≥90th Percentile	PSA Level >3 μg/Liter		Positive MRI Results†		PSA Level >3 μg/Liter and Positive MRI Results†	
	Cancer Detected (N=187)	Cancer Detected (N=69)	Cancer Missed (N=118)	Cancer Detected (N=61)	Cancer Missed (N=125)	Cancer Detected (N=30)	Cancer Missed (N=156)
	number of participants (percent)						
Low or very low	84 (44.9)	17 (24.6)	67 (56.8)	16 (26.2)	68 (54.4)	2 (6.7)	82 (52.6)
Intermediate favorable	63 (33.7)	24 (34.8)	39 (33.1)	17 (27.9)	46 (36.8)	6 (20.0)	57 (36.5)
Intermediate unfavorable	28 (15.0)	19 (27.5)	9 (7.6)	18 (29.5)	10 (8.0)	14 (46.7)	14 (9.0)
High or very high	12 (6.4)	9 (13.0)	3 (2.5)	10 (16.4)	1 (0.8)	8 (26.7)	3 (1.9)



Participants with Detected Cancer, with Stratification According to Screening Method and Gleason Score.

Shown is the number of participants with prostate cancer detected with the use of polygenic risk score alone and polygenic risk score combined with prostate-specific antigen (PSA) level, with PI-RADS score on MRI, with both PSA level and PI-RADS score, and with PSA level, PSA density, and PI-RADS score. Participants with detected cancer are grouped according to Gleason score. Gleason pattern is the measure of how aggressive the cancer looks on microscopic examination; scores range from 1 to 5, with higher scores indicating a more aggressive appearance. For the groups that include PI-RADS score, the number of participants with cancer totals 186 of the overall 187 because one participant was unable to undergo MRI owing to claustrophobia.



Absolute Risk of Prostate Cancer.

Shown is the 10-year absolute risk of prostate cancer (estimated from the iCARE22 algorithm) for all 6393 participants who agreed to screening and for whom we calculated a polygenic risk score, stratified according to participant age, family history of prostate cancer, and polygenic risk score. A threshold of 3.5 to 4% for the 10-year absolute risk of prostate cancer has been suggested as generating the greatest number of quality-adjusted life-years from risk-based screening and was used to calculate the 3.8% cutoff in this study.

Discussion

Our results show that offering targeted screening to participants in at least the 90th percentile of genetic risk distribution as determined by a polygenic risk score resulted in the detection of prostate cancer warranting clinical management in 55.1% of these participants and radical treatment in 21.4% of those with cancer classified as unfavorable intermediate risk or higher. The current diagnostic pathway for suspected prostate cancer in the United Kingdom involves either a high PSA level (>2.5 µg per liter in persons <50 years of age, >3.5 µg per liter in persons 50 to 59 years of age, or >4.5 µg per liter in persons 60 to 69 years of age) or an abnormal digital rectal examination followed by a referral for MRI. If a lesion is present or there is other clinical concern, biopsy is indicated. If the participants of the BARCODE1 study had followed this pathway, prostate cancer would have been missed in 42.5% of those with clinically significant disease, and a prostate cancer diagnosis would have been avoided in 97.6% of those with clinically insignificant disease.

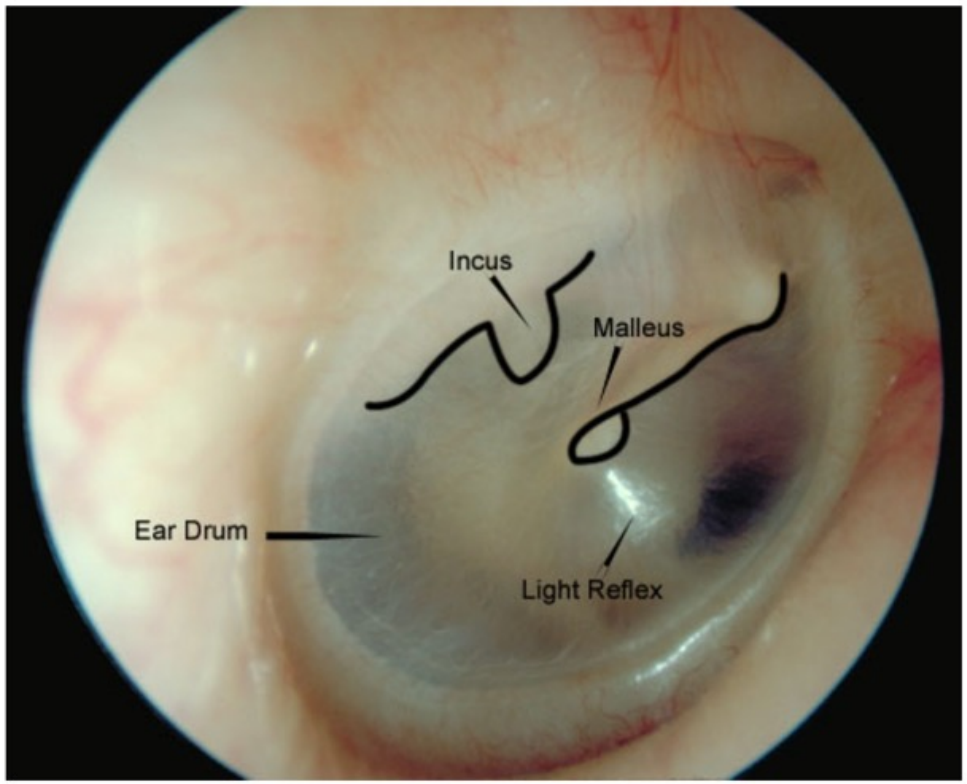
Of note, prostate cancer was detected at biopsy in 40.0% of the participants who underwent the procedure, and 55.1% of these participants had a Gleason score of 7 or higher. In the ERSPC, the decision to perform biopsy was based on PSA level, and 35.5% of the participants who underwent biopsy were found to have prostate cancer. In the BARCODE1 study, when we only included in the analysis participants with a polygenic risk score in the 90th percentile or higher and a PSA level greater than 3.0 µg per liter, we found that 75.4% of the participants with detected cancer had a Gleason score of 7 or higher. In the ERSPC, the positive predictive value of a PSA level greater than 3.0 µg per liter with respect to having biopsy-confirmed prostate cancer was 24.1%.

EDITORIAL

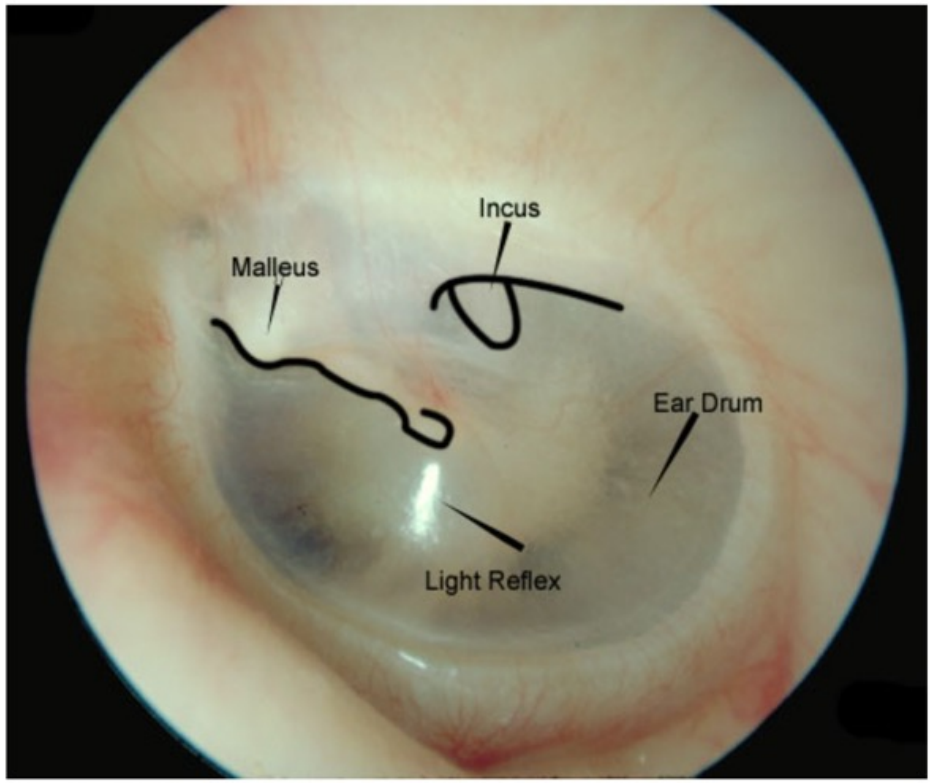
A Polygenic Risk Score in Practice

A polygenic risk score does not yield a diagnosis of disease; rather it is a risk factor that may be included as part of a screening program. The genotyping panel used to calculate polygenic risk scores in the study by McHugh et al. is validated only for men of European ancestry and performs less well among men of African and other ancestries.
McHugh et al. examined the outcomes of a workup in men with a polygenic risk score in at least the 90th percentile for risk of prostate cancer. Of 6393 participants who had their polygenic risk score calculated with the use of DNA extracted from saliva, 745 had a score in at least the 90th percentile of risk in the population, and 468 agreed to undergo MRI and biopsy. A total of 187 participants received a diagnosis of prostate cancer at a median age of 64 years, of whom 103 had disease classified as intermediate or higher risk and therefore warranted further treatment according to National Comprehensive Cancer Network criteria. Of these 103 men, 74 (71.8%) had cancer that would not have been detected with the use of the screening recommendations currently used in the United Kingdom because these participants had either a PSA level lower than the action threshold or an MRI result that would not have led to a recommendation for biopsy. A total of 370 men had an MRI result that would not have led to a recommendation for biopsy; 125 received a diagnosis of prostate cancer, of whom 57 had a Gleason score of 7 or higher (scores range from 6 to 10, with higher scores indicating a more aggressive form of prostate cancer).
Thus, if a screening program started with an assessment of a polygenic risk score, a substantial number of clinically significant cases would be discovered that otherwise would have been missed.

Im Mittelohr befinden sich drei Gehörknöchelchen: Hammer (oder Malleus), Amboss (oder Incus) und Steigbügel (oder Stapes).

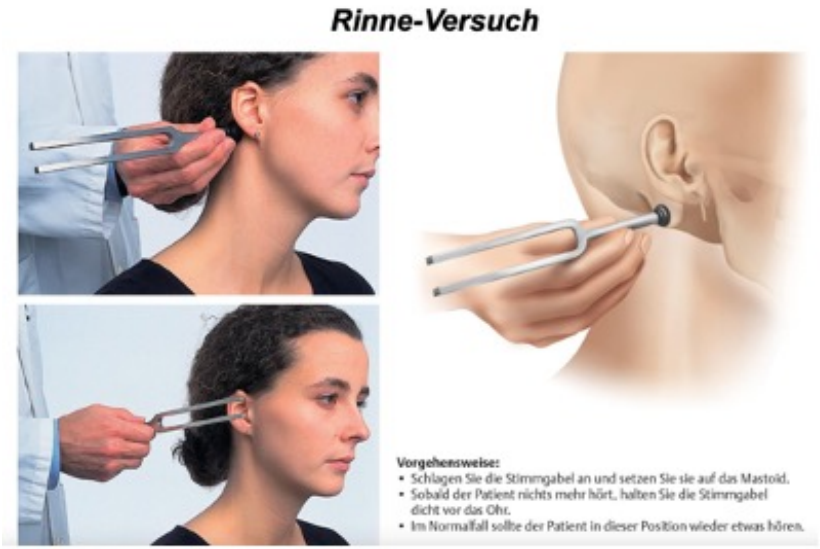


Normal Right Ear Drum
The ear drum is often transparent and looks like a stretched piece of clear plastic. The drum is approximately the size of a dime, with the newborn ear drum the same size as the adult. The malleus is the middle ear bone which is attached to the drum and easily identified. The middle ear space can be seen through the ear drum and a portion of the incus (another middle ear bone) can be identified.



Normal Left Ear Drum
This is a left ear drum of a ten year old. The drum looks healthy and has a nice gray color to it.

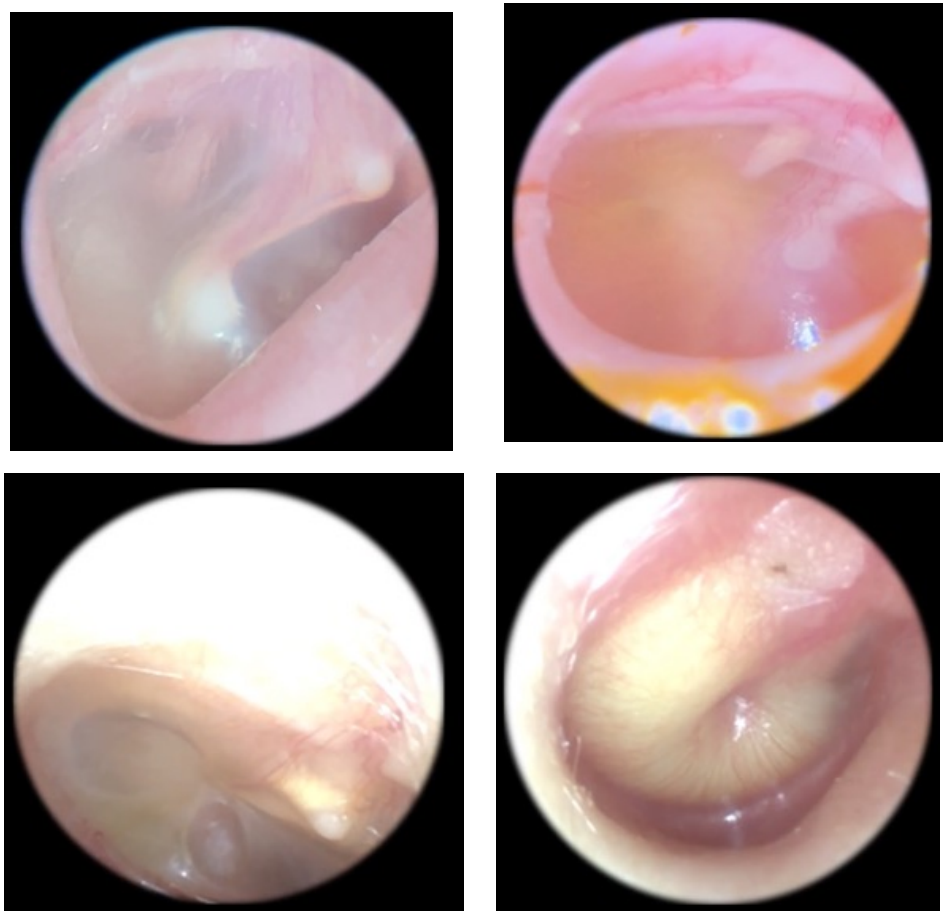
Ein Stimmgabeltest ist ein einfaches Hörtestverfahren, das mit einer schwingenden Stimmgabel durchgeführt wird. Es kann Hinweise auf Hörstörungen oder Funktionsstörungen des Nervensystems geben



CLINICAL PRACTICE

Otitis Media in Young Children

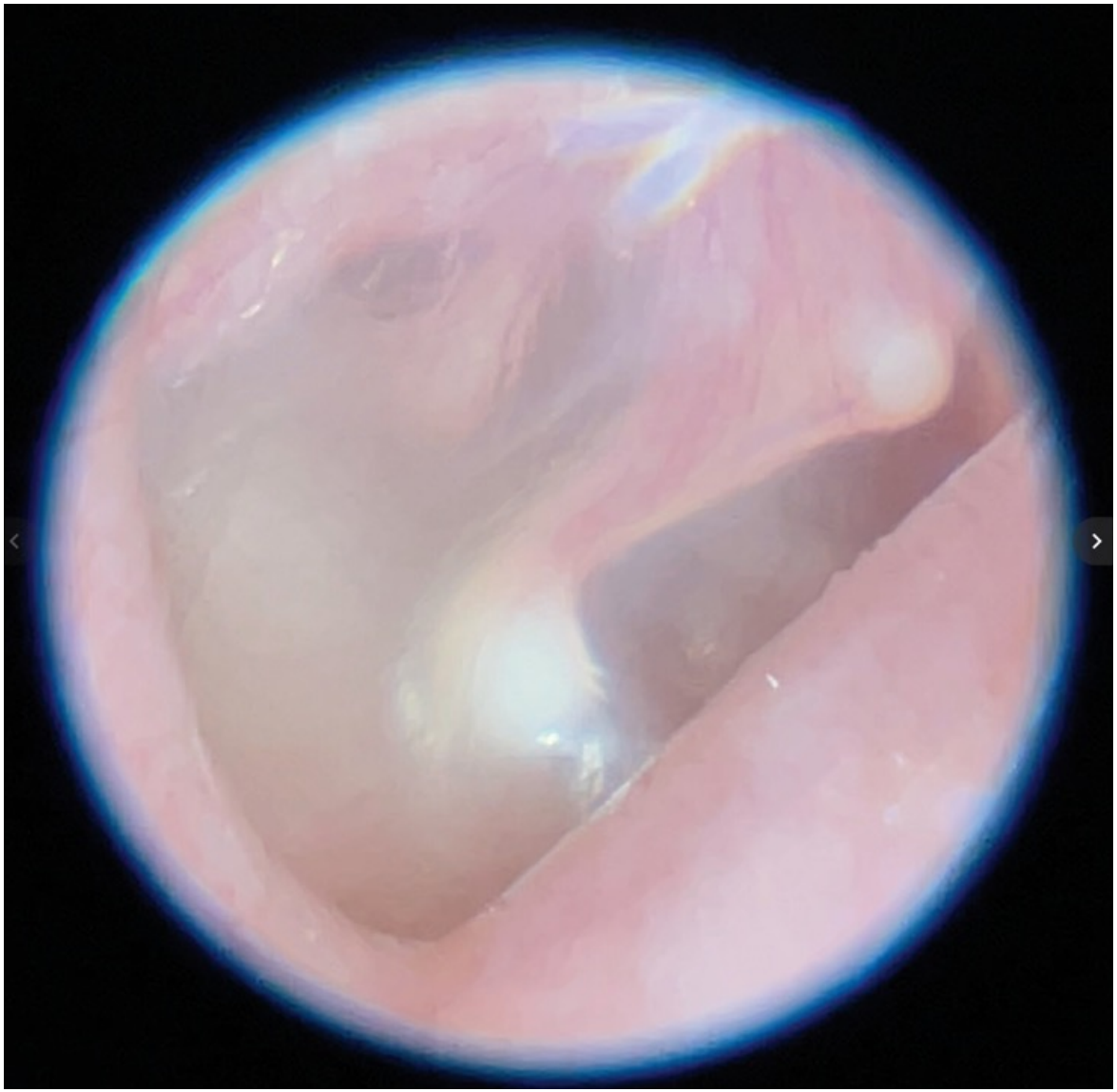
An otherwise-healthy 9-month-old girl in whom symptoms of an upper respiratory tract infection had developed 4 days earlier presents with a 1-day history of increased fussiness and difficulty sleeping reported by a parent. On examination, she is afebrile and slightly fussy. Her right tympanic membrane, which can be visualized only partially owing to the presence of cerumen, appears opacified. How would you treat this child?



Du hast weniger als 0,10 sek

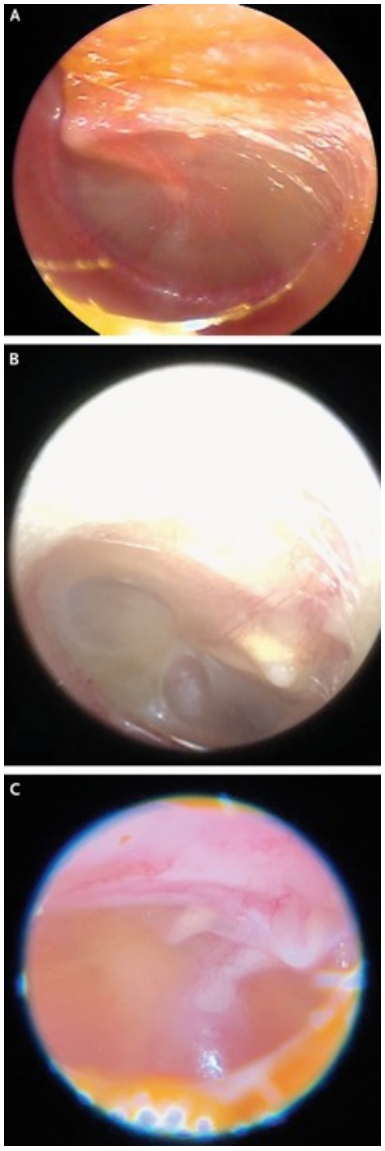
Otitis Media in Young Children

- Acute otitis media is a bacterial infection that occurs almost exclusively after a viral upper respiratory tract infection.
- Common pathogens include *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*.
- Bulging of the tympanic membrane is a defining feature.
- Children with mild or moderate symptoms can be either treated with antibiotic agents or closely observed.
- High-dose amoxicillin (80 to 90 mg per kilogram of body weight per day, divided into two doses) remains the first-line treatment. Amoxicillin–clavulanate therapy warrants consideration in children in whom *H. influenzae* is likely to predominate (i.e., those who have received antibiotics in the previous 30 days, have conjunctivitis–otitis syndrome, or have spontaneous rupture of the tympanic membrane).
- Treatment with antibiotics for 10 days resulted in less treatment failure and less use of rescue antibiotics than treatment for 5 days.
- Tympanocentesis is indicated in children with acute otitis media who have had treatment failure with multiple rounds of antibiotic therapy.
- Among children with recurrent acute otitis media, the incidence of acute otitis media during a 2-year period was similar among those who had placement of a tympanostomy tube and those who received episodic antibiotic treatment.



Normal Tympanic Membrane.

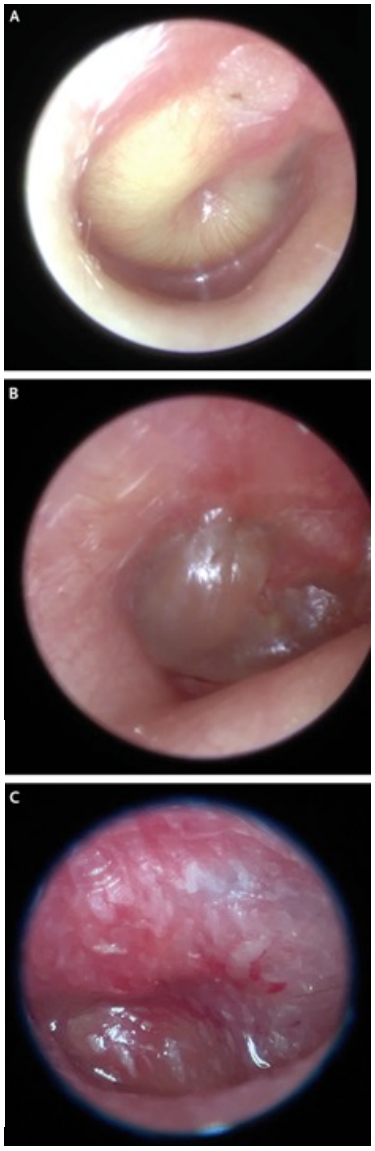
The normal tympanic membrane is translucent and pearly gray and has a ground-glass appearance that enables a clear view of the short process and the manubrium of the malleus.



Manifestations of Otitis Media with Effusion.

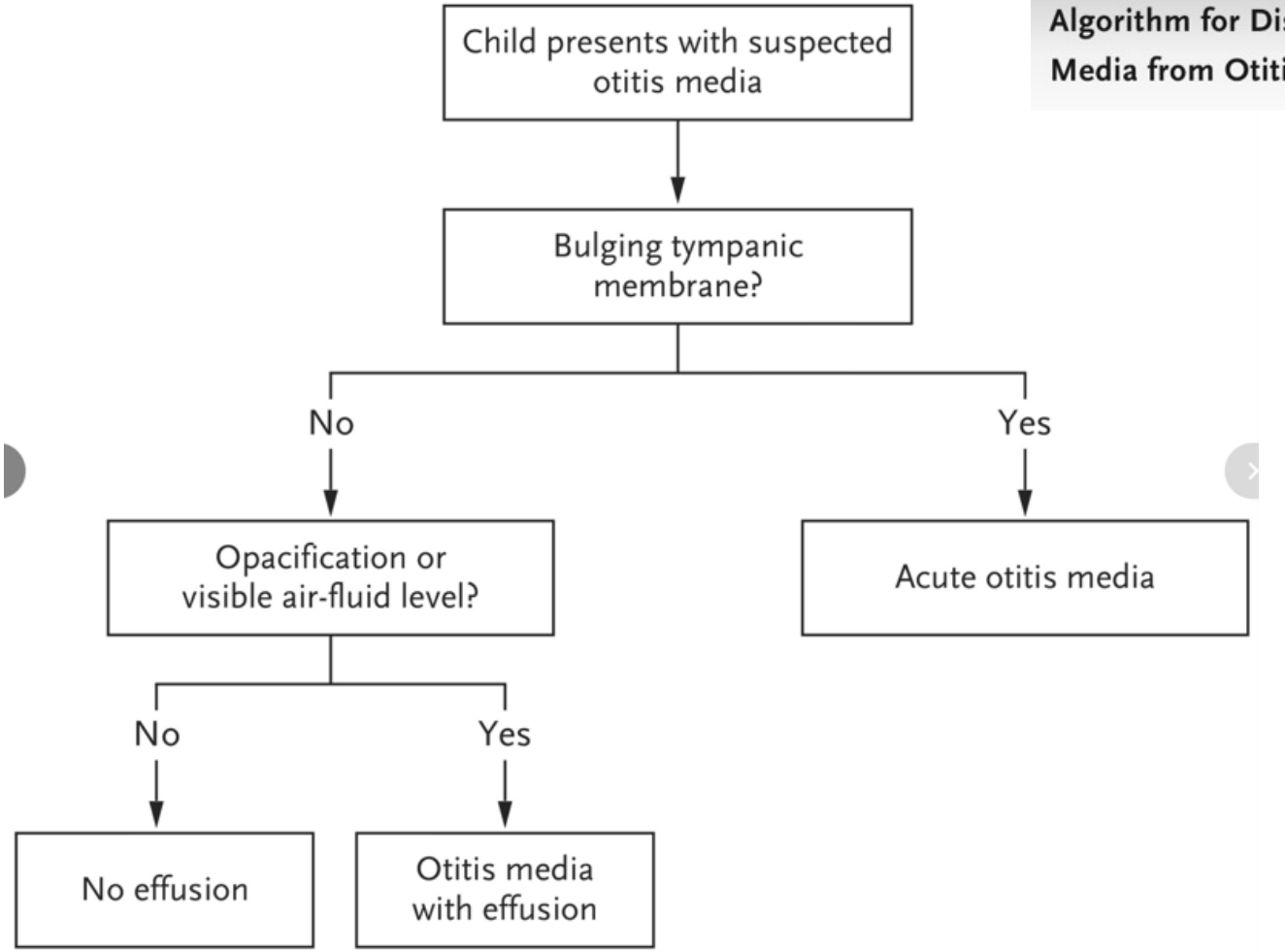
Panel A shows an opaque neutral tympanic membrane, Panel B an opaque tympanic membrane with visible air-fluid levels, and Panel C an amber tympanic membrane.

An amber tympanic membrane can indicate otitis media with effusion (OME)



Manifestations of Acute Otitis Media.

Panel A shows a bulging tympanic membrane, Panel B bullous myringitis (bulging tympanic membrane with bullae), and Panel C cobblestoning of the tympanic membrane (bulging tympanic membrane with microperforations).



Algorithm for Distinguishing Acute Otitis Media from Otitis Media with Effusion.

Management

Many issues influence strategies for the treatment of acute otitis media. These issues include the age of the child, the severity of symptoms, and the relative risk of observation as compared with treatment.

To date, 13 randomized trials have examined the efficacy of antibiotics as compared with placebo for eradicating symptoms of acute otitis media in children. The outcomes that were investigated varied among these trials: 5 trials reported data on ear pain, and 8 reported data on composite outcomes that may or may not have included ear pain.

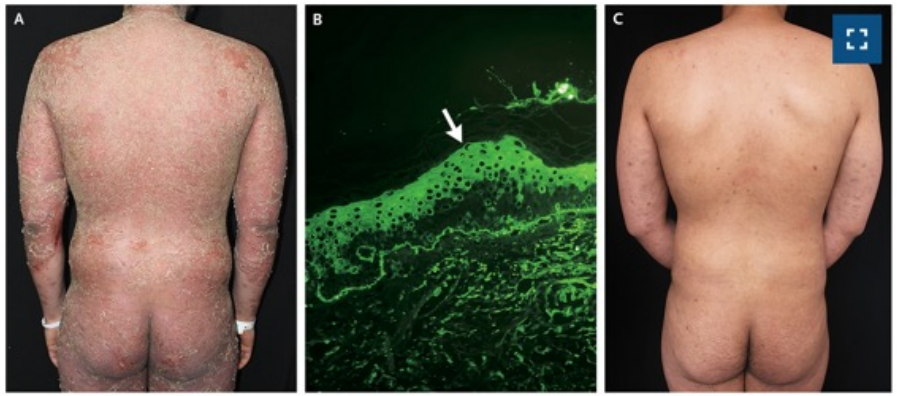
Children assigned to receive antibiotics had a 29% lower risk of persistent symptoms at 2 to 3 days, a 24% lower risk of persistent symptoms at 4 to 7 days, and a 67% lower risk of persistent symptoms at or before 10 to 12 days than those who had been assigned to receive placebo. The corresponding number needed to treat with antibiotics to achieve symptom eradication at these time points were 20 at 2 to 3 days, 17 at 4 to 7 days, and 7 at or before 10 to 12 days. No significant difference in symptom eradication was noted during the first 24 hours, but a difference would not be expected given the pharmacokinetics of the agents being used. The use of antibiotics halved the risk of contralateral acute otitis media episodes (from 19% to 10%; number needed to treat, 11) and reduced the risk of tympanic-membrane perforations by two thirds (from 5% to 2%; number needed to treat, 33). Of note, in 11 of the 13 trials, a large proportion of the enrolled children had nonbulging tympanic membranes, which could have biased the pooled results toward the null. In the 1 trial that measured symptoms with the use of a validated scale, the risk of persistent symptoms was 67% lower among children randomly assigned to receive amoxicillin–clavulanate than among those who had been assigned to receive placebo (nnt = 7).

Conclusions and Recommendations

With regard to the child in the vignette, I would first determine the severity and trajectory of symptoms of acute otitis media by having a detailed discussion with the parent. The child was fussy approximately half the time when awake and slept only a few hours at night. Next, with the help of assistants who could securely hold the child's head, hands, and body, I would remove cerumen from the child's external auditory canal. If the right tympanic membrane was intact and moderately bulging, I would discuss the pros and cons of amoxicillin treatment with the parent. I would also recommend acetaminophen for the management of symptoms.

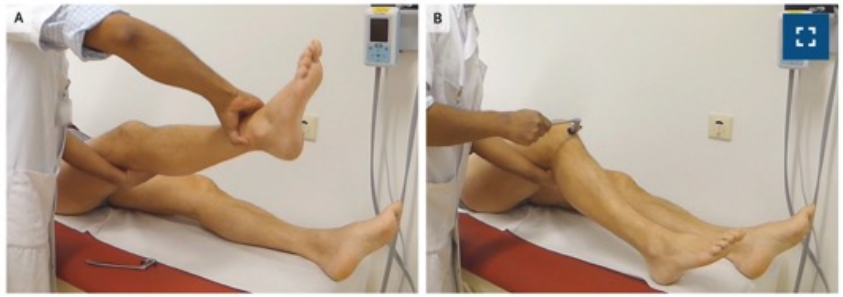
IMAGES IN CLINICAL MEDICINE

Pemphigus Foliaceus



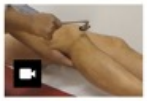
A 22-year-old man presented to the dermatology clinic with a 1-year history of a red, scaly rash on his face and body. On physical examination, widespread erythroderma with overlying erosions, scaling, and crusting was observed (Panel A). The oral mucosa was spared. A skin biopsy from the back showed superficial acantholysis (the loss of adhesion between keratinocytes). Direct immunofluorescence of the biopsy specimen showed intercellular IgG antibodies against desmoglein-1 in the superficial layers of the epidermis (Panel B, arrow). Testing for anti–desmoglein-1 antibodies was not available. A diagnosis of pemphigus foliaceus — thought perhaps to be an endemic subtype seen in South America — was made. Pemphigus foliaceus is a type of pemphigus — a set of autoimmune blistering skin disorders — that develops in the superficial epidermis. It typically manifests with subcorneal blisters that turn into eroded, scaly lesions. If the lesions coalesce and spread across the body, erythroderma may develop. Unlike pemphigus vulgaris, pemphigus foliaceus typically spares mucous membranes. Treatment with systemic glucocorticoids, azathioprine, and later rituximab was given. Six months after the first rituximab infusion, the lesions had been markedly reduced (Panel C).

Postexercise Facilitation of Reflexes in the Lambert–Eaton Myasthenic Syndrome



A 54-year-old man presented to the neurology clinic with a 5-month history of weakness and autonomic dysfunction. He initially had leg fatigue at the end of long walks and later had difficulty biking uphill and climbing up stairs. He also noted dry mouth and diminished morning erections. On physical examination, there was 4/5 strength in the proximal muscle groups. Patellar deep-tendon reflexes were absent at rest; however, after voluntary muscle contraction (Panel A), the reflexes briefly reappeared, a finding known as postexercise facilitation of reflexes (Panel B; see video). Testing for voltage-gated calcium-channel antibodies was positive. Repetitive nerve-stimulation testing showed a decrement in compound muscle action potential of more than 10% with low rates of stimulation and an increment in compound muscle action potential of 240% after voluntary muscle contraction. A diagnosis of the Lambert–Eaton myasthenic syndrome — an autoimmune disorder of the presynaptic neuromuscular junction — was made. Postexercise facilitation of reflexes is present in a minority of patients with this syndrome. This facilitation of reflexes occurs because the accumulation of intracellular calcium in the presynaptic terminal permits a transient bypass of the antibody effect, thereby facilitating a release of acetylcholine from reserves. Treatment with amifampridine and cancer screenings were initiated owing to the potentially paraneoplastic nature of the disease. Eight years after the initiation of treatment, the patient was asymptomatic.

VIDEO



Postexercise Facilitation of Reflexes 0m 28s

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Case 10-2025: A 32-Year-Old Woman with Flank Pain, Fever, and Hypoxemia

A 32-year-old woman was admitted to this hospital because of flank pain, fever, and hypoxemia.

Two weeks before the current presentation, sharp, intermittent pain in the left flank developed. Two days before the current presentation, the pain worsened in intensity, became more constant, and was associated with nausea. The next day, the patient had multiple episodes of vomiting. On the morning of the current presentation, she noted a dry cough and a subjective feeling of warmth, although she had not checked her temperature at home. She presented to an urgent care clinic affiliated with her primary care physician's office for evaluation.

In the urgent care clinic, no increased urinary frequency, dysuria, or hematuria was present, and she had no shortness of breath. The temporal temperature was 38.1°C, the blood pressure 107/75 mm Hg, the pulse 113 beats per minute, the respiratory rate 20 breaths per minute, and the oxygen saturation 95% while she was breathing ambient air. Physical examination revealed abdominal tenderness on palpation of the left lower quadrant, but no tenderness was detected when the costovertebral angles were tapped. The white-cell count was 19,000 per microliter (reference range, 3800 to 10,800) with a neutrophilic predominance. The blood level of albumin was 2.8 g per deciliter (reference range, 3.3 to 5.5), and carbon dioxide 23 mmol per liter (reference range, 24 to 29); the anion gap was 18 mmol per liter (reference range, 10 to 20). Urinalysis showed 3+ blood (reference value, negative) and 3+ protein.

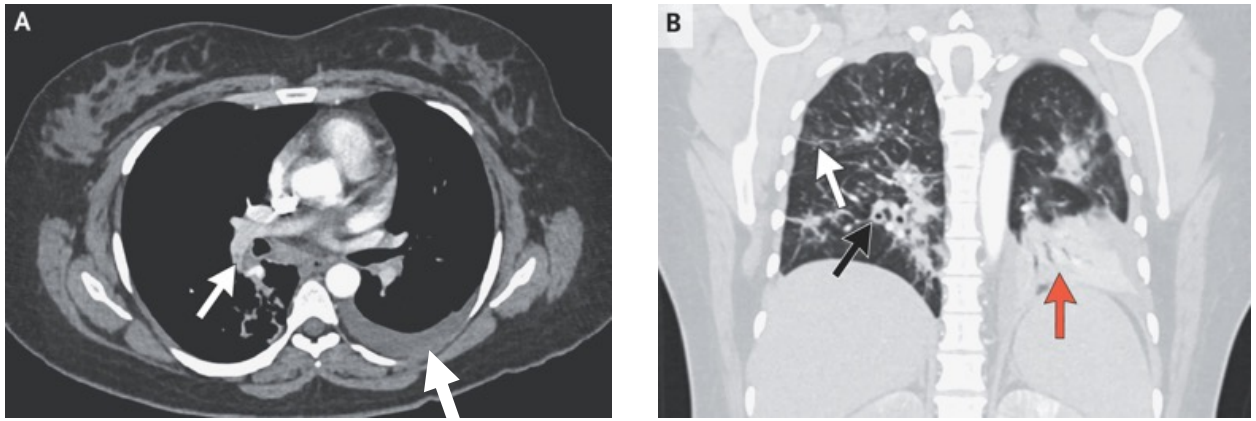
Laboratory Data.

Variable	Reference Range, Adults, Urgent Care Clinic	On Initial Presentation, Urgent Care Clinic	Reference Range, Adults, This Hospital†	On Current Presentation, This Hospital
Sodium (mmol/liter)	138–146	138	135–145	138
Potassium (mmol/liter)	3.5–4.9	3.7	3.4–5.0	3.5
Chloride (mmol/liter)	98–109	101	98–108	104
Carbon dioxide (mmol/liter)	24–29	23	23–32	22
Urea nitrogen (mg/dl)	8–26	11	8–25	11
Creatinine (mg/dl)	0.6–1.3	1.1	0.60–1.50	0.93
Glucose (mg/dl)	70–105	147	70–110	127
Anion gap (mmol/liter)	10–20	18	3–17	12
Calcium (mg/dl)	—	—	8.5–10.5	8.0
Hematocrit (%)	35.0–45.0	40.7	36.0–46.0	42.7
Hemoglobin (g/dl)	11.7–15.5	13.5	12.0–16.0	14.1
White-cell count (per μl)	3800–10,800	19,000	4500–11,000	16,020
Differential count (per μl)				
Neutrophils	1500–7800	16,460	1800–7700	14,210
Lymphocytes	850–3900	1400	1000–4800	1240
Monocytes	200–950	1120	200–1200	400
Eosinophils	20–500	10	0–900	0
Basophils	0–200	10	0–300	40
Bands	—	—	0–100	130
Platelet count (per μl)	140,000–400,000	190,000	150,000–400,000	173,000
Alkaline phosphatase (U/liter)	42–141	88	30–100	104
Alanine aminotransferase (U/liter)	10–47	19	7–33	18
Aspartate aminotransferase (U/liter)	11–38	14	9–32	17
Total bilirubin (mg/dl)	0.2–1.6	0.7	0.0–1.0	0.4
Direct bilirubin (mg/dl)	—	—	0.0–0.3	<0.2
Total protein (g/dl)	6.4–8.1	6.6	6.0–8.3	7.0
Albumin (g/dl)	3.3–5.5	2.8	3.3–5.0	3.3
Lactic acid (mmol/liter)	—	—	0.5–2.0	2.2
Lactate dehydrogenase (U/liter)	—	—	110–210	278
International normalized ratio	—	—	0.9–1.1	1.2
C-reactive protein (mg/liter)	—	—	0–8.0	199.9
Erythrocyte sedimentation rate (mm/hr)	—	—	0–19	40

No blood gases are reported

Urinalysis revealed 3+ blood (reference value, negative), 3+ protein (reference value, negative), more than 100 red cells per high-power field (reference range, 0 to 2), and 10 to 20 white cells per high-power field (reference value, <10). The ratio of protein to creatinine in urine was 3.5 (reference value, <0.15), a finding that suggests a urinary protein level of approximately 3.5 g per day. The glycated hemoglobin level was 6.2% (reference range, 4.3 to 5.6). A test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA was negative. Blood was obtained for culture, and imaging studies were performed. (Whether or not casts were present was not stated.)

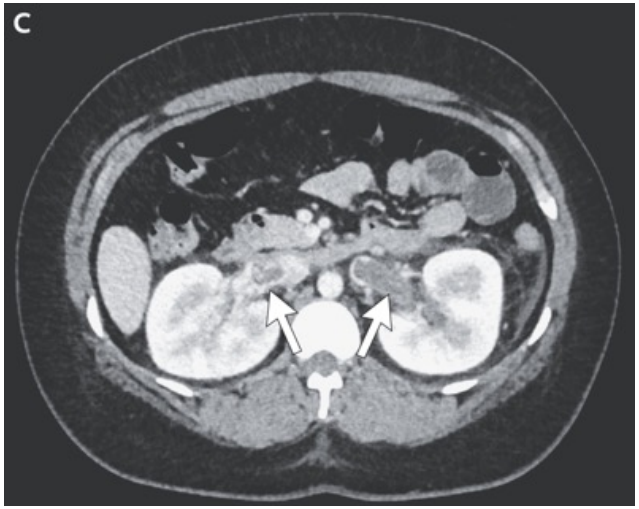
On examination, the temporal temperature was 39.6°C, the blood pressure 102/58 mm Hg, the pulse 122 beats per minute, the respiratory rate 28 breaths per minute, and the oxygen saturation 96% while she was receiving oxygen through a nasal cannula at a rate of 3 liters per minute. The body-mass index (the weight in kilograms divided by the square of the height in meters) was 30.1. The patient appeared uncomfortable. No oral ulcers, alopecia, or rash was present. The results of a joint examination were normal. On auscultation, inspiratory and expiratory course crackles were noted in both lungs. The heart sounds were tachycardic but otherwise normal. She had pain on palpation of the left lower abdomen. No edema was present.



Pleura Erguss

Contrast-Enhanced CT Images of the Chest and Abdomen.

An axial image of the chest (Panel A) shows poor opacification of the pulmonary arteries; however, a partial filling defect is present in the right lower lobar pulmonary artery (arrow). A coronal image of the chest in a lung window (Panel B) shows bronchial wall thickening (black arrow), patchy peribronchiolar ground-glass opacities (white arrow), and dependent consolidation and atelectasis in the left lower lobe (orange arrow). An axial image of the abdomen and pelvis (Panel C) shows a nearly occlusive thrombus in the left renal vein and a nonocclusive thrombus in the right renal vein (arrows).



Urinalysis revealed 3+ blood (reference value, negative), 3+ protein (reference value, negative), more than 100 red cells per high-power field (reference range, 0 to 2), and 10 to 20 white cells per high-power field (reference value, <10). The ratio of protein to creatinine in urine was 3.5 (reference value, <0.15), a finding that suggests a urinary protein level of approximately 3.5 g per day. The glycated hemoglobin level was 6.2% (reference range, 4.3 to 5.6). A test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA was negative. Blood was obtained for culture, and imaging studies were performed.

CT of the abdomen and pelvis, performed after the administration of intravenous contrast material, revealed a nearly occlusive thrombus in the left renal vein and a nonocclusive thrombus in the right renal vein without thrombus or compression in the iliac veins. Early heterogeneous parenchymal enhancement of the kidneys and moderate perinephric stranding were observed. No evidence of cancer was seen in the chest, abdomen, or pelvis.

Differential Diagnosis

Imaging revealed multiple venous thromboemboli, including a suspected pulmonary embolism and bilateral renal vein thromboses. Areas of interlobular septal thickening with associated ground-glass opacity were observed, a finding that could be consistent with diffuse alveolar hemorrhage.

Pulmonary–Renal Syndrome

Pulmonary–renal syndrome is characterized by the combination of diffuse alveolar hemorrhage and glomerulonephritis. In addition to the imaging findings, this patient's cough, dyspnea, and fever are also consistent with diffuse alveolar hemorrhage. This potentially life-threatening and organ-threatening condition has a wide array of causes, with antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis being the most common. Other, less common causes of pulmonary–renal syndrome include anti–glomerular basement membrane disease, systemic lupus erythematosus (SLE), antiphospholipid syndrome, and cryoglobulinemic vasculitis.

Nephrotic Syndrome

Nephrotic syndrome is defined by heavy proteinuria (urinary protein excretion of >3.5 g per day), hypoalbuminemia, and peripheral edema. Although this patient did not have peripheral edema, the episodes of vomiting and recurrent nausea may have resulted in a volume-depleted state, which can mask clinically detectable edema.

Hypercoagulable State

Venous and arterial thromboemboli are well-documented complications of nephrotic syndrome. Reported incidences of thrombotic events among patients with nephrotic syndrome vary, with deep venous thrombosis occurring in approximately 15% of patients, pulmonary embolism in 10 to 30%, and renal vein thrombosis in 25 to 37%. Among patients with nephrotic syndrome, the overall incidence of thrombotic events is higher in adults (25%) than children (3%).

Causes of Nephrotic Syndrome

A variety of underlying disease processes can cause nephrotic syndrome. This patient had no known diabetes, a common cause of nephrotic syndrome, and no history of a chronic inflammatory condition (e.g., chronic osteomyelitis or inflammatory bowel disease), which can lead to secondary amyloidosis and nephrotic syndrome.

Minimal Change Disease and Focal Segmental Glomerulosclerosis

Minimal change disease and FSGS are podocytopathies that commonly result in nephrotic syndrome. Both conditions are characterized by the histopathological finding of podocyte foot process effacement on electron microscopy.

Membranous Nephropathy

One of the most common causes of nephrotic syndrome in adults, membranous nephropathy is frequently associated with venous thromboembolism. Membranous nephropathy is characterized by deposition of immune complexes along the glomerular basement membrane, which compromises podocyte integrity and results in proteinuria.

Membranous nephropathy is most often a primary disorder in adults. Secondary causes include autoimmune diseases (e.g., membranous lupus nephropathy), infections (e.g., hepatitis B, hepatitis C, and syphilis), cancer (e.g., solid tumors), complications of stem-cell transplantation (e.g., graft-versus-host disease), medications (e.g., nonsteroidal antiinflammatory drugs and penicillamine), and dietary supplements (e.g., alpha lipoic acid). In approximately 70 to 80% of patients, primary membranous nephropathy is caused by autoantibodies directed against the M-type phospholipase A2 receptor (PLA2R) on podocytes. Other target antigens, such as thrombospondin type-1 domain-containing 7A and neural epidermal growth factor–like 1, have also been identified but are much less common causes of membranous nephropathy.

A kidney biopsy remains the diagnostic standard for membranous nephropathy. However, serum testing for anti-PLA2R antibodies is sensitive and highly specific for the diagnosis of membranous nephropathy, and it allows for noninvasive diagnosis in patients with nephrotic syndrome, preserved kidney function, and no evidence of other causes, such as diabetes or cancer.

Diagnostic Testing

The diagnostic tests in this case were a serum enzyme-linked immunosorbent assay (ELISA) and indirect immunofluorescence testing for circulating anti-PLA2R antibodies. Indirect immunofluorescence testing detects the presence of circulating anti-PLA2R autoantibodies with the use of cultured cells expressing recombinant PLA2R and fluorescently labeled secondary antibodies to visualize the antibody binding under a fluorescence microscope. In this patient, indirect immunofluorescence testing was positive for circulating anti-PLA2R antibodies. The ELISA was positive for anti-PLA2R antibodies, with a level of 400.3 RU per milliliter (reference range, <14).

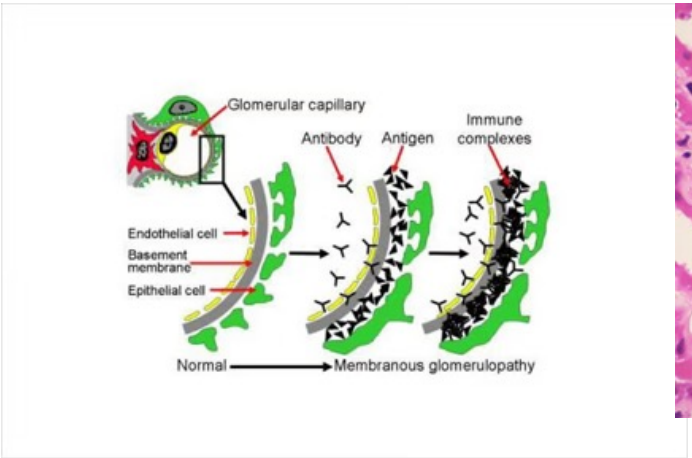
Laboratory Diagnosis

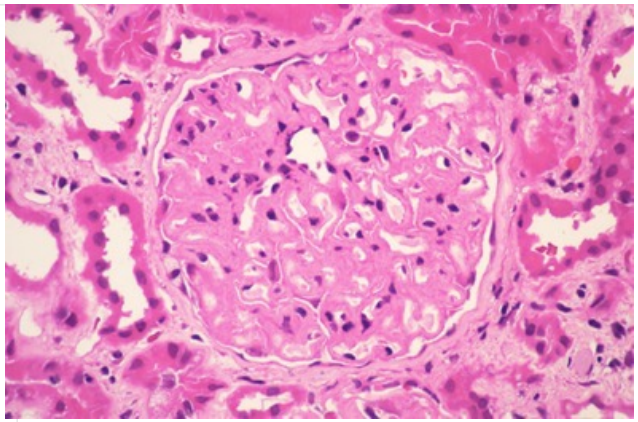
Phospholipase A2 receptor–associated membranous nephropathy.

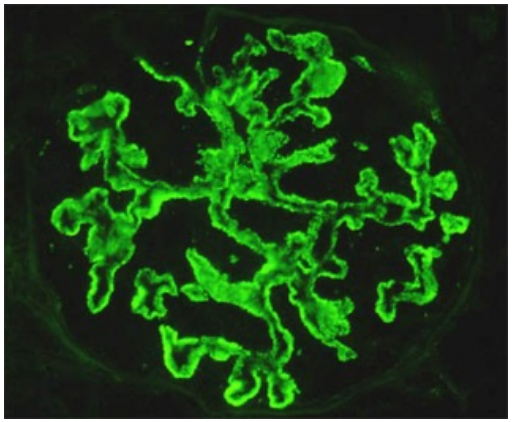
Discussion of Management

A combination therapy regimen that includes cyclophosphamide, glucocorticoids, and rituximab, which is used at this hospital for several types of glomerular disease, has shown remarkable efficacy in an observational cohort study of membranous nephropathy, with complete remission occurring in 83% of patients at 24 months. Such an aggressive regimen is not needed in all cases of membranous nephropathy; however, it would be a reasonable regimen in this case owing to the high-risk features and pulmonary embolic disease in this patient.

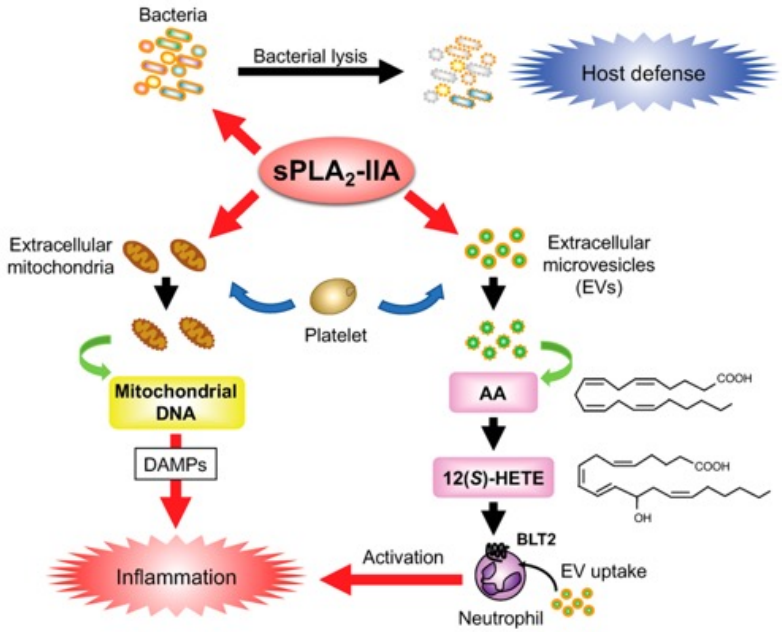
Two months after the patient started treatment, the serum test for anti-PLA2R antibodies was negative, indicating immunologic remission. Within 3 months after starting immunosuppression and supportive measures, the urinary protein level had decreased to 1.79 g per day, indicating partial proteinuric remission. Venous thromboembolism was considered to be provoked in the context of membranous nephropathy, and treatment with warfarin was discontinued after three consecutive normal serum albumin levels (>3.5 g per deciliter). She continues to receive treatment with rituximab, which is planned for a duration of 2 years. After treatment with rituximab is stopped, the serum anti-PLA2R antibody level and urinary protein levels will be monitored every 3 to 4 months for potential relapse.

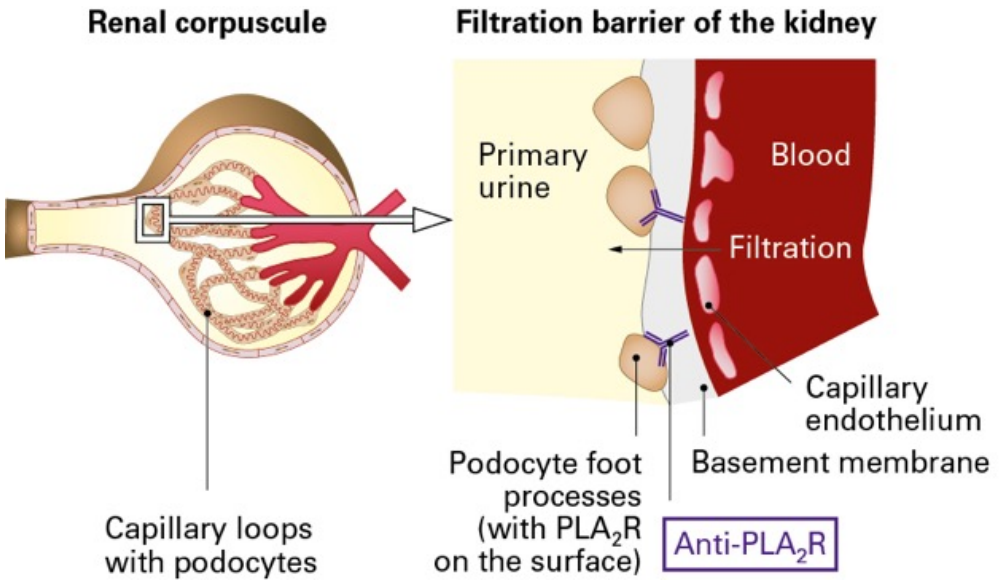






Phospholipase A2 (PLA2) ist ein Enzym, das Fettsäuren von Phospholipiden abspaltet. Es spielt eine wichtige Rolle bei der Verdauung, Entzündungen und der Synthese von Prostaglandinen. Phospholipase-A2-Rezeptor (PLA2R) ist ein Typ-1-Transmembranprotein, das mehrere Typen von Phospholipase A_2 bindet. PLA2R ist einer der vier bei Säugetieren vorkommenden Mannose-Rezeptoren. PLA2R wird beim Menschen hauptsächlich in den Nieren von den Podozyten des Nierenkörperchens exprimiert.





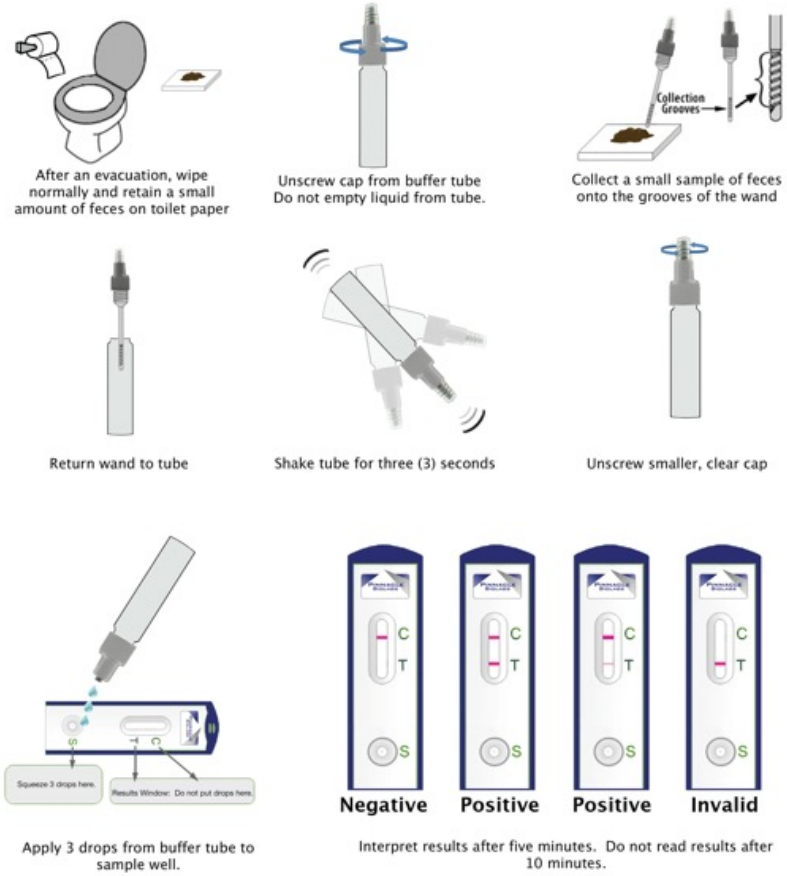
M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy

Laurence H Beck Jr [1], Ramon G B Bonegio, Gérard Lambeau, David M Beck, David W Powell, Timothy D Cummins, Jon B Klein, David J Salant

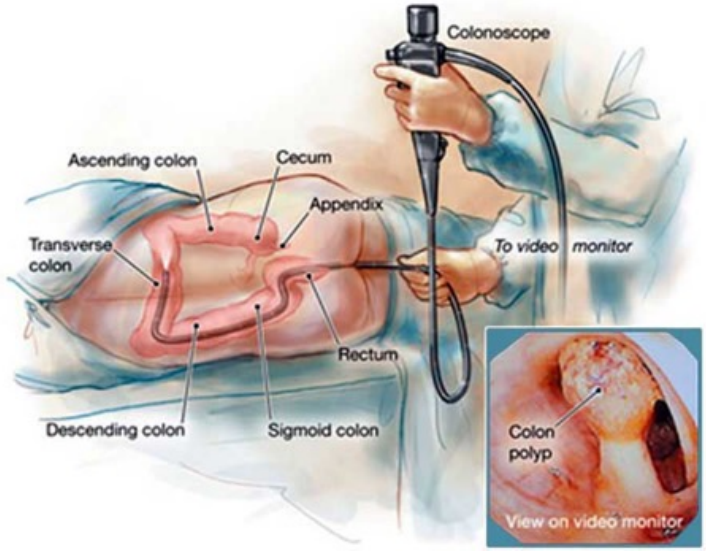
N Engl J Med. 2009 Jul 2;361(1):11-21.

The phospholipase A2 receptor (PLA2R) regulates a variety of biological responses, including cell proliferation, migration, and lipid mediator production. It also helps clear certain types of secretory phospholipase A2 (sPLA2).

Ein fäkaler immunchemischer Test (FIT) ist ein Stuhltest, der nach verstecktem Blut im Stuhl sucht. Der Test kann zu Hause durchgeführt werden und ist schmerzfrei.



Eine Colonoscopie, auch Koloskopie oder Darmspiegelung genannt, ist eine Untersuchung des Dickdarms. Sie wird mit einem Endoskop, dem Koloskop, durchgeführt.



Effect of invitation to colonoscopy versus faecal immunochemical test screening on colorectal cancer mortality (COLONPREV): a pragmatic, randomised, controlled, non-inferiority trial

Summary

Background Colonoscopy and the faecal immunochemical test are accepted strategies for colorectal cancer screening in the average-risk population (ie, people aged ≥50 years without personal or family history of colorectal cancer). In this trial, we aimed to compare whether invitation to screening with faecal immunochemical test was non-inferior to colonoscopy in a screening programme.

Methods COLONPREV was a pragmatic, randomised, controlled, non-inferiority trial done at 15 tertiary hospitals across eight regions of Spain. Eligible participants were presumptively healthy and aged between 50 years and 69 years without a personal history of colorectal cancer, adenoma or inflammatory bowel disease, family history of hereditary or familial colorectal cancer (ie, two or more first-degree relatives with colorectal cancer or one diagnosed before age 60 years), severe comorbidities, or previous colectomy. Participants were randomly assigned (1:1) to one-time colonoscopy or biennial faecal immunochemical test before invitation to screening. The primary endpoint was colorectal cancer mortality at 10 years, assessed in the intention-to-screen population. An absolute difference of less than 0·16 percentage points was required to show non-inferiority. This trial was registered with ClinicalTrials.gov, NCT00906997.

Biennial = alle zwei Jahre

Findings Between June 1, 2009, and Dec 31, 2021, 57 404 individuals were randomly assigned to receive an invitation for colonoscopy (n=28 708) or the faecal immunochemical test (n=28 696). The intention-to-screen population consisted of 26 332 individuals in the colonoscopy group and 26 719 in the faecal immunochemical test group. In the intention-to-screen population, participation in any form of screening was 31·8% in the colonoscopy group and 39·9% in the faecal immunochemical test group (risk ratio [RR] 0·79 [95% CI 0·77 to 0·82]). Faecal immunochemical testing was non-inferior to colonoscopy with regard to the risk of colorectal cancer mortality at 10 years: the risk was 0·22% (55 deaths) in the colonoscopy group and 0·24% (60 deaths) in the faecal immunochemical test group (risk difference –0·02 [95% CI –0·10 to 0·06; RR 0·92 [95% CI 0·64 to 1·32]; $p_{non\text{-}inferiority}$=0·0005).

Interpretation Participation in screening was higher among individuals invited to faecal immunochemical test screening than colonoscopy screening. On the basis of participation observed in this study, a faecal immunochemical test-based programme was non-inferior to a colonoscopy-based programme for colorectal cancer-related mortality.

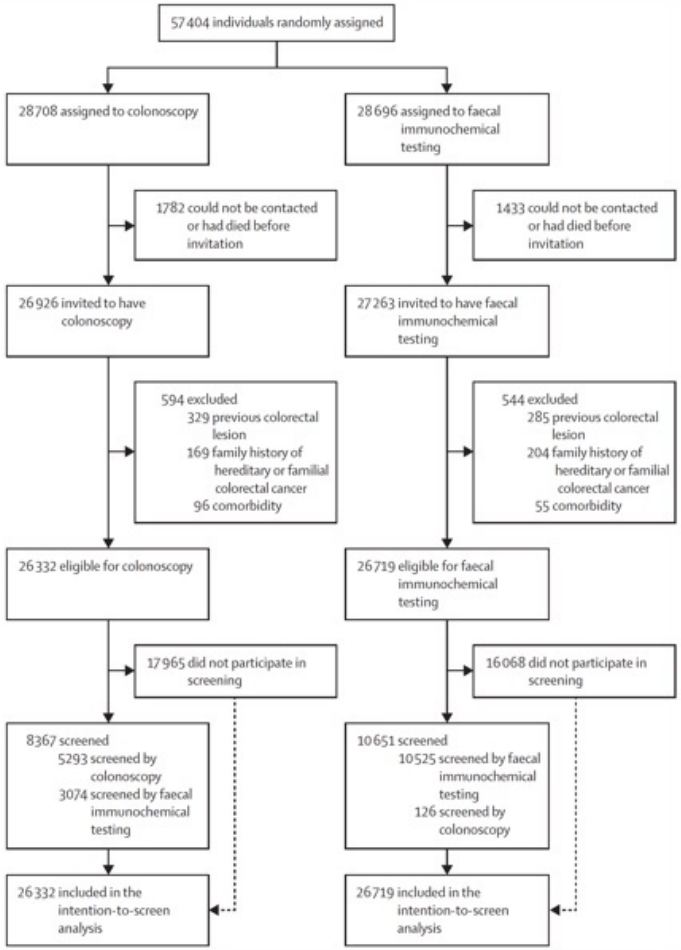


Figure 1: **Trial profile**
The number of participants included in each of the analysis populations (intention-to-screen, as-screened, and per-protocol populations) are shown in the appendix (p 11). The number of eligible individuals shown in this figure differs from that in the previously published preliminary results of the COLONPREV study[18] because 1245 additional participants could not be contacted after being randomly assigned because they had died before randomisation or had an inaccurate mailing address, and due to permanent exclusions among participants recruited in subsequent rounds of the study after the publication of the preliminary results.

	Colonoscopy (n=26 332)		Faecal immunochemical test (n= 26 719)		Colonoscopy versus faecal immunochemical test	
	Individuals with event, n	10-year risk % (95% CI)	Individuals with event, n	10-year risk % (95% CI)	Risk difference (95% CI)	Risk ratio (95% CI)
Colorectal cancer-related mortality	55	0·22% (0·16 to 0·28)	60	0·24% (0·18 to 0·30)	−0·02 (−0·1 to 0·06)	0·92 (0·64 to 1·32)
Colorectal cancer incidence	286	1·13% (1·00 to 1·26)	314	1·22% (1·09 to 1·36)	−0·09 (−0·28 to 0·10)	0·92 (0·79 to 1·08)
All-cause mortality*	1989	7·64% (7·32 to 8·01)	2034	7·68% (7·36 to 7·96)	−0·04 (−0·50 to 0·42)	0·99 (0·94 to 1·06)

*All-cause mortality was a post-hoc endpoint.

Table 1: **Primary and key selected secondary endpoints in the intention-to-screen analyses**

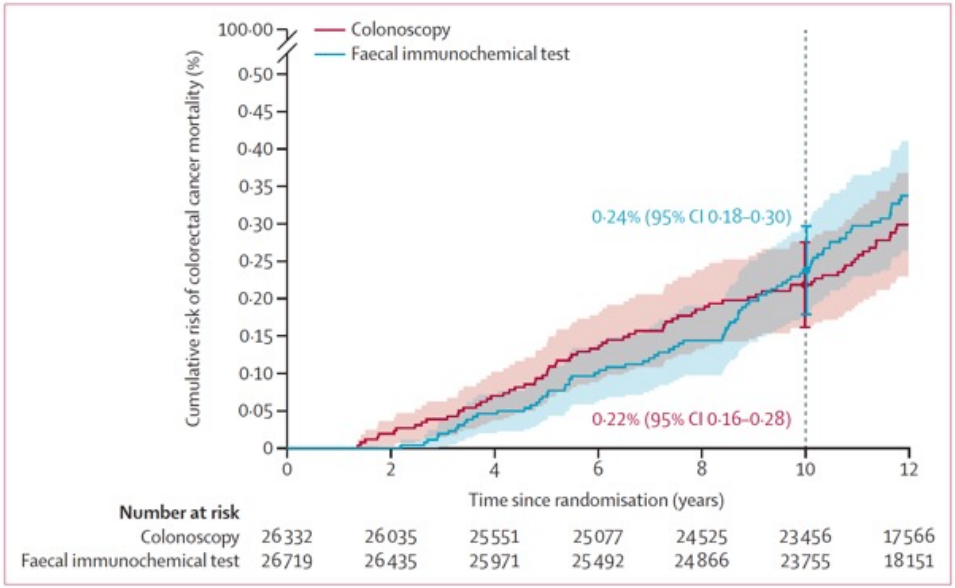


Figure 2: **Cumulative risk of colorectal cancer mortality at 10 years in the intention-to-screen analysis population**
Shaded areas indicate 95% CIs.

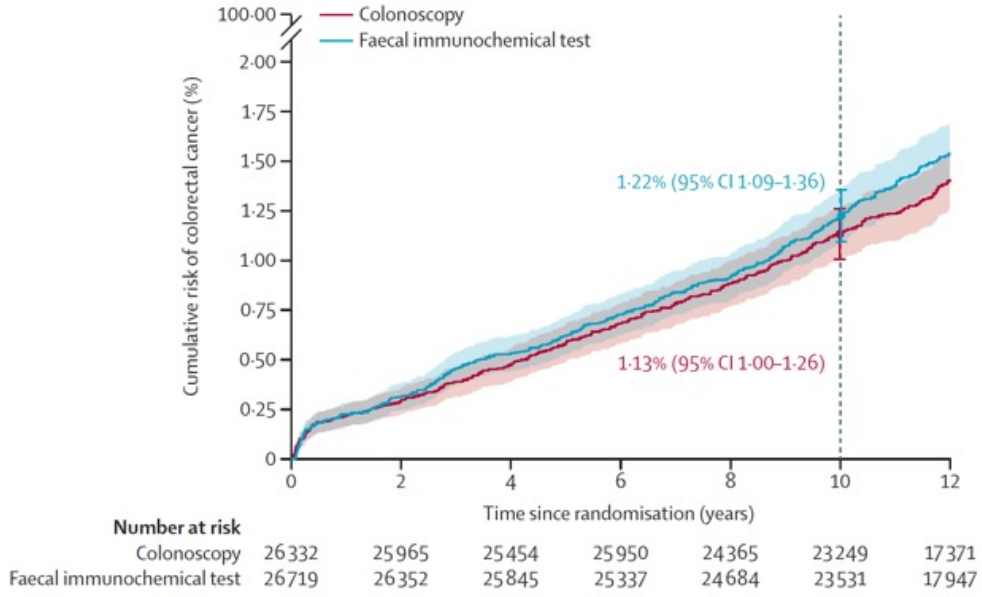


Figure 3: **Cumulative risk of colorectal cancer at 10 years in the intention-to-screen population**
Shaded areas indicate 95% CIs.

	Colonoscopy (n=26 332)	Faecal immunochemical test (n=26 719)	OR (95% CI)†	p value
Colorectal polyposis	46 (0·2%)	19 (0·1%)	2·50 (1·46–4·27)	<0·0001
Advanced colorectal lesion‡	853 (3·2%)	630 (2·4%)	1·39 (1·25–1·54)	<0·0001
Non-advanced colorectal lesion§	1176 (4·5%)	391 (1·5%)	3·17 (2·82–3·56)	<0·0001
Most advanced lesion¶				
Colorectal polyposis	46 (0·2%)	19 (0·1%)	NA	NA
Advanced colorectal lesion	839 (3·2%)	616 (2·3%)	NA	NA
Non-advanced colorectal lesion	1167 (4·4%)	372 (1·4%)	NA	NA

Data are n (%), unless otherwise specified. OR=odds ratio. NA=not applicable. *The diagnostic yield was calculated as the number of individuals with true positive results divided by the number of individuals who were eligible to undergo screening (intention-to-treat analysis) and limited to screen-detected lesions. †Adjusted for age, sex, and participating centre. ‡Defined as an adenoma measuring ≥10 mm in diameter, with villous architecture (>25%), high-grade dysplasia or intramucosal carcinoma, or a serrated lesion measuring ≥10 mm in diameter or with dysplasia. §Defined as a tubular adenoma measuring <10 mm in diameter with low-grade dysplasia, or a serrated lesion measuring <10 mm in diameter without dysplasia. ¶Individuals were classified according to the most advanced colorectal lesion.

Table 2: **Diagnostic yield of colonoscopy and faecal immunochemical test with respect to premalignant neoplastic lesions***

Research in context

Evidence before this study

We searched PubMed from database inception to June 17, 2024 for randomised controlled trials published in English that assessed the efficacy of colonoscopy and faecal immunochemical test for screening of colorectal cancer in average-risk individuals (ie, people aged ≥50 years without personal or family history of colorectal cancer). We used the following search terms: ("colorectal cancer" OR "colorectal neoplasm" OR "colon cancer") AND ("colonoscopy" OR "faecal immunochemical test" OR "faecal blood testing") AND "screening". Three randomised trials were identified: the TARGET-C study, comparing one-time colonoscopy, annual faecal immunochemical test, and annual risk-adapted screening; the CONFIRM study, comparing one-time colonoscopy and annual faecal immunochemical test; and the SCREESCO trial, comparing one-time colonoscopy, biennial faecal immunochemical testing, and no intervention. None of the studies reported results on colorectal cancer mortality or incidence. Several studies have shown that colorectal cancer screening is effective and cost-effective in individuals with average risk (ie, people aged ≥50 years without personal or family history of colorectal cancer). For this purpose, organised screening programmes are preferred over opportunistic approaches because they ensure coverage and equity of access, thereby maximising the effectiveness of the screening process. The faecal immunochemical test and colonoscopy are accepted strategies for colorectal cancer screening, the faecal immunochemical test being predominantly implemented in Europe and Australia, whereas colonoscopy is the dominant screening modality in the USA. Nevertheless, randomised controlled trials comparing the efficacy of colonoscopy and the faecal immunochemical test in programmatic screening are needed. In an interim analysis done on completion of the first screening round of the COLONPREV study, we demonstrated that individuals in the faecal immunochemical test group were more likely to participate in screening than those in the colonoscopy group. In this baseline examination, the numbers of participants in whom colorectal cancer was identified were similar in the two study groups. However, comparative data on the effectiveness of both screening strategies in reducing colorectal cancer-related mortality, colorectal cancer incidence, and all-cause mortality at 10 years were missing.

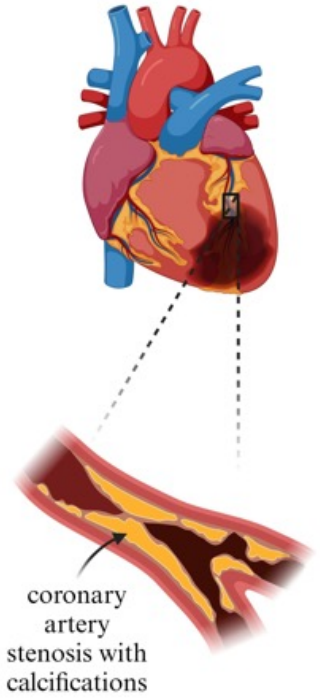
Added value of this study

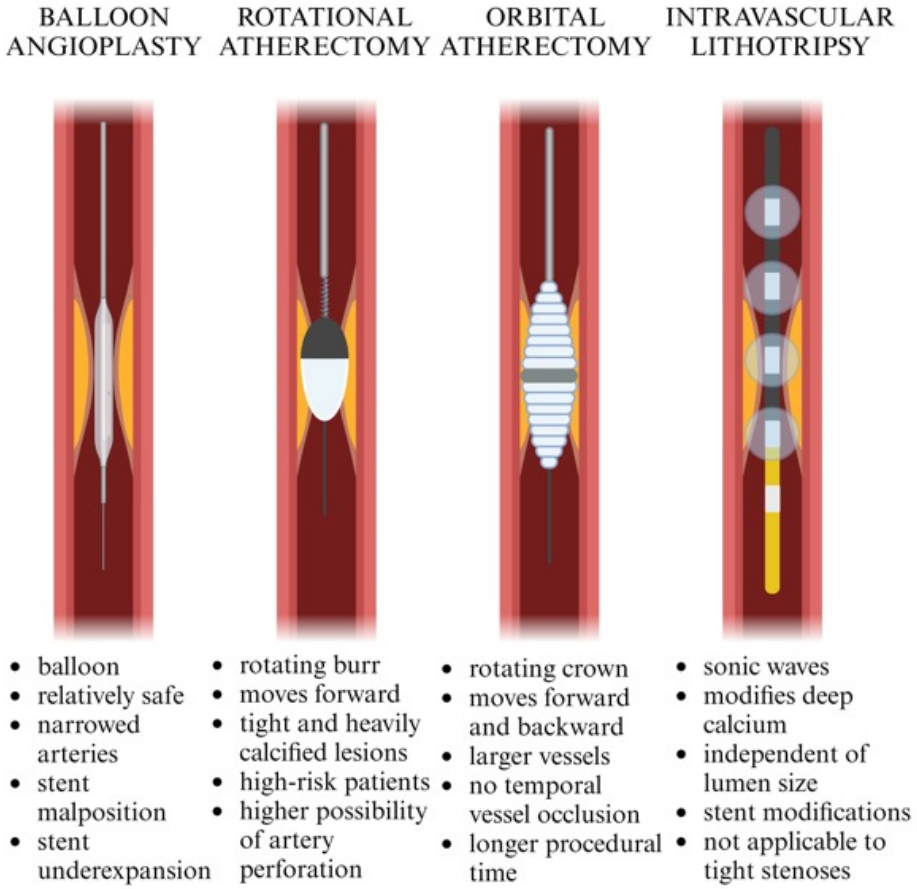
This pragmatic, randomised, controlled, non-inferiority trial demonstrated that 31·8% of participants in the colonoscopy group and 39·9% of participants in the faecal immunochemical test group participated in screening (risk ratio [RR] 0·79 [95% CI 0·77 to 0·82]). Additionally, invitation to faecal immunochemical test screening was non-inferior to invitation to colonoscopy screening with regard to risk of colorectal cancer mortality at 10 years (0·22% [55 deaths] in the colonoscopy group; 0·24% [60 deaths] in the faecal immunochemical test group; risk difference −0·02 [95% CI −0·10 to 0·06]; RR 0·92 [0·64 to 1·32]; $p_{non\text{-}inferiority}$=0·0005). For colorectal cancer incidence (RR 0·92 [0·79 to 1·08]) and for all-cause mortality (RR 0·99 [0·94 to 1·06]) both strategies appeared to be also similar. Additionally, secondary analyses suggested that both strategies reduced the risk of colorectal cancer mortality with respect to those individuals who did not participate in screening, and reductions in colorectal cancer incidence and death seemed larger with colonoscopy than faecal immunochemical test.

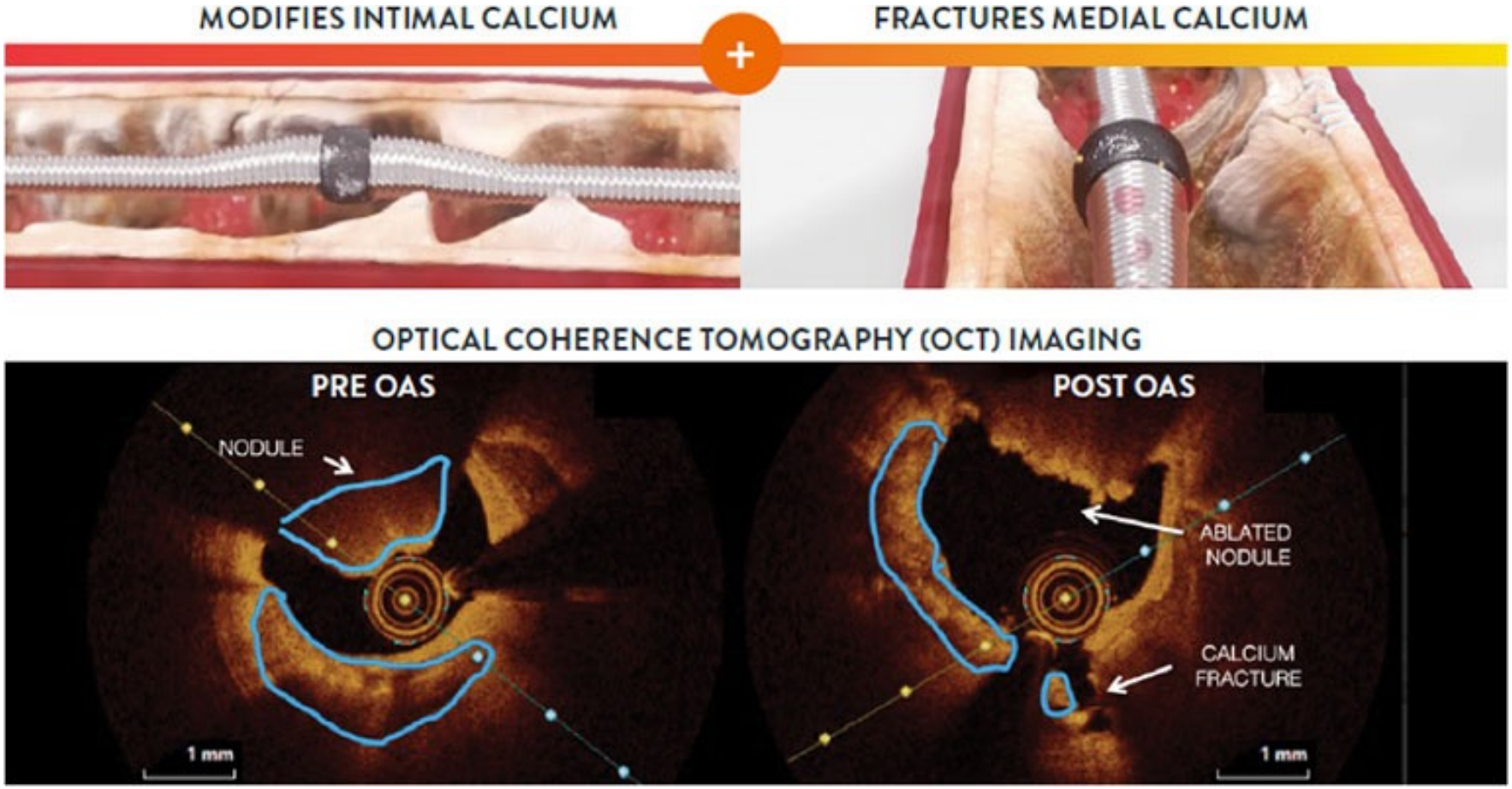
Implications of all the available evidence

The COLONPREV study demonstrates that participation in colorectal cancer screening was higher among participants invited to faecal immunochemical test than to colonoscopy. Invitation to a faecal immunochemical test-based programme was non-inferior to a colonoscopy-based programme in terms of colorectal cancer-related mortality. Accordingly, a less invasive approach, such as faecal immunochemical test, has been validated as an effective strategy for population-based, organised colorectal cancer screening, with potentially significant implications for global health-care policies.

Orbital atherectomy (OA) is a procedure that uses a device with a diamond-coated crown to ablate and modify calcified plaque in arteries, particularly in preparation for percutaneous coronary intervention (PCI) or other endovascular procedures, improving stent expansion and outcomes.






MODIFIES INTIMAL CALCIUM
+
FRACTURES MEDIAL CALCIUM
OPTICAL COHERENCE TOMOGRAPHY (OCT) IMAGING
PRE OAS
NODULE
1 mm
POST OAS
ABLATED NODULE
CALCIUM FRACTURE
1 mm

Orbital atherectomy versus balloon angioplasty before drug-eluting stent implantation in severely calcified lesions eligible for both treatment strategies (ECLIPSE): a multicentre, open-label, randomised trial

Summary

Background Coronary artery calcification is common among patients undergoing percutaneous coronary intervention (PCI), and severe coronary artery lesion calcification is associated with increased procedural complexity, stent under-expansion, and high rates of intraprocedural complications and out-of-hospital adverse events. Whether calcium ablation before stent implantation can mitigate these adverse events is not currently established. We aimed to prospectively compare orbital atherectomy with a balloon angioplasty-based strategy before stent implantation for the treatment of severely calcified coronary lesions.

Methods In this multicentre, open-label, randomised controlled trial conducted at 104 medical centres in the USA, patients (aged ≥18 years) with severely calcified coronary lesions were randomly assigned (1:1) to orbital atherectomy or balloon angioplasty before PCI with drug-eluting stents using a web-based system (block sizes of four and six) and stratified by intended treatment of single versus multiple lesions and enrolling site. Randomly assigned lesions were deemed by operators to be eligible for both treatment strategies. Operators and patients were not masked to treatment. The two powered coprimary study endpoints were target vessel failure at 1 year (a composite of cardiac death, target vessel myocardial infarction, or ischaemia-driven target vessel revascularisation) and post-procedural minimal stent area at the site of maximal calcification, as assessed by intravascular optical coherence tomography in an imaging patient cohort. Primary analyses were by intention-to-treat. The trial is registered at ClinicalTrials.gov NCT03108456, and 2-year follow-up is ongoing.

Findings From March 27, 2017, to April 13, 2023, 2005 patients with 2492 lesions were randomly assigned to lesion preparation with orbital atherectomy (1008 patients with 1250 lesions) or balloon angioplasty (997 with 1242 lesions) before stent implantation. Median patient age was 70·0 years (IQR 64·0–76·0). 541 (27·0%) of 2005 patients were female and 1464 (73·0%) were male. Angiographically severe calcium was confirmed by the core laboratory in 1088 (97·1%) of 1120 lesions assigned to orbital atherectomy and 1068 (97·0%) of 1101 lesions assigned to balloon angioplasty. PCI was guided by intravascular imaging in 627 (62·2%) of 1008 patients in the orbital atherectomy group and 619 (62·1%) of 997 in the balloon angioplasty group. Target vessel failure events within 1 year occurred in 113 of 1008 patients in the orbital atherectomy group (1-year target vessel failure 11·5% [95% CI 9·7 to 13·7]) and in 97 of 997 patients in the balloon angioplasty group (10·0% [8·3 to 12·1]; absolute difference 1·5% [96% CI –1·4 to 4·4]; hazard ratio 1·16 [96% CI 0·87 to 1·54], p=0·28). Among those in the optical coherence tomography substudy cohort (276 patients with 286 lesions in the orbital atherectomy group and 279 patients with 292 lesions in the balloon angioplasty group), the mean minimal stent area at the site of maximal calcification was 7·67 mm² (SD 2·27) in the orbital atherectomy group and 7·42 mm² (2·54) in the balloon angioplasty group (mean difference 0·26 [99% CI –0·31 to 0·82]; p=0·078). Cardiac death events within 1 year occurred in 39 of 1008 patients in the orbital atherectomy group and in 26 of 997 in the balloon angioplasty group.

Interpretation Routine treatment with orbital atherectomy before drug-eluting stent implantation did not increase minimal stent area or reduce the rate of target vessel failure at 1 year compared with a balloon angioplasty-based approach in severely calcified lesions deemed eligible for both treatment strategies. These data support a balloon-first approach for most calcified coronary artery lesions that can be crossed and dilated before stent implantation, guided by intravascular imaging.

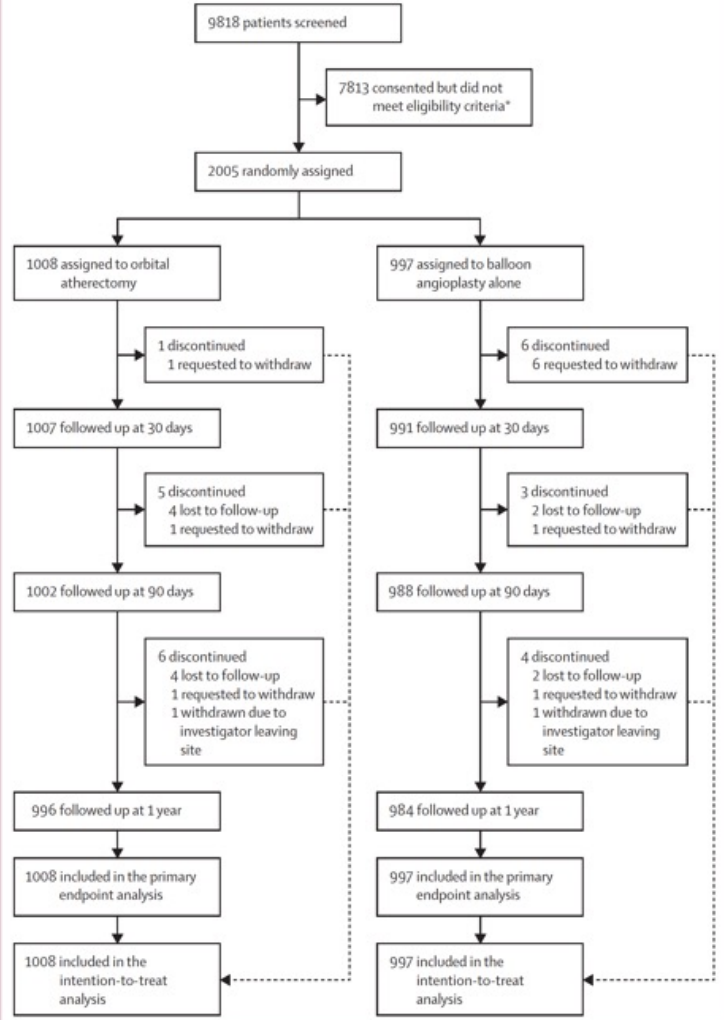


Figure 1: **Trial profile**
Patients who were lost to follow-up or withdrew were censored at the time of last data availability. *Reasons for ineligibility were not captured.

	Orbital atherectomy group (n=1008)	Balloon angioplasty group (n=997)
Age, years	70·0 (65·0–76·0)	71·0 (64·0–76·0)
Sex		
Male	742 (73·6%)	722 (72·4%)
Female	266 (26·4%)	275 (27·6%)
Ethnicity		
Hispanic or Latino*	90 (8·9%)	81/994 (8·1%)
Not Hispanic or Latino*	918 (91·1%)	913/994 (91·9%)
Race		
Native American or Alaska Native	5/995 (0·5%)	2/989 (0·2%)
Asian	22/995 (2·2%)	18/989 (1·8%)
Black or African American	93/995 (9·3%)	100/989 (10·1%)
Native Hawaiian or other Pacific Islander	3/995 (0·3%)	2/989 (0·2%)
White	848/995 (85·2%)	828/989 (83·7%)
Other	21/995 (2·1%)	33/989 (3·3%)
More than one race selected	3/995 (0·3%)	6/989 (0·6%)
BMI, kg/m²	29·2 (25·8–33·4)	29·3 (25·7–33·1)
History of hypercholesterolemia	886/1007 (88·0%)	869/996 (87·2%)
History of hypertension	910 (90·3%)	900 (90·3%)
History of diabetes	434 (43·1%)	447 (44·8%)
Treated with insulin	185 (18·4%)	179 (18·0%)
Current smoker (within 1 month of enrolment)	129 (12·8%)	125 (12·5%)
History of chronic kidney disease	234 (23·2%)	245 (24·6%)
Requiring haemodialysis	60 (6·0%)	52 (5·2%)
eGFR, mL/min per 1·73 m²	70·1 (53·5–83·2)	67·9 (52·3–83·4)
Left ventricular ejection fraction	55·0% (50·0–61·0%)	55·0% (50·0–61·0%)
Previous myocardial infarction	262 (26·0%)	272 (27·3%)
Previous stroke or transient ischaemic attack	88 (8·7%)	112 (11·2%)
Peripheral vascular disease	138 (13·7%)	146 (14·6%)
Previous PCI	440 (43·7%)	466 (46·7%)
Previous coronary artery bypass surgery	92 (9·1%)	109 (10·9%)
Presentation with stable angina or ACS without elevated biomarker	789 (78·3%)	798 (80·0%)
Presentation with recent myocardial infarction or biomarker positive ACS	219 (21·7%)	199 (20·0%)

Data are n (%) or median (IQR). ACS=acute coronary syndrome. PCI=percutaneous coronary intervention. *These were the terms used at the time of data collection.

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

	Orbital atherectomy group (n=1008)	Balloon angioplasty group (n=997)	Difference (95% CI)	p value
Number of target lesions treated	1·0 (1·0 to 1·0)	1·0 (1·0 to 1·0)	0·0 (–0·1 to 0·0)	0·44*
Two or more	170 (16·9%)	180 (18·1%)	–1·2% (–4·5 to 2·1)	0·48
Number of target vessels treated	1·0 (1·0 to 1·0)	1·0 (1·0 to 1·0)	0	0·046*
Two or more	23 (2·3%)	38 (3·8%)	–1·5% (–3·0 to 0·0)	0·046
Non-target vessels treated during the index procedure	126 (12·5%)	117 (11·7%)	0·8% (–2·1 to 3·6)	0·60
Any femoral artery access site†	480 (47·6%)	465 (46·6%)	1·0% (–3·4 to 5·3)	0·66
No femoral access site	528 (52·4%)	532 (53·4%)	–1·0% (–5·3 to 3·4)	0·66
Haemodynamic support	8 (0·8%)	7 (0·7%)	0·1% (–0·7 to 0·8)	0·81
Temporary pacemaker‡	45 (4·5%)	19 (1·9%)	2·6% (1·0 to 4·1)	0·0011
Guide extension catheter used	216 (21·4%)	222 (22·3%)	–0·8% (–4·5 to 2·8%)	0·65
Number of guide wires used	2·7 (1·4)	2·2 (1·4)	0·6 (0·4 to 0·7)	<0·0001*
Number of balloon catheters used	3·6 (2·3)	4·0 (2·8)	–0·4 (–0·6 to –0·2)	0·017*
Orbital atherectomy attempted	997 (98·9%)	37 (3·7%)	95·2% (93·9 to 96·5)	..
Orbital atherectomy performed	990 (98·2%)	37 (3·7%)	94·5% (93·1 to 95·9)	..
Microcatheter or over-the-wire balloon used	424 (42·1%)	165 (16·5%)	25·5% (21·7 to 29·3)	<0·0001
Any intravascular imaging performed§	627 (62·2%)	619 (62·1%)	0·1% (–4·1 to 4·4)	0·96
Optical coherence tomography	408 (40·5%)	411 (41·2%)	–0·7% (–5·1 to 3·6)	0·73
Intravascular ultrasound	258 (25·6%)	255 (25·6%)	0·0% (–3·8 to 3·8)	0·99
Total contrast volume, mL	165·0 (120·0 to 220·0)	150·0 (100·0 to 200·0)	19·4 (11·4 to 27·3)¶	<0·0001‖
Total procedure time, min	68·0 (49·0 to 90·5)	52·0 (36·0 to 74·0)	13·1 (10·1 to 16·2)¶	<0·0001‖

Data are median (IQR), n (%), or mean (SD), unless otherwise specified. *p values based on a t test or Wilcoxon test. †Any femoral access used. ‡43 pacemakers in the orbital atherectomy group and 18 pacemakers in the control group were placed prophylactically (pre-percutaneous coronary intervention). §Optical coherence tomography and intravascular ultrasound were used in some patients. ¶Differences between continuous variables are differences between mean values with 95% CIs. ‖p values based on Chi squared test or Fisher's exact test.

Table 2: **Procedural characteristics**

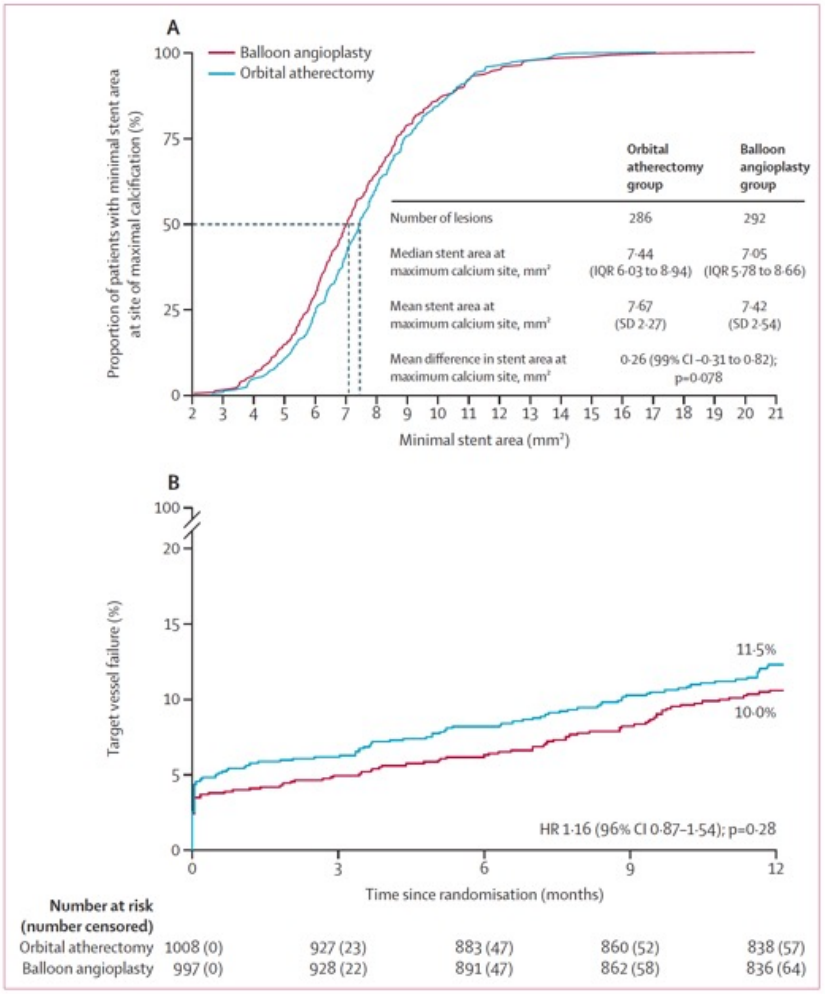


***Figure 2*: Primary outcome results**

(A) Cumulative distribution function of minimal stent area at the site of maximal calcification. The y-axis is the proportion of patients with minimal stent area equal to or lesser than the corresponding minimal stent area on the x-axis. (B) Kaplan–Meier estimates of the percentage of patients with target vessel failure at 1-year follow-up.

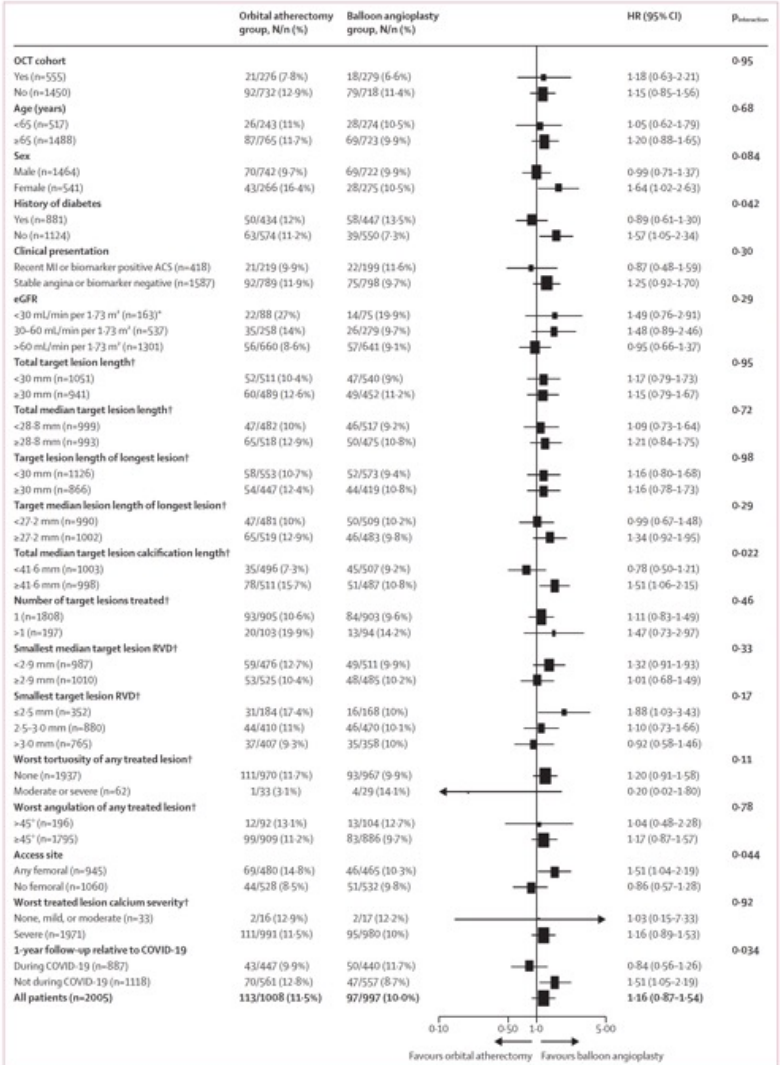


***Figure 3*: 1-year rates of target vessel failure in prespecified subgroups**

ACS=acute coronary syndrome. eGFR=estimated glomerular filtration rate. MI=myocardial infarction. OCT=optical coherence tomography. RVD=reference vessel diameter. *Patients with eGFR <30 mL/min per 1·73m² includes those on chronic haemodialysis. †Angiographic core laboratory-reported variables.

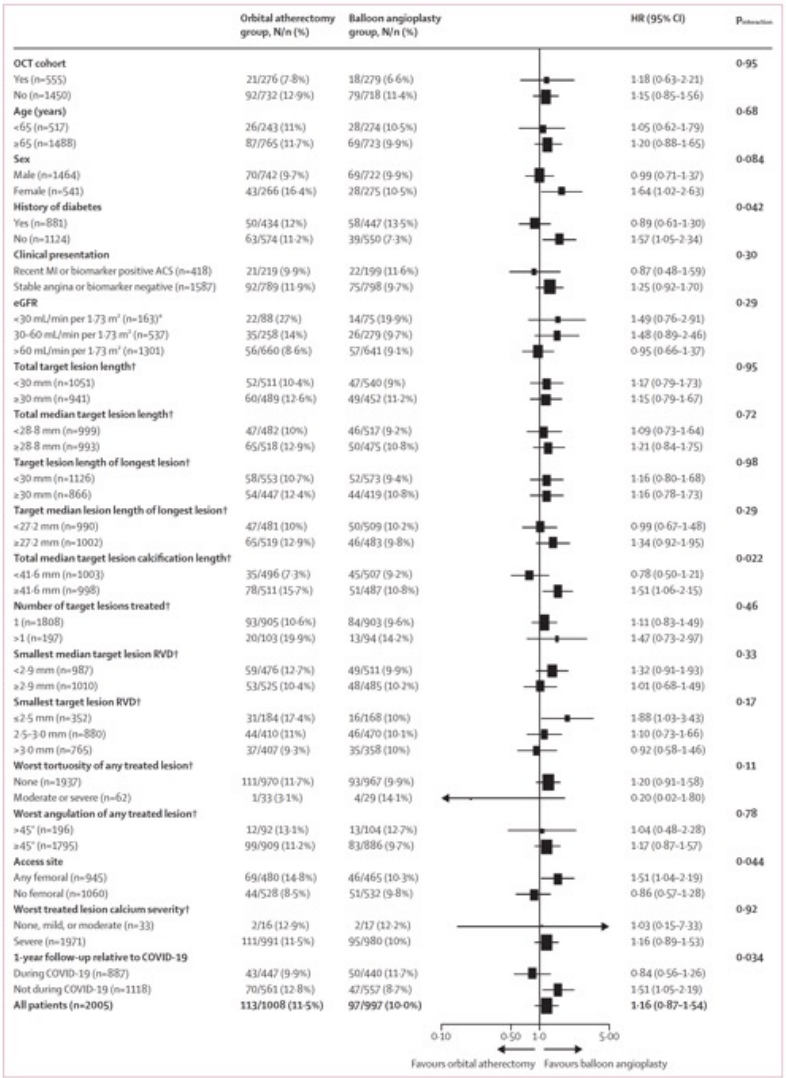


Figure 3: **1-year rates of target vessel failure in prespecified subgroups**
ACS=acute coronary syndrome. eGFR=estimated glomerular filtration rate. MI=myocardial infarction. OCT=optical coherence tomography. RVD=reference vessel diameter. *Patients with eGFR <30 mL/min per 1·73m² includes those on chronic haemodialysis. †Angiographic core laboratory-reported variables.

	Orbital atherectomy group (n=1008)	Balloon angioplasty group (n=997)	Hazard ratio (96% or 95% CI)*	p value
Primary endpoint				
Target vessel failure	113 (11·5%)	97 (10·0%)	1·16 (0·87–1·54)†	0·28
Components and other endpoints				
All-cause death	61 (6·2%)	53 (5·5%)	1·14 (0·79–1·65)	0·48
Cardiac	39 (4·0%)	26 (2·7%)	1·49 (0·91–2·45)	0·12
Vascular	4 (0·4%)	2 (0·2%)	1·99 (0·36–10·84)	0·43
Non-cardiovascular	18 (1·9%)	25 (2·6%)	0·71 (0·39–1·31)	0·28
All myocardial infarction	80 (8·1%)	74 (7·6%)	1·07 (0·78–1·47)	0·65
Procedural	41 (4·1%)	34 (3·4%)	1·19 (0·76–1·88)	0·45
Non-procedural	41 (4·3%)	40 (4·2%)	1·02 (0·66–1·57)	0·94
Target vessel-related	55 (5·6%)	43 (4·4%)	1·27 (0·85–1·89)	0·24
Non-target vessel-related	27 (2·8%)	32 (3·4%)	0·84 (0·50–1·39)	0·49
Ischaemia-driven revascularisation, any	81 (8·5%)	76 (8·1%)	1·06 (0·78–1·45)	0·70
Ischaemia-driven TVR	40 (4·2%)	41 (4·4%)	0·97 (0·63–1·49)	0·88
Ischaemia-driven TLR	32 (3·4%)	32 (3·4%)	0·99 (0·61–1·62)	0·98
Ischaemia-driven TVR (non-TLR)	15 (1·6%)	16 (1·7%)	0·93 (0·46–1·88)	0·84
Ischaemia-driven non-TVR	57 (6·0%)	44 (4·7%)	1·30 (0·88–1·92)	0·19
Stent thrombosis (definite or probable)	11 (1·1%)	4 (0·4%)	2·74 (0·87–8·59)	0·085
Definite	8 (0·8%)	4 (0·4%)	1·99 (0·60–6·61)	0·26
Probable	3 (0·3%)	0	..	..
Timing of stent thrombosis				
Acute (ie, <24 h)	1 (0·1%)	2 (0·2%)	0·49 (0·04–5·45)	0·57
Subacute (ie, 24 h–30 days)	6 (0·6%)	1 (0·1%)	5·97 (0·72–49·59)	0·10
Late (ie, >30 days–1 year)	4 (0·4%)	1 (0·1%)	3·99 (0·45–35·73)	0·22

Data are number of events (Kaplan–Meier estimates), unless otherwise specified. p values are based on a Cox proportional hazards model. TLR= target lesion revascularisation. TVR=target vessel revascularisation. *The only hazard ratio with a 96% CI is target vessel failure (primary endpoint), all others have 95% CIs. †The estimated hazard ratio for target vessel failure at 1 year was 1·16 (96% CI 0·89–1·52).

Table 3: **Clinical outcomes at 1 year**

Research in context

Evidence before this study

The incidence of coronary artery calcification is increasing as the population ages, and because coronary artery calcification impedes vessel dilation and stent delivery during percutaneous coronary intervention, severe calcification is associated with procedural complications, stent under-expansion, and increased rates of early and late adverse clinical outcomes. Although additional technologies (beyond balloon angioplasty alone) have been specifically designed to modify coronary calcium before stent implantation, comparative clinical outcome data supporting the use of these technologies are scarce. We searched PubMed on Jan 5, 2025, with the search terms "atherectomy", "orbital OR rotational OR laser", "coronary", and "calc*" for randomised trials published in English and identified two randomised trials comparing atheroablation with balloon angioplasty alone for preparation of severely calcified lesions. In these studies, rotational atherectomy before stent implantation in severely calcified lesions had higher rates of strategy success than balloon angioplasty alone but did not improve event-free survival. Data for other advanced calcium-modification devices, including orbital atherectomy and intravascular lithotripsy, are largely limited to intravascular imaging-based observations alone (one randomised trial of lithotripsy compared with rotational atherectomy) or observational studies without a randomised control group.

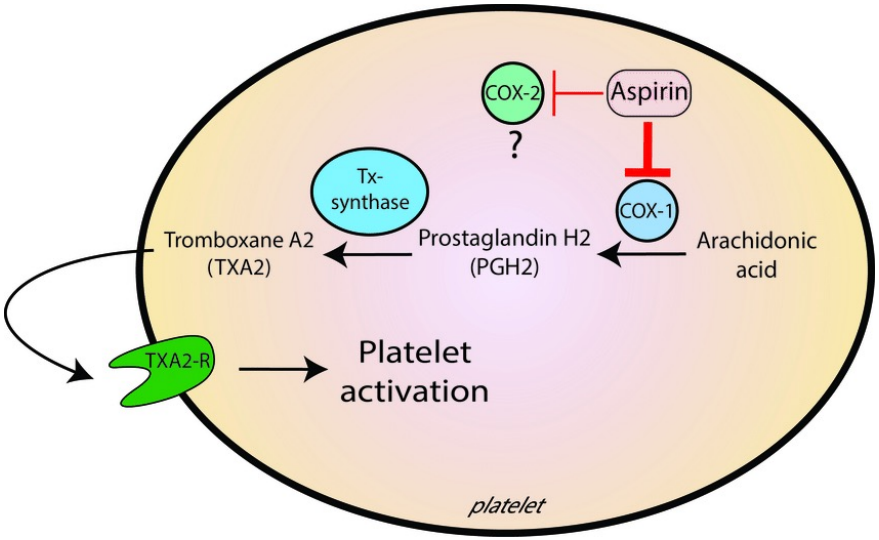
Added value of this study

In this multicentre, randomised clinical trial in patients with severely calcified lesions for which the operator believed atherectomy was not absolutely required, calcium modification with orbital atherectomy did not increase minimal stent area or reduce the 1-year rate of target vessel failure compared with balloon angioplasty alone before drug-eluting stent implantation. Consistent with the 2024 European Society of Cardiology guidelines, most procedures in this trial were guided by intravascular imaging, which has been shown to improve clinical outcomes after stenting of complex lesions. These findings indicate that adequate stent expansion and low rates of adverse outcomes are achievable with a balloon angioplasty-based strategy in a large proportion of severely calcified lesions if meticulous attention is paid to lesion preparation before contemporary stent implantation. These data further suggest that the conventional definition of severe calcification based on the coronary angiogram alone might be insufficient to identify lesions that might optimally benefit from advanced calcium modification strategies.

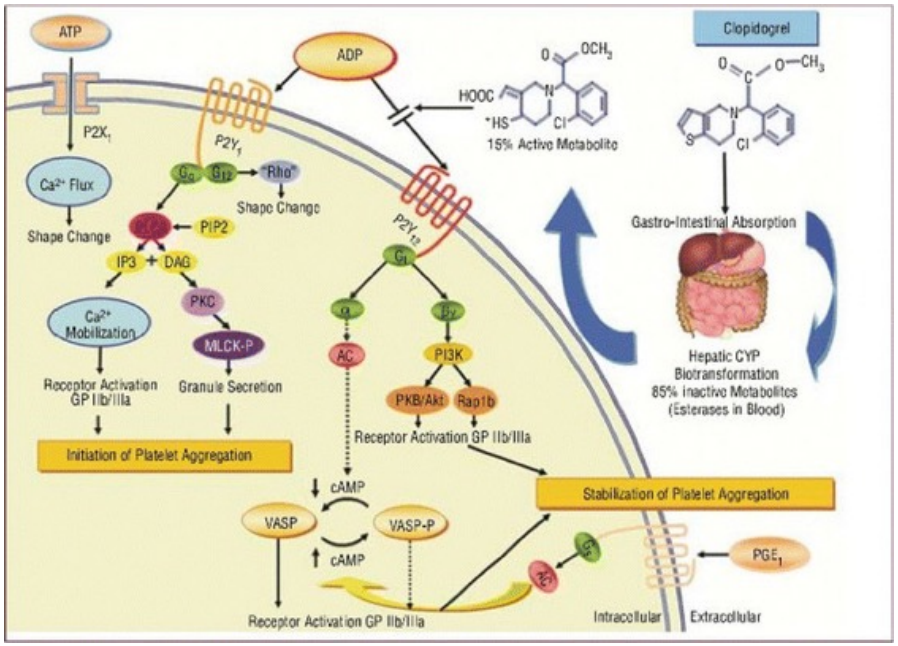
Implications of all the available evidence

These findings support a balloon-first approach to most calcified coronary artery lesions that can be crossed and dilated before stent implantation, guided by intravascular imaging.

Aspirin can be used to prevent thrombosis, particularly arterial thrombosis.

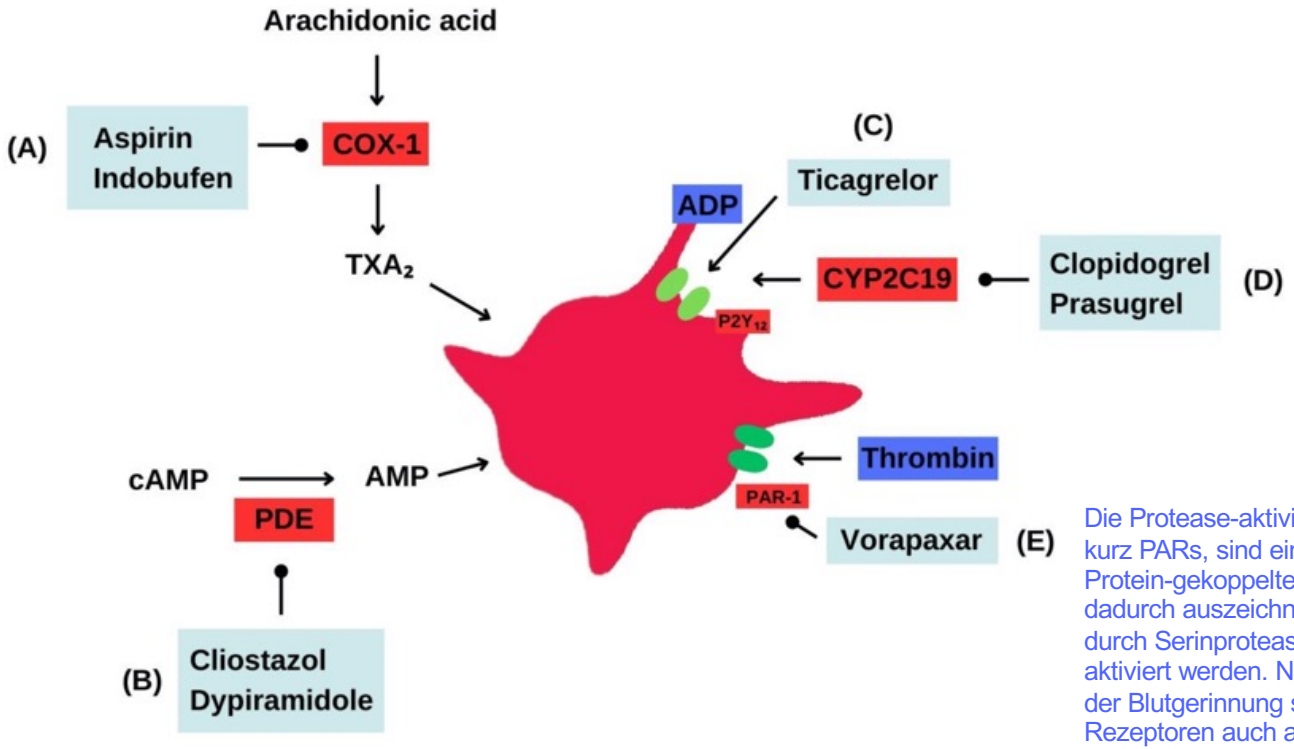


Clopidogrel is a pro-drug, which binds to P2Y12 receptors irreversibly, rendering the receptor unable to respond to adenosine diphosphate (ADP), thus reducing platelet function. Its effect on platelet function lasts for the lifetime of the affected platelet.



VASP vasodilator stimulated phosphoprotein

Dual antiplatelet therapy (DAPT) ist eine Behandlung, die das Risiko von Blutgerinnseln, Herzinfarkten und Schlaganfällen senkt. Sie wird mit zwei verschiedenen Medikamenten durchgeführt, die die Blutplättchen daran hindern, sich zu verklumpen (zumeist ASS + Clopidogrel).



Die Protease-aktivierten Rezeptoren, kurz PARs, sind eine Familie von G-Protein-gekoppelten Rezeptoren, die sich dadurch auszeichnen, dass sie durch Serinproteasen (v.a. Thrombin) aktiviert werden. Neben ihrer Rolle bei der Blutgerinnung sind Protease-aktivierte Rezeptoren auch an Entzündungs- und Verdauungsprozessen beteiligt. Vorapaxar ist ein oral einsetzbarer Thrombozytenaggregationshemmer aus der Gruppe der PAR-1-Antagonisten.

Efficacy and safety of clopidogrel versus aspirin monotherapy in patients at high risk of subsequent cardiovascular event after percutaneous coronary intervention (SMART-CHOICE 3): a randomised, open-label, multicentre trial

Summary

Background The optimal strategy for long-term antiplatelet maintenance for patients who underwent percutaneous coronary intervention (PCI) remains uncertain. This study aimed to compare the efficacy and safety of clopidogrel versus aspirin monotherapy in patients who completed a standard duration of dual antiplatelet therapy (DAPT) following PCI with drug-eluting stents.

Methods In this multicentre, randomised, open-label trial, patients aged 19 years or older at high risk of recurrent ischaemic events (previous myocardial infarction at any time before enrolment, medication-treated diabetes, or complex coronary lesions) who completed a standard duration of DAPT after PCI were randomly assigned (1:1) to receive clopidogrel (75 mg once a day) or aspirin (100 mg once a day) oral monotherapy at 26 sites in South Korea. The primary endpoint was the cumulative incidence of a composite of death from any cause, myocardial infarction, or stroke, assessed in the intention-to-treat population. Adverse events were captured as part of the secondary endpoints. This trial is registered with ClinicalTrials.gov (NCT04418479). It is closed to accrual and extended follow-up is ongoing.

Findings Between Aug 10, 2020, and July 31, 2023, 5542 patients were assessed for eligibility and 5506 were randomly assigned (2752 to clopidogrel monotherapy and 2754 to aspirin monotherapy). The median time between PCI and randomisation was 17·5 months (IQR 12·6–36·1 months). During a median follow-up period of 2·3 years (IQR 1·6–3·0), the primary endpoint occurred in 92 patients in the clopidogrel group and 128 patients in the aspirin group (Kaplan–Meier estimated 3-year incidence 4·4% [95% CI 3·4–5·4] *vs* 6·6% [5·4–7·8]; hazard ratio 0·71 [95% CI 0·54–0·93]; p=0·013). Death from any cause occurred in 50 patients in the clopidogrel group and 70 in the aspirin group (2·4% [1·6–3·1] *vs* 4·0% [2·9–5·0] at 3 years; 0·71 [0·49–1·02]); myocardial infarction in 23 patients in the clopidogrel group and 42 in the aspirin group (1·0% [0·6–1·4] *vs* 2·2% [1·4–2·9] at 3 years; 0·54 [0·33–0·90]); and stroke in 23 in the clopidogrel group and 29 in the aspirin group (1·3% [0·7–2·0] *vs* 1·3% [0·8–1·7] at 3 years; 0·79 [0·46–1·36]). There was no difference in the risk of bleeding between the clopidogrel and aspirin groups (3·0% [2·0–3·9] *vs* 3·0% [2·2–3·9] at 3 years; 0·97 [0·67–1·42]). Clopidogrel was not associated with a higher incidence of any adverse event compared with aspirin.

Interpretation Among patients who were at high risk of recurrent ischaemic events and who completed the standard duration of DAPT following PCI, clopidogrel monotherapy, compared with aspirin monotherapy, significantly reduced the cumulative incidence of a composite of death from any cause, myocardial infarction, and stroke, without an apparent increase in the risk of bleeding.

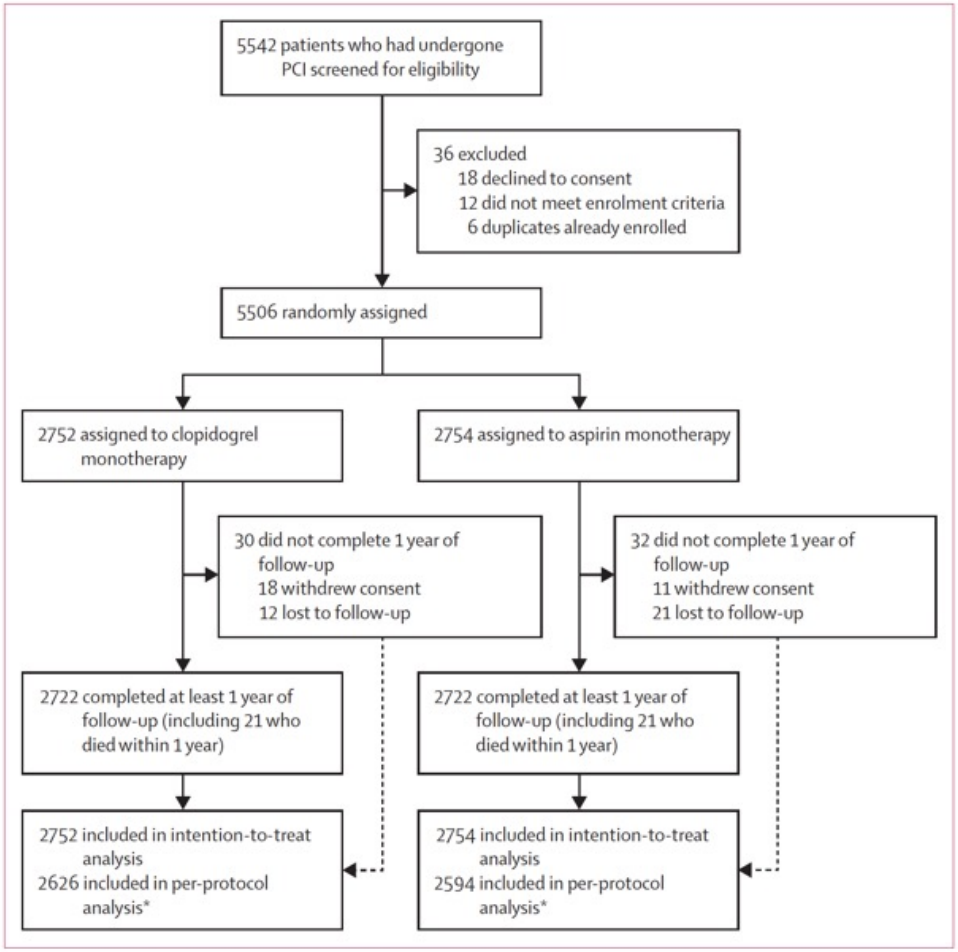


Figure 1: **Trial profile**

In accordance with the protocol, the primary endpoint was assessed at 1 year after the last patient was enrolled, with all patients having a minimum of 12 months of follow-up. The primary analysis was done in the intention-to-treat population. PCI=percutaneous coronary intervention. *126 patients in the clopidogrel group and 160 in the aspirin group deviated from the protocol and were not included in the per-protocol analysis.

	Clopidogrel group (n=2752)	Aspirin group (n=2754)
Age, years	66·0 (58·0–73·0)	65·0 (58·0–73·0)
Sex*		
Male	2240 (81·4%)	2264 (82·2%)
Female	512 (18·6%)	490 (17·8%)
Enrolment criteria		
Previous myocardial infarction	1283 (46·6%)	1269 (46·1%)
Medication-treated diabetes	1039 (37·8%)	1050 (38·1%)
Complex PCI	2113 (76·8%)	2072 (75·2%)
BMI, kg/m²	24·9 (23·0–27·0)	24·8 (23·1–26·9)
Diagnosis at index PCI		
Chronic coronary syndrome	672 (24·4%)	662 (24·0%)
Unstable angina	797 (29·0%)	823 (29·9%)
Non-ST-segment elevation myocardial infarction	678 (24·6%)	652 (23·7%)
ST-segment elevation myocardial infarction	605 (22·0%)	617 (22·4%)
Hypertension	1756 (63·8%)	1690 (61·4%)
Diabetes	1119 (40·7%)	1128 (41·0%)
Dyslipidaemia	1626 (59·1%)	1604 (58·2%)
Current smoking	448 (16·3%)	488 (17·7%)
Chronic kidney disease†	242 (8·8%)	260 (9·4%)
Previous stroke	76 (2·8%)	66 (2·4%)
Peripheral vascular disease	23 (0·8%)	22 (0·8%)
Previous history of major bleeding	15 (0·5%)	21 (0·8%)
Left ventricular ejection fraction, %‡	60·0% (55·0–65·0)	60·0% (55·0–65·0)
Haemoglobin concentration, g/dL	13·8 (1·7)	13·8 (1·7)
Platelet count, ×10³ cells per L	216·6 (66·6)	215·6 (61·3)
Estimated glomerular filtration rate§, mL/min per 1·73 m²	86·7 (19·5)	86·2 (19·9)
LDL cholesterol concentration, mmol/L	1·55 (0·57)	1·56 (0·56)
High bleeding risk defined by ARC	427 (15·5%)	448 (16·3%)
Time from PCI to randomisation, months	17·3 (12·7–36·1)	17·7 (12·6–36·2)
≤12 months of DAPT before randomisation	368 (13·4%)	372 (13·5%)
DAPT regimen before randomisation		
Aspirin plus clopidogrel	1702 (61·8%)	1729 (62·8%)
Aspirin plus prasugrel	304 (11·0%)	341 (12·4%)
Aspirin plus ticagrelor	746 (27·1%)	684 (24·8%)
Medications at randomisation		
Statin	2708 (98·4%)	2714 (98·5%)
Ezetimibe	1717 (62·4%)	1730 (62·8%)
β blocker	1524 (55·4%)	1565 (56·8%)
ACE inhibitor or ARB	1755 (63·8%)	1762 (64·0%)
Gastrointestinal protection medication	792 (28·8%)	844 (30·6%)
Proton-pump inhibitor	545 (19·8%)	589 (21·4%)
Potassium-competitive acid blocker	100 (3·6%)	115 (4·2%)
Histamine-2 receptor blocker or others	153 (5·6%)	150 (5·4%)

Data are mean (SD), median (IQR), or n (%). ACE=angiotensin-converting enzyme. ARB=angiotensin receptor blocker. ARC=Academic Research Consortium. DAPT=dual antiplatelet therapy. PCI=percutaneous coronary intervention. *Only biological sex was reported. †Defined as kidney damage (pathological abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies) or an estimated glomerular filtration rate of less than 60 mL/min per 1·73 m². ‡Data on left ventricular ejection fraction were available for 2436 (88·5%) patients in the clopidogrel group and 2434 (88·4%) in the aspirin group. §The estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease method.

Table 1: **Baseline patient characteristics**

	Clopidogrel group (n=2752)	Aspirin group (n=2754)	Hazard ratio (95% CI)
Primary endpoint			
Major adverse cardiac and cerebrovascular events*	92 (4·4% [3·4–5·4])	128 (6·6% [5·4–7·8])	0·71 (0·54–0·93), p=0·013
Secondary endpoints			
Death from any cause	50 (2·4% [1·6–3·1])	70 (4·0% [2·9–5·0])	0·71 (0·49–1·02)
Death from cardiovascular cause	33 (1·4% [0·9–2·0])	42 (2·1% [1·4–2·8])	0·79 (0·50–1·24)
Death from non-cardiovascular cause	17 (1·0% [0·4–1·5])	28 (1·9% [1·1–2·6])	0·60 (0·33–1·10)
Myocardial infarction†	23 (1·0% [0·6–1·4])	42 (2·2% [1·4–2·9])	0·54 (0·33–0·90)
Stroke	23 (1·3% [0·7–2·0])	29 (1·3% [0·8–1·7])	0·79 (0·46–1·36)
Ischaemic stroke	20 (1·0% [0·5–1·5])	25 (1·1% [0·6–1·6])	0·79 (0·44–1·43)
Haemorrhagic stroke	3 (0·3% [0·0–0·8])	4 (0·2% [0·0–0·3])	0·74 (0·17–3·30)
Stent thrombosis‡	1 (0% [0·0–0·0])	5 (0·2% [0·0–0·4])	0·20 (0·02–1·68)
Death from any cause or myocardial infarction	71 (3·2% [2·4–4·1])	109 (5·9% [4·7–7·1])	0·65 (0·48–0·87)
Death from cardiovascular cause or myocardial infarction	54 (2·3% [1·6–3·0])	81 (4·1% [3·1–5·1])	0·66 (0·47–0·94)
Death from cardiovascular cause, myocardial infarction, or stroke	76 (3·6% [2·7–4·5])	103 (4·9% [3·9–6·0])	0·73 (0·54–0·98)
Death from cardiovascular cause, myocardial infarction, or stent thrombosis	54 (2·3% [1·6–3·0])	81 (4·1% [3·1–5·1])	0·66 (0·47–0·94)
Bleeding (BARC type 2, 3, or 5)	53 (3·0% [2·0–3·9])	55 (3·0% [2·2–3·9])	0·97 (0·67–1·42)
Major bleeding (BARC type 3 or 5)	26 (1·6% [0·9–2·3])	26 (1·3% [0·8–1·8])	1·00 (0·58–1·73)
Upper gastrointestinal clinical event§	58 (2·8% [2·0–3·6])	90 (4·9% [3·7–6·0])	0·65 (0·47–0·90)
Gastrointestinal ulcer or bleeding	24 (1·3% [0·7–1·8])	32 (1·6% [1·0–2·1])	0·76 (0·45–1·29)
Gastrointestinal ulcer	8 (0·6% [0·0–1·1])	15 (0·7% [0·0–1·1])	0·54 (0·23–1·28)
Gastrointestinal bleeding	21 (1·1% [0·6–1·6])	25 (1·4% [0·8–2·0])	0·85 (0·48–1·52)
Gastro-oesophageal reflux disease	23 (1·0% [0·6–1·5])	47 (2·6% [1·7–3·4])	0·49 (0·30–0·81)
Net adverse clinical event¶	111 (5·4% [4·2–6·5])	142 (7·3% [6·0–8·6])	0·78 (0·61–0·99)
Target-lesion revascularisation	32 (1·7% [1·0–2·3])	40 (2·0% [1·3–2·7])	0·80 (0·50–1·27)
Target-vessel revascularisation	42 (2·2% [1·4–2·9])	50 (2·6% [1·8–3·4])	0·84 (0·56–1·27)
Any revascularisation	81 (4·2% [3·1–5·2])	87 (4·5% [3·4–5·5])	0·94 (0·69–1·27)

Values are n (Kaplan-Meier estimated % at 3 years [95% CI]) or hazard ratio (95% CI). The database for the analysis was locked on Oct 31, 2024. Clinical endpoints were evaluated in the intention-to-treat population during the overall study period (ie, from the time of randomisation to the day of the first occurrence of a primary endpoint event, the day of the last office visit or telephone follow-up, or the day of death during follow-up). BARC=Bleeding Academic Research Consortium. *Composite of death from any cause, myocardial infarction, or stroke. †Defined according to the Fourth Universal Definition. ‡Defined according to Academic Research Consortium criteria (definite or probable). §Composite of overt bleeding of gastroduodenal origin, overt upper gastrointestinal bleeding of unknown origin, occult gastrointestinal bleeding with a documented decrease in haemoglobin concentration of at least 2 g/dL, symptomatic gastroduodenal ulcer or at least five erosions, symptomatic gastro-oesophageal reflux disease, upper gastrointestinal obstruction, or perforation. ¶Composite of death from any cause, myocardial infarction, stroke, or major bleeding (BARC type 3 or 5).

Table 2: **Primary and secondary endpoints in the intention-to-treat population**

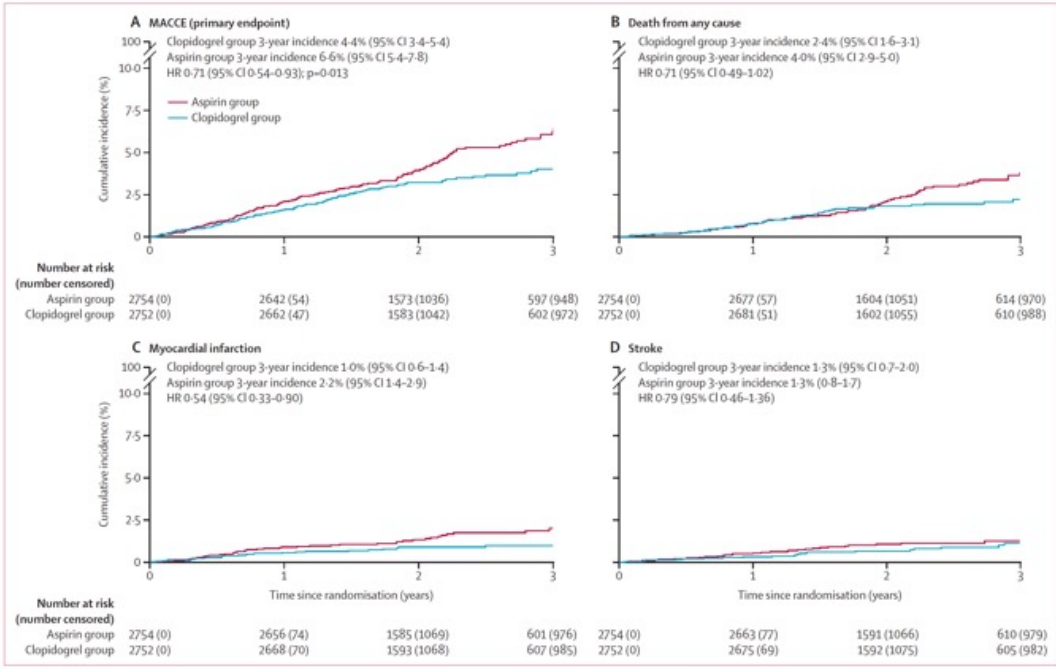


Figure 2: **Cumulative incidence of MACCE (A), death from any cause (B), myocardial infarction (C), and stroke (D) at 3 years**
Note: y-axes are broken. HR=hazard ratio. MACCE=major adverse cardiac and cerebrovascular events.

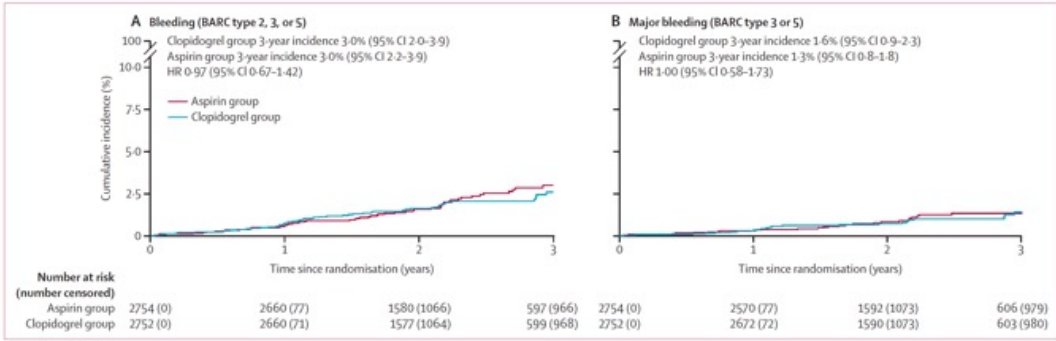


Figure 3: **Cumulative incidence of BARC type 2, 3, or 5 bleeding (A) and BARC type 3 or 5 bleeding (B) at 3 years**
Note: y-axes are broken. HR=hazard ratio. BARC=Bleeding Academic Research Consortium.

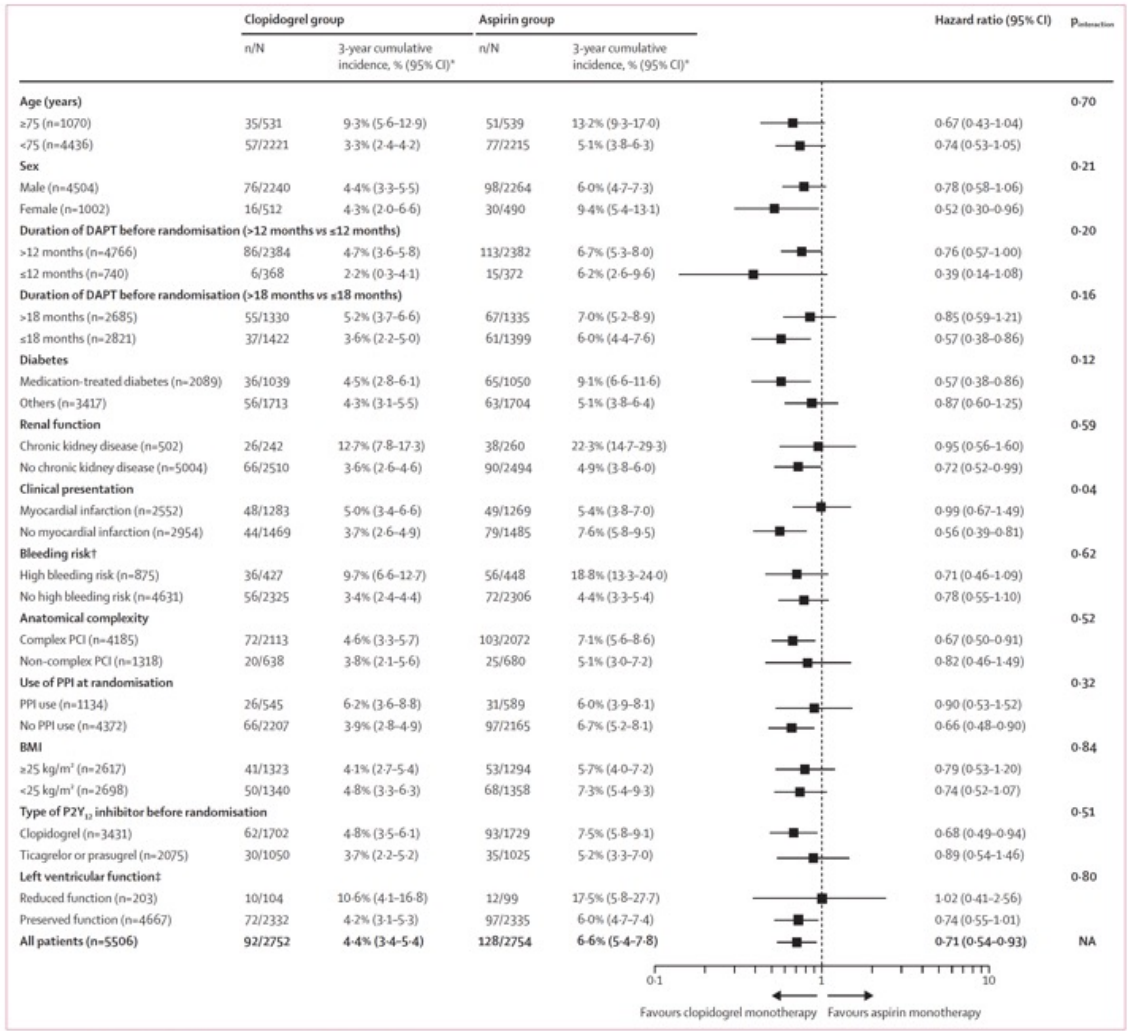


Figure 4: **Subgroup analysis for MACCE (primary endpoint) at 3 years**

DAPT=dual antiplatelet therapy. MACCE=major adverse cardiac and cerebrovascular events. NA=not applicable. PCI=percutaneous coronary intervention. PPI=proton-pump inhibitor. *Percentages (95% CI) are estimated 3-year cumulative incidence from Kaplan–Meier analysis. †Defined according to Academic Research Consortium criteria. ‡Left ventricular function was assessed by ejection fraction from echocardiography; an ejection fraction of 40% or less was defined as reduced function.

Research in context

Evidence before this study

After percutaneous coronary intervention (PCI) with a current-generation drug-eluting stent, dual antiplatelet therapy (DAPT) remains a cornerstone strategy to prevent recurrent ischaemic events in patients with coronary artery disease. After completion of a standard duration of DAPT, indefinite aspirin monotherapy is recommended for secondary prevention, but the optimal long-term antiplatelet strategy after PCI remains uncertain. We searched PubMed for relevant publications in English up to Feb 28, 2025, using the terms "single antiplatelet therapy", "long-term maintenance", "secondary prevention", "percutaneous coronary intervention", "drug-eluting stent", "aspirin", "clopidogrel", and "$P2Y_{12}$ inhibitor". We identified three randomised clinical trials comparing outcomes with aspirin versus $P2Y_{12}$ inhibitor monotherapy in patients treated with PCI after standard DAPT. The HOST-EXAM trial showed that clopidogrel monotherapy, compared with aspirin monotherapy, significantly reduced the incidence of adverse clinical events after standard DAPT maintenance following PCI with a drug-eluting stent. A landmark analysis of the GLOBAL LEADERS trial compared outcomes in patients treated with ticagrelor versus aspirin monotherapy beyond 1 year after PCI. During the second year, the ischaemic composite endpoint (all-cause death, any myocardial infarction, or stroke) was lower with ticagrelor monotherapy than with aspirin monotherapy, but Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding was numerically higher in the ticagrelor group. The 1-year landmark analysis of the STOPDAPT-2 trial showed that clopidogrel was numerically, but not significantly, superior to aspirin for cardiovascular events (cardiovascular death, myocardial infarction, definite stent thrombosis, or stroke) without a difference in major bleeding.

Added value of this study

SMART-CHOICE 3 was a large randomised trial comparing clopidogrel monotherapy against aspirin monotherapy for long-term maintenance therapy in patients with a high ischaemic risk (previous myocardial infarction, medication-treated diabetes, or complex coronary artery lesions) who completed a standard duration of DAPT after PCI. Clopidogrel monotherapy was associated with a significantly reduced risk of major adverse cardiac and cerebrovascular events, particularly myocardial infarction, compared with aspirin monotherapy. To our knowledge, SMART-CHOICE 3 is the first trial to show a benefit of clopidogrel monotherapy over aspirin monotherapy on a hard ischaemic endpoint after PCI. There was no difference in the incidence of BARC type 2, 3, or 5 bleeding between the clopidogrel and aspirin groups. The risk of upper gastrointestinal clinical events was lower in the clopidogrel group than in the aspirin group.

Implications of all the available evidence

Among patients with coronary artery disease who were at high risk of recurrent ischaemic events and completed the standard duration of DAPT after PCI, clopidogrel monotherapy was associated with a reduced risk of a composite of death from any cause, myocardial infarction, or stroke compared with aspirin monotherapy, without an increase in major bleeding. This trial adds to previous evidence supporting clopidogrel monotherapy as an alternative to aspirin for long-term secondary prevention in PCI patients at high risk of ischaemic events, by demonstrating that clopidogrel offers enhanced protection against ischaemic events without an apparent increase in bleeding.

The *Lancet* Commission on rethinking coronary artery disease: moving from ischaemia to atheroma

Executive summary

Coronary artery disease has long been understood through the paradigm of epicardial coronary artery obstruction, causing myocardial ischaemia (a mismatch between myocardial blood supply and demand). However, this model, which focuses on diagnosing and managing coronary artery disease based on ischaemia and cardiovascular events, is flawed. By the time ischaemia manifests, it is often too late for optimal intervention, limiting the effectiveness of treatment options. Despite decades of medical advances, coronary artery disease continues to be a leading cause of morbidity and mortality globally, highlighting the inadequacy of this traditional ischaemia-centric model.

The central limitation of current approaches is the focus on the temporary solutions of restoring myocardial blood flow after obstruction, rather than tackling the underlying disease. Coronary artery disease, caused by atherosclerosis, often results in myocardial infarction through mechanisms that emerge earlier in the progression of disease. The focus of medical care has predominantly been on the recognition of symptoms and treatment of acute events, missing opportunities for early detection and prevention of disease. Billions of dollars in health-care funding continue to be spent on identifying and managing coronary ischaemia; yet, the dominant mechanisms for myocardial infarction are atherosclerotic plaque rupture or erosion and, to a lesser extent, erupted calcified nodules that can emerge at a much earlier stage of the disease.

This Commission advocates for a shift in the conceptual framework of coronary artery disease. We suggest reclassifying the condition as atherosclerotic coronary artery disease (ACAD), moving away from the traditional emphasis on ischaemia and acute cardiac events towards a more systematic understanding of atherosclerosis. This reframing will enable the identification and management of the disease much earlier in its course, potentially saving millions of lives worldwide.

Risk of ACAD develops over a lifetime, beginning in utero, progressing through childhood and adolescence, and continuing into older age. The early stages of disease, which involve the formation of atherosclerotic plaques, are often undetected. A major shift is needed from acute event-centred care to strategies focused on early diagnosis, prevention, and management of atherosclerosis. In this new framework, ACAD should be recognised across all stages, from the earliest signs of atheroma formation to the advanced stages of disease. Our goals should not just to be to manage symptoms and events but to prevent the disease from developing in the first place and, where possible, reverse its course.

Key messages

Atherosclerotic coronary artery disease (ACAD) clinical pathways must be refocused away from ischaemia and towards atherosclerosis

- ACAD death rates are forecasted to increase by 19·2% in lower-middle-income countries and by 4·2% in upper-middle-income countries between 2022 and 2050. ACAD is projected to remain the leading cause of death, responsible for the death of 10·5 million people annually by 2050
- The focus of management of coronary artery disease needs to shift from the late stages of the disease, coronary artery obstruction and resultant ischaemia and infarction, towards strategies aimed at early prevention, regression, and cure of atherosclerosis

ACAD should be seen as a lifetime continuum from early life through to older age

- This new perspective would move the focus from diagnosis after the development of ischaemia or a cardiovascular event towards defining lifetime risk for an individual or a population at the earliest opportunity

The onset of ACAD can be prevented with early risk factor modification

- ACAD and associated cardiovascular events must be recognised as preventable. Complete elimination of known behavioural and metabolic risk factors by 2050 would reduce the rate of ACAD deaths by 82·1% and save 8·7 million lives per year globally

Effective strategies for early screening and detection of ACAD are needed

- These strategies should aim to maximise the effect of therapies to delay, halt, and revert the process of atherosclerosis by using targeted screening and detection earlier in the life course

Implementation of current approaches to ACAD needs to be improved

- Implementation of evidence-based knowledge in ACAD is poor and variable, contributing to avoidable death, disability, and waste of resources
- Stakeholders should support implementation efforts to maximise the uptake of known effective strategies for ACAD prevention and treatment globally and equitably

Local and global disparities in prevention, diagnosis, treatment, and outcomes of all people at risk of and with ACAD must be addressed

- Research in ACAD is not representative of diverse populations and might not be transferable to all settings
- Practical and pragmatic research must be promoted and conducted by stakeholders that is inclusive of routine health care using decentralised and adaptive platforms of interventions that allow a greater proportion of diverse patients to be randomised within clinical trials with lifelong follow-up

New therapies to eradicate atherosclerosis must be developed

- The eradication of atherosclerosis is possible with transformative research

A global standard of data collection and dissemination to inform population-based decision making in ACAD should be established

- A systematic international approach can generate and make data accessible for research and policy
- The necessary resources and legislation should be provided by stakeholders to embed sustainable, integrated, standardised, accessible, and accurate databases of key health indicators in ACAD within all countries, with fair and easily accessible mechanisms

The ACAD health-care workforce and research infrastructure should be aligned towards early detection and prevention

- The current workforce is focused on diagnosis and treatment of late-stage disease. This focus is variable, inequitable, and not resilient to economic, social, and environmental challenges and catastrophes
- The global workforce must be trained to redirect delivery of care to prevention, detection, and management of earlier stages of ACAD, considering the relevant national context

Research funding must reflect the global burden of ACAD

- Current research resources and investment are not commensurate to the global burden of morbidity and mortality attributable to ACAD. Without additional investment, the global incidence of acute coronary syndromes will double by 2050
- Research funding must increase to match the burden of disease and support transformational research to improve outcomes worldwide

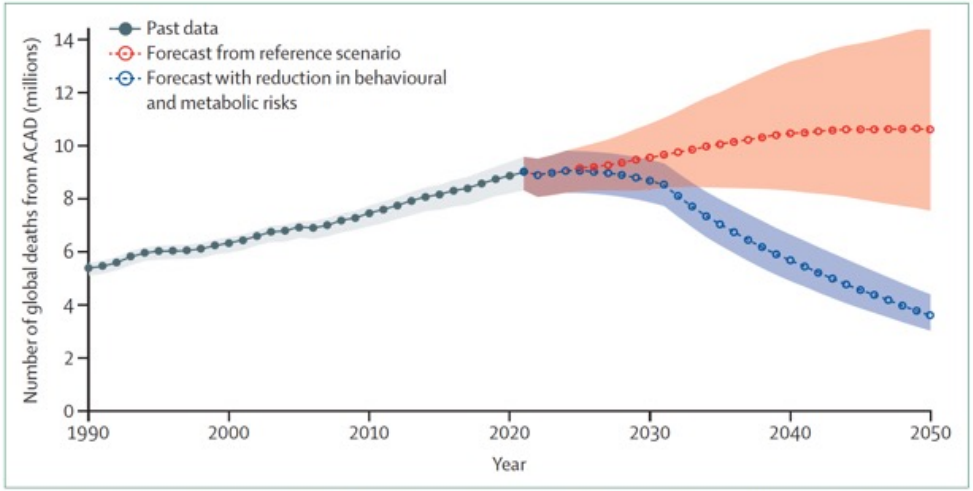


Figure 1: **Number of deaths from ACAD from 1990 to 2021 and projection to 2050 with and without elimination of metabolic and behavioural risk factors**

Raw data were acquired from the Institute for Health Metrics and Evaluation through the Global Burden of Disease Foresight and Results tools. Data from 1990 to 2021 are based on past observations.[10] Data from 2022 to 2050 are forecasted.[11] The forecasted data consists of two scenarios: a reference scenario and an improved behavioural and metabolic risks scenario (with 5-year delay). In both scenarios, the risk, demographic, and environmental factors were first forecasted until 2050 and then used to regress the mortality trends. Under the improved behavioural and metabolic risks scenario, the original study assumed that: (1) metabolic risks, high adult BMI, high systolic blood pressure, high LDL-cholesterol, and high fasting plasma glucose, are linearly eliminated by 2050; (2) exposure to non-optimal diet is eliminated by 2050; (3) the number of smokers reduces linearly until reaching zero in 2050; and (4) there are no new smokers after 2022.[11] For each measurement, the mean value and the 95% uncertainty interval (from percentile 2·5–97·5; shown as shaded areas) were used. Data were visualised using the Matplotlib, Seaborn, and GeoPandas packages in Python programming. No imputation and alteration of the data was performed. ACAD=atherosclerotic coronary artery disease.

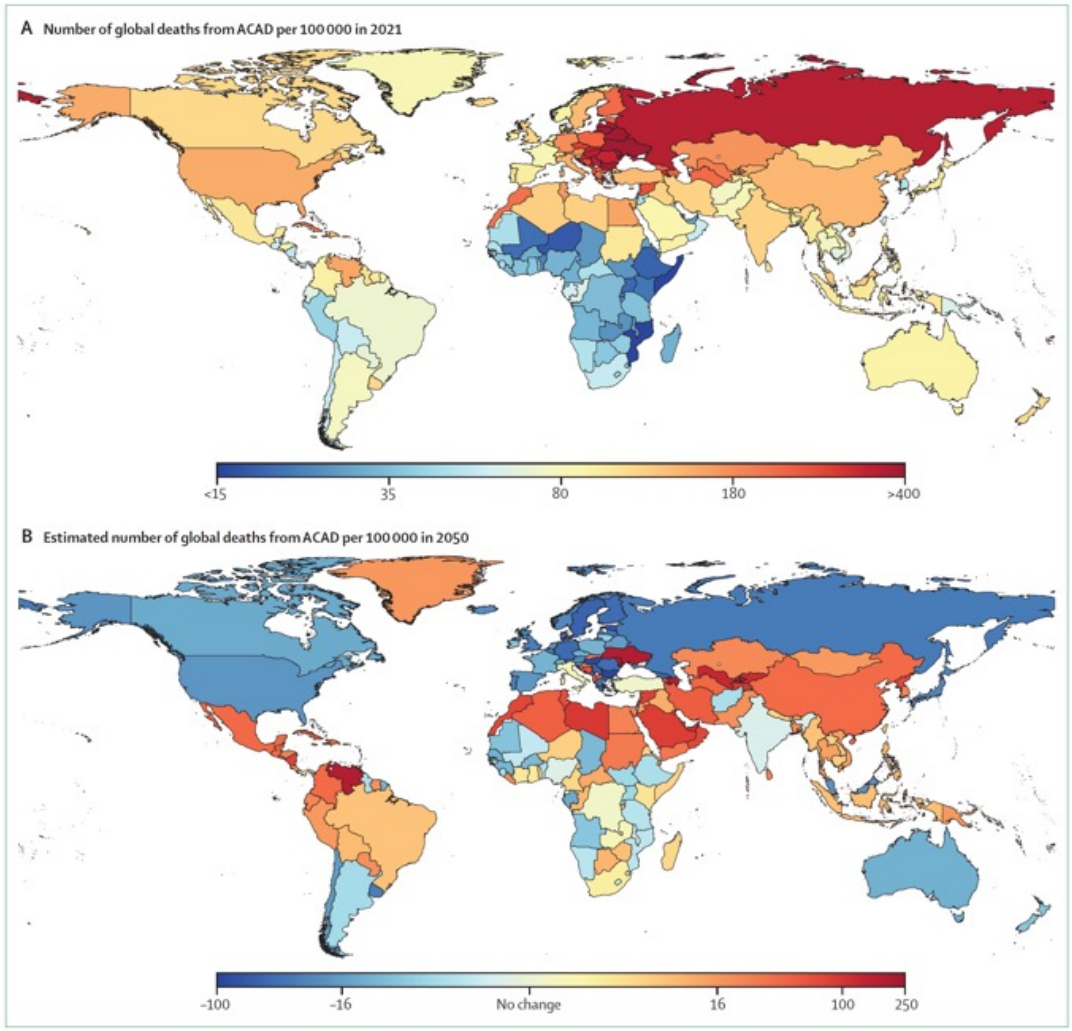


Figure 2: **Projected change in number of ACAD deaths from 2021 to 2050**

(A) Number of global deaths from ACAD per 100 000 population in 2021. (B) Projected change in global deaths from ACAD per 100 000 population from 2021 to 2050. Global Burden of Disease estimates for ischaemic heart disease were used to construct choropleth maps. ACAD=atherosclerotic coronary artery disease.

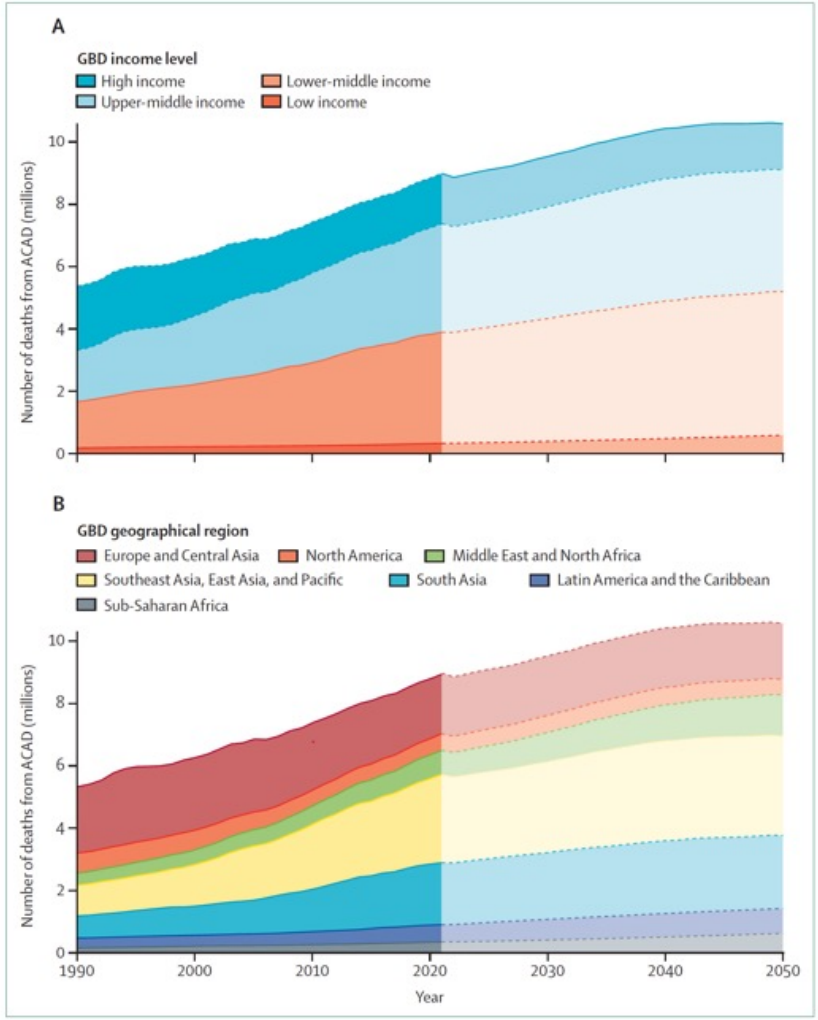


Figure 3: **Absolute number of deaths from ACAD by income and geographical region, current and projected to 2050**

(A) Deaths by income level. (B) Deaths by geographical region. Estimates are from the GBD model and definitions. ACAD=atherosclerotic coronary artery disease. GBD=Global Burden of Disease.

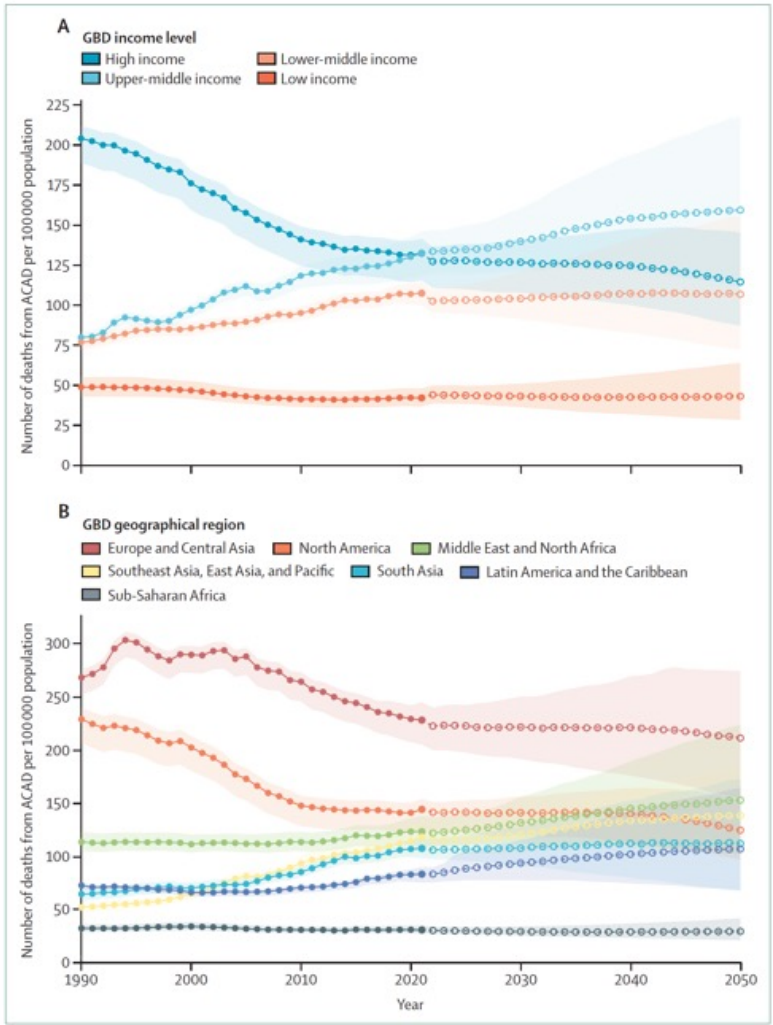


Figure 4: **Number of deaths from ACAD per 100 000 population by income and geographicalregion, current and projected to 2050**

(A) Deaths by income level. (B) Deaths by geographical region. Data are from GBD estimates. ACAD=atherosclerotic coronary artery disease. GBD=Global Burden of Disease.

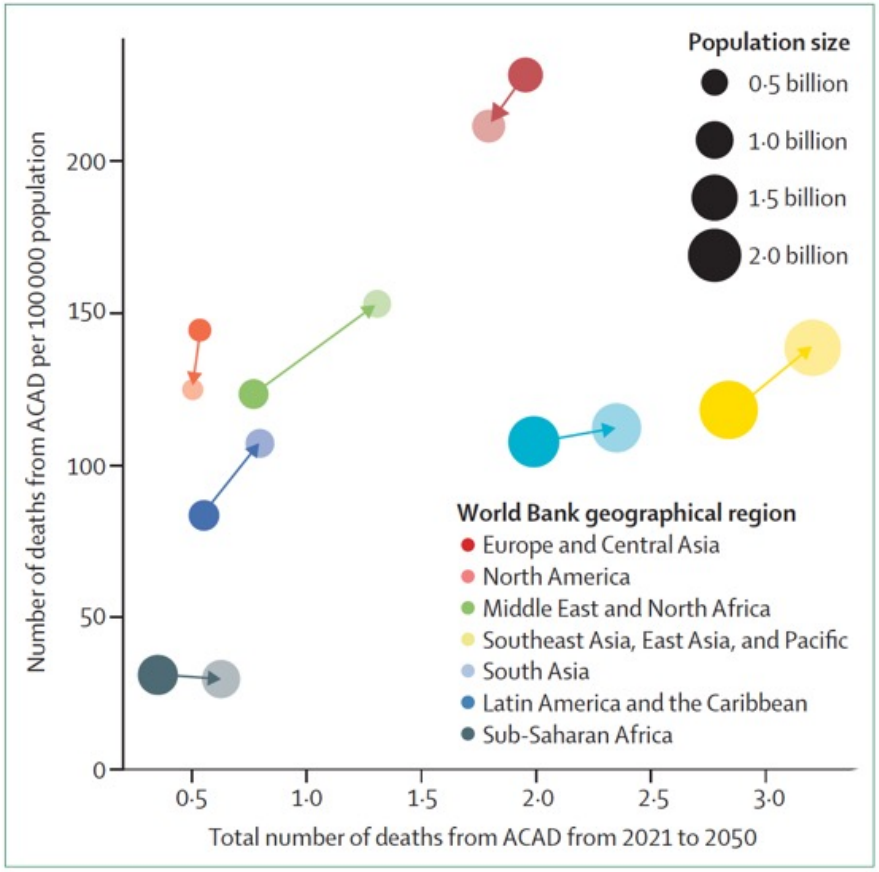


Figure 5: **Projected changes in absolute numbers of deaths from ACAD by geographical regions from 2021 to 2050**

Dark-coloured circles indicate number of deaths in 2021 from ACAD. Light-coloured circles indicate the projected change over time to 2050. Population size in each geographical region is represented by size of circle. Data from Global Burden of Disease models. ACAD=atherosclerotic coronary artery disease.

	ICD-11 code	Definition	Proposed update
Acute ischaemic heart disease	BA41	Acute myocardial infarction is described as ST elevation myocardial infarction (BA41.0) and non-ST elevation myocardial infarction (BA41.1)	Include mechanism of myocardial infarction in coding to distinguish between atherosclerotic and non-atherosclerotic causes
Chronic ischaemic heart disease	BA52	Coronary atherosclerosis of native arteries (BA52.0), bypass grafts (BA52.1 and BA52.2), or unspecified (BA5Z); subcodes for severity focused on single vessel (XS2V) versus multiple vessel (XS8U) disease; codes used to associate with angina and myocardial infarction	Recode to a new umbrella term of atherosclerotic coronary artery disease, focused on coronary artery atheroma; include codes that identify the stages of disease from early atheroma through to extensive atherosclerosis

Table 1: **Current classification of ischaemic heart disease and proposed updates to promote global reporting of atherosclerotic coronary artery disease**

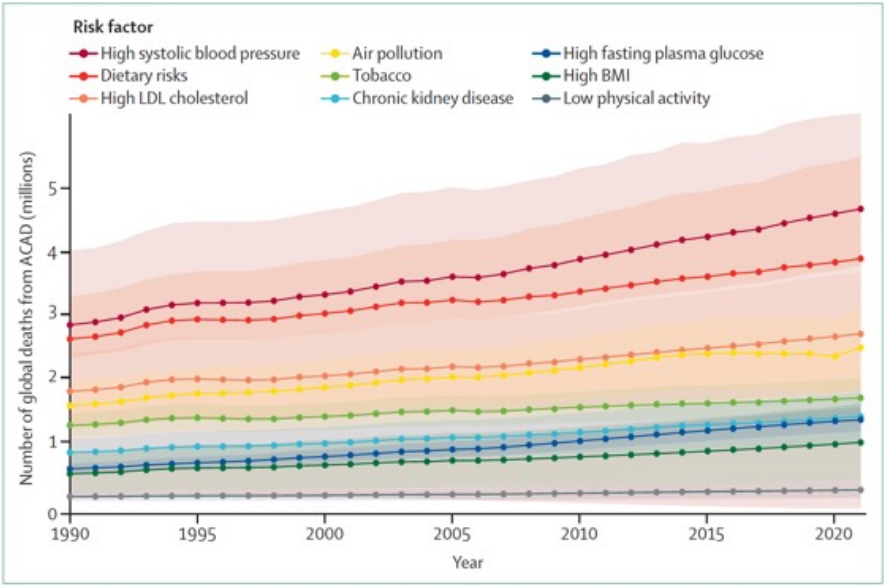


Figure 6: **Contribution of leading risk factors to global ACAD deaths between 1990 and 2021**
Data are from Global Burden of Disease models. ACAD=atherosclerotic coronary artery disease. Dietary risk is defined as a diet low in fruits, vegetables, legumes, whole grains, fibre, nuts and seeds, seafood omega-3 fatty acids, calcium, polyunsaturated acids, and milk, as well as a diet high in red meat, processed meat, sugar-sweetened beverages, sodium, and trans fatty acids.

Panel 1: Addressing risk factors for atherosclerotic coronary artery disease

- Obesity, sedentary behaviour, poor diet, hypertension, and diabetes constitute an epidemic of risk factors that begin in early life with risk exposure even in utero. These risk factors are particularly relevant in high-income and middle-income countries and are also becoming more prevalent in low-income countries. Screening for risk factors for atherosclerosis should therefore begin earlier in life
- Control of traditional risk factors continues to be crucial in reducing the burden of atherosclerotic coronary artery disease (ACAD). Global ACAD risk factor data do not capture important regional and intracountry and intercountry differences that require personalised approaches to mitigate individual ACAD risk
- Identification of novel ACAD risk factors, encompassing not only biological but also social and technological factors, will provide further opportunities to improve health outcomes and to reduce disparities within and between regions
- Multi-measure and multi-territory longitudinal studies are required to understand the relationship between risk factors and health outcomes from ACAD over time

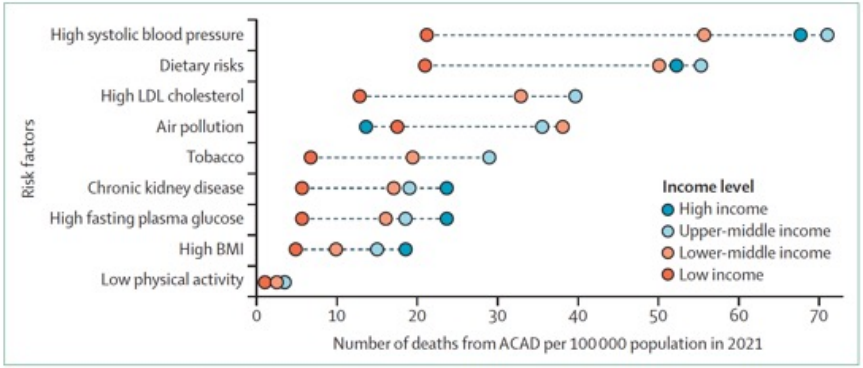


Figure 7: **Leading risk factor contributions to ACAD DALYs by income level for 2021**
Data are from Global Burden of Disease models. ACAD=atherosclerotic coronary artery disease. DALYs=daily-adjusted life-years.

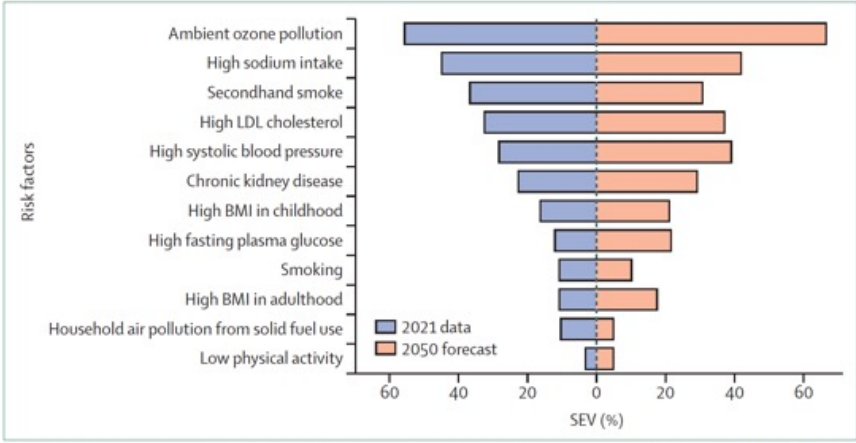


Figure 8: **Global prevalence of leading risk factors contributing to all causes of death between 2021 and projected to 2050**
SEV is the ratio between the weighted average of the excess risks among individuals in the global population and the maximum excess risk. Data are from Global Burden of Disease models. This metric includes both the prevalence of the exposure and the extent to which such exposure would affect the disease. SEV is 0% when everyone in the population has no excess risk and 100% when everyone is at maximum risk. For a dichotomous risk factor, SEV is equivalent to the prevalence. SEV=summary exposure value.

Panel 2: Atherosclerotic coronary artery disease prevention targets

- Recognise and prioritise the role of primordial prevention of atherosclerotic coronary artery disease (ACAD)
- Research the effect of screening for risk factors and starting preventive strategies earlier in life to reduce lifelong risk of ACAD
- Understand the trajectory of ACAD risk factors and the initiation of preventive strategies in childhood and adolescence within populations with increased genetic and environmental risk
- Establish early detection strategies using diverse tools that measure disease activity or directly visualise atherosclerosis
- Develop tools incorporating multimodal data computed by appropriate predictive models, including using artificial intelligence, with a focus on early detection and longitudinal assessment of risk
- Further evaluate the effectiveness of long-acting therapies, vaccines, polypills, and novel therapies on cardiovascular disease risk factors, patient adherence, and ACAD outcomes
- Evaluate genetic testing and genomic-based therapies in preventing ACAD
- Repurpose proven therapeutics into different populations (eg, GLP-1 receptor agonists for prevention of ACAD beyond individuals with diabetes and obesity)

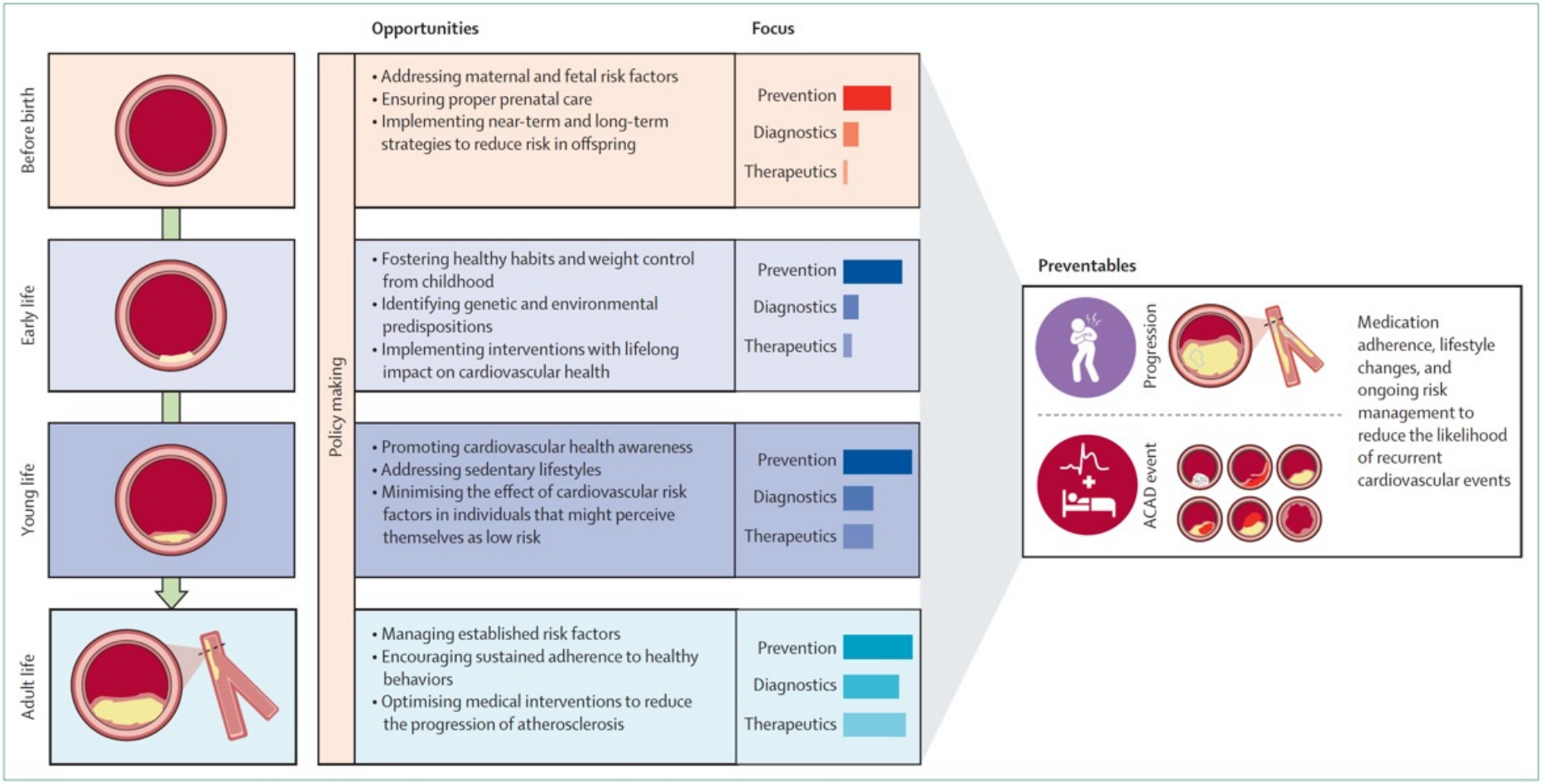


Figure 9: **Opportunities and strategies to prevent atherosclerotic coronary artery disease over the life course**
Early life defined as age 0–3 years. Young life defined as age 4–17 years. Adult life defined as age 18 years and older. ACAD=atherosclerotic coronary artery disease.

	Primordial prevention		Primary prevention	Secondary prevention
	Prenatal population	Birth, childhood, and adolescence without risk factors (low risk for ACAD)	Greater than low risk for ACAD and established ACAD risk factors	Past acute event (high risk) and symptomatic stable ACAD (moderate risk)
Tobacco use	Risk of harm to fetus	Major modifiable risk	Major modifiable risk	Major modifiable risk
Raised blood pressure	Pre-eclampsia and hypertensive disorders are associated with increased risk of ACAD in offspring for several generations	Observed risk	Major modifiable risk[143]	Major modifiable risk
LDL-cholesterol	Elevated maternal LDL cholesterol during pregnancy associated with increased risk of dyslipidaemia in adult offspring[144]	LDL-cholesterol modification modelled to be cost-effective down to population 10-year risk of 2·5%	Major modifiable risk	Major modifiable risk
Diabetes or insulin resistance	Gestational diabetes causes macrosomia, possible accelerated metabolic risk in fetus, and long-term risk of ACAD in mother	Threshold for treatment of impaired fasting glucose to prevent ACAD remains unclear	Major modifiable risk	Major modifiable risk
Chronic kidney disease			Major modifiable risk (with some uncertainty in patients who undergo dialysis)[145,146]	Major modifiable risk (with some uncertainty in patients who undergo dialysis)[145,146]
Physical activity		Observed risk	Observed risk	Major modifiable risk (exercise-based cardiac rehabilitation reduces recurrent events)
Inflammation	Pre-term birth associated with inflammation, ACAD in the mother, and unknown fetal risk[147–149]	Observational data of inflammation associated with risk of ACAD	Observational data of inflammation associated with risk of ACAD[150–152]	Major modifiable risk (anti-inflammatory treatment reduces cardiovascular events)[153]
Infectious		Infection (eg, HIV) in childhood and adolescence associated with risk of ACAD[154,155]	HIV, hepatitis C, periodontitis, COVID-19, and influenza associated with risk of ACAD	Infection prevention after myocardial infarction or in coronary artery disease reduces risk of cardiovascular disease events or death (eg, influenza vaccine)[156]
Drug use disorders[157]	Risk of harm to fetus	Cocaine, amphetamine, and cannabinoids associated with risk of ACAD	Cocaine, amphetamine, cannabinoids associated with risk of ACAD	Cocaine, amphetamine, cannabinoids associated with risk of ACAD
Obesity	Maternal obesity associated with increased cardiovascular disease in offspring[158]	Contributes to hypertension, diabetes, and sleep apnoea	Contributes to hypertension, diabetes, and sleep apnoea	Contributes to hypertension, diabetes, and sleep apnoea
Diet		Little evidence for DASH diet[159]	Little evidence for Mediterranean or DASH diet[159,160]	Little evidence for Mediterranean diet[161]
Low birthweight	Low birthweight independently associated with future risk of ACAD[162]	Low birthweight independently associated with future risk of ACAD[162]	NA	NA
Genetic risk (monogenetic)		Strong monogenic risk (familial hypercholesterolaemia or dyslipidaemias)	Strong monogenic risk (familial hypercholesterolaemia or dyslipidaemias)	Variable risk (benefits of target therapy vary)[163–168]
Vaping, e-cigarettes, and nicotine replacement therapy			Observational data of increased risk of acute myocardial infarction[169]	Observational data of increased risk of acute myocardial infarction[169]
Atherogenic lipids			Observational association with ACAD	Observational association with ACAD
Mental health			Depression, anxiety, and psychosocial stressors associated with risk of ACAD[170–174]	Depression, anxiety, and psychosocial stressors associated with increased cardiovascular events
Environmental		Air pollutants, fine particulates, and heavy metals associated with risk of ACAD[175]	Air pollutants, fine particulates, and heavy metals associated with risk of ACAD[175]	Unknown benefit of reduction in exposure
Autoimmune and inflammatory diseases[176–180]		Unknown long-term risk when early in life	Associated with risk of ACAD but not independently of other risk factors; increased levels of inflammation seem to drive major adverse outcomes despite normal cholesterol levels (ie, the lipid paradox)	Targeted therapies have unknown benefit, especially with the lipid paradox
Sleep disorders[181,182]			Observational data of long sleep and short sleep duration associated with risk of ACAD[183]	Unknown risk in secondary prevention
Polycystic ovary syndrome			Associated with risk of ACAD but not independent to other risk factors[184,185]	Unknown benefit of treatment to prevent secondary events
Metabolic dysfunction-associated steatotic liver disease			Associated with risk of ACAD	Unknown; potential for incretin-based drugs (eg, GLP-1 receptor agonists)[186]
Sex hormone exposure			Associated with ACAD risk; unknown whether strategies (eg, hormone use) mitigate risk or cause harm[187–189]	
Genetic risk (polygenetic)			Polygenic scores might reclassify risk; unclear therapeutic benefit	Unknown benefit of targeted therapy

Figure 10: **Summary of evidence on risk factor exposure with ACAD according to primordial, primary, and secondary prevention interventions**
Green=modifiable risk factors with multiple studies showing that intervention on this risk factor leads to improved cardiovascular outcomes. Yellow=risk factors with some data, but the efficacy of an intervention on cardiovascular outcomes has not been established. Red=minimal or no supporting data. ACAD=atherosclerotic coronary artery disease. DASH=Dietary Approaches to Stop Hypertension. NA=not applicable.

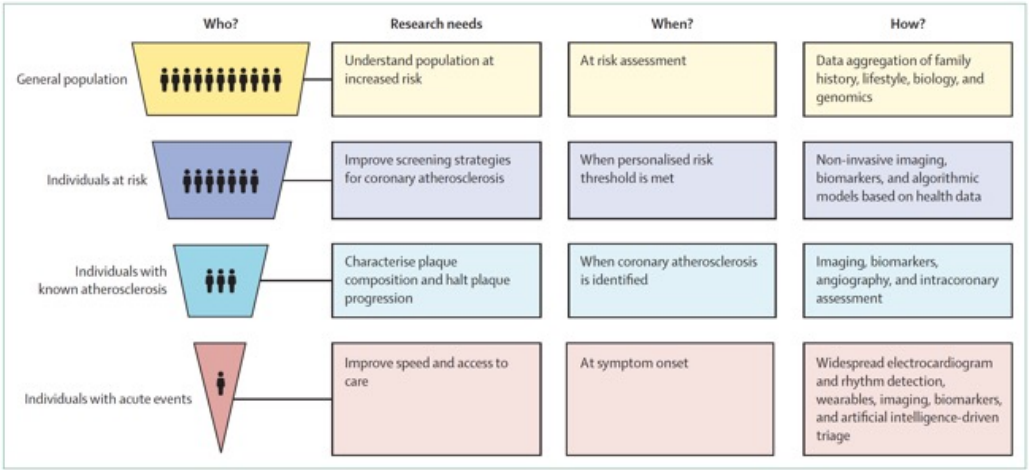


Figure 11: **Guidance on screening and investigation of atherosclerotic coronary artery disease**

Panel 3: Screening strategies for atherosclerotic coronary artery disease (ACAD)

- Develop and test strategies for early atherosclerotic coronary artery disease (ACAD) detection through screening asymptomatic individuals
- Focus on imaging to detect plaque burden and morphology, with consideration of cost-effectiveness and safety (ie, minimising radiation exposure)
- Conduct research assessing long-term outcomes of early ACAD detection strategies and strengthen evidence for surrogate endpoints, such as the halting or regressing of atherosclerosis

Panel 4: Steps to improve diagnosis of atherosclerotic coronary artery disease

- Develop strategies to foster broader access to effective diagnostic strategies for atherosclerotic coronary artery disease in resource-limited settings, including access to timely care for acute and high-risk coronary artery disease
- Develop accurate diagnostic tools to detect biological processes and mechanisms (eg, plaque burden and morphology or inflammation) to predict future risk, with consideration of cost-effectiveness and safety

Panel 5: Targeting atheroma before the end phenotype of ischaemia is established

- Examine whether, and how, some people benefit more from existing and new treatments and the efficacy of personalisation
- Develop new treatments that could reverse, cure, or eradicate atherosclerosis
- Identify broadly applicable and locally effective strategies to increase uptake of, and adherence to, proven treatments
- Reassess benefits of established treatments to identify obsolete therapies and adapt therapies to new indications

	Specific drugs	Challenges	Future research goals
Lipid-lowering agents	Statins, ezetimibe, bempedoic acid, and PCSK9 inhibitors (eg, evolocumab, alirocumab, inclisiran)	Poor implementation or up-titration in eligible people; public mistrust and suspicion regarding benefits and side-effects; low adherence rates; unclear optimal timing, duration, or indications for deprescribing	Investigate the ideal therapeutic goals according to risk groups; develop strategies to build public trust and understanding; develop strategies to reduce nocebo and side-effects
Blood-pressure lowering agents	ACE-I, ARB, calcium-channel blockers, β blockers, diuretics	Large proportion of population globally at risk with undiagnosed or untreated hypertension; little evidence investigating low blood pressure targets in acute coronary syndrome	Establish treatment targets for blood pressure in the early phase after acute coronary syndrome; define strategies to improve detection of hypertension on a broad scale
Antianginals	Nitrates (short-acting for acute angina or long-acting for angina prophylaxis), β blockers; calcium-channel blockers (non-dihydropyridine agents such as verapamil or diltiazem), dihydropyridine agents (eg, long-acting nifedipine and amlodipine), ivabradine; nicorandil, ranolazine, trimetazidine	Previous evidence of efficacy often based on surrogate and non-patient centred outcomes; variable treatment response; clinically significant side-effects; unclear efficacy of single therapy versus combined therapy; scarce evidence on strategies to personalise treatment	Develop new approaches to targeted antianginal medication and strategies based on endotype of disease and patient characteristics
Antiplatelets and antithrombotics	Antiplatelets and antithrombotics (administered for pretreatment, peri-interventional, postinterventional, and maintenance treatment); low-dose aspirin, oral and intravenous P2Y12 inhibitors (eg, Ticagrelor, prasugrel and cangrelor), glycoprotein IIb-IIIa antagonists (eg abciximab and tirofiban), direct oral anticoagulants (eg, rivaroxaban), factor XIa inhibitors	High risk of bleeding; variation in treatment response for some agents; uncertainty around which patient groups benefit most from which treatment combination or duration	Individualise choice and duration of dual *vs* single antiplatelet therapy according to ischaemic and bleeding risk; individualise platelet function and genetic polymorphisms; role of using antithrombin (eg, factor XIa inhibitor) in addition to antiplatelet therapy after acute coronary syndrome
β blockers	Cardio-selective β blockers (eg, carvedilol, bisoprolol, and extended-release metoprolol), non-selective (eg, propanolol)	Contemporary trials show limited benefit in patient groups without impaired LVEF; side-effect profile (eg, fatigue, bradycardia, hypotension, and worsening heart failure when decompensated)	Ascertain improvement in quality of life, exercise, and angina in stable patients with ACAD; identify which subgroups benefit after myocardial infarction or stable ACAD, with preserved LVEF; identify ways to reduce side-effects
RAAS inhibitors	ACE-I, ARB, sacubitril–valsartan	ACE-I and ARB commonly used after myocardial infarction and in coronary artery disease management; limited data in context of evolving contemporary medical therapy; minimal outcome data in preserved LVEF after myocardial infarction; no additional improvement in cardiovascular outcomes with new agents (sacubitril–valsartan) *vs* ACE-I	Investigate whether RAAS blockers reduce cardiovascular events in patients with coronary artery disease and typical left ventricular function; investigate benefit in context of contemporary coronary artery disease therapy
Glucose-lowering agents	SGLT2 inhibitors, GLP-1 receptor agonists	Polypharmacy with associated challenges in adherence	Identify further indications for use in different groups
Anti-inflammatory agents	Colchicine, allopurinol IL-6 inhibitors, monoclonal antibody IL-1β (canakinumab)	Minimal data on risk reduction; side-effect profile and infection risk	Measure outcome data; quantify frequency and define side-effect profile

ACAD=atherosclerotic coronary artery disease. ACE-I=angiotensin converting enzyme inhibitor. ARB=angiotensin II receptor blockers. LVEF=left ventricular ejection fraction. RAAS=renin–angiotensin–aldosterone system.

Table 2: **Current pharmacological treatments, challenges, and research needs for atherosclerotic coronary artery disease**

	Challenges	Future research goals
Patients with diabetes	Diffuse and extensive coronary artery disease; high mortality and repeat revascularisation rates	Ascertain the possible synergy between drugs and medical devices in diabetes
Older patients	Comorbidities; increased risk of bleeding complications and periprocedural events (for both surgical and percutaneous revascularisation); complex lesions (eg, bifurcations, calcifications, and tortuosity)	Perform more studies of revascularisation specifically recruiting older people and inclusive of patients who are frail and at high risk, with multiple comorbidities
Patients with chronic kidney disease	High rates of complex and calcified plaques; increased risk of acute kidney injury and bleeding	Perform research on acute kidney injury minimisation strategies; improved tools for management of calcified plaques; increase recruitment of people with kidney disease into clinical trials
Patients with left ventricular dysfunction	Role of percutaneous coronary intervention remains uncertain; uncertainties exist regarding the most suitable method to assess myocardial viability and whether myocardial viability can predict outcomes with revascularisation	Perform randomised studies with standardised viability assessment and quantification; develop new tools to assess viability; perform studies assessing the role of percutaneous coronary intervention with physiology and imaging guidance, studies defining the optimal role of ventricular support devices during revascularisation, and studies defining the prognostic importance of complete anatomical or functional revascularisation

Table 3: **Challenges and opportunities for future research in revascularisation for specific subgroups**

Panel 6: Improving diversity of participants in clinical trials

Barriers to representation

- Difficulty in accessing study sites
- Familial or caregiver responsibilities
- Cultural or language barriers, screen failure, and not being considered for screening
- Socioeconomic barriers
- Participant concerns about safety
- Limited inclusion criteria
- Poor data collection on relevant non-cardiac history

Strategies to improve representation

- Establish research sites in locations where potential participants already receive health care; provide language assistance for individuals with limited language proficiency; make reasonable modifications for persons with disabilities; and use remote (telephone or online) recruitment processes and study designs
- Reduce burdens due to trial and study participation (eg, number or frequency of study-related procedures or visits, use of local laboratory and imaging, and telehealth)
- Develop a diverse pool of investigators and staff, sustained community engagement, and screening protocols that promote unbiased screening; and promote communication adjusted to patient needs, enhancing transparency and trust
- Improve access by providing assistance with issues such as transportation
- Ensure prevalence-adjusted representation of individuals in cardiovascular clinical trials across relevant age or other categories
- Consider important previous factors from early life (eg, pre-eclampsia, endometriosis, or polycystic ovary syndrome)

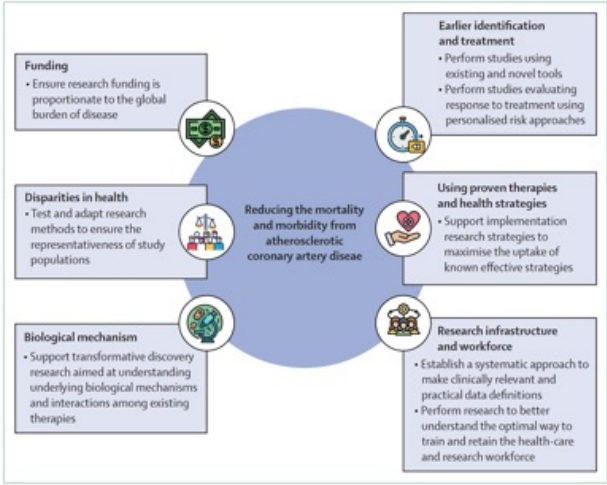


Figure 12: **Recommended actions to lower mortality and morbidity from atherosclerotic coronary artery disease**

Panel 7: Key targets for research

- Health services research in atherosclerotic coronary artery disease (ACAD) is required to improve health outcomes by increasing the delivery of existing clinically effective therapies
- The cost-effectiveness of clinical interventions needs to be identified to inform real-world prices and encourage appropriate allocation of scarce resources
- Collection methods of population health data should be applied to health-care systems to allow modelling for resilience testing
- Research into strategies and policies should be funded to increase the numbers of women and under-represented ethnic and racial groups in the ACAD workforce

Panel 8: Evaluation of health-care delivery for atherosclerotic coronary artery disease

Gaps in delivery of health care for atherosclerotic coronary artery disease (ACAD)

- Worse ACAD outcomes of unclear cause
- Low adherence to performance metrics
- Scarce resources misallocated to low value therapies
- Treatments misallocated to patients at low risk
- Primary prevention risk scores not correctly indicating risk in different populations
- Health-care workforce insufficiently prepared to address care gaps, such as control of ACAD risk factors
- Overdependence on traditional care models
- Minimal ACAD workforce at the primary care level
- Poor allocation of health-care workers in diverse settings

Suggested research methods to address gaps

- Inductive qualitative methods
- Pragmatic trials of health-care delivery mechanisms (eg, nudges) to increase adherence; and pragmatic trials of alternative health-care delivery mechanisms as alternatives to traditional care (eg, home hospital, blood pressure checks in barbershops, and electronic consults)
- Decision analysis and cost-effectiveness simulations that use both effect estimates and costs that apply to local settings, including low-income and middle-income countries
- Observational comparative effectiveness research using large observational datasets adequately powered for heterogeneous treatment effects
- Trials of educational interventions to serve vulnerable populations
- Inclusive transnational clinical registries that reflect a full range of diverse populations in different countries, including low-income and middle-income countries

Panel 9: Health policy and public education goals

- Public education needs to target the prevention of atherosclerotic coronary artery disease (ACAD) from during pregnancy, childhood, adolescence, and throughout the life course
- Governments should prioritise funding of public health strategies for ACAD and a healthy built environment
- Policy is needed to combat the global epidemic of obesity, diabetes, hypertension, and poor diet

Panel 10: Key targets for research in health policy and public education

- Rigorously test new health policies to evaluate efficacy in reducing risk factors, burden of atherosclerotic coronary artery disease (ACAD), and improving ACAD outcomes, including a focus on cost-effectiveness
- Establish the most effective methods using digital technologies and online platforms to engage a wide range of people in diverse economies
- Find optimal ways to engage more people, particularly of diverse representation, to participate in population-based research

Conclusion

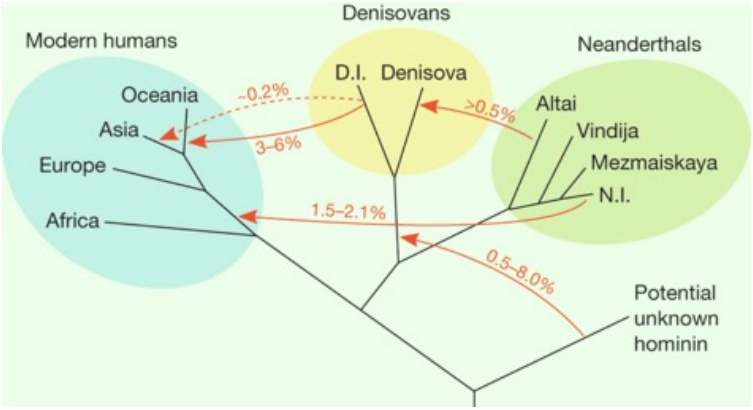
Refocusing and reframing the definition and discussion of coronary artery disease from late-stage ischaemia and acute coronary events to early detection of coronary artery atheroma and prevention of advanced ACAD has the potential to save 8·7 million lives globally every year. Acute coronary syndrome events must be recognised as a failure of upstream care, missed opportunities for early intervention, and should be seen as avoidable consequences of a preventable disease.

The current definition and ICD codes for ischaemic heart disease constrain the ability to devise clinical pathways for early diagnosis, effective prevention, and cure of the disease. We argue that it is necessary to measure and define coronary atherosclerosis at a much earlier stage, when the opportunity to make an impact is greatest. By the time ischaemia and obstruction develop, prevention is no longer possible, and the effectiveness of interventions on morbidity and mortality are greatly reduced.

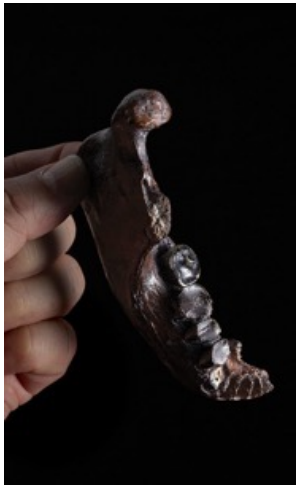
Coronary artery disease must be recognised across all stages of atherosclerosis, from the onset of atheroma through to end-stage disease. Throughout this Commission, we have aimed to redefine the conceptual framework of coronary artery disease—from the traditional model centred on ischaemia to a continuous disease with multiple stages throughout the life course. The disease begins with precursor features even in utero, which can develop through to childhood and adolescence, progressing as individuals age. Only after redefining coronary artery disease as ACAD can data based on this new definition be collected and used to inform future advances in health care.

Strategies must be developed to prevent the onset of atherosclerosis, diagnose the disease early, and improve the implementation of known effective strategies for those who have already developed the disease. Achieving these goals, and ensuring the delivery of global and equitable care, will require investment, training, and development of a workforce focused on early risk factor modification, diagnosis, and prevention of atherosclerosis rather than diagnosis and treatment of cardiovascular events and end-stage disease.

Die Denisova-Menschen waren eine Population der Gattung Homo, die eng verwandt ist mit den Neandertalern und wie diese den anatomisch modernen Menschen (Homo sapiens) nahe steht, jedoch genetisch von beiden Arten unterschieden werden kann. In der englischsprachigen Fachliteratur werden sie Denisova hominins oder kurz Denisovans genannt



Series/ Epoch	Stage/ Age	millions of years ago
Anthropocene[1]		1950 CE
Holocene		0.0117
Pleistocene	Upper	0.126
	Middle	0.781
	Calabrian	1.806
	Gelasian	2.588



PALEOANTHROPOLOGY

A subtropical Denisovan

Denisovans are a Pleistocene hominin lineage first identified genomically and known from only a few fossils. Although genomic studies suggest that they were widespread throughout Asia, fossils of this group have thus far only been identified from regions with cold climates, Siberia and Tibet. Tsutaya *et al.* used ancient proteomic analysis on a previously unidentified hominin mandible from Taiwan and identified it as having belonged to a male Denisovan. This identification confirms previous genomic predictions of the group's widespread occurrence, including in warmer climates. The robust nature of this mandible is similar to that seen in a Denisovan mandible from Tibet, suggesting that this is a consistent trait for the lineage. —Sacha Vignieri

A male Denisovan mandible from Pleistocene Taiwan

Denisovans are an extinct hominin group defined by ancient genomes of Middle to Late Pleistocene fossils from southern Siberia. Although genomic evidence suggests their widespread distribution throughout eastern Asia and possibly Oceania, so far only a few fossils from the Altai and Tibet are confidently identified molecularly as Denisovan. We identified a hominin mandible (Penghu 1) from Taiwan (10,000 to 70,000 years ago or 130,000 to 190,000 years ago) as belonging to a male Denisovan by applying ancient protein analysis. We retrieved 4241 amino acid residues and identified two Denisovan-specific variants. The increased fossil sample of Denisovans demonstrates their wider distribution, including warm and humid regions, as well as their shared distinct robust dentognathic traits that markedly contrast with their sister group, Neanderthals.

Retrieved proteome sequences

Before processing Penghu 1, we optimized sample preparation methods using two faunal specimens from the same locality to minimize damage to Penghu 1 (supplementary text S1). Endogenous proteins were successfully retrieved from ~5 mg each of faunal bone, dentine, and enamel. Mandibular bone and dental enamel were identified as the most promising tissues for extraction, with richer and better preserved protein profiles. We tested 13 different protein extraction and digestion options through 44 measurement sessions using liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS). On the basis of the results obtained from the analysis of the faunal specimens, we processed Penghu 1 by combining (i) a digestion-free approach and (ii) workflows that included digestion with three different endoproteases, without removing the demineralizing agent.

Penghu 1 belonged to a Denisovan

Among the 4241 amino acid residues from the 51 proteins recovered in Penghu 1, five sites of variation from five proteins were Denisovanspecific or phylogenetically relevant variations.

Two derived amino acid sequence variants associated with Denisovans were identified in ameloblastin (AMBN; M273V) and collagen α-2(I) chain (COL1A2; R996K) of Penghu 1, with depths of 17 and 28 peptides, respectively. Both AMBN and COL1A2 had substantial sequence coverage in our dataset for Penghu 1 (35.8 and 67.7% respectively). The Denisovan-type variant of AMBN (M273V) has less than 1% frequency for the corresponding single-nucleotide polymorphism (SNP) allele (rs564905233) in most modern human populations but has a frequency of 21.22% (*n* = 104) in the Philippines. Genetic evidence suggests that the Philippines is one of the regions of Denisovan introgression. The derived variant of COL1A2 (R996K) has so far been found only in Penghu 1, Xiahe 1, Xiahe 2, and Denisova 3.

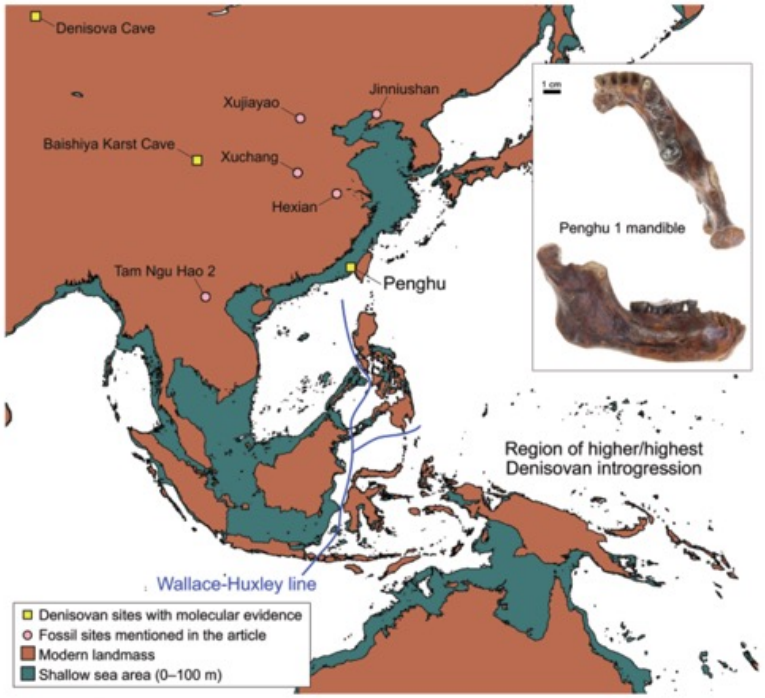


Fig. 1. Map showing the distribution of known, molecularly determined Denisovan fossils and photos of Penghu 1. Fossil sites are also shown. (Inset) Photos of Penghu 1 show the (top) superior and (bottom) right lateral views. [Photos by Y.K. and C.-H.C.]

Table 1. Amino acid residues related to taxon-specific variation among hominins. The numbers of peptides that cover the position with good quality in Penghu 1 are shown. The corresponding residues in other Denisovans, the residues and the number of sequenced Neanderthal individuals with the coverage of the position, variants that can be seen in modern human SNP databases, and the corresponding residues in apes are also shown. Dashes indicate the sequence for that residue has not been obtained.

Protein	Uniprot accession	Position	Number of peptides	Penghu 1 proteome	Xiahe 1 proteome	Xiahe 2 proteome	Denisova 3 genome	Neanderthal genomes	Human genomes	Ape genomes
AMBN	Q9NP70	273	17	V	–	–	V	M (*n* = 8)	M, (V)	M
COL1A2	P08123	996	28	K	K	K	K	R (*n* = 7)	R	R
COL2A1	P02458	583	1	E	G	E	E	E (*n* = 7)	E	E
COL5A2	P05997	1211	6/2	V/E	–	–	E	E (*n* = 7)	E	E
COL11A1	P12107	1535	2/1	S/(P)	–	–	P	P (*n* = 6)	S, P	P

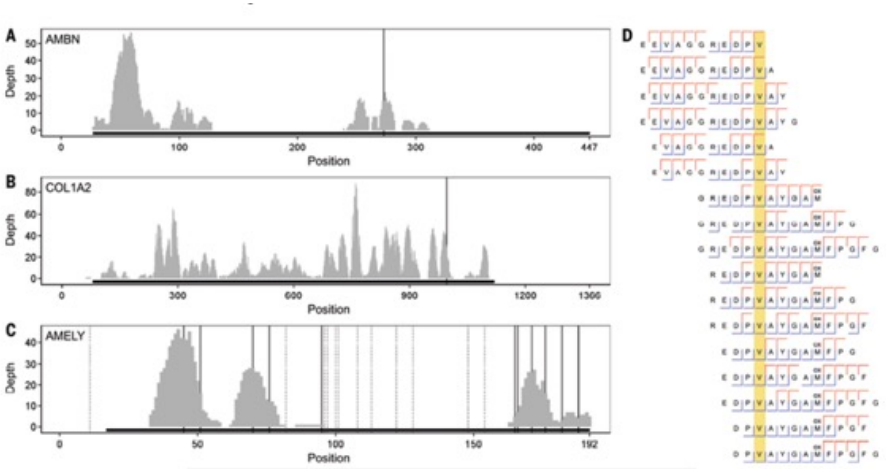


Fig. 2. Details of the Denisovan-specific and male-specific peptides identified from Penghu 1. (**A** to **C**) The depth and amino acid coverage of (A) AMBN, (B) COL1A2, and (C) AMELY identified from Penghu 1, based on manually validated peptide counts. The regions of the mature protein without the signal sequence and propeptide are indicated with the black solid bars under the histograms. Positions with Denisovan-specific variants in AMBN and COL1A2, and male-specific variants in AMELY, covered in Penghu 1, are indicated with vertical solid lines. Uncovered positions with male-specific amino acid residues are indicated with vertical dotted lines in AMELY. Only AMELY-specific peptides are shown in (C); including peptides shared with AMELX would further improve coverage to 100% for amelogenin (table S19 and fig. S21). (**D**) Supporting peptides of the Denisovan-specific residue (M273V) in AMBN, aligned and highlighted for the subject position. The numbers of each annotated y- and b-ion are provided in fig. S12. Single-letter abbreviations for the amino acid residues are as follows: E, Glu; G, Gly; K, Lys; M, Met; P, Pro; R, Arg; S, Ser; and V, Val. In the variants, other amino acids were substituted at certain locations; for example, M273V indicates that methionine at position 273 was replaced by valine.

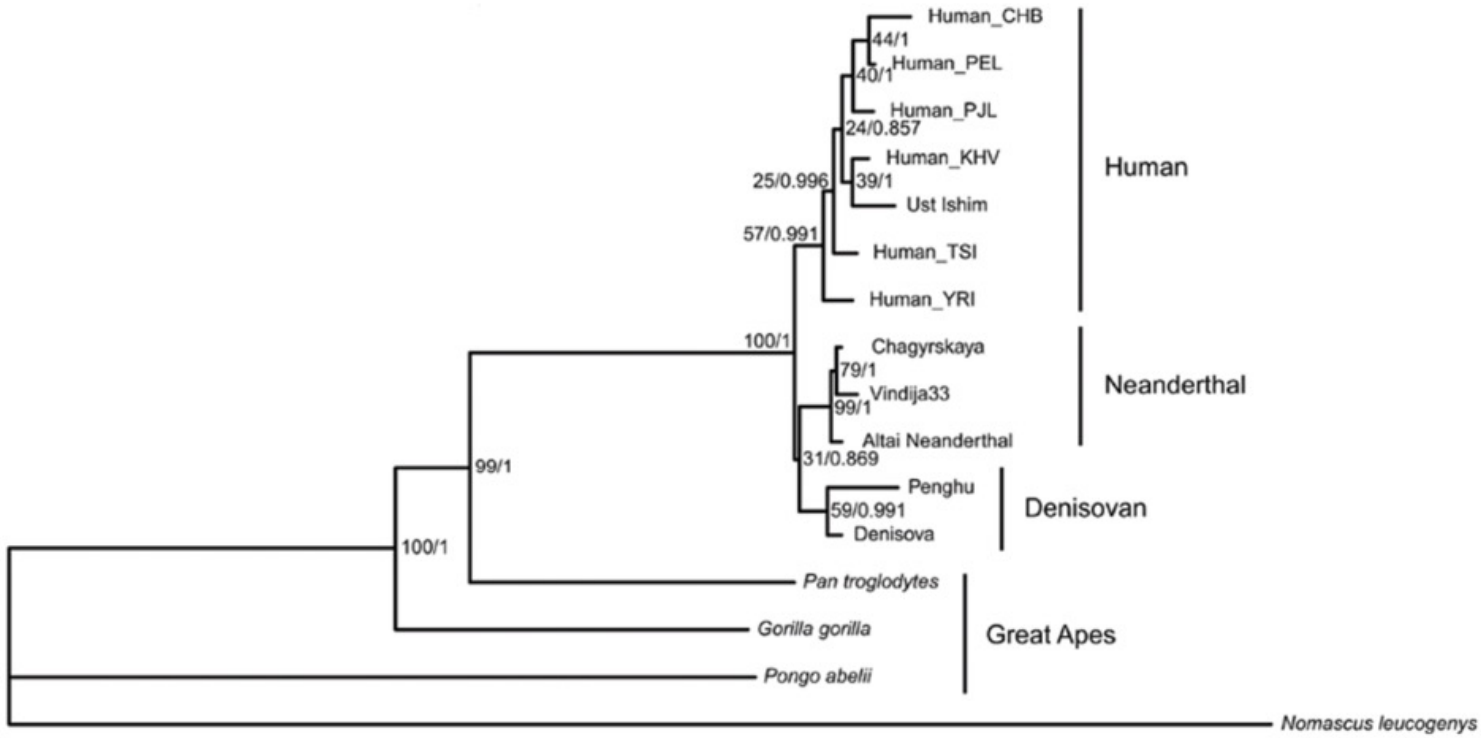


Fig. 3. Phylogenetic tree constructed from a total of 3318 amino acid positions of 22 proteins by using maximum likelihood and Bayesian models. Node values indicate maximum likelihood (0 to 100%) by use of iqtree2 and Bayesian probability (0 to 1) by use of BEAST, respectively.

Discussion

The high-quality palaeoproteomic data obtained from Penghu 1, enabled by relatively good fossil preservation and optimized protein extraction methods, indicates that Penghu 1 belonged to a male Denisovan. Two diagnostic positions in the Denisovan variant of AMBN and COL1A2 were covered with more than 19 peptides. The Denisovan-related variant of AMBN adds additional support to our arguments because this position was not observed in previous proteomic studies of Denisovan specimens or tentative Denisovan specimens. Because proteome composition varies among tissues, and the occurrence of variations in protein sequences is lower than in DNA, even two phylogenetically informative residues generally provide confident support. Phylogenetic trees constructed by using two different methods both indicated that Penghu 1 clustered with Denisova 3. Additionally, 11 AMELY specific positions were covered with amaximum depth of 44 peptides in Penghu 1, indicating that the specimen is a male.

These findings provide insights into the Middle to Late Pleistocene archaic hominins in continental eastern Asia. First, Penghu 1 expands the known geographic range of Denisovans with direct molecular evidence. Penghu is located ~4000 km southeast of Denisova Cave and ~2000 km southeast of Xiahe. The identification of Penghu 1 as a Denisovan mandible confirms the inference from modern human genomic studies that Denisovans were widely distributed in eastern Asia. The presence of Denisovans in diverse geographical and climatic zones—from a continental climate with long, cold winters (Denisova Cave; 51°N); to an alpine subarctic climate associated with a high altitude (3280 m above sea level) (Xiahe; 35°N); to the warmer, more humid climate of a low latitude (Penghu: 23°N)—demonstrates their adaptational flexibility. Although the palaeoclimate of Taiwan during glacial periods of low sea levels was colder than today, previous elemental analysis showed a roughly contemporaneous occurrence of water buffalo (*Bubalus*) with Penghu 1. *Bubalus* is a representative animal of present-day Southeast Asia, implying a contrasting environment with southern Siberia and Tibet. Such an environment is compatible with the preferred habitats of Denisovans estimated by recent model simulations.

A PRACTICAL FORESTER
(A subject that had attention all through Mr. Roosevelt's Presidency.)
From the *Pioneer Press* (St. Paul)

During his presidency, Roosevelt issued nearly 10 times more conservation-directed executive orders than any predecessor. Many lands started out as preserves, but were expanded by later presidents and made into national forests.

A cornerstone of his actions focused on the issue of conservation, and Roosevelt set aside more national parks and nature preserves than all of his predecessors combined. At the time, Roosevelt's executive action was controversial, and many of his actions were brought before a court.

Trump administration orders half of national forests open for logging

The Trump administration has removed environmental protections covering more than half of the land managed by the U.S. Forest Service as part of the president's aim to significantly bolster the U.S. logging industry.

In a memo issued Thursday, Agriculture Secretary Brooke Rollins said "heavy-handed federal policies" have prevented the United States from making use of its "abundance of timber resources that are more than adequate to meet our domestic timber production needs."

The directive, which established an "Emergency Situation Determination," comes a month after President Donald Trump signed an executive order seeking changes to forest management to increase timber production by 25 percent.

Die CCC-Arbeiter wurden für ein Jahr in work camps untergebracht, erhielten Verpflegung, Unterkunft sowie ein Gehalt von mindestens 30 US-Dollar im Monat, von denen 25 US-Dollar an die Familienangehörigen in der Heimat geschickt werden mussten. Jedes Camp war einer Bundesbehörde zugeordnet, die die Projekte koordinierte. Schwerpunkte lagen im Straßenbau, bei Flussbefestigungen, Aufforstung, der Anlage von Feuerbeobachtungstürmen in Waldgebieten und dem Kampf gegen Waldbrände, touristischen Infrastrukturmaßnahmen in Nationalparks, State Parks und anderen Schutzgebieten und Gedenkstätten, Bewässerungseinrichtungen für die Viehzucht und Trockenlegung von Feuchtgebieten für die Landwirtschaft.