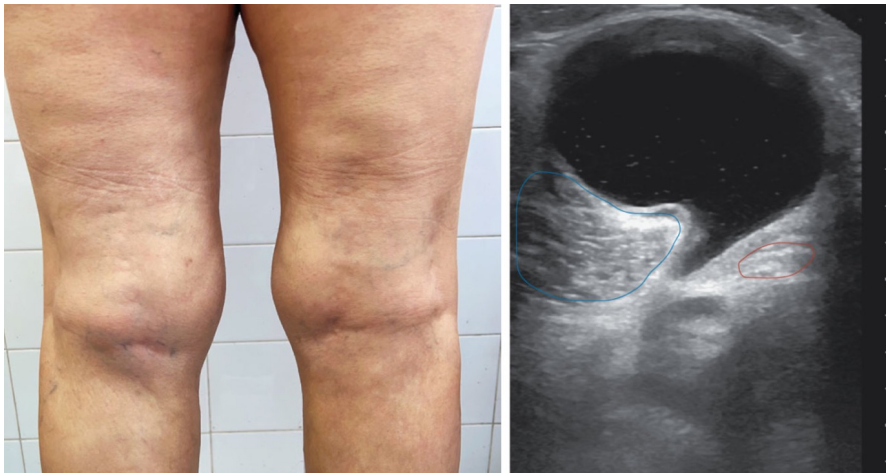
https://www.mdc-berlin.de/de/veroeffentlichungstypen/clinical-journal-club

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 diagnosis of a popliteal synovial cyst — also known as a Baker's cyst — was made. This results when synovial fluid from the knee joint flows into and accumulates in the gastrocnemius–semimembranosus bursa. Baker's cysts are associated with underlying joint disorders, including osteoarthritis, traumatic injury, or inflammatory arthritis (as in this case). Imaging is not always required to make the diagnosis but may help rule out other conditions.

A 63-year-old woman with psoriatic arthritis involving her knees presented for evaluation of 9-months of pain in the left knee. Physical examination was notable for a nontender, palpable mass in the left popliteal fossa. Point-of-care musculoskeletal ultrasonography is shown. What is the most likely diagnosis?

Cruciate ligament cyst

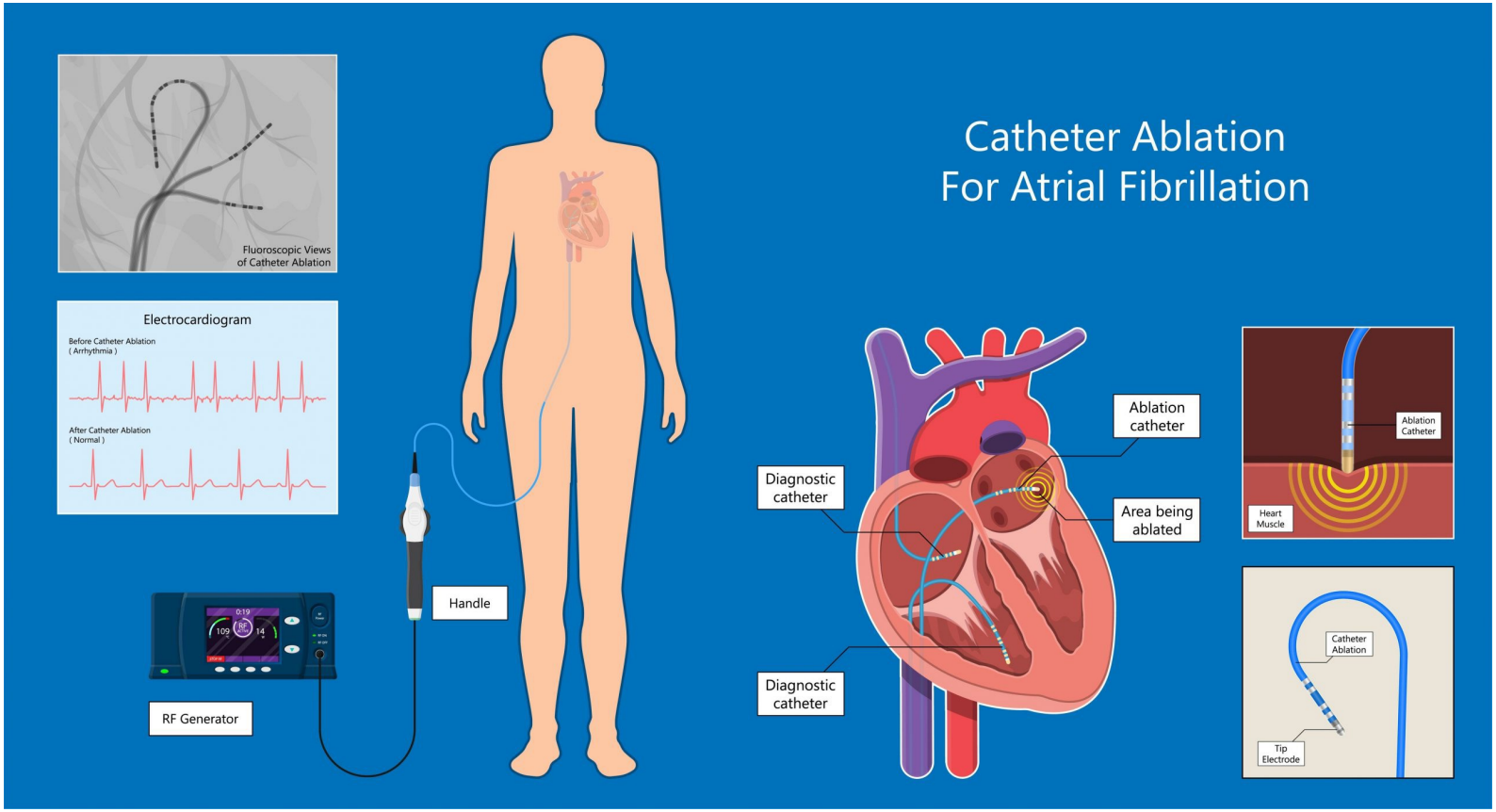
Deep vein thrombosis

Pes anserine bursitis

● Popliteal synovial cyst (Baker's Cyst)

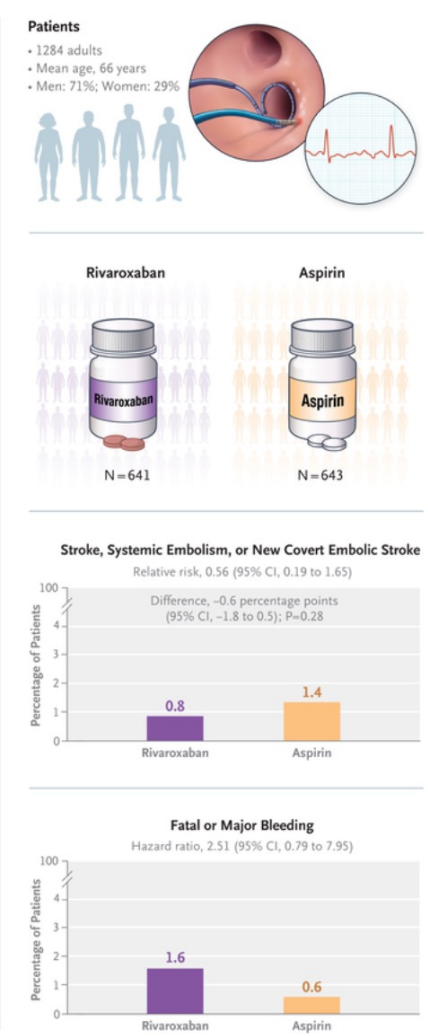
Pseudothrombophlebitis

After atrial fibrillation (AF) ablation, oral anticoagulation (OAC) is typically continued for at least **two months** in all patients to prevent clots due to post-procedure inflammation, with the decision for **long-term OAC** depending on the individual's **stroke risk (CHA2DS2-VASc score)**



Antithrombotic Therapy after Successful Catheter Ablation for Atrial Fibrillation

Whether successful catheter ablation for atrial fibrillation eliminates the need for long-term oral anticoagulant therapy is unknown. We conducted an international, open-label, randomized, blinded-outcome-assessment trial involving 1284 patients who had undergone successful catheter ablation for atrial fibrillation at least 1 year earlier and had a CHA_2DS_2-VASc score (scores range from 0 to 9, with higher scores indicating a higher risk of stroke) of 1 or more (or ≥2 for women or for patients in whom vascular disease was a risk factor). Patients were randomly assigned to receive either aspirin (at a dose of 70 to 120 mg daily, depending on availability in the local jurisdiction) or rivaroxaban (at a dose of 15 mg) and followed for 3 years. Magnetic resonance imaging (MRI) of the head was performed after enrollment and at 3 years. The primary outcome was a composite of stroke, systemic embolism, or new covert embolic stroke (defined by ≥1 new infarct measuring ≥15 mm on MRI) at 3 years.



Catheter ablation is an established therapy for the treatment of atrial fibrillation and is superior to medical therapy in reducing the recurrence and burden of atrial fibrillation. A low burden of atrial fibrillation has been associated with a decreased risk of stroke, but it is unclear whether successful catheter ablation reduces the risk of stroke enough that the risk–benefit ratio does not support the need for oral anticoagulant therapy. Consequently, current guidelines state that anticoagulation should be continued indefinitely after atrial fibrillation ablation on the basis of the patient's stroke risk profile and not the apparent success of the procedure. These recommendations are based on evidence from small, nonrandomized studies.

The risks and benefits of ongoing anticoagulation after successful atrial fibrillation ablation remain unclear. The purpose of this trial was to evaluate whether ongoing anticoagulation with rivaroxaban would be superior to aspirin for the prevention of stroke, systemic embolism, and covert embolic stroke in patients with risk factors for stroke who had undergone successful catheter ablation for atrial fibrillation.

Patients

Eligible patients had undergone successful catheter ablation for nonvalvular atrial fibrillation at least 1 year before enrollment. A successful ablation procedure was defined by no clinical evidence of any atrial arrhythmia and no atrial arrhythmia lasting longer than 30 seconds on at least one 24-hour Holter monitor study between 2 and 6 months after the ablation procedure and on at least one 24-hour Holter monitor study at any time after 6 months after the ablation procedure.

Interventions

Patients were randomly assigned in a 1:1 ratio to receive either aspirin at a dose of 70 to 120 mg daily (depending on availability in the local jurisdiction) or rivaroxaban at a dose of 15 mg daily. Aspirin was chosen because, although it may provide minimal benefit for a reduction in the risk of stroke in patients with atrial fibrillation who have a very low risk of stroke, it may provide greater benefit in patients with a higher stroke risk. Rivaroxaban at a dose of 15 mg has pharmacokinetic properties that are similar to those of the 20-mg dose but with a lower bleeding risk, and the 15-mg dose has been evaluated in other trials.

Outcomes

The primary outcome was a composite of stroke, systemic embolism, or new covert embolic stroke detected by MRI of the head at 3 years. Covert embolic stroke was defined by at least one new cerebral infarct measuring at least 15 mm that was detected between the baseline MRI and the MRI at 3 years.

Characteristic	Rivaroxaban (N=641)	Aspirin (N=643)
Demographics		
Age — yr	66.3±7.1	66.3±7.6
Male sex — no. (%)	458 (71.5)	459 (71.4)
Atrial fibrillation history		
Median time since first atrial fibrillation ablation (IQR) — mo	19.3 (13.9–35.7)	19.3 (14.2–31.3)
Median time since most recent atrial fibrillation ablation (IQR) — mo	16.4 (13.4–25.2)	16.5 (13.6–25.2)
Total no. of ablations for atrial fibrillation or atrial tachyarrhythmia — no. (%)		
1	484 (75.5)	504 (78.4)
2	133 (20.7)	105 (16.3)
≥3	24 (3.7)	34 (5.3)
Type of atrial fibrillation — no. (%)		
Paroxysmal	431 (67.2)	421 (65.5)
Persistent	204 (31.8)	212 (33.0)
Long-standing persistent	6 (0.9)	10 (1.6)
Total HAS-BLED score†	1.4±0.9	1.3±0.8
Coexisting conditions		
Hypertension — (%)	442 (69.0)	434 (67.5)
Diabetes — (%)	96 (15.0)	77 (12.0)
Stroke — (%)		
Ischemic	7 (1.1)	17 (2.6)
Hemorrhagic	0	2 (0.3)
Uncertain	3 (0.5)	6 (0.9)
Transient ischemic attack — (%)	18 (2.8)	25 (3.9)
Coronary artery disease — (%)	74 (11.5)	68 (10.6)
Ischemic cardiomyopathy — (%)	9 (1.4)	6 (0.9)
Nonischemic cardiomyopathy — (%)	15 (2.3)	20 (3.1)
Peripheral vascular disease — (%)	9 (1.4)	9 (1.4)
Clinically significant carotid artery disease — (%)	2 (0.3)	4 (0.6)
CHA_2DS_2-VASc score‡		
Mean	2.2±1.1	2.2±1.1
Distribution — no. (%)		
1	194 (30.3)	196 (30.5)
2	241 (37.6)	243 (37.8)
3	138 (21.5)	127 (19.8)
≥4	68 (10.6)	77 (12.0)
Echocardiography§		
Ejection fraction — %	61.8±7.1	61.5±7.3
Left ventricular function — no. (%)		
Normal	476 (99.2)	453 (97.8)
Abnormal	4 (0.8)	10 (2.2)
Mild impairment	4 (0.8)	6 (1.3)
Moderate impairment	0	3 (0.6)
Severe impairment	0	1 (0.2)
Left atrial diameter — mm¶	40.7±16.0	40.4±19.2

Primary and Secondary Efficacy Outcomes.

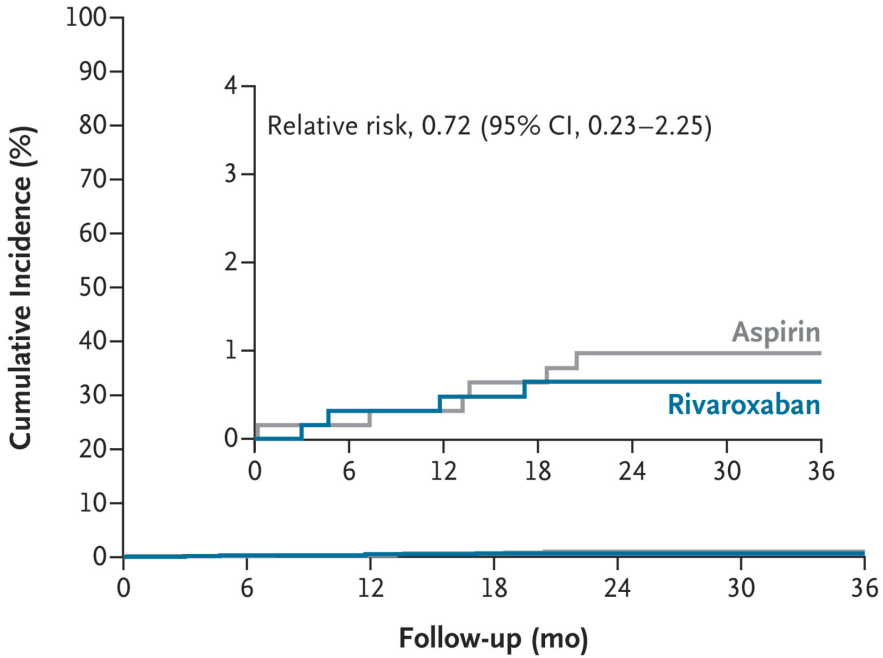
Outcome	Rivaroxaban (N=641)	Aspirin (N=643)	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)†
Primary composite outcome: stroke, systemic embolism, or new covert embolic stroke				
No. of patients (%)	5 (0.8)	9 (1.4)	0.56 (0.19 to 1.65)	−0.6 (−1.8 to 0.5)‡
Annualized rate — events per 100 patient-yr	0.31	0.66	—	—
Components of primary outcome				
All stroke				
No. of patients (%)	5 (0.8)	7 (1.1)	0.72 (0.23 to 2.25)	−0.3 (−1.4 to 0.7)
Annualized rate — events per 100 patient-yr	0.31	0.58	—	—
Systemic embolism				
No. of patients (%)	0	0	—	—
Annualized rate — events per 100 patient-yr	0	0	—	—
New covert embolic stroke				
No. of patients (%)	0	2 (0.3)	0	−0.3 (−0.7 to 0.1)
Annualized rate — events per 100 patient-yr	0	0.08	—	—
Other secondary outcomes				
All stroke or systemic embolism				
No. of patients (%)	5 (0.8)	7 (1.1)	0.72 (0.23 to 2.25)	−0.3 (−1.4 to 0.7)
Annualized rate — events per 100 patient-yr	0.29	0.58	—	—
Transient ischemic attack				
No. of patients (%)	1 (0.2)	5 (0.8)	0.20 (0.02 to 1.71)	−0.6 (−1.4 to 0.1)
Annualized rate — events per 100 patient-yr	0.05	0.26	—	—

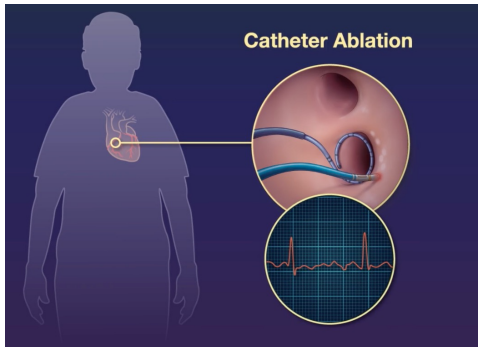
CHADS2 – VASc Score		
C	Congestive Heart Failure	1
H	Hypertension (>140/90 mmHg)	1
A	Age ≥ 75	2
D	Diabetes Mellitus	1
S_2	Prior TIA or stroke	2
V	Vascular disease (MI, aortic plaque etc)	1
A	Age 65-74	1
Sc	Sex category (Female = 1 pt)	1

Endpoint and Safety are both P=NS

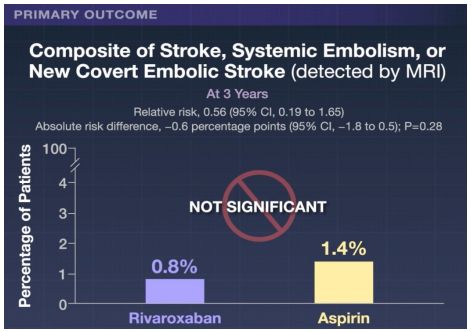
Safety Outcomes.

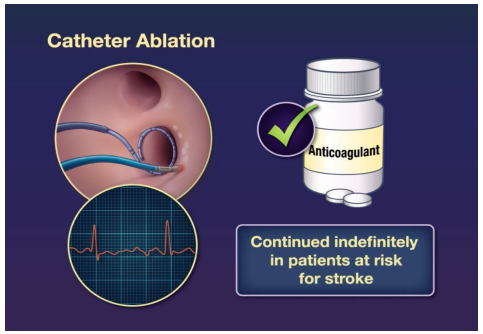
Outcome	Rivaroxaban (N=641)	Aspirin (N=643)	Hazard Ratio (95% CI)
	no. of patients (%)		
Primary composite safety outcome: fatal bleeding or major bleeding	10 (1.6)	4 (0.6)	2.51 (0.79–7.95)
Secondary safety outcomes			
Fatal bleeding	0	0	—
Major bleeding	10 (1.6)	4 (0.6)	2.51 (0.79–7.95)
Intracranial bleeding	5 (0.8)	1 (0.2)	5.02 (0.59–42.81)
Gastrointestinal bleeding	3 (0.5)	2 (0.3)	1.50 (0.25–8.97)
Other major bleeding	2 (0.3)	1 (0.2)	2.01 (0.18–22.07)
Minor bleeding	74 (11.5)	20 (3.1)	3.71 (2.29–6.01)
Clinically relevant nonmajor bleeding	35 (5.5)	10 (1.6)	3.51 (1.75–7.03)
Composite of major bleeding or minor bleeding	83 (12.9)	23 (3.6)	3.62 (2.31–5.67)
Death from any cause	10 (1.6)	7 (1.1)	1.43 (0.55–3.74)

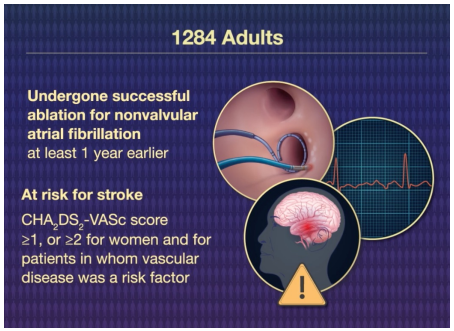


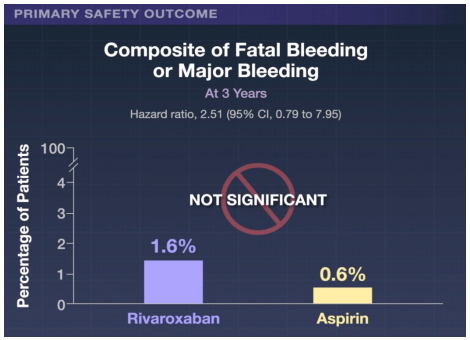

Catheter Ablation


Rivaroxaban
?
Aspirin
Prevention of adverse events in this population

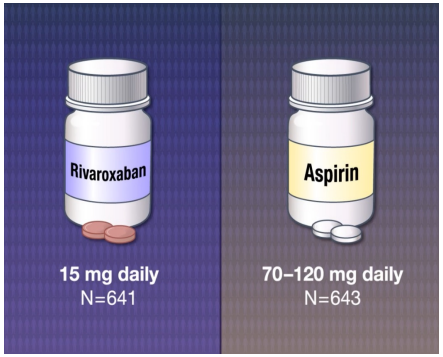

PRIMARY OUTCOME
Composite of Stroke, Systemic Embolism, or New Covert Embolic Stroke (detected by MRI)
At 3 Years
Relative risk, 0.56 (95% CI, 0.19 to 1.65)
Absolute risk difference, −0.6 percentage points (95% CI, −1.8 to 0.5); P=0.28
Percentage of Patients
100
4
3
2
1
0
NOT SIGNIFICANT
0.8%
1.4%
Rivaroxaban
Aspirin

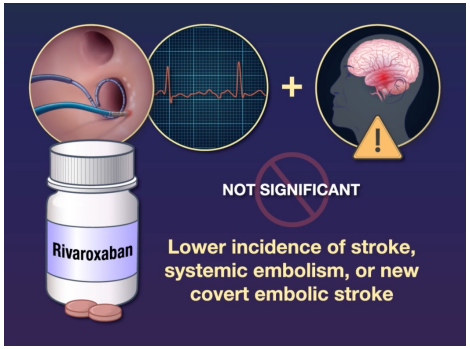

Catheter Ablation
Anticoagulant
Continued indefinitely in patients at risk for stroke


1284 Adults
Undergone successful ablation for nonvalvular atrial fibrillation
at least 1 year earlier
At risk for stroke
CHA2DS2-VASc score ≥1, or ≥2 for women and for patients in whom vascular disease was a risk factor
!

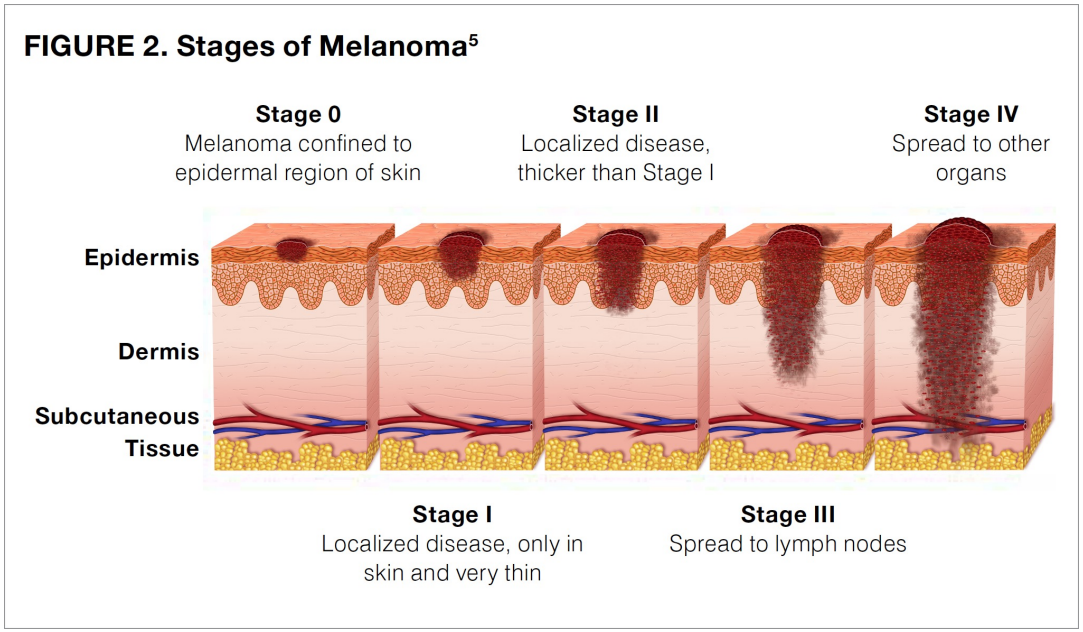

PRIMARY SAFETY OUTCOME
Composite of Fatal Bleeding or Major Bleeding
At 3 Years
Hazard ratio, 2.51 (95% CI, 0.79 to 7.95)
Percentage of Patients
100
4
3
2
1
0
NOT SIGNIFICANT
1.6%
0.6%
Rivaroxaban
Aspirin

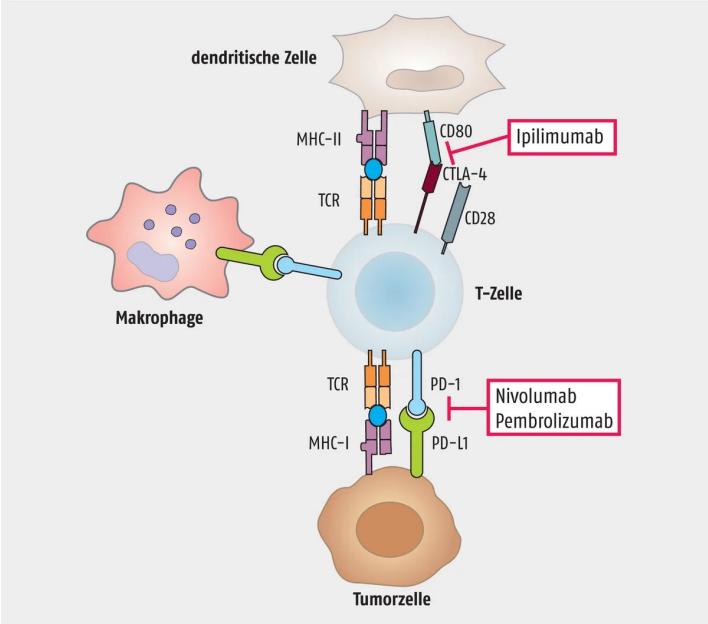

Catheter Ablation
Anticoagulant
STUDY
STUDY
?


Rivaroxaban
Aspirin
15 mg daily
N=641
70–120 mg daily
N=643


+
!
NOT SIGNIFICANT
Rivaroxaban
Lower incidence of stroke, systemic embolism, or new covert embolic stroke

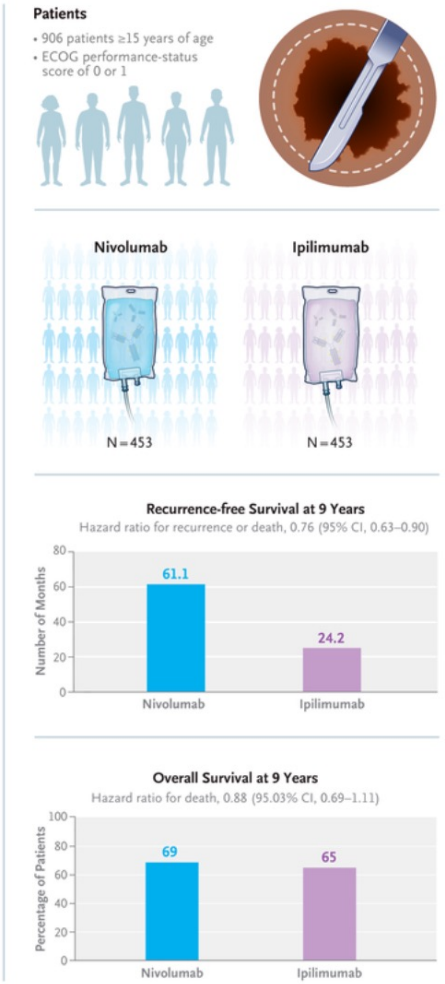
Melanoma and Checkpoint inhibition





Nivolumab for Resected Stage III or IV Melanoma at 9 Years

In the CheckMate 238 trial, patients with resected stage IIIB–C or stage IV melanoma who were treated with nivolumab had longer recurrence-free survival than those who received ipilimumab. Data were needed on longer-term survival. We randomly assigned patients in a 1:1 ratio to receive an intravenous infusion of nivolumab (at a dose of 3 mg per kilogram of body weight every 2 weeks) or ipilimumab (at a dose of 10 mg per kilogram every 3 weeks for four doses, then every 12 weeks) for up to 1 year or until disease recurrence or the occurrence of unacceptable toxic effects. Randomization was stratified according to disease stage and status with respect to programmed cell death ligand 1. The primary end point was recurrence-free survival; secondary end points included overall and distant metastasis–free survival and safety.



Adjuvant systemic treatment of patients with high-risk resectable stage III or IV melanoma with nivolumab, pembrolizumab, ipilimumab, or dabrafenib plus trametinib in patients with *BRAF* mutations has improved recurrence-free survival and is now a recommended standard of care. Data from the primary analysis of the CheckMate 238 trial involving patients with stage IIIB–C or IV resected melanoma showed that adjuvant nivolumab was superior to ipilimumab with respect to recurrence-free survival and distant metastasis–free survival; nivolumab also had a more favorable safety profile. Further analyses showed that longer recurrence-free and distant metastasis–free survival with nivolumab was maintained in most clinically relevant subgroups of patients, particularly in those with either stage IIIB or IIIC disease and regardless of *BRAF* mutational status.

Here, we provide the final results from CheckMate 238, with a minimum follow-up of 9 years, including updated post hoc analyses and a new competing-risk analysis for the probability of death from melanoma. In addition, we evaluated the effect of the timing of drug administration on survival and safety on the basis of evidence suggesting that circadian timing can have an effect on the efficacy of immunotherapy.

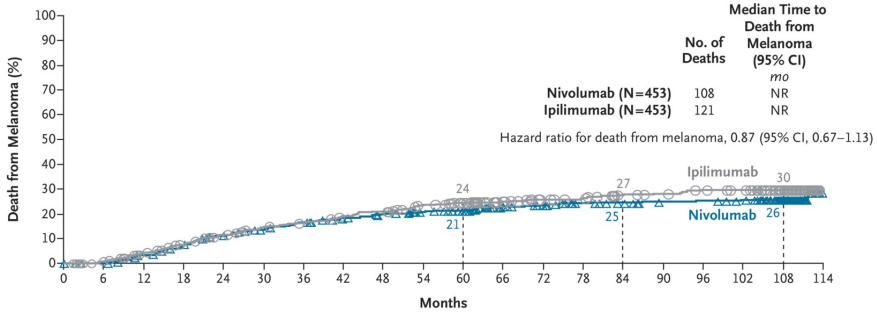
End Points and Assessments

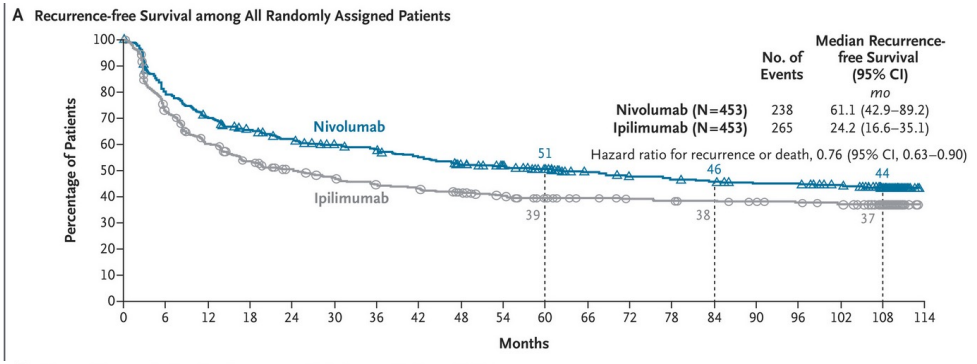
The primary end point was recurrence-free survival in the intention-to-treat population. According to an amendment to the protocol (available with the full text of this article at NEJM.org), follow-up was extended beyond 5 years, but surveillance scans were not required after 60 months; recurrence-free survival beyond the 60-month database lock was assessed by means of investigator reports of disease recurrence or a new primary lesion. For patients who did not have disease recurrence or a new primary lesion or did not start subsequent therapy, data regarding recurrence-free survival were censored at their last follow-up visit.

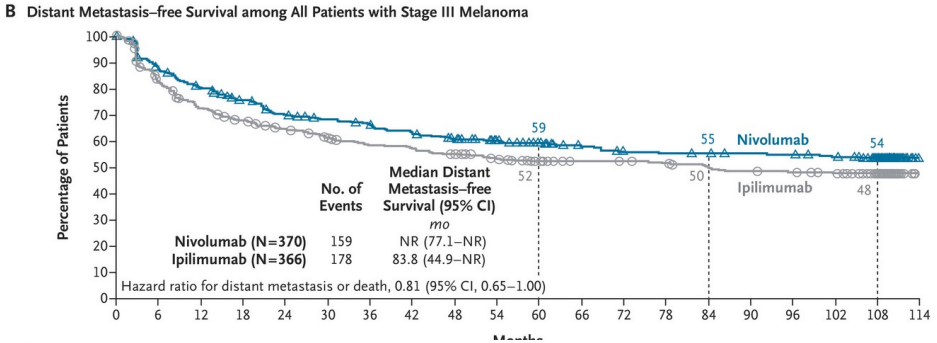
Follow-up was extended beyond 5 years, but surveillance scans were not required after 60 months; recurrence-free survival beyond the 60-month database lock was assessed according to the investigator report of disease recurrence or a new primary lesion. Confirmation questions about the absence of new recurrence were added to the survival follow-up case-report form after the 60-month follow-up period. For patients who did not have disease recurrence or a new primary lesion or did not start subsequent therapy, data regarding recurrence-free survival were censored at their last follow-up visit.

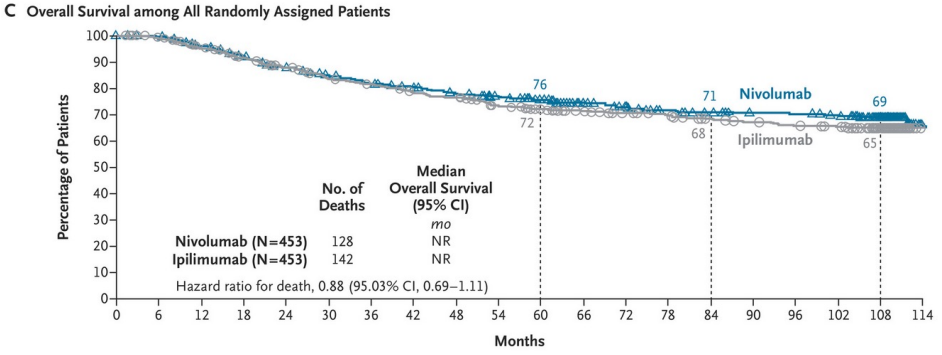
Subsequent Therapy.

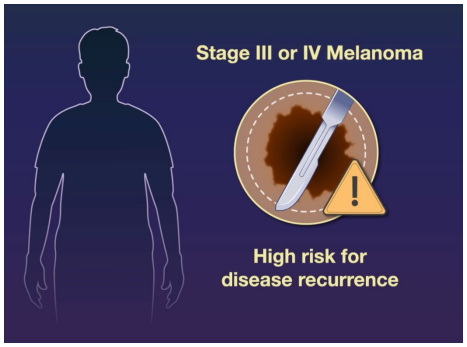
Variable	Nivolumab (N=453)	Ipilimumab (N=453)
	number (percent)	
Patients with recurrence	232 (51.2)	250 (55.2)
Patients who received any subsequent therapy	205 (45.3)	230 (50.8)
Radiotherapy	42 (9.3)	48 (10.6)
Surgery	102 (22.5)	89 (19.6)
Systemic therapy	169 (37.3)	202 (44.6)
Immunotherapy	120 (26.5)	167 (36.9)
Nivolumab†	64 (14.1)	85 (18.8)
Pembrolizumab	35 (7.7)	93 (20.5)
Ipilimumab†	77 (17.0)	36 (7.9)
BRAF inhibitor‡	72 (15.9)	71 (15.7)
MEK or NRAS inhibitor‡	66 (14.6)	76 (16.8)
Experimental drug	19 (4.2)	20 (4.4)
Chemotherapy	48 (10.6)	56 (12.4)

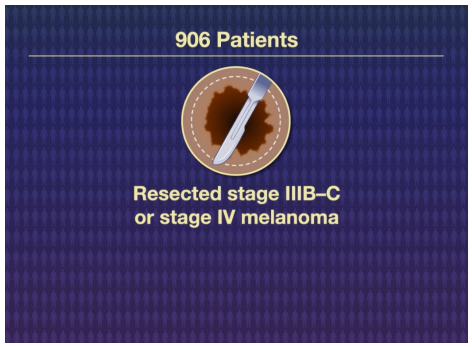


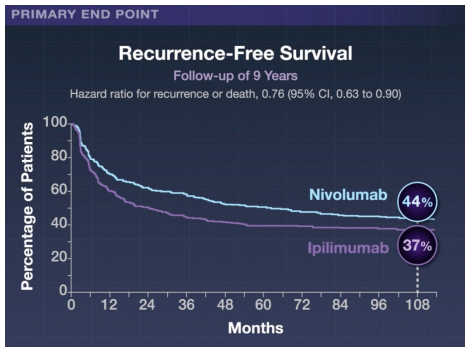




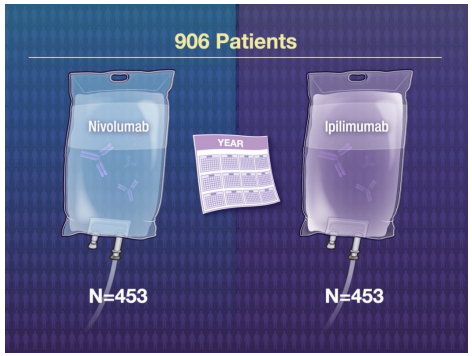


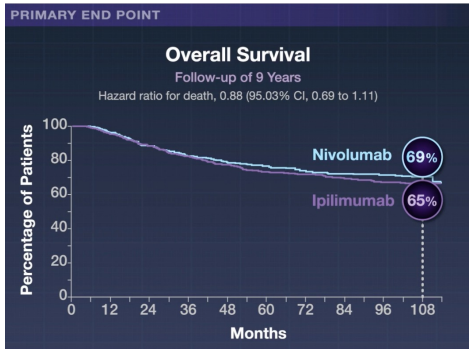

Stage III or IV Melanoma
High risk for disease recurrence

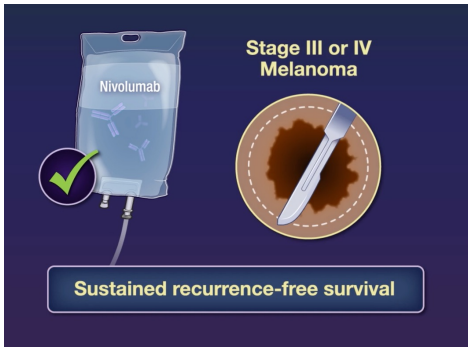

906 Patients
Resected stage IIIB–C or stage IV melanoma


PRIMARY END POINT
Recurrence-Free Survival
Follow-up of 9 Years
Hazard ratio for recurrence or death, 0.76 (95% CI, 0.63 to 0.90)
Percentage of Patients
Nivolumab
44%
Ipilimumab
37%
Months

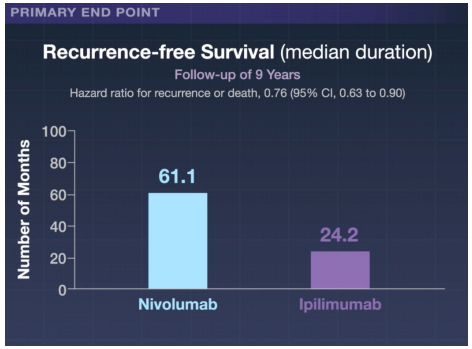

Nivolumab
CheckMate 238 Trial
Ipilimumab
Longer recurrence-free survival


906 Patients
Nivolumab
YEAR
Ipilimumab
N=453
N=453


PRIMARY END POINT
Overall Survival
Follow-up of 9 Years
Hazard ratio for death, 0.88 (95.03% CI, 0.69 to 1.11)
Percentage of Patients
Nivolumab
69%
Ipilimumab
65%
Months

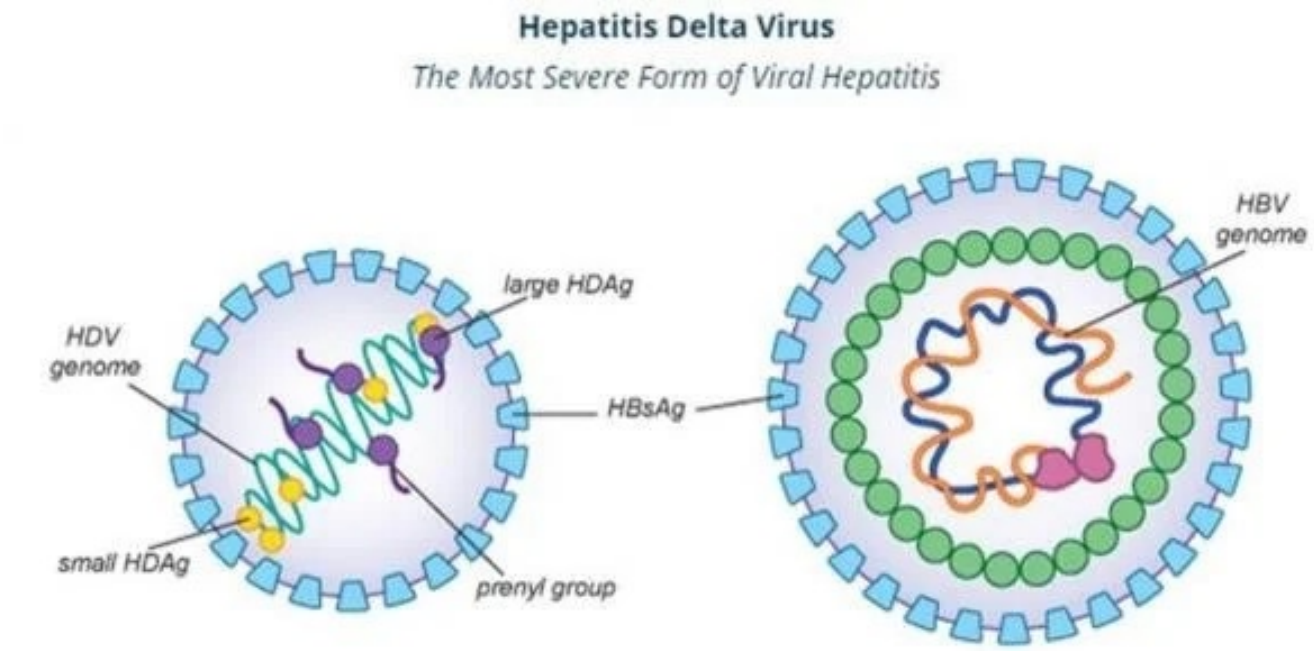

Nivolumab
Stage III or IV Melanoma
Sustained recurrence-free survival


Nivolumab
CheckMate 238 Trial
Ipilimumab
Longer-term follow-up was needed to assess survival outcomes


PRIMARY END POINT
Recurrence-free Survival (median duration)
Follow-up of 9 Years
Hazard ratio for recurrence or death, 0.76 (95% CI, 0.63 to 0.90)
Number of Months
61.1
24.2
Nivolumab
Ipilimumab

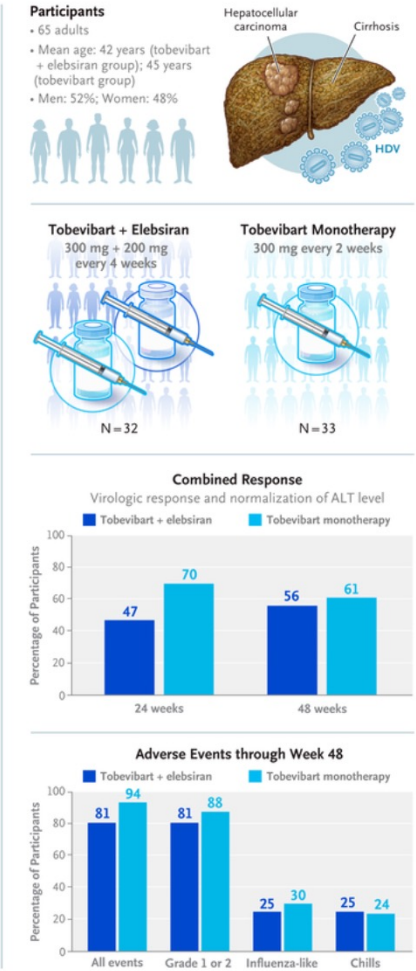

No new late adverse events were reported

Hepatitis D (auch Hepatitis Delta genannt) ist die schwerste Form der chronischen Virushepatitis und betrifft weltweit etwa 15 bis 20 Millionen Menschen. Das Hepatitis-D-Virus (HDV) ist ein unvollständiges RNA-Virus, das für seine Vermehrung zwingend das Oberflächenprotein des **Hepatitis-B-Virus (HBV)** benötigt. Eine Infektion kann daher nur gemeinsam mit oder nach einer bestehenden Hepatitis-B-Infektion auftreten.



A Phase 2 Trial of Tobevibart plus Elebsiran in Hepatitis D

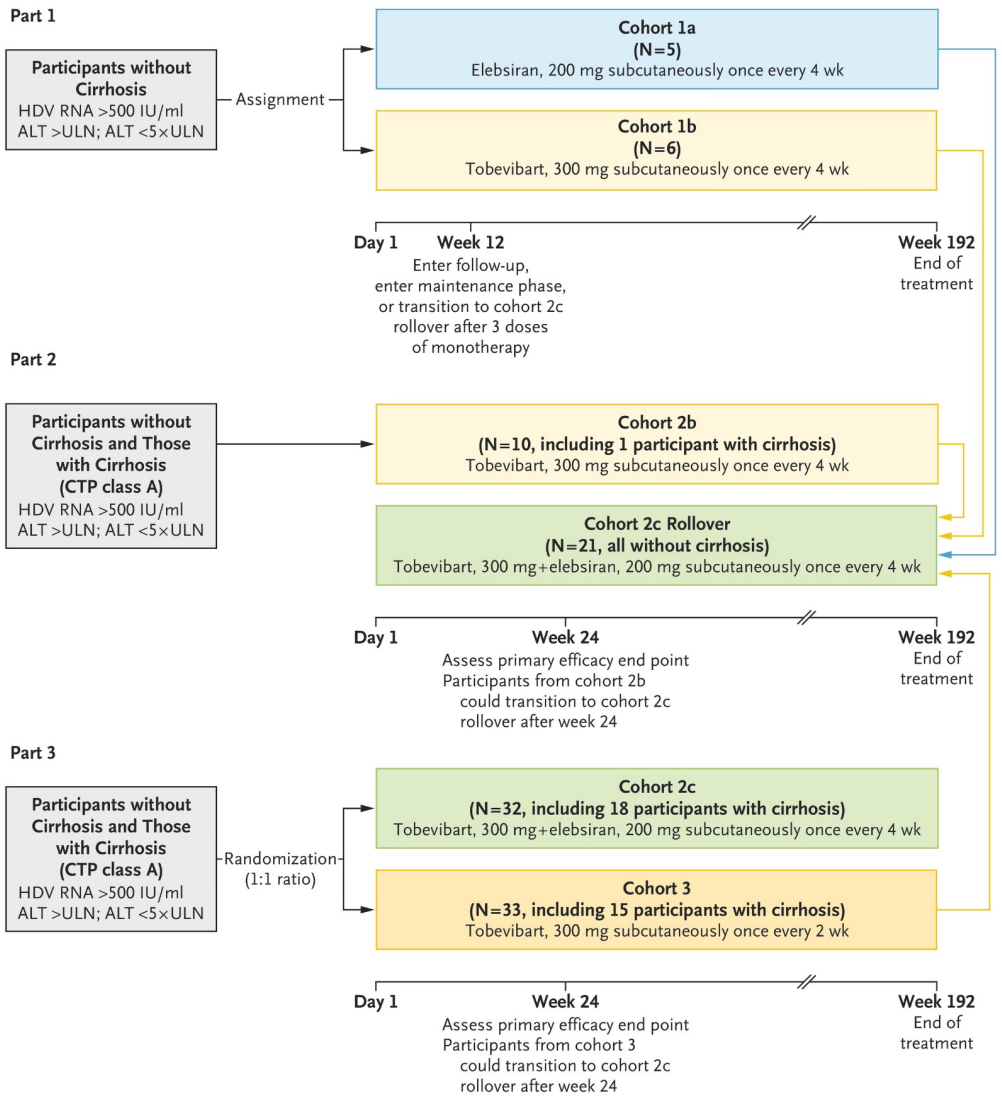
Both tobevibart (a monoclonal antibody) and elebsiran (a small interfering RNA) target hepatitis B virus surface antigen (HBsAg). Their efficacy and safety in the treatment of chronic hepatitis D virus (HDV) infection are unknown. In this ongoing, phase 2, open-label trial, we randomly assigned participants to receive tobevibart plus elebsiran every 4 weeks or tobevibart monotherapy every 2 weeks. The primary end point was a combined response, defined by an HDV RNA level below the limit of detection or a decrease in the HDV RNA level of at least 2 $\log_{10}$ IU per milliliter from baseline (virologic response) and normalization of the alanine aminotransferase (ALT) level, at week 24.



Hepatitis D virus (HDV), also known as hepatitis delta virus, is a satellite RNA virus that requires hepatitis B virus (HBV) surface antigen (HBsAg) for entry and propagation within hepatocytes. Globally, HDV infection affects approximately 12 million persons. Chronic HDV infection, the most severe form of chronic viral hepatitis, is associated with increased risks of cirrhosis, hepatocellular carcinoma, and death and has limited treatment options. Bulevirtide, an entry inhibitor that reduces viral spreading, is available in some regions and is the only agent approved by the European Medicines Agency for long-term treatment of HDV. Finite therapy with pegylated interferon (peginterferon) alfa is recommend in the European Association for the Study of the Liver guidelines; however, it has limited efficacy and is contraindicated in many patients owing to side effects. In the MYR 301 trial, 12% of participants who received bulevirtide at a dose of 2 mg per day had undetectable HDV RNA (also known as target not detected, or TND; no amplification during reverse-transcriptase–polymerase-chain-reaction [RT-PCR] assay) at week 48 despite either an undetectable HDV RNA level or a decrease in the HDV RNA level of at least 2 $\log_{10}$ IU per milliliter in 71% of participants. In addition, bulevirtide requires daily subcutaneous injections, has minimal effect on HBsAg, and is associated with a high risk of relapse after the end of treatment.

Studies of bulevirtide led to an improved understanding of the on-treatment responses associated with long-term control of HDV infection. Findings from these studies suggest that the most relevant goal of therapy is complete viral suppression, as indicated by undetectable HDV RNA.

Tobevibart and elebsiran have complementary mechanisms of action. Tobevibart is a broadly neutralizing anti-HBsAg monoclonal antibody that neutralizes HBV and HDV and blocks viral entry into hepatocytes. Elebsiran is a small interfering RNA (siRNA) that targets HBV messenger RNA and reduces HBsAg production. The ongoing phase 2 SOLSTICE trial is evaluating the efficacy and safety of tobevibart alone or combined with elebsiran for up to 192 weeks in participants with chronic HDV infection. Here, we report results through week 48, a key time point for evaluating HDV therapies.



Overview of Trial Design.

The SOLSTICE trial was conducted in three parts. In **part 1** (cohorts 1a and 1b), participants without cirrhosis (those with liver stiffness of <12 kPa or a liver biopsy showing no cirrhosis [Metavir stage F0 through F3] within 12 months before screening and a platelet count of >150,000 cells per cubic millimeter) were assigned to receive either elebsiran at a dose of 200 mg subcutaneously (cohort 1a) or tobevibart at a dose of 300 mg subcutaneously every 4 weeks (cohort 1b) up t week 12. Participants who did not have a combined response (hepatitis D virus [HDV] RNA level below the limit of detection or a decrease in the HDV RNA level of ≥2 $\log_{10}$ IU per milliliter [virologic response] and normalization of the alanine aminotransferase [ALT] level) at week 12 could transition to tobevibart plus elebsiran (cohort 2c rollover) c enter follow-up. Participants who had a combined response at week 12 could enter a maintenance phase in which the dose of tobevibart or elebsiran monotherapy was reduced to every 8 weeks. In **part 2**, participants without cirrhosis received tobevibart at a dose of 300 mg subcutaneously every 4 weeks (cohort 2b) for up to 192 weeks. Participants without a decrease in the HDV RNA level of at least 1 $\log_{10}$ IU per milliliter at week 24 could transition to tobevibart plus elebsiran (cohort 2c rollover). Cohort 2c rollover is ongoing; the cohort comprises participants receiving tobevibart plus elebsiran who transitioned from any monotherapy cohort. The figure reflects cohort 2c rollover at the week 48 time point of part 3. In **part 3**, participants were randomly assigned in a 1:1 ratio to receive either tobevibart (300 mg) plus elebsiran (200 mg) subcutaneously every 4 weeks (cohort 2c) or tobevibart (300 mg) subcutaneously every 2 weeks (cohort 3). Participants from cohort 3 who did not have a decrease in the HDV RNA level of at least 1 $\log_{10}$ IU per milliliter at week 24 could transition to tobevibart plus elebsiran every 4 weeks (cohort 2c rollover). These cohorts included both participants without cirrhosis and those with compensated cirrhosis (Child–Turcotte–Pugh [CTP] class A; liver stiffness of ≥12 kPa or a liver biopsy showing cirrhosis [Metavir stage F4] within 12 months before screening and a platelet count of >90,000 cells per cubic millimeter). The primary end point was a combined response at week 24. The trial includes an interventional treatment period of up to 192 weeks. Participant replacement was allowed according to the protocol to ensure an adequate sample size for descriptive analysis. Part 3 also includes cohort 5, which includes participants without cirrhosis with a baseline hepatitis B virus surface antigen level of less than 10,000 IU per milliliter and liver stiffness of less than 8 kPa. Participants in this cohort received elebsiran at a dose of 200 mg every 4 weeks up to week 12 and then transitioned to cohort 2c rollover. At the time of this report, not all participants in cohort 5 had completed the three planned doses of elebsiran. ULN denotes upper limit of the normal range.

Assessments

To quantify serum HDV RNA, the RoboGene HDV DNA quantification kit, version 2.0 (Roboscreen Diagnostics), was used on the Roche LightCycler 480 Instrument II after manual RNA extraction with the INSTANT Virus RNA/DNA Kit (Analytik Jena) on a 400-µl sample. The RoboGene assay has a limit of detection of 14 IU per milliliter and a lower limit of quantification of 63 IU per milliliter. An HDV RNA level below the limit of detection or below the lower limit of quantification includes all values below the threshold and undetectable HDV RNA (target not detected, or TND; no amplification during RT-PCR assay). Normalization of the ALT level was defined as an ALT level below the upper limit of the normal range (40 IU per milliliter in men and 33 IU per milliliter in women). HBsAg was measured with the use of the Roche Elecsys HBsAg II assay, with a lower limit of quantification of 0.05 IU per milliliter. Safety assessments included documentation of adverse events (those that emerged or worsened on or after the date of the start of the trial drug up to 30 days after permanent discontinuation of the trial drug), serious adverse events, and clinical laboratory measurements.

End Points

The primary efficacy end point was a combined response, defined by an HDV RNA level below the limit of detection or a decrease in the HDV RNA level of at least 2 $\log_{10}$ IU per milliliter from baseline (virologic response) and normalization of the ALT level, at week 24 in cohort 2c (excluding cohort 2c rollover) and cohort 3. The primary safety end point was the evaluation of adverse events and serious adverse events. Secondary end points included a combined response at weeks 12 and 48 and a virologic response, an HDV RNA level below the limit of detection, an HDV RNA level below the lower limit of quantification, undetectable HDV RNA, and normalization of the ALT level at weeks 12, 24, and 48. Undetectable HDV RNA is highlighted as a key virologic end point in regulatory guidance.[22] The change from baseline in the HBsAg level was an exploratory end point.

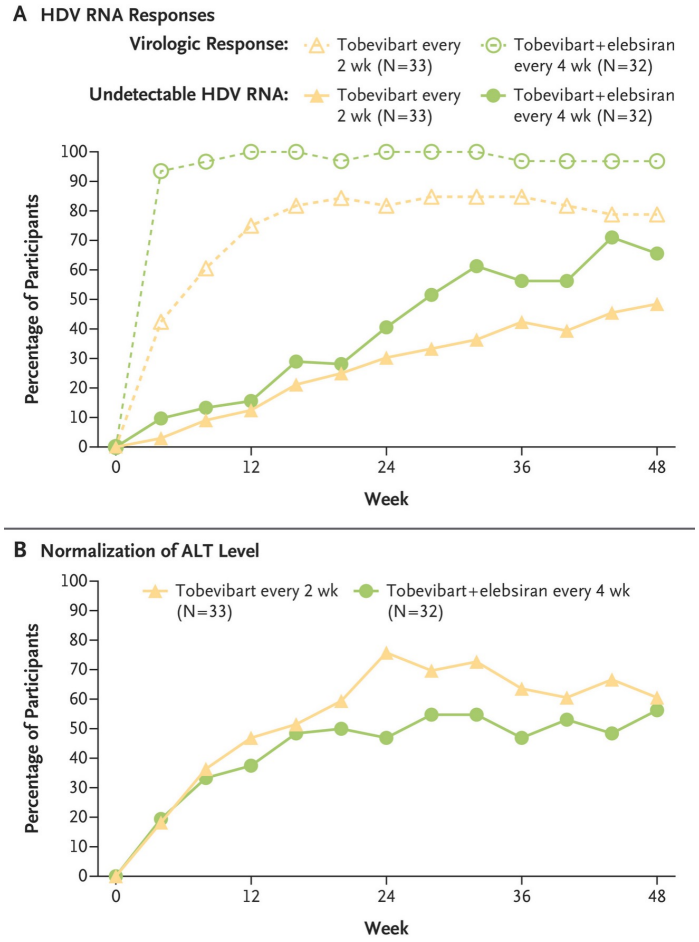
Characteristic	Tobevibart plus Elebsiran Every 4 Wk (N=32)	Tobevibart Every 2 Wk (N=33)
Age — yr	42±8	45±9
Male sex — no. (%)	18 (56)	16 (48)
Race — no. (%)†		
White	25 (78)	28 (85)
Asian	2 (6)	1 (3)
Black	4 (12)	2 (6)
Other	1 (3)	2 (6)
Body-mass index‡		
Mean	27±4	26±4
<30 — no. (%)	26 (81)	26 (79)
Cirrhosis — no. (%)§	18 (56)	15 (45)
Liver stiffness — kPa	13.5±7.3	13.5±8.7
Serum HDV RNA level — $\log_{10}$ IU/ml	5.7±1.2	5.6±1.1
HDV genotype — no. (%)¶		
1	31 (97)	32 (97)
5	1 (3)	1 (3)
HBeAg not detected — no. (%)	29 (91)	25 (76)
Serum HBsAg level — $\log_{10}$ IU/ml	3.7±0.6	3.7±0.8
Serum HBV DNA level — $\log_{10}$ IU/ml	0.7±0.7	0.7±0.8
ALT level — U/liter	83±47	76±59
Concomitant NA therapy — no. (%)	32 (100)	33 (100)
Tenofovir disoproxil fumarate	10 (31)	9 (27)
Tenofovir disoproxil	11 (34)	12 (36)
Entecavir	11 (34)	13 (39)
Previously exposed to agent with HDV activity — no. (%)	17 (53)	18 (55)
Interferon alfa	16 (50)	14 (42)
Bulevirtide	4 (12)	6 (18)
Lonafarnib	2 (6)	3 (9)
Other	2 (6)	1 (3)

Primary and Key Secondary End Points.

Response	Week 24		Week 48	
	Tobevibart plus Elebsiran Every 4 Wk (N=32)	Tobevibart Every 2 Wk (N=33)	Tobevibart plus Elebsiran Every 4 Wk (N=32)	Tobevibart Every 2 Wk (N=33)
Combined response†				
No. of participants	15	23	18	20
Percentage of participants (95% CI)	47 (29–65)	70 (51–84)	56 (38–74)	61 (42–77)
According to cirrhosis status — no./total no. (%)				
Present	8/18 (44)	10/15 (67)	10/18 (56)	10/15 (67)
Absent	7/14 (50)	13/18 (72)	8/14 (57)	10/18 (56)
Undetectable HDV RNA‡				
No. of participants	13	10	21	16
Percentage of participants (95% CI)	41 (24–59)	30 (16–49)	66 (47–81)	48 (31–67)
According to cirrhosis status — no./total no. (%)				
Present	9/18 (50)	4/15 (27)	13/18 (72)	6/15 (40)
Absent	4/14 (29)	6/18 (33)	8/14 (57)	10/18 (56)
HDV RNA level below LOD or decrease of ≥2 $\log_{10}$ IU/ml from baseline				
No. of participants	32	27	31	26
Percentage of participants (95% CI)	100 (89–100)	82 (65–93)	97 (84–100)	79 (61–91)
According to cirrhosis status — no./total no. (%)				
Present	18/18 (100)	13/15 (87)	17/18 (94)	12/15 (80)
Absent	14/14 (100)	14/18 (78)	14/14 (100)	14/18 (78)
Normalization of ALT level				
No. of participants	15	25	18	20
Percentage of participants (95% CI)	47 (29–65)	76 (58–89)	56 (38–74)	61 (42–77)
According to cirrhosis status — no./total no. (%)				
Present	8/18 (44)	10/15 (67)	10/18 (56)	10/15 (67)
Absent	7/14 (50)	15/18 (83)	8/14 (57)	10/18 (56)
HBsAg level <10 IU/ml				
No. (%)	28 (88)	7 (21)	29 (91)	7 (21)
According to cirrhosis status — no./total no. (%)				
Present	14/18 (78)	4/15 (27)	15/18 (83)	4/15 (27)
Absent	14/14 (100)	3/18 (17)	14/14 (100)	3/18 (17)

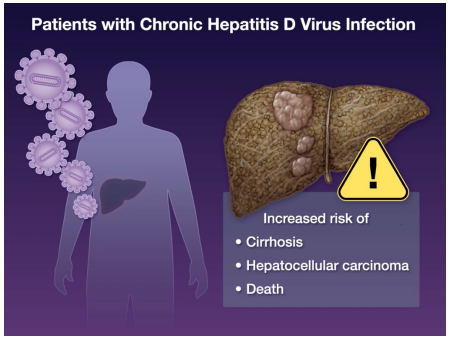
Summary of Safety Assessments in Participants through Week 48.

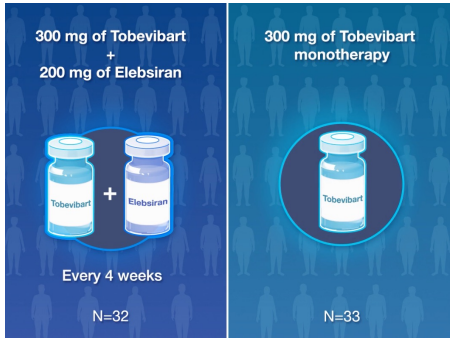
Event	Tobevibart plus Elebsiran Every 4 Wk (N=32)	Tobevibart Every 2 Wk (N=33)
	no. of participants (%)	
Any adverse event	26 (81)	31 (94)
Grade 1 or 2: mild or moderate	26 (81)	29 (88)
Grade 3: severe	0	1 (3)†
Grade 4: life-threatening	0	1 (3)‡
Adverse events in >10% of participants in either group		
Chills	8 (25)	8 (24)
Influenza-like illness	8 (25)	10 (30)
Pyrexia	7 (22)	3 (9)
Headache	6 (19)	7 (21)
Fatigue	2 (6)	4 (12)
Myalgia	2 (6)	8 (24)
Dizziness	1 (3)	4 (12)
Nausea	1 (3)	4 (12)
Treatment-related adverse event	23 (72)	26 (79)
Related to elebsiran	22 (69)	—
Related to tobevibart	22 (69)	25 (76)
Any serious adverse event	0	1 (3)†
Influenza-like symptoms§	22 (69)	24 (73)
Injection-site reaction	3 (9)	1 (3)
Adverse event leading to interruption of trial drug	0	1 (3)
Adverse event leading to discontinuation of trial drug	0	3 (9)†¶
Adverse event leading to death	0	0
Grade 3 or 4 laboratory abnormalities: neutrophil count <1000/mm^3	3 (9)	5 (15)

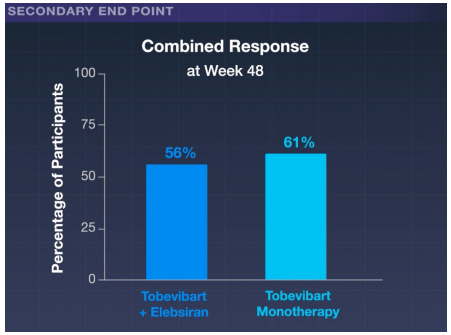


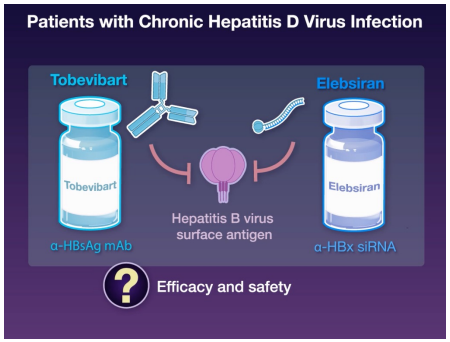
HDV RNA Responses and Normalization of ALT Level over Time among Participants Who Received Tobevibart plus Elebsiran or Tobevibart Monotherapy.

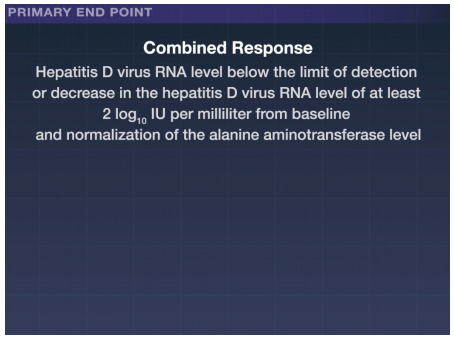
Participants were randomly assigned to receive either tobevibart plus elebsiran every 4 weeks (cohort 2c) or tobevibart every 2 weeks (cohort 3) through subcutaneous administration. Panel A shows the percentage of participants who had a virologic response, which was defined as an HDV RNA level below the limit of detection or a decrease in the HDV RNA level of at least 2 $\log_{10}$ IU per milliliter from baseline (open symbols), and the percentage of participants who had undetectable HDV RNA (also known as target not detected, or TND; no amplification during reverse-transcriptase–polymerase-chain-reaction assay) (closed symbols) over time for both cohorts. The assay used to measure HDV RNA had a lower limit of quantification of 63 IU per milliliter and a limit of detection of 14 IU per milliliter. Panel B shows the percentage of participants with normalization of the ALT level, which was defined as an ALT level below the ULN (40 IU per milliliter in men and 33 IU per milliliter in women).


Patients with Chronic Hepatitis D Virus Infection
Increased risk of
• Cirrhosis
• Hepatocellular carcinoma
• Death

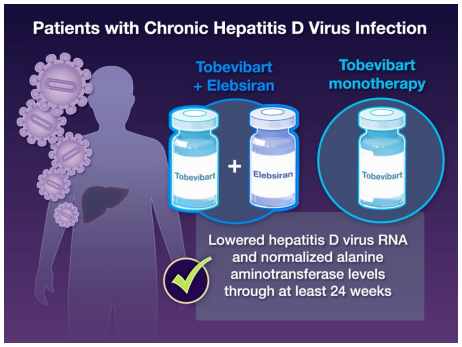

300 mg of Tobevibart
+
200 mg of Elebsiran
Tobevibart
Elebsiran
Every 4 weeks
N=32
300 mg of Tobevibart
monotherapy
Tobevibart
N=33

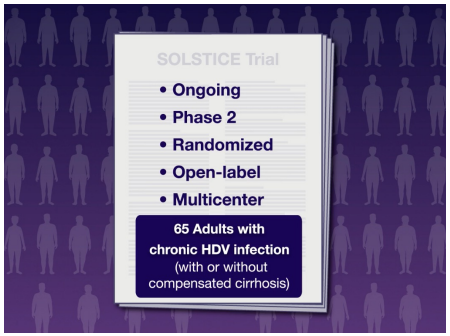

SECONDARY END POINT
Combined Response
at Week 48
Percentage of Participants
100
75
50
25
0
56%
61%
Tobevibart
+ Elebsiran
Tobevibart
Monotherapy

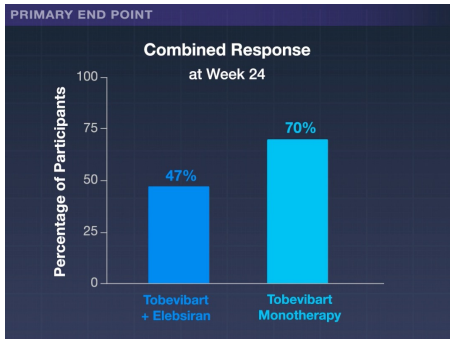

Patients with Chronic Hepatitis D Virus Infection
Tobevibart
Elebsiran
Tobevibart
Elebsiran
Hepatitis B virus
surface antigen
α-HBsAg mAb
α-HBx siRNA
Efficacy and safety

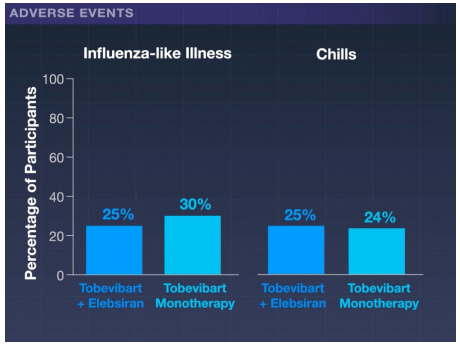

PRIMARY END POINT
Combined Response
Hepatitis D virus RNA level below the limit of detection
or decrease in the hepatitis D virus RNA level of at least
2 log10 IU per milliliter from baseline
and normalization of the alanine aminotransferase level

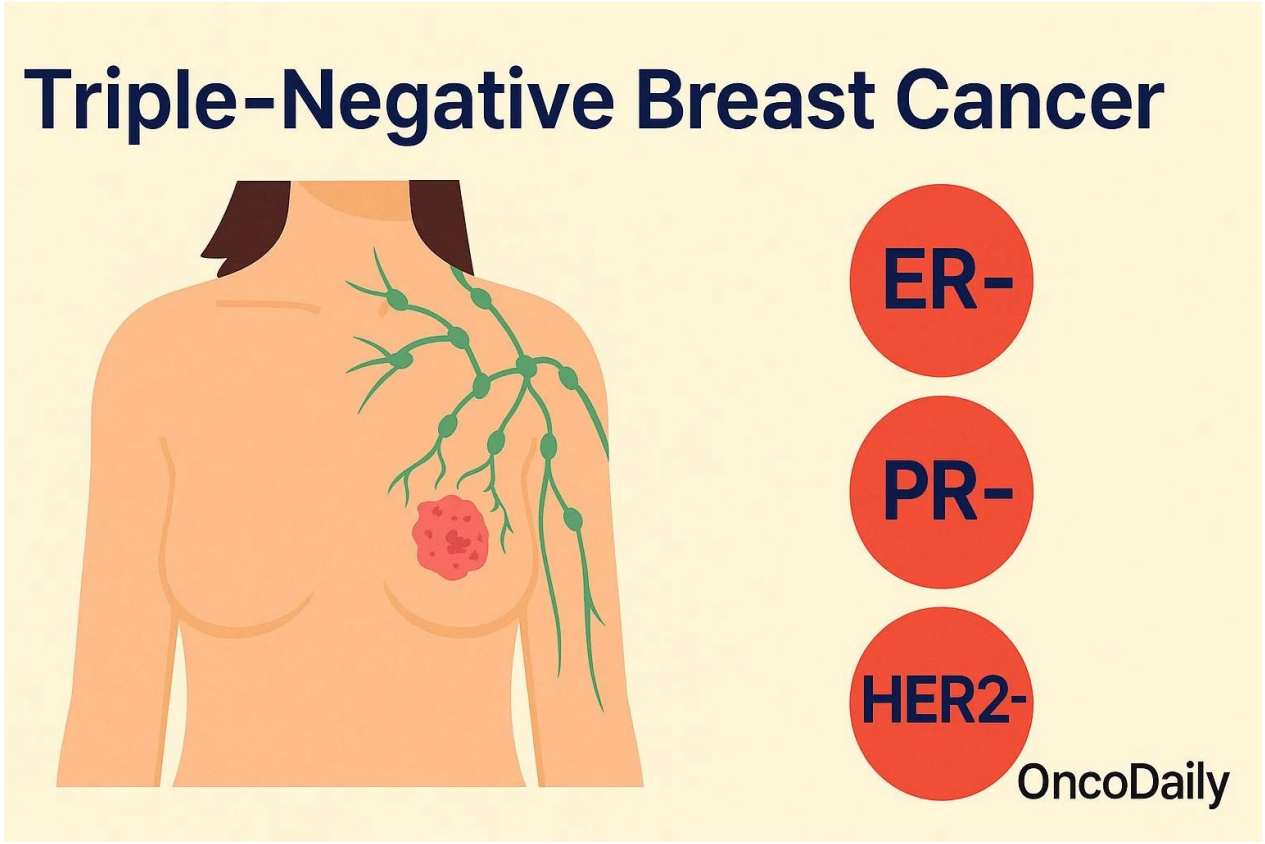

ADVERSE EVENTS
Most adverse events were mild or
moderate across treatment groups


Patients with Chronic Hepatitis D Virus Infection
Tobevibart
+ Elebsiran
Tobevibart
monotherapy
Tobevibart
Elebsiran
Tobevibart
Lowered hepatitis D virus RNA
and normalized alanine
aminotransferase levels
through at least 24 weeks


SOLSTICE Trial
• Ongoing
• Phase 2
• Randomized
• Open-label
• Multicenter
65 Adults with
chronic HDV infection
(with or without
compensated cirrhosis)


PRIMARY END POINT
Combined Response
at Week 24
Percentage of Participants
100
75
50
25
0
47%
70%
Tobevibart
+ Elebsiran
Tobevibart
Monotherapy

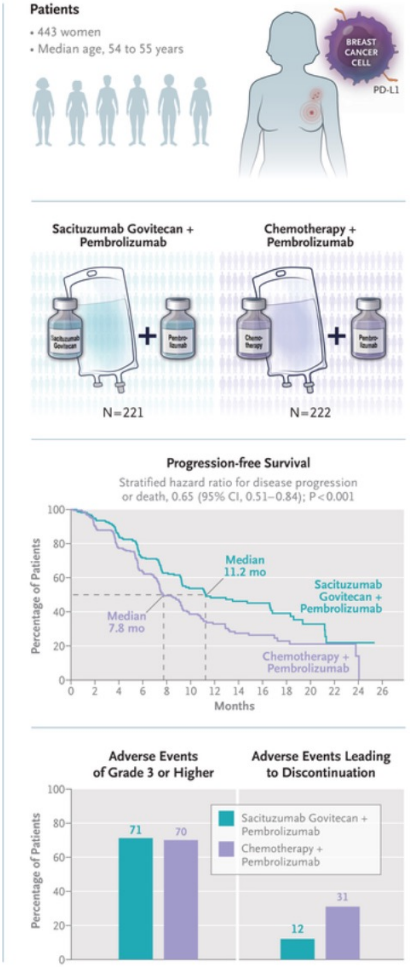

ADVERSE EVENTS
Influenza-like Illness
Chills
Percentage of Participants
100
80
60
40
20
0
25%
30%
25%
24%
Tobevibart
+ Elebsiran
Tobevibart
Monotherapy
Tobevibart
+ Elebsiran
Tobevibart
Monotherapy



Patients with triple-negative breast cancer (TNBC) do not strictly have to be PD-L1 positive (often referred to as PD-1/PD-L1 status) to receive nivolumab, but they are significantly more likely to benefit if they are. Studies show higher response rates and longer survival in PD-L1 positive TNBC, although some PD-L1 negative patients may still derive benefit.

Sacituzumab Govitecan plus Pembrolizumab for Advanced Triple-Negative Breast Cancer

Triple-negative breast cancer is an aggressive breast cancer subtype, and there remains an unmet need to improve outcomes in patients with previously untreated, programmed death ligand 1 (PD-L1)–positive, locally advanced unresectable or metastatic triple-negative breast cancer. In this phase 3, open-label, international trial, we randomly assigned patients in a 1:1 ratio to receive sacituzumab govitecan plus pembrolizumab or chemotherapy plus pembrolizumab. The primary end point was progression-free survival as assessed by blinded independent central review. Secondary end points included overall survival, objective response (complete or partial response) and duration of response as assessed by blinded independent central review, and safety.



Approximately 40% of cases of triple-negative breast cancer are programmed death ligand 1 (PD-L1)–positive. The preferred treatment option for patients with previously untreated, PD-L1–positive, metastatic triple-negative breast cancer is the programmed cell death protein 1 (PD-1) immune checkpoint inhibitor pembrolizumab with chemotherapy, on the basis of the phase 3 KEYNOTE-355 trial in which pembrolizumab plus chemotherapy (taxanes or gemcitabine–carboplatin) resulted in significantly longer progression-free survival than chemotherapy alone (median, 9.7 months vs. 5.6 months), as well as longer overall survival (median, 23.0 months vs. 16.1 months), among patients whose tumors expressed PD-L1 (combined positive score, ≥10; the combined positive score is the number of PD-L1–staining tumor cells, lymphocytes, and macrophages divided by the total number of viable tumor cells, multiplied by 100). Despite the improvement achieved with this treatment combination, an opportunity to further improve outcomes in earlier treatment lines for patients with PD-L1–positive metastatic triple-negative breast cancer exists, because approximately half of patients with metastatic triple-negative breast cancer do not receive treatment beyond first-line therapy.

Sacituzumab govitecan is a trophoblast cell-surface antigen 2 (Trop-2)–directed antibody–drug conjugate composed of a humanized anti–Trop-2 monoclonal antibody attached to the topoisomerase I inhibitor SN-38 through a hydrolyzable linker. Sacituzumab govitecan is approved in multiple countries for the treatment of persons with metastatic triple-negative breast cancer after at least two previous systemic therapies (at least one in the context of metastatic disease) on the basis of the phase 3 ASCENT trial, which showed significant improvements in progression-free and overall survival with sacituzumab govitecan as compared with chemotherapy. Here, we report the primary results from the ASCENT-04/KEYNOTE-D19 trial of sacituzumab govitecan plus pembrolizumab as compared with chemotherapy plus pembrolizumab in patients with previously untreated, locally advanced unresectable or metastatic triple-negative breast cancer whose tumors express PD-L1.

Patients

We conducted this phase 3, open-label, randomized trial at 186 sites in 28 countries. We enrolled adults with locally advanced unresectable or metastatic triple-negative breast cancer with no previous therapy for advanced disease and whose tumors were PD-L1–positive (combined positive score, ≥10). Both triple-negative status (<1% of tumor cells positive for estrogen receptor or progesterone receptor and a HER2 immunohistochemistry [IHC] result of 0, 1+, or 2+ with negative in situ hybridization) and PD-L1 expression (assessed with the PD-L1 IHC 22C3 pharmDx assay.

Trial Design and Treatments

Eligible patients were randomly assigned in a 1:1 ratio to receive sacituzumab govitecan at a dose of 10 mg per kilogram of body weight intravenously on days 1 and 8 and pembrolizumab at a dose of 200 mg intravenously on day 1 of 21-day cycles or chemotherapy of the physician's choice (paclitaxel at a dose of 90 mg per square meter of body-surface area or nanoparticle albumin-bound paclitaxel at a dose of 100 mg per square meter on days 1, 8, and 15 of 28-day cycles or gemcitabine at a dose of 1000 mg per square meter plus carboplatin at a dose targeting an area under the concentration–time curve of 2 mg per milliliter per minute on days 1 and 8 of 21-day cycles, administered intravenously) and pembrolizumab at a dose of 200 mg on day 1 of 21-day cycles.

End Points and Assessments

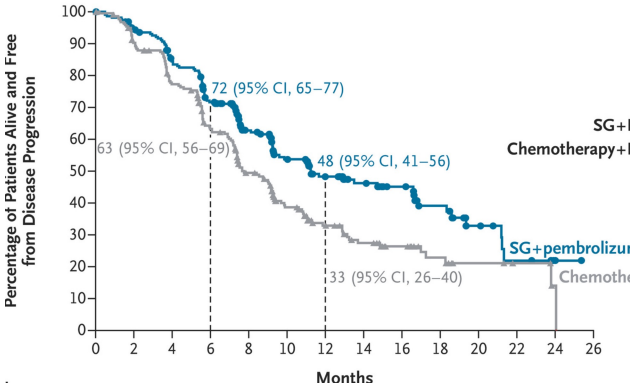
The primary end point was progression-free survival, defined as the time from the date of randomization to the date of disease progression or death (whichever occurred first), as assessed by blinded independent central review. Key secondary end points included overall survival and objective response.

Characteristic	Sacituzumab Govitecan plus Pembrolizumab (N=221)	Chemotherapy plus Pembrolizumab (N=222)
Median age (range) — yr	54 (23–88)	55 (27–82)
Age ≥65 yr — no. (%)	58 (26)	57 (26)
Female sex — no. (%)	221 (100)	222 (100)
Race or ethnic group — no. (%)†		
White	139 (63)	118 (53)
Asian	43 (19)	63 (28)
American Indian or Alaska Native	14 (6)	13 (6)
Black	13 (6)	11 (5)
Other or not specified	12 (5)	17 (8)
Geographic region — no. (%)‡		
Canada, the United States, or western Europe	85 (38)	85 (38)
Rest of the world	136 (62)	137 (62)
ECOG performance-status score — no. (%)§		
0	156 (71)	154 (69)
1	65 (29)	67 (30)
PD-L1–positive status — no. (%)¶	221 (100)	222 (100)
Disease status — no. (%)‖		
Metastatic at initial diagnosis	75 (34)	75 (34)
Recurrent within 6–12 mo after completion of curative-intent treatment	40 (18)	40 (18)
Recurrent >12 mo after completion of curative-intent treatment	106 (48)	107 (48)
Metastatic site — no. (%)		
Lymph nodes	159 (72)	154 (69)
Lung	111 (50)	95 (43)
Liver	55 (25)	57 (26)
Bone	61 (28)	45 (20)
Brain	8 (4)	6 (3)
Other**	81 (37)	71 (32)
Previous anti–PD-1 or anti–PD-L1 therapy — no. (%)††	9 (4)	11 (5)
Chemotherapy received during trial — no. (%)‡‡		
Taxane	—	113 (51)
Gemcitabine plus carboplatin	—	107 (49)

Additional Efficacy End Points.

Variable	Sacituzumab Govitecan plus Pembrolizumab (N=221)	Chemotherapy plus Pembrolizumab (N=222)
No. of deaths	53	61
Median overall survival (95% CI) — mo	NR (25.6–NR)	NR (NR–NR)
Objective response (95% CI) — %†	60 (53–66)	53 (46–60)
Stratified odds ratio vs. chemotherapy plus pembrolizumab (95% CI)	1.3 (0.9–1.9)	
Best overall response — no. (%)		
Complete response	28 (13)	18 (8)
Partial response	104 (47)	100 (45)
Stable disease	70 (32)	70 (32)
For ≥6 mo	23 (10)	29 (13)
Progressive disease	9 (4)	26 (12)
Not evaluable	10 (5)	8 (4)
Median time to response (range) — mo‡	1.9 (1.0–9.3)	1.9 (1.1–11.4)
Median duration of response (95% CI) — mo‡	16.5 (12.7–19.5)	9.2 (7.6–11.3)

Common chemotherapies for triple negative breast cancer may include an anthracycline such as Adriamycin, alkylating agents such as cyclophosphamide, and a taxane, such as Taxol or Taxotere. Fluorouracil (5FU) may be given as well.



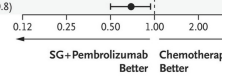
	No. of Patients	No. of Events	Median Progression-free Survival (95% CI)
			mo
SG+Pembrolizumab	221	109	11.2 (9.3–16.7)
Chemotherapy+Pembrolizumab	222	140	7.8 (7.3–9.3)

Stratified hazard ratio for disease progression or death, 0.65 (95% CI, 0.51 to 0.84)
P<0.001

Kaplan–Meier Estimate of Progression-free Survival.

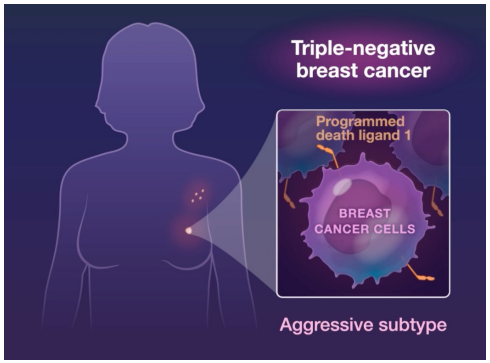
Progression-free survival was assessed by blinded independent central review among all the patients who had undergone randomization. The two-sided P value was derived from a stratified log-rank test. SG denotes sacituzumab govitecan.

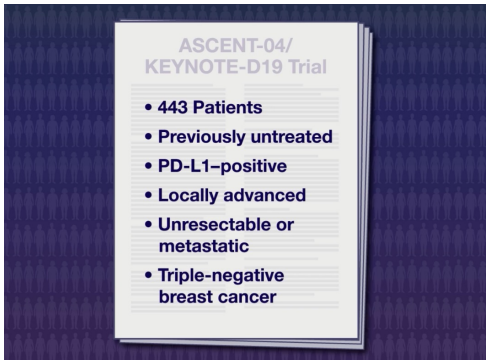
Subgroup	No. of Patients		Median Progression-free Survival (95% CI)		Unstratified Hazard Ratio for Diseas or Death (95% CI)
	SG+ Pembrolizumab	Chemotherapy+ Pembrolizumab	SG+ Pembrolizumab	Chemotherapy+ Pembrolizumab	
			mo		
Intention-to-treat population	221	222	11.2 (9.3–16.7)	7.8 (7.3–9.3)	
Age					
<65 yr	163	165	11.3 (9.3–16.8)	7.5 (7.0–9.2)	
≥65 yr	58	57	11.1 (7.5–NR)	9.3 (7.3–13.2)	
ECOG performance-status score					
0	156	154	12.9 (9.3–16.8)	8.7 (7.3–9.9)	
≥1	65	67	9.2 (7.5–18.3)	7.5 (5.6–9.3)	
Geographic region					
Canada, the United States, or western Europe	85	85	11.7 (7.5–19.4)	7.4 (5.7–9.9)	
Rest of the world	136	137	11.2 (9.3–16.7)	8.4 (7.4–9.3)	
Disease status					
Metastatic at initial diagnosis	75	75	8.1 (7.3–18.6)	7.7 (6.1–11.9)	
Recurrent, 6–12 mo after completion of curative-intent treatment	40	40	9.9 (5.7–16.8)	7.2 (4.4–9.1)	
Recurrent, >12 mo after completion of curative-intent treatment	106	107	16.6 (11.0–NR)	8.7 (7.3–10.8)	
Previous anti–PD-1 or anti–PD-L1 therapy					
Yes	9	11	7.5 (0.9–NR)	6.6 (2.1–NR)	
No	212	211	11.7 (9.3–16.8)	7.8 (7.4–9.3)	
Chemotherapy selected before randomization					
Taxane	116	114	11.1 (8.6–16.7)	9.2 (7.2–12.9)	
Gemcitabine–carboplatin	105	108	11.3 (9.2–21.2)	7.4 (6.9–9.0)	
Race					
White	139	118	11.1 (9.2–21.2)	7.7 (6.9–10.8)	
Asian	43	63	16.7 (7.5–NR)	8.7 (7.2–9.9)	
Other	35	28	11.3 (7.4–16.6)	6.0 (3.8–7.5)	
History of liver metastasis					
Yes	55	57	7.3 (5.5–9.3)	5.6 (5.4–8.5)	
No	166	165	16.6 (11.1–21.2)	9.0 (7.4–9.9)	
History of brain metastasis					
Yes	8	6	5.7 (0.5–NR)	3.7 (1.3–NR)	
No	213	216	11.7 (9.3–16.8)	8.4 (7.4–9.3)	
Menopausal status					
Premenopausal	81	77	9.3 (7.4–19.4)	7.4 (5.6–9.3)	
Postmenopausal	140	145	12.9 (9.3–18.3)	8.4 (7.4–10.8)	

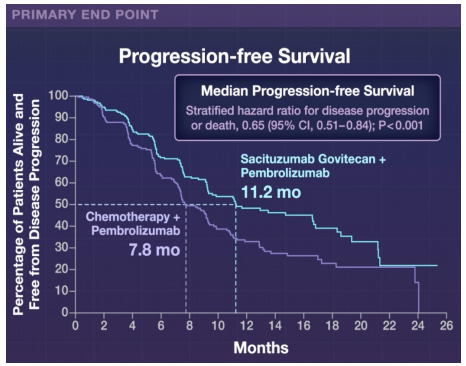


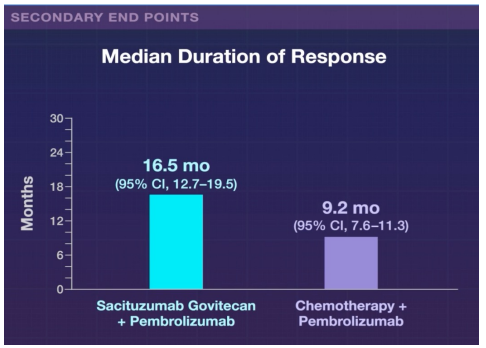
Subgroup Analysis of Progression-free Survival.

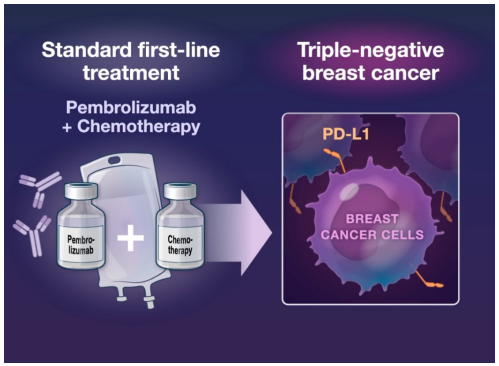
Progression-free survival was assessed by blinded independent central review among all the patients who had undergone randomization. Hazard ratios and 95% confidence intervals were estimated with the use of an unstratified Cox proportional-hazards model. Analyses for stratification factors were conducted with the use of values from the interactive voice-response or Web-response system. Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability. Although patients were included in the stratified subgroups with respect to disease status at the values listed in the figure, according to the clinical database the distribution of patients was as follows: in the group assigned to receive sacituzumab govitecan plus pembrolizumab, 74 patients had disease that was metastatic at initial diagnosis, 39 had disease that had recurred within 6 to 12 months after treatment, and 108 had disease that had recurred more than 12 months after treatment; in the group assigned to receive chemotherapy plus pembrolizumab, 74 had disease that was metastatic at initial diagnosis, 48 had disease that had recurred within 6 to 12 months after treatment, and 100 had disease that had recurred more than 12 months after treatment. Although 20 patients were included in the stratified subgroup for previous exposure to anti–programmed cell death protein 1 (PD-1) or anti–programmed death ligand 1 (PD-L1) therapy (on the basis of investigator selection of "yes" at enrollment in the trial in the interactive voice-response or Web-response system), only 6 patients were later determined to have actually received previous treatment with anti–PD-1 or anti–PD-L1 agents according to the clinical database (3 in each treatment group). Race was reported by the patients. NR denotes not reached.

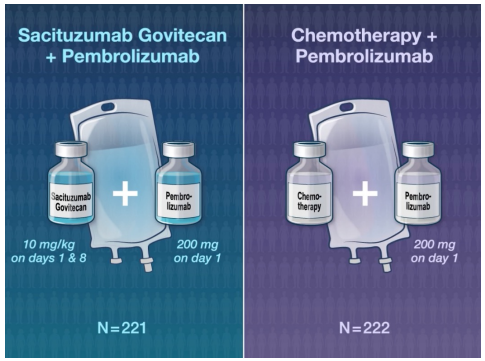

Triple-negative breast cancer
Programmed death ligand 1
BREAST CANCER CELLS
Aggressive subtype

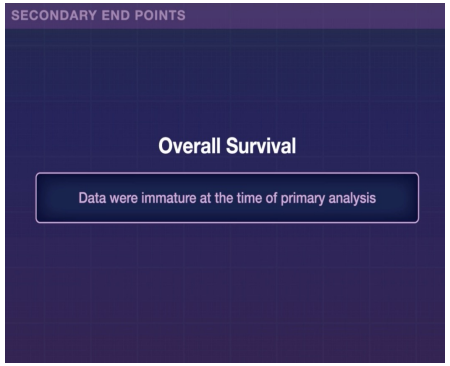

ASCENT-04/ KEYNOTE-D19 Trial
• 443 Patients
• Previously untreated
• PD-L1–positive
• Locally advanced
• Unresectable or metastatic
• Triple-negative breast cancer

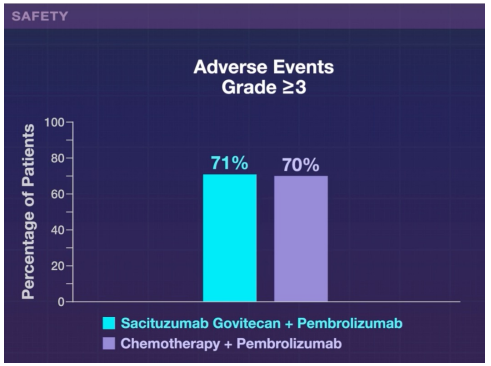

PRIMARY END POINT
Progression-free Survival
Median Progression-free Survival
Stratified hazard ratio for disease progression or death, 0.65 (95% CI, 0.51–0.84); P<0.001
Sacituzumab Govitecan + Pembrolizumab
11.2 mo
Chemotherapy + Pembrolizumab
7.8 mo
Percentage of Patients Alive and Free from Disease Progression
Months

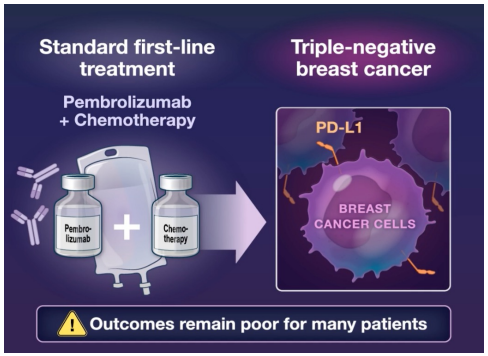

SECONDARY END POINTS
Median Duration of Response
Months
16.5 mo
(95% CI, 12.7–19.5)
9.2 mo
(95% CI, 7.6–11.3)
Sacituzumab Govitecan + Pembrolizumab
Chemotherapy + Pembrolizumab

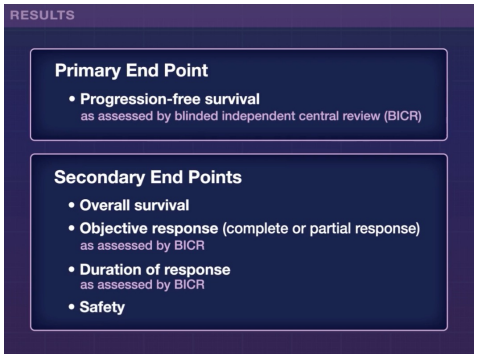

Standard first-line treatment
Pembrolizumab + Chemotherapy
Triple-negative breast cancer
PD-L1
BREAST CANCER CELLS

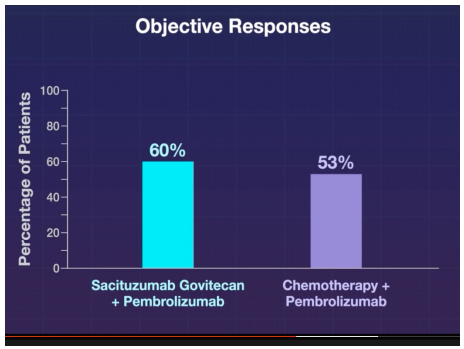

Sacituzumab Govitecan + Pembrolizumab
10 mg/kg on days 1 & 8
200 mg on day 1
N=221
Chemotherapy + Pembrolizumab
200 mg on day 1
N=222

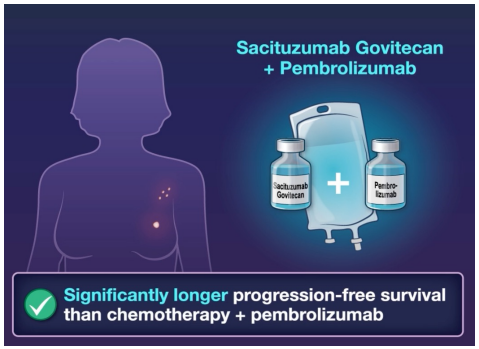

SECONDARY END POINTS
Overall Survival
Data were immature at the time of primary analysis


SAFETY
Adverse Events Grade ≥3
Percentage of Patients
71%
70%
Sacituzumab Govitecan + Pembrolizumab
Chemotherapy + Pembrolizumab

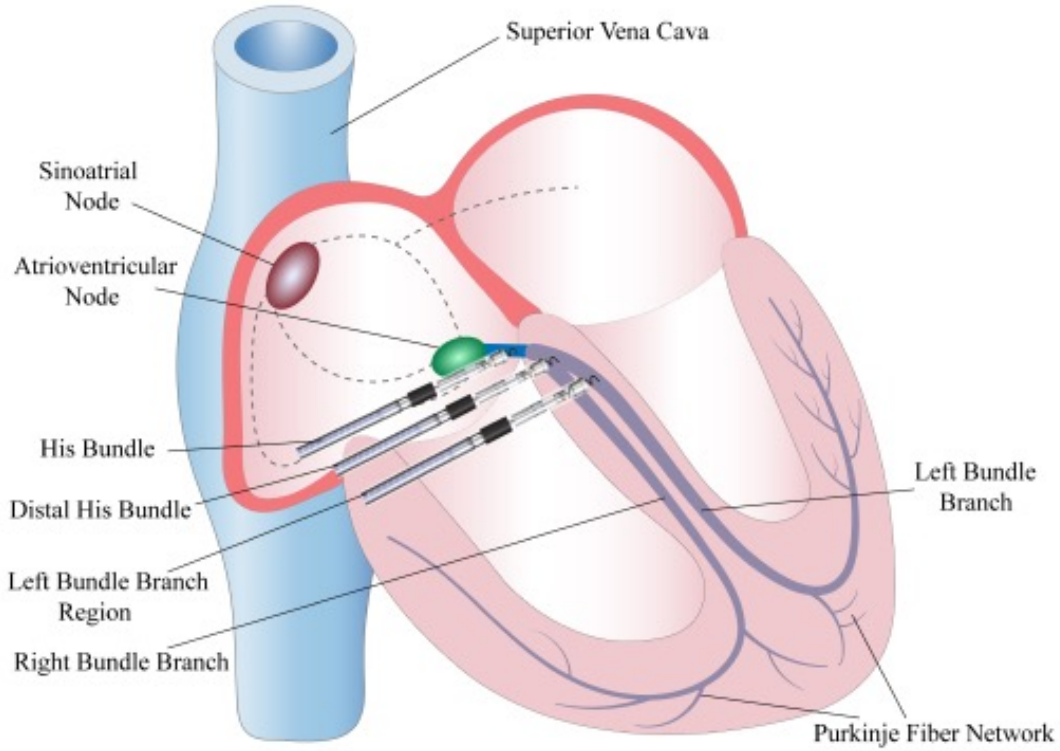

Standard first-line treatment
Pembrolizumab + Chemotherapy
Triple-negative breast cancer
PD-L1
BREAST CANCER CELLS
Outcomes remain poor for many patients


RESULTS
Primary End Point
• Progression-free survival as assessed by blinded independent central review (BICR)
Secondary End Points
• Overall survival
• Objective response (complete or partial response) as assessed by BICR
• Duration of response as assessed by BICR
• Safety


Objective Responses
Percentage of Patients
60%
53%
Sacituzumab Govitecan + Pembrolizumab
Chemotherapy + Pembrolizumab


Sacituzumab Govitecan + Pembrolizumab
Significantly longer progression-free survival than chemotherapy + pembrolizumab

Physiological cardiac pacing (CPP) is any form of pacing designed to restore or preserve the natural synchrony of the heart's contraction.



REVIEW ARTICLE

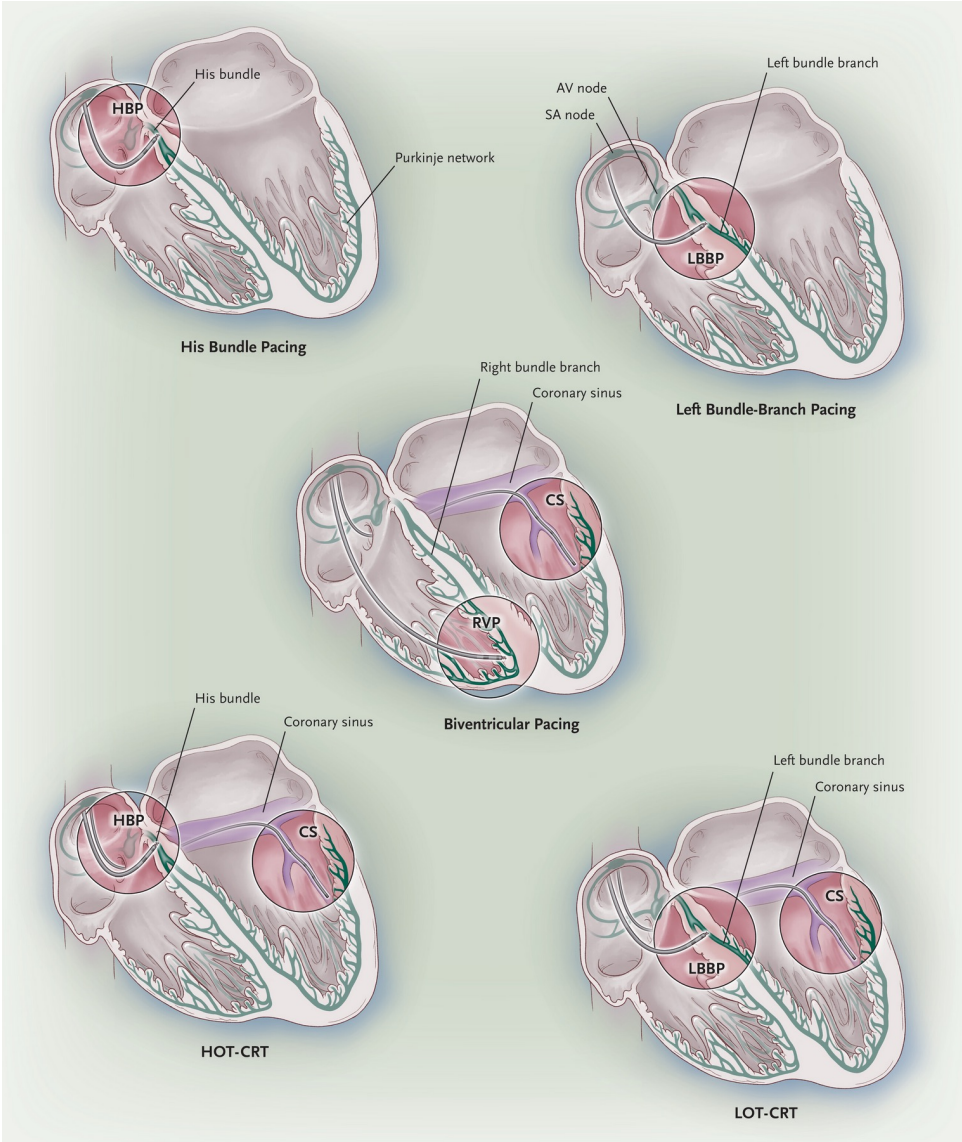
Physiologic Pacing in Heart Failure

Summary

Cardiac physiologic pacing, also known as cardiac resynchronization therapy, is indicated in patients with heart failure, reduced left ventricular ejection fraction (LVEF) of 50% or less, and either a high (or anticipated high) ventricular pacing burden or a wide QRS complex. Traditionally, physiologic pacing has been achieved with biventricular pacing with a right ventricular lead and a coronary sinus branch lead. Randomized trials involving more than 10,000 patients with heart failure have shown clinical, exercise, and quality-of-life benefits associated with biventricular pacing, as well as improved LVEF and reduced mitral regurgitation and ventricular volumes. These benefits are greatest in patients with left bundle-branch block and a QRS duration of 150 msec or longer. Recent studies support targeting the His bundle or left bundle branch as an alternative cardiac physiologic pacing strategy. Ongoing randomized trials are expected to more clearly define the comparative efficacy and safety of conduction system pacing as compared with biventricular pacing.

Biventricular Pacing for Cardiac Physiologic Pacing

The human conduction system ensures that mechanical contractions of the heart maintain atrioventricular, intraventricular, and interventricular synchrony. When activation of the right and left ventricles is dyssynchronous, with left bundle-branch block or pacing of the right ventricular myocardium, left ventricular function may decrease. This decrease in function is more likely to occur in patients who already have reduced left ventricular systolic function. The primary approach to overcoming left ventricular dyssynchrony in patients with heart failure with reduced ejection fraction has been biventricular pacing, with a lead introduced through the coronary sinus into a lateral or posterolateral coronary sinus venous branch to capture the epicardium. Alternatively, when placement of the left ventricular lead through the coronary sinus is not possible, a lead may be placed directly on the left ventricular epicardium during an open or thoracoscopic surgical procedure. Biventricular pacing achieves its salutary effect by synchronizing the activation of the right ventricular endocardium with that of the left ventricular epicardium by means of a pacing or implantable cardioverter–defibrillator (ICD) lead placed in the right ventricle, which results in reverse ventricular remodeling. Activation proceeds from cell to cell in the myocardium without directly engaging the conduction system, resulting in a fusion of the electrical wavefronts from stimulation of the right ventricle and left ventricle. Challenges to successful biventricular pacing include a lack of appropriate target vessels in the coronary sinus in which to place leads, lead dislodgement, lateral myocardial scarring, and differential benefit relative to both QRS morphologic features and QRS duration. Device algorithms have been developed to optimize pacing by fusing intrinsic conduction down the right bundle branch with pacing from the coronary sinus lead.



Lead Configurations.

Shown are the lead configurations for His bundle pacing (HBP), left bundle-branch pacing (LBBP), biventricular pacing, His bundle-branch–optimized cardiac resynchronization therapy (HOT-CRT), and left bundle-branch–optimized cardiac resynchronization therapy (LOT-CRT). AV denotes atrioventricular, CS coronary sinus, RVP right ventricular pacing, and SA sinoatrial node.

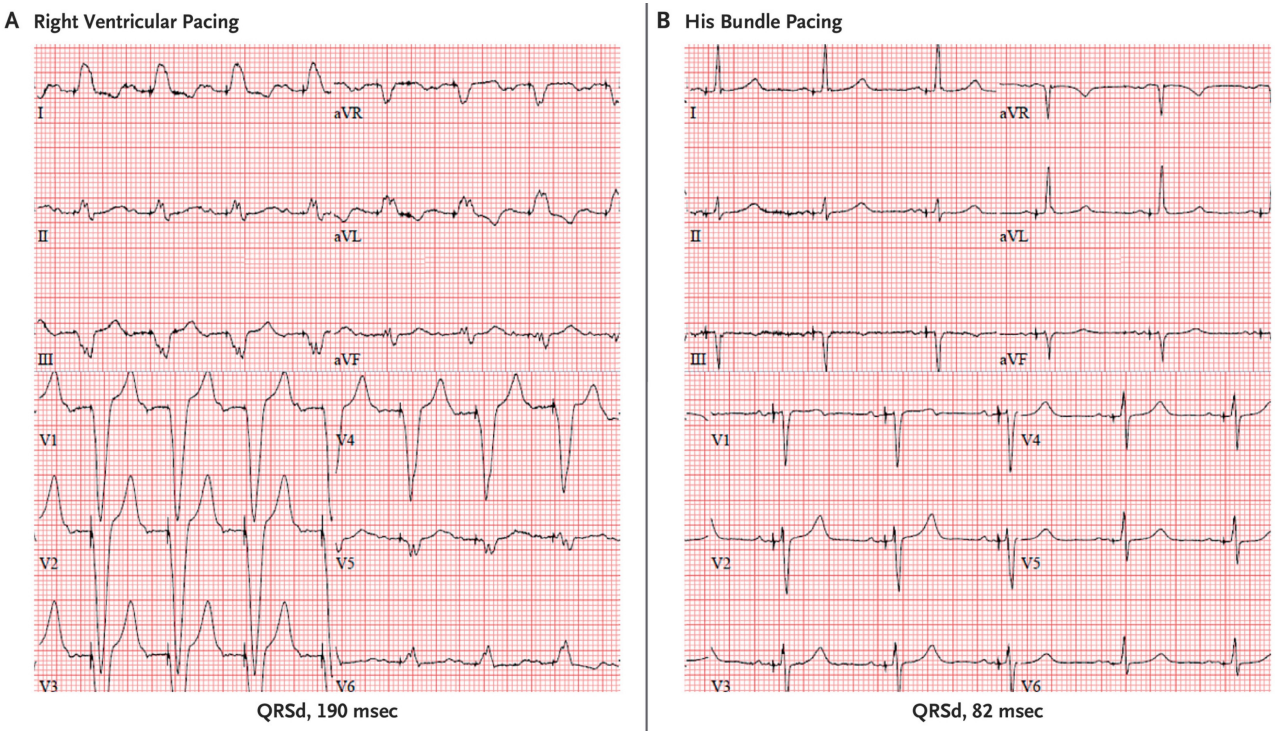
KEY POINTS

Physiologic Pacing in Heart Failure

- Cardiac physiologic pacing can be achieved with biventricular pacing with a right ventricular lead and coronary sinus lead or conduction system pacing by way of the His bundle or left bundle branch. It is indicated in patients with heart failure, left ventricular ejection fraction (LVEF) of 50% or less, and high or anticipated high ventricular pacing burden and left ventricular resynchronization in patients with a wide QRS complex.
- Randomized trials of biventricular pacing in more than 10,000 patients with heart failure have shown improved LVEF, reduced mitral regurgitation and left ventricular volumes, enhanced quality of life and exercise capacity, fewer hospitalizations for heart failure, and improved survival. The greatest benefit is seen in patients who have a left bundle-branch block with a QRS duration of 150 msec or longer, whereas biventricular pacing may be of negligible benefit when the QRS duration is 130 msec or less.
- Retrospective studies suggest that conduction system pacing may offer benefits equal to or greater than biventricular pacing. Ongoing randomized trials will clarify the relative efficacy and safety of cardiac physiologic pacing as compared with biventricular pacing.

Trials of Cardiac Physiologic Pacing with Biventricular Pacing.

Trial	Type or Comparison	NYHA Class	LVEF	SR or AF	QRS	LBBB or IVCD	Primary End Point	Primary End-Point Results
			%		msec	%		
Early trials								
MUSTIC-SR (48 patients)[4]	Single-blind, cross-over CRT on or off	III	≤35	SR	>150	87	6MWT, peak VO_2, LVEF, NYHA class, QOL, MR	Improved peak VO_2, LVEF, NYHA class, QOL, MR
MUSTIC AF (43 patients)[5]†	Single-blind crossover CRT on or off	III	≤35	AF	≥200	NA	6MWT, peak VO_2, QOL	Improved 6MWT, QOL
MIRACLE (453 patients)[8]	CRT vs. medical care	III, IV	≤35	SR	≥130	NA	6-mo QOL, NYHA class, 6MWT	Improved QOL, NYHA class, 6MWT
PATH-CHF (41 patients)[9]	Single-blind, cross-over CRT on or off	III, IV	≤35	SR	>120	97	VO_2, QOL, 6MWT, LVEF, NYHA class	Trend toward an improvement in all primary and secondary end points with BIVP
MIRACLE ICD (369 patients)[10]	Double-blind, parallel controlled, ICD vs. CRT CRT on or off	III, IV	≤35	SR	≥130	94	6-mo QOL, NYHA class, 6MWT	Improved QOL, NYHA class, 6MWT
CONTAK CD (490 patients)[11]	ICD vs. CRT CRT on or off	II–IV	≤35	SR	≥120	46	At 6 mo, death from any cause, hospitalization for HF, and VT or VF requiring device intervention	Decreased HF progression; improved peak VO_2, NYHA class, QOL, LV volumes
MIRACLE ICD II (186 patients)[12]	ICD vs. CRT, double blind, parallel-controlled CRT on or off	II	≤35	SR	≥130	83.4	VO_2, NYHA class, QOL, 6MWT, LV volumes, and LVEF at 6 mo; composite clinical response	No change in exercise capacity; improved LV volumes, LVEF, and composite clinical responses
Large RCTs								
COMPANION (1520 patients)[13]	Three groups: ICD with CRT, CRT without ICD, or optimal medical therapy	III, IV	≤35	SR	≥120	86	Death from any cause or hospitalization for any cause	Both CRT and ICD with CRT better than optimal medical therapy alone
CARE-HF (813 patients)[14]	CRT vs. optimal medical therapy	III, IV	≤35	SR	≥120	95	Death from any cause or unplanned cardiovascular hospitalization	CRT better than optimal medical therapy
MADIT-CRT (1820 patients)[15]	ICD with CRT vs. ICD alone	I, II	≤30	SR	≥130	70.5	Death from any cause or HF events	CRT better than optimal medical therapy
RAFT (1798 patients)[16]	ICD with BIVP vs. ICD alone	II, III	≤30	SR or AF	≥120	72	Death from any cause or hospitalization for HF	CRT did not reduce mortality but did reduce HF events
REVERSE (610 patients)[17]	CRT with ICD if LVEF ≤35% CRT alone if LVEF ≥36% and ≤40% CRT on or off over 12 mo	I, II	≤40	SR	≥120	60.5	HF clinical score composite	Clinical composite score better with CRT (with or without ICD)
RCTs in HF, QRS ≤120 to 130 msec								
NARROW-CRT (120 patients)[18]‡	CRT and ICD vs. DDD and ICD	II, III	≤35	SR	<120	NA	HF clinical composite response	CRT associated with better HF clinical composite response
LESSER-EARTH (85 patients)[19]†	CRT or ICD CRT on or off	None§	≤35	SR	<120	NA	Submaximal exercise duration with VO_2, QOL, reverse LV remodeling	CRT did not improve exercise capacity, symptoms, QOL or reverse LV remodeling
EchoCRT (809 patients)[20]†‡	CRT or ICD CRT on or off	III, IV	≤35	SR	≤130	NA	Death from any cause or HF hospitalization	CRT did not decrease mortality or HF hospitalization
RethinQ (172 patients)[21]	CRT or ICD CRT on or off	III	≤35	SR	≤130	NA	VO_2 at 6 mo	CRT did not improve VO_2
ESTEEM-CRT (68 patients)[22]	CRT or ICD CRT on or off	III	≤35	SR	≤130	NA	Hemodynamics (LV dP–dt[max]) at the time of implantation and chronic exercise performance, echo-determined reverse remodeling	CRT did not improve hemodynamics at the time of implantation, long-term exercise performance, or reverse remodeling
RCT of HF prevention, substantial RV pacing								
BLOCK HF (691 patients)[23]	Pacemaker indicated for AV block Double-blind randomization to BIVP or RVP If LVEF ≤35%, patients randomly assigned to ICD with BIVP or without BIVP ¶	I–III	≤50	SR or AF	NA	NA	Death from any cause, HF-related urgent care, or ≥15% increase in LVESI	BIVP reduced mortality and morbidity, improved clinical outcomes, QOL, HF symptoms



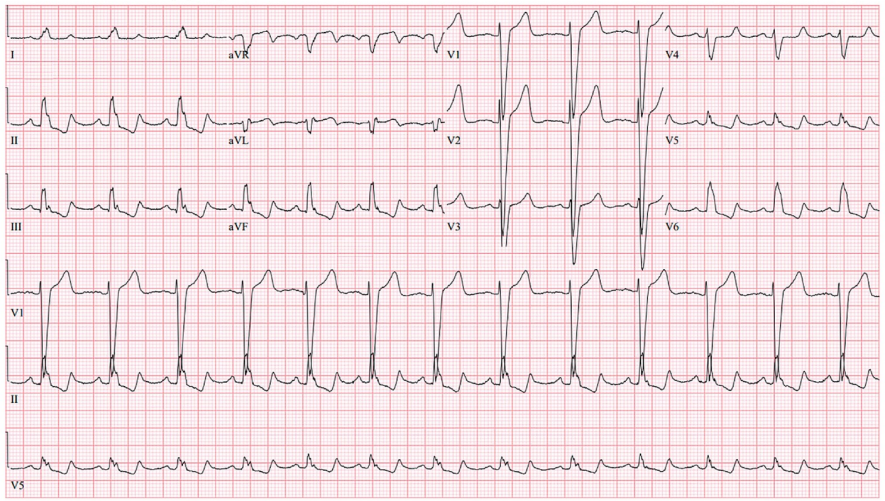
His Bundle Pacing Shown on Electrocardiogram (ECG).

Panel A shows an ECG of right ventricular pacing with a paced QRS duration (QRSd) of 190 msec. In this patient, who had complete heart block at baseline and a left ventricular ejection fraction (LVEF) of 60 to 65%, pacing-induced cardiomyopathy developed, leading to a LVEF of 35 to 40% with 100% right ventricular pacing. Panel B shows an ECG of His bundle pacing with a paced QRSd of 82 msec. Upgrading the patient's pacemaker to a His bundle pacemaker improved the LVEF to a range of 60 to 65%.

Trials and Studies of Conduction System Pacing for Cardiac Physiologic Pacing.

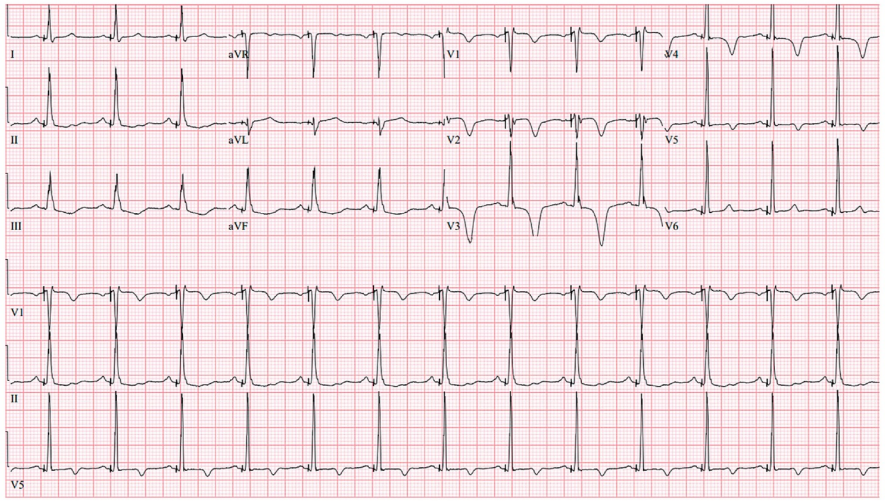
Trial	Type or Comparison	NYHA Class	LVEF	SR or AF	QRS	LBBB	Primary End Points	Primary End-Point Results
			%		*msec*	%		
Early Trials								
Lustgarten et al. (29 patients)[37]	Randomized crossover, BIVP vs. HisBP at 6 mo with crossover and 12-mo follow-up	II, III	<40	SR	138–186	96	QOL, NYHA class, 6MWT, LVEF	No differences between HisBP and BIVP
His-SYNC (41 patients)[38]	Single-blinded crossover, His CRT vs. BIV CRT	II–IV	≤35	SR	>120	70	LVEF, LVESV, NYHA class, QOL at 6 and 12 mo	High crossover rate, no differences
His-Alternative (50 patients)[39]	Single-blinded crossover, His CRT vs. BIV CRT	II–IV	≤35	SR	>130 (women), >140 (men)	100	QRS, NYHA class, 6MWT, LVEF, LVESV, success of implanting a His bundle lead at 6 mo	No differences based on intention-to-treat analysis
LBBP-RESYNC (40 patients)[39]	Nonischemic cardiomyopathy and LBBB, LBBP-CRT vs. BIV-CRT, single-blinded	II–IV	≤40	SR	≥140	100	6-mo LVEF, LVESV, NT-pro BNP, NYHA class, 6MWT, QRS duration	Improved LVEF in LBBP-CRT
LEVEL-AT (70 patients)[40]	Single-blinded, randomized, BIV-CRT vs. CSP	NA	≤35	SR	>130 (LBBB), ≥150 (non-LBBB)	97	LV activation time, LVESV, HF hospitalization at 6 mo	No differences
ALTERNATIVE-AF (50 patients)[41]	Randomized, crossover, persistent AF after AVNA to HisBP vs. BIVP	II–IV	≤40	AF	≤120 or RBBB	NA	LVEF, LVEDD, NYHA class, BNP, QOL at 9 mo	Improved LVEF with HisBP
HOPE-HF (167 patients)[42]	Randomized, crossover at 6 mo, HisBP vs. no pacing, PR ≥200ms	I–IV	≤40	SR	≤140 or RBBB		Peak VO_2, QOL, LVEF	No differences in peak VO_2 or LVEF; improvement of QOL with HisBP
Observational Studies								
Vijayaraman et al. (477 patients)[44]	Observational two-center study, BIVP vs. CSP, mean follow-up of 27 mo	II–IV	≤35	SR	≥120	52	Death from any cause or unplanned CV hospitalization	Greater reduction in HF hospitalization with CSP in all patients and patients with LBBP, better LVEF and narrower QRS duration with CSP
Diaz et al. (371 patients)[45]	Observational multicenter study, BIVP vs. LBBAP, mean follow-up of 11.3 mo	II–IV	≤35–40	SR	≥120	91	HF hospitalization and death from any cause; NYHA class, ECG	Higher LVEF and fewer HF hospitalizations with CSP
Vijayaraman et al., I-CLAS (1778 patients)[46]	Observational 15-center, international study; BIVP vs. LBBAP, mean follow-up of 36 mo	II–IV	≤35	SR	≥120	61	Death from any cause or HF hospitalization	Greater reduction in composite of death from any cause and HF hospitalization with LBBAP in all patients and patients with LBBB, greater LVEF improvement and narrower QRS duration with LBBAP
Herweg et al., I-CLAS (1414 patients)[47]	Propensity-matched, observational, 15-center, international study, BIVP vs. LBBAP, mean follow-up of 32 mo	II–IV	≤35	SR	≥120	61	VT or VF, new-onset AF	Lower incidence of sustained VT or VF and new-onset AF with LBBAP than with BVP
Zhu et al. (259 patients)[48]	Observational two-center study, BIVP vs. LBBP and LVSP, mean follow-up of 28.8 mo	I–IV	<50	SR	>130 with LBBB, ≥150 with no LBBB and LVEF ≤35% or advanced AVB and LVEF <50%	63	Death from any cause or HF hospitalization or ECG measures of LV remodeling	Greater reduction in primary end-point events with LBBP than with BIVP or LVSP; death from any cause higher with LVSP than with BIVP
Vijayaraman et al., I-CLAS (1004 patients)[49]	Observational 16-center international study, BIVP vs. CSP (HisBP and LBBAP), mean follow-up of 49 mo	II–IV	36–50	SR	>120 with LBBB or expected RVP >40%	33	Death from any cause or HF hospitalization	Greater reduction in composite of death from any cause and HF hospitalization with CSP
Ongoing Trials								
LEAP (470 patients) NCT04595487	LVSP vs. RVP	NA	>40	SR, AF	2nd or 3rd AVB or atrial arrhythmia with slow VR; expected VP >20%	NA	Combined death, hospitalization for HF, and decline in LVEF by >10%	Enrolling; 12-mo follow-up
OptimPacing (683 patients) NCT04624763	LBBP vs. RVP	I–III	>35	SR, AF	2nd or 3rd AV block or persistent or permanent AF with VR <50 bpm	NA	Combined death, hospitalization for HF, and PICM	Enrolling; 36-mo follow-up
LEFT HF (1280 patients) NCT05015660	LBBP vs. RVP	NA	>35	SR	High-degree AVB and anticipated RVP >90%	NA	Combined CV death, HF events, and increase in LVESV by 15%	Enrolling; 36-mo follow-up
PROTECT-HF (2600 patients) NCT05815745	HisBP or LBBP vs. RVP	NA	>35	SR, AF	Any AVB or infrahisian block with pacing indication, or AF with slow ventricular rate, or planned AV node ablation	NA	Combined mortality and incidence of HF events	Enrolling; 78-mo follow-up
Left vs. Left RCT (2136 patients) NCT05650658	HisBP or LBBP vs. BIVP	NA	≤50	SR, AF	QRSd ≥130 or anticipated RVP >40%, or upgrade to CRT due to RVP >40%	NA	Combined death and HF hospitalization	Enrolling; 66-mo follow-up

A LBBB-Induced Cardiomyopathy



QRSd, 138 msec

B Left Bundle-Branch Pacing



QRSd, 86 msec

Left Bundle-Branch Pacing Shown on ECG.

Panel A shows baseline ECG findings in a patient with left bundle-branch block (LBBB)–induced cardiomyopathy (QRSd, 138 msec) with an LVEF of 30 to 35%. Panel B shows an ECG from the same patient with left bundle-branch pacing and a paced QRSd of 86 msec. With left bundle-branch pacing, the LVEF improved to 50 to 54%. Right bundle-branch morphologic features in lead V_1 indicate either left bundle-branch pacing or left ventricular septal pacing. Additional pacing maneuvers are performed to distinguish between left bundle-branch pacing and left ventricular septal pacing. In this case, left bundle-branch pacing was confirmed.

Clinical Considerations for the Treatment of Patients with Physiologic-Pacing Devices

Heart-Failure and Electrophysiology Clinics

A multidisciplinary approach to cardiac physiologic pacing, which involves collaborative efforts in combined heart-failure and electrophysiology clinics, promotes guideline-directed medical therapy and the selection of appropriate physiologic pacing strategies. This integrated-care model has been associated with improved patient outcomes, including enhanced quality of care, increased patient engagement, improved medication safety, reduced hospitalization rates, and decreased mortality.

Magnetic Resonance Imaging (MRI)

MRI conditionality (manufacturer-defined conditions under which a pacing device is safe in the setting of an MRI) is important, given the frequent use of MRI scanning in multiple clinical situations. Some leads and pacing systems used for conduction system pacing are labeled as MRI conditional. Ongoing clinical trials are expected to provide sufficient safety data that will lead to the MRI-conditional labeling of multiple leads and pacing systems.

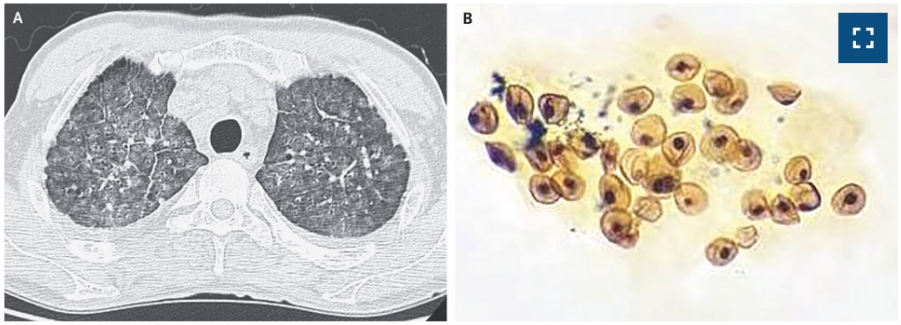
Lead Extraction

Experience with lead extraction is growing. Leads used for conduction system pacing can either be lumenless (not stylet driven because there is no inner lumen) or stylet driven. In one study, the success of lead extractions for lumenless leads was reported to be 100%, although there were retained distal fragments in 1% of the patients. It is reassuring that minor complications occurred in only 2.1% of the patients. Extraction of ICD or pacemaker leads becomes more difficult the longer the leads are implanted. Given the relatively recent emergence of conduction system pacing leads, dwell time is short, with a mean (±SD) of 22±26 months. There are limited data on extraction of stylet-driven leads implanted in either the His or left bundle-branch positions.

Future Directions

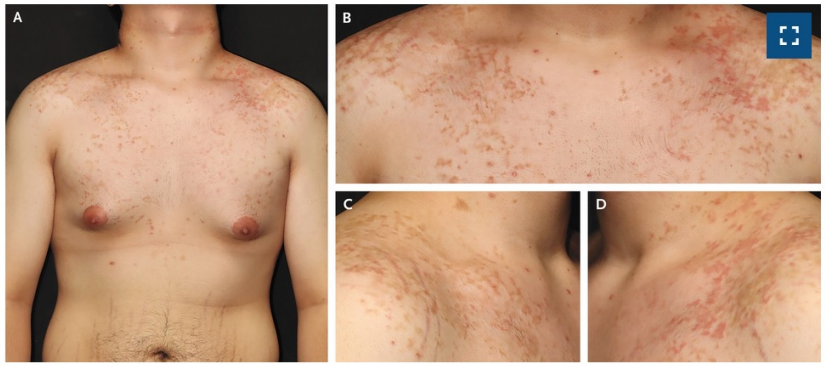
Physiologic pacing is a dynamic field with ongoing developments on multiple fronts. The role of biventricular pacing is well established for the treatment of patients with abnormal cardiac function and conduction system disease and is supported by multiple large randomized trials with clinically relevant end points, including mortality. The body of evidence is rapidly increasing for conduction system pacing, with special emphasis on left bundle-branch pacing. Ongoing randomized clinical trials will establish the relative efficacy and safety of conduction system pacing as compared with biventricular pacing. If the two pacing strategies are equivalent, other factors may play a role in making the appropriate choice. His bundle pacing and left bundle-branch pacing involve a simpler system and shorter procedural times for implantation than biventricular pacing, with potential downstream favorable consequences that include reduced cost, lower radiation dose, lower contrast dose, and increased battery life. Reduced costs may further be derived from less-expensive generators and fewer or less-expensive leads. CRT ICD or pacemaker generators (intended for use with biventricular pacing) are much more expensive than an ICD alone or pacemakers without CRT capability — the type of generators used for conduction system pacing. Also, pacing leads are less expensive than the coronary-sinus left ventricular leads used in biventricular pacing systems. In addition, because the His bundle pacing or left bundle-branch pacing lead provides the dual functions of pacing and cardiac resynchronization, only one lead, rather than the two needed for biventricular pacing, is needed. Furthermore, conduction system pacing will probably replace traditional right-ventricular pacing for indications of symptomatic sinus-node dysfunction and atrioventricular block.

Pneumocystis jirovecii Pneumonia



A 60-year-old man with recently diagnosed human immunodeficiency virus (HIV) infection presented to the infectious diseases clinic with a 10-day history of fever, dry cough, and shortness of breath. Treatment for HIV infection had not yet been started. His respiratory rate was 32 breaths per minute, heart rate 120 beats per minute, blood pressure 105/75 mm Hg, and oxygen saturation 89% while he was breathing ambient air. The physical examination revealed cyanosis of the lips but no abnormalities on lung auscultation. A chest radiograph showed diffuse interstitial infiltrates. Computed tomography of the chest showed diffuse nodules and ground-glass opacities with thickened interlobular septa (Panel A). Laboratory studies were notable for a CD4 count of 56 cells per microliter (reference range, 550 to 1440), HIV load of 76,200 copies per milliliter (reference value, <20) and elevated 1,3-β-D-glucan and lactate dehydrogenase levels. Gomori methenamine silver staining of bronchoalveolar lavage fluid showed multiple round structures with thick walls (Panel B), a finding consistent with the cystic form of the fungus *Pneumocystis jirovecii*. Metagenomic sequencing of the bronchoalveolar lavage fluid confirmed the diagnosis of *P. jirovecii* pneumonia. Treatment with trimethoprim–sulfamethoxazole and methylprednisolone was started. Nine days after presentation, the patient died of progressive respiratory failure.

Prurigo Pigmentosa



A previously healthy 20-year-old man presented to the dermatology clinic with a 4-week history of an itchy rash on his upper chest and shoulders. Two months before presentation, he had started a carbohydrate-restricted ketogenic diet for weight loss. Physical examination was notable for symmetric, erythematous papules and underlying reticulated hyperpigmentation on the upper chest (Panels A and B [close-up view]), anterior neck (Panel A), and shoulders (Panels C and D show the right and left shoulders, respectively). Striae were also seen on the lower abdomen. Histopathological analysis of a skin-biopsy specimen obtained from the left side of the chest revealed spongiosis with perivascular lymphocytic infiltrates in the dermis. Direct immunofluorescence was negative for IgA, IgE, IgG, IgM, C3, and fibrinogen. A diagnosis of prurigo pigmentosa — also known as keto rash — was made. Prurigo pigmentosa is an inflammatory dermatosis that manifests as pruritic, erythematous papules on the chest, back, or neck that may progress to a reticular pattern over time. It has been associated with ketosis in the context of ketogenic diets, diabetes mellitus, and fasting. A biopsy is not required if the diagnosis can be made on the basis of clinical features. Treatment involves tetracycline therapy and resolution of ketosis. The patient was advised to stop his ketogenic diet and was given a 2-week course of oral doxycycline. At 1 week of follow-up, the rash had abated.

Case 3-2026: A 58-Year-Old Woman with Diplopia and Fever

A 58-year-old woman was admitted to this hospital because of diplopia and fever. Three weeks before the current presentation, the patient underwent lumbar hemilaminectomy, facetectomy, and foraminotomy on the left side, with excision of a herniated disk and decompression of the nerve root, at another hospital. On postoperative day 1, back pain increased substantially, and oxycodone was prescribed. Owing to the back pain, which did not abate after oxycodone treatment, and the development of left leg pain with resultant limited mobility, prednisone was prescribed on postoperative day 3.

On postoperative day 4, the patient was readmitted to the other hospital. The blood levels of glucose and electrolytes were normal, as were the results of tests of kidney function; other laboratory test results are shown in Table 1. Magnetic resonance imaging (MRI) of the lumbar spine, performed after the administration of intravenous contrast material, reportedly showed postsurgical changes and an epidural fluid collection, measuring 16 mm in diameter, on the left side at the level of the fifth lumbar vertebra; a radiograph of the left leg was reportedly normal, and ultrasonography showed no deep venous thrombosis in the legs. Treatment with intravenous dexamethasone and oral acetaminophen, cyclobenzaprine, celecoxib, gabapentin, hydromorphone, and tramadol was administered.

Seven days before the current presentation, leg pain persisted, and the patient noticed a new erythematous rash on her legs, chest, buttocks, back, and cheeks. She contacted her primary care physician and reported that the rash had started as hives and had then become “welts.” The tympanic temperature measured by the patient at home was 39.1°C, and she was instructed by her primary care physician to take diphenhydramine and ibuprofen and to stop taking all other medications except gabapentin.

Six days later, the patient was evaluated by her primary care physician, who prescribed oral doxycycline for a presumed skin infection. The next day, fever recurred, the right eyelid became swollen and painful with motion, and horizontal diplopia developed. The patient presented to the emergency department of this hospital.

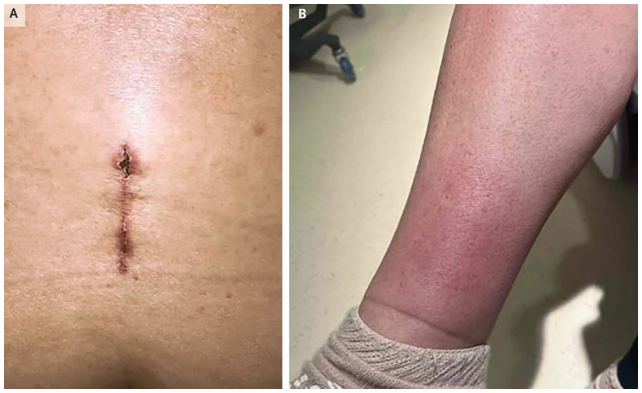
Variable	Reference Range, Adults, Other Hospital	Approximately 2 Wk before the Current Presentation, Other Hospital	Reference Range, Adults, This Hospital*	On Initial Evaluation, This Hospital
Hemoglobin (g/dl)	12.0–16.0	12.1	12.0–16.0	10.6
Hematocrit (%)	36.0–46.0	35.2	36.0–46.0	31.8
White-cell count (per μl)	4000–11,000	11,790	4500–11,000	6530
Platelet count (per μl)	150,000–350,000	434,000	150,000–400,000	200,000
Erythrocyte sedimentation rate (mm/hr)	—	—	0–30	95
C-reactive protein (mg/liter)	—	—	0.0–8.0	117.8

On evaluation in the emergency department, the patient reported ongoing leg pain and fever but no chills or diaphoresis, although she recalled that she had had 3 days of chills and body aches before the lumbar surgery. Aside from diplopia, which decreased with covering one eye, she did not report worsening visual acuity or changes in color vision. She had no hearing loss, sinus or ear symptoms, headache, neck stiffness, weakness, falls, or paresthesia (except for chronic numbness in the toes of the left foot). She reported a persistent erythematous rash on her legs. She had no weight change, photosensitivity associated with the rash, oral or genital ulcers, Raynaud’s phenomenon, jaw claudication, dysphagia, lightheadedness, dyspnea, or chest pain. No pulmonary, gastroenterologic, or genitourinary symptoms were present.

Medical history included lumbar spondylosis and disk protrusion with radiculopathy, type 2 diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease, colonic polyps, obstructive sleep apnea, asthma, allergic rhinitis, eczema, anxiety, and periodic limb movement disorder. Medications included gabapentin, aspirin, rosuvastatin, losartan, hydrochlorothiazide, and sertraline, as well as clonazepam as needed. Amoxicillin had caused lip swelling, and lisinopril had caused a cough. The patient had received vaccinations against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

The patient worked in education and lived in a coastal suburban area of eastern Massachusetts with her husband and dog. She frequently walked her dog in a wooded area. Recent travel included a trip to Europe; she had had no specific animal, food, or insect exposures. She occasionally drank wine and did not use tobacco or other substances. Her family history included hyperlipidemia and coronary artery disease in her father, mother, and brother. Her father also had diabetes and diverticulosis, and her maternal grandmother had had breast cancer.

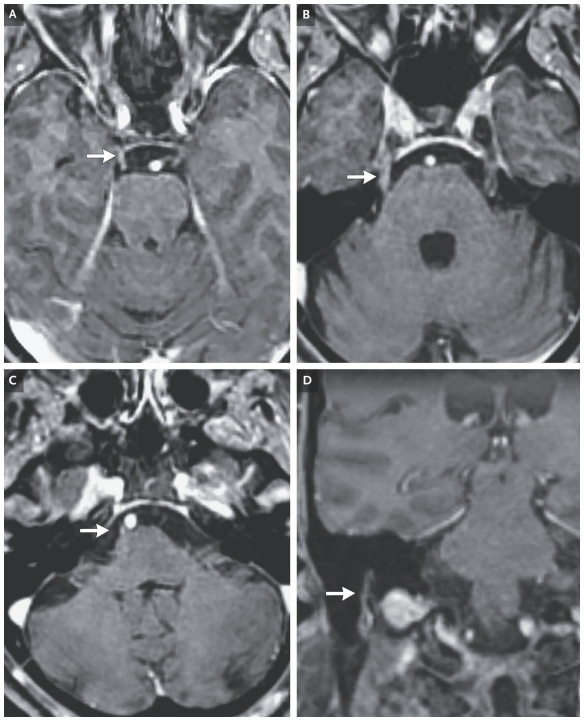
Ophthalmologic examination revealed right esotropia, which was worse with attempted abduction, and slight ptosis, with the right pupil slightly smaller than the left pupil. No conjunctival erythema or scleral icterus was present. The remainder of the neurologic examination, including evaluation of other cranial-nerve function, strength, sensation, reflexes, and coordination, was normal. The lumbar surgical-incision site was well-approximated and clean, without drainage or fluctuance. Confluent erythematous macules, measuring approximately 5 cm in diameter overall, were present on the right lower leg and buttocks, without palpable purpura. There was no palpable lymphadenopathy.



Clinical Photographs.

The incision site of lumbar hemilaminectomy, which had been performed 3 weeks before the current presentation, is shown (Panel A). On arrival at the emergency department, the patient had confluent erythematous macules on the right lower leg (Panel B) and buttocks (not shown).

The blood levels of electrolytes, glucose, albumin, globulin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and creatine kinase were normal, as were the white-cell count and differential count and the results of tests of kidney function; other laboratory test results are shown in. Tests for SARS-CoV-2, influenza A and B viruses, human immunodeficiency virus types 1 and 2, and hepatitis C virus antibodies were negative. Urinalysis was normal. A chest radiograph was normal. Computed tomographic (CT) angiography of the head and neck, performed after the administration of intravenous contrast material, showed no intracranial vascular abnormality. MRI of the head, performed after the administration of intravenous contrast material, showed no infarct or mass, but enhancement was noted along cranial nerves III, V, VI, and VII on the right side. Treatment with intravenous acyclovir and oral doxycycline, acetaminophen, ibuprofen, and diazepam was administered. The patient was admitted to the neurology unit of this hospital. Diagnostic tests were performed, and management decisions were made.



MRI of the Head and Neck.

Gadolinium-enhanced axial (Panels A, B, and C) and coronal (Panel D) T1-weighted images of the head and neck show smooth enhancement along cranial nerves III (Panel A, arrow), V (Panel B, arrow), VI (Panel C, arrow), and VII (Panel D, arrow) on the right side.

Autoimmune or inflammatory disease

Systemic rheumatic (sarcoidosis, ANCA-associated vasculitis, IgG4-related disease, Sjögren's syndrome, systemic lupus erythematosus, or Behçet's disease)

Neurologic (multiple sclerosis, Guillain–Barré syndrome, neuromyelitis optica, or Tolosa–Hunt syndrome)

Cancer (perineural spread of tumor cells, metastatic disease, primary nerve tumors, or lymphoma)

Infection

Bacterial (typical bacterial infection [e.g., with staphylococcus or streptococcus species], brucellosis, tuberculosis, listeria infection, syphilis, Lyme disease, or *Borrelia miyamotoi* infection)

Viral

Herpesvirus infection (varicella–zoster virus infection, herpes simplex virus type 1 infection, or Epstein–Barr virus infection)

Arbovirus infection (West Nile virus infection, Powassan virus infection, eastern equine encephalitis, or western equine encephalitis)

Fungal (cryptococcal infection, aspergillosis, or mucormycosis)

Other condition (a physiologic finding in a healthy person, ophthalmoplegia, migraine, ischemia, surgery, head trauma, or radiation exposure)

Discussant

Multiple aspects of this case suggest Lyme disease. Lyme disease is a tickborne infection caused by the spirochete *B. burgdorferi*. Lyme disease is endemic in the northeastern United States, where this patient resides, and she probably had tick exposures through frequent dog walking. A single expanding erythema migrans rash is the initial clinical sign of the disease in many patients, occurring within days to several weeks after a tick bite. This patient did not recall a tick bite or an initial erythema migrans rash, but the absence of those findings does not rule out the diagnosis of Lyme disease. Erythema migrans may be accompanied by flulike symptoms, headache, and malaise. Infection may then disseminate and cause further skin lesions, including a rash with multiple erythema migrans lesions, which could explain the rash this patient described on her legs, chest, buttocks, back, and cheeks. Disseminated infection can also cause neurologic, cardiac, and joint disease. Neurologic involvement occurs in 15% of cases of Lyme disease. Lyme neuroborreliosis is characterized by lymphocytic meningitis, painful radiculitis, and cranial neuropathies. Approximately 43% of persons with Lyme neuroborreliosis have cranial-nerve involvement, most commonly with cranial nerve VII, followed by cranial nerve III. Facial palsy is the most common manifestation of Lyme neuroborreliosis in the United States. Bannwarth's syndrome, a subset of Lyme neuroborreliosis that is more common in Europe than in the United States, involves a triad of painful radiculopathy, cerebrospinal fluid (CSF) lymphocytic pleocytosis, and cranial neuritis. Although this patient's leg pain may be related to recent surgery or worsening of previous nerve-root compression, the description could be consistent with radiculitis. Some patients with Lyme neuroborreliosis may have multiple nerve palsies or radiographic enhancement, as was seen in this patient; cranial-nerve enhancement may also be clinically occult.

Although the month of presentation was not included in the case history provided, I inquired specifically and learned that the patient presented in July, the peak month of onset of neurologic manifestations of Lyme disease. I think that the most likely diagnosis is Lyme neuroborreliosis. The diagnostic test of choice would be serologic testing for antibodies against *B. burgdorferi*. If a lumbar puncture was performed, CSF antibody testing could be performed to ultimately determine the CSF–serum antibody index.

Diagnostic Testing

The major diagnostic tests for Lyme disease detect antibody responses to *B. burgdorferi*. The standard two-tiered approach first measures IgM and IgG responses to *B. burgdorferi*, either separately or together, with an enzyme immunoassay, usually with the use of a *B. burgdorferi* whole-cell sonicate. Then, in samples with an equivocal or positive response, Western blot (or line blot) analysis for IgM and IgG is performed. However, a positive IgM response alone should be used only to support the diagnosis of Lyme disease during the first month of infection; after that time, patients usually have an IgG response, which is more specific than an IgM response.

The Food and Drug Administration has approved a modified two-tiered approach involving two enzyme immunoassays that each determine IgM and IgG responses to different *B. burgdorferi* antigens. The modified approach is more sensitive than the standard two-tiered approach during early infection. However, the standard two-tiered approach provides more information and therefore may be helpful in more complicated cases even in patients with early disease (such as the patient in this case), as well as in patients with late disease. CSF testing must account for the passive transfer of IgG across the blood–brain barrier. Therefore, concomitant serum and CSF samples are needed to test for IgG against *B. burgdorferi*, and the results are adjusted on the basis of total IgG levels in both types of samples. In this patient, serologic testing was performed with the use of the modified approach, which showed positive IgM and IgG responses to B. burgdorferi, as is typically seen in patients with acute Lyme neuroborreliosis.

Final Diagnosis

Lyme neuroborreliosis and coinfection with *Babesia microti*.

A sedentary lifestyle—defined as excessive sitting or low energy expenditure—significantly increases the risk of premature death, with risks comparable to smoking or obesity. Sitting for over eight hours a day without exercise raises mortality risk by nearly 38%, with 1 in 6 deaths attributed to inactivity. It doubles the risk of cardiovascular disease, diabetes, and obesity.

Deaths potentially averted by small changes in physical activity and sedentary time: an individual participant data meta-analysis of prospective cohort studies

Summary

Background The effects of small, realistic changes in physical activity and sedentary behaviour on population-level mortality are unclear. We aimed to estimate the proportion of deaths preventable by 5-min and 10-min incremental increases in moderate-to-vigorous intensity physical activity (MVPA) and 30-min and 60-min reductions in daily sedentary time.

Methods We did an individual participant data meta-analysis of prospective cohort studies. We included studies with device-measured physical activity and sedentary time. We estimated the proportion of deaths prevented (potential impact fractions; PIFs) by changes in (1) the approximately 20% least active participants (high-risk approach) and (2) all participants except the approximately 20% most active (population-based approach). We calculated PIFs from adjusted hazard ratios estimated for 5-min and 10-min increases in MVPA and 30-min and 60-min reductions in sedentary time from observed levels across the activity distribution.

Findings We included seven cohorts from Norway, Sweden, and the USA (n=40 327; 4895 deaths). Data from the UK Biobank (n=94 719; 3487 deaths) were analysed separately. A 5-min/day increase in MVPA in the least active participants might prevent 6·0% (95% CI 4·3–7·4) of all deaths. A similar increase in MVPA in all participants except the most active might prevent 10·0% (6·3–13·4) of all deaths. Reducing sedentary time by 30 min/day might prevent 3·0% (2·0–4·1) of all deaths in the high-risk approach and 7·3% (4·8–9·6) in the population-based approach. Results from the UK Biobank were of a smaller magnitude but still substantial—eg, reducing sedentary time by 30 min/day in all except the most active participants was associated with preventing 4·5% (2·8–6·1) of total deaths.

Interpretation Small and realistic increases in MVPA of 5 min/day might prevent up to 6% of all deaths in a high-risk approach and 10% of all deaths in population-based approach. Reducing sedentary time by 30 min/day might prevent a smaller, but still meaningful, proportion of deaths in the two risk scenarios.

	ABC (n=719), Sweden*		HAI (n=4271), Sweden†		NHANES (n=3871), USA‡		REGARDS (n=7276), USA§	
	Women	Men	Women	Men	Women	Men	Women	Men
Participants	399 (55·5%)	320 (44·5%)	2172 (50·9%)	2099 (49·1%)	1958 (50·6%)	1913 (49·4%)	3964 (54·5%)	3312 (45·5%)
Deaths	31 (7·8%)	47 (14·7%)	33 (1·5%)	58 (2·8%)	524 (26·8%)	617 (32·3%)	729 (18·4%)	918 (27·7%)
Follow-up time, years	14·3 (1·7)	13·9 (2·3)	3·8 (1·9)	3·9 (1·9)	13·5 (3·3)	12·9 (3·8)	9·9 (3·2)	9·6 (3·3)
Age, years	54·6 (9·1)	55·5 (9·1)	70·4 (0·2)	70·4 (0·3)	60·6 (12·9)	60·5 (12·9)	68·2 (8·7)	69·8 (8·3)
Age ≥60 years	117 (29·3%)	103 (32·2%)	2172 (100%)	2099 (100%)	1020 (52·1%)	984 (51·4%)	3298 (83·2%)	2945 (88·9%)
Sedentary time, min/day	509 (96·1)	529 (103)	550 (82·7)	563 (85·8)	498 (112)	511 (125)	693 (82·2)	689 (83·6)
Total physical activity, min/day	369 (101)	365 (110)	293 (74·5)	284 (78·6)	341 (101)	343 (111)	148 (71·8)	161 (76·4)
Light-intensity physical activity, min/day	340 (89·9)	330 (96·9)	263 (68·4)	249 (71·9)	327 (94·2)	320 (99·6)	141 (66·8)	151 (69·9)
Moderate-to-vigorous intensity physical activity, min/day	29·6 (31·6)	35·0 (30·6)	30·4 (24·0)	34·4 (26·4)	13·9 (16·5)	23·6 (24·8)	6·7 (11·6)	10·0 (15·2)
BMI, kg/m²	25·6 (3·9)	26·0 (2·9)	26·3 (4·6)	26·7 (3·7)	29·1 (6·6)	28·3 (5·3)	28·8 (6·3)	28·3 (4·7)
BMI ≥30 kg/m²	51 (12·8%)	30 (9·4%)	403 (18·6%)	351 (16·7%)	735 (37·5%)	575 (30·1%)	1453 (36·7%)	968 (29·2%)
Smoking								
Never	164 (41·1%)	126 (39·4%)	1077 (49·6%)	959 (45·7%)	1159 (59·2%)	681 (35·6%)	2272 (57·3%)	1350 (40·8%)
Former	121 (30·3%)	131 (40·9%)	934 (43·0%)	1016 (48·4%)	497 (25·4%)	808 (42·2%)	1277 (32·2%)	1619 (48·9%)
Current	114 (28·6%)	63 (19·7%)	161 (7·4%)	124 (5·9%)	302 (15·4%)	424 (22·2%)	415 (10·5%)	343 (10·4%)
Education								
Primary	120 (30·1%)	117 (36·6%)	266 (12·2%)	391 (18·6%)	529 (27·0%)	577 (30·2%)	255 (6·4%)	172 (5·2%)
High school	145 (36·3%)	117 (36·6%)	890 (41·0%)	831 (39·6%)	515 (26·3%)	440 (23·0%)	2069 (52·2%)	1489 (45·0%)
University	134 (33·6%)	86 (26·9%)	1016 (46·8%)	877 (41·8%)	914 (46·7%)	896 (46·8%)	1640 (41·4%)	1651 (49·8%)
History of cardiovascular disease¶	6 (1·5%)	22 (6·9%)	120 (5·5%)	333 (15·9%)	255 (13·0%)	339 (17·7%)	336 (8·5%)	553 (16·7%)
History of cancer¶	12 (3·0%)	8 (2·5%)	816 (37·6%)	481 (22·9%)	255 (13·0%)	216 (11·3%)	222 (12·1%)‖	314 (14·5%)‖
Diabetes¶	9 (2·3%)	11 (3·4%)	130 (6·0%)	226 (10·8%)	269 (13·7%)	271 (14·2%)	505 (12·7%)	482 (14·6%)

Data are n (%) or mean (SD). ABC=Activity, Behaviour, Change. HAI=Healthy Aging Initiative. NHANES=National Health and Nutrition Examination Survey. REGARDS=Reasons for Geographical and Racial Differences in Stroke. *ActiGraph 7164 (lower back). †ActiGraph GT3X+ (right hip). ‡ActiGraph 7164 (right hip). §Actical (right hip). ¶Binary variables (yes or no). ‖Percentages calculated out of 1836 women and 2172 men with non-missing observations.

Table 1: **Descriptive characteristics of the ABC, HAI, NHANES, and REGARDS cohorts**

	WHS (n=16 316), USA*		NNPAS (n=2208), Norway†		Tromsø study (5666), Norway‡		UK Biobank Study (94 719), UK§	
	Women	Men	Women	Men	Women	Men	Women	Men
Participants	16 316 (100%)	0	1168 (52·9%)	1040 (47·1%)	3025 (53·4%)	2641 (46·6%)	53 449 (56·4%)	41 270 (43·6%)
Deaths	1584 (9·7%)	..	37 (3·2%)	77 (7·4%)	97 (3·2%)	143 (5·4%)	1414 (2·6%)	2073 (5·0%)
Follow-up time, years	8·8 (1·6)	..	9·0 (0·7)	8·8 (1·0)	7·1 (0·5)	7·0 (0·7)	8·0 (0·8)	7·9 (0·9)
Age, years	72·0 (5·7)	..	55·8 (11·0)	57·1 (10·7)	62·9 (10·3)	63·4 (10·1)	61·8 (7·7)	63·0 (7·9)
Age ≥60 years	16 316 (100%)	..	415 (35·5%)	418 (40·2%)	2066 (68·3%)	1895 (71·8%)	32 209 (60·3%)	27 327 (66·2%)
Sedentary time, min/day	503 (103)	..	548 (83·2)	579 (86·8)	714 (82·0)	727 (89·6)	547 (104)	586 (111)
Total physical activity, min/day	388 (101)	..	337 (83·0)	314 (88·4)	327 (83·1)	312 (88·8)	360 (102)	325 (105)
Light-intensity physical activity, min/day	353 (87·3)	..	303 (75·7)	277 (80·6)	299 (75·7)	280 (78·5)	325 (95·9)	276 (94·7)
Moderate-to-vigorous intensity physical activity, min/day	35·3 (29·8)	..	33·7 (23·4)	37·2 (26·5)	27·9 (22·0)	31·4 (25·4)	35·2 (30·0)	49·6 (38·5)
BMI, kg/m²	26·2 (5·0)	..	25·1 (4·2)	26·4 (3·4)	26·8 (4·7)	27·7 (3·9)	26·3 (4·8)	27·3 (4·0)
BMI ≥30 kg/m²	3186 (19·5%)	..	136 (11·6%)	136 (13·1%)	643 (21·3%)	623 (23·6%)	9721 (18·2%)	8602 (20·8%)
Smoking								
Never	8242 (50·5%)	..	535 (45·8%)	451 (43·4%)	1222 (40·4%)	1002 (37·9%)	32 602 (61·0%)	21 602 (52·3%)
Former	7506 (46·0%)	..	397 (34·0%)	426 (41·0%)	1421 (47·0%)	1350 (51·1%)	17 713 (33·1%)	16 307 (39·5%)
Current	568 (3·5%)	..	236 (20·2%)	163 (15·7%)	382 (12·6%)	289 (10·9%)	3134 (5·9%)	3361 (8·1%)
Education								
Primary	0	..	199 (17·0%)	185 (17·8%)	932 (30·8%)	678 (25·7%)	4229 (7·9%)	3598 (8·7%)
High school	8105 (49·7%)	..	443 (37·9%)	408 (39·2%)	800 (26·4%)	801 (30·3%)	26 544 (49·7%)	19 152 (46·4%)
University	8211 (50·3%)	..	526 (45·0%)	447 (43·0%)	1293 (42·7%)	1162 (44·0%)	22 676 (42·4%)	18 520 (44·9%)
History of cardiovascular disease¶	680 (4·2%)	..	55 (4·7%)	118 (11·3%)	206 (6·8%)	403 (15·3%)	1690 (3·2%)	3529 (8·6%)
History of cancer¶	1931 (11·8%)	..	76 (6·5%)	68 (6·5%)	300 (9·9%)	286 (10·8%)	7565 (14·2%)	4119 (10·0%)
Diabetes¶	1482 (9·1%)	..	35 (3·0%)	65 (6·3%)	164 (5·4%)	184 (7·0%)	1283 (2·4%)	1963 (4·8%)

Data are n (%) or mean (SD). NNPAS=Norwegian National Physical Activity Survey. WHS=Women's Health Study. *ActiGraph GT3X+ (right hip). †ActiGraph GT1M (right hip). ‡ActiGraph wGT3X-BT (right hip). §Axivity AX3 (wrist). ¶Binary variables (yes or no).

Table 2: **Descriptive characteristics of the WHS, NNPAS, Tromsø study, and UK Biobank Study cohorts**

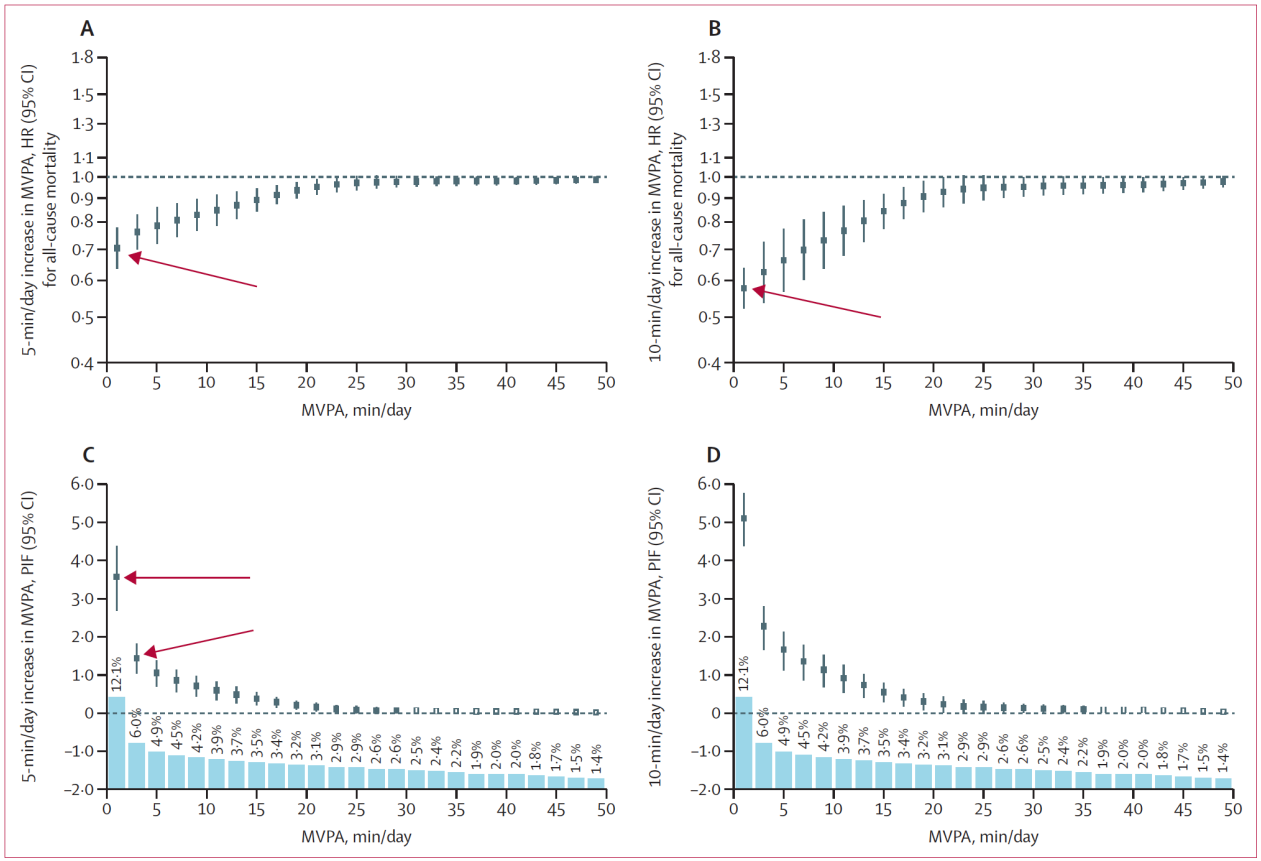


Figure 1: **MVPA and mortality risk in the accelerometer consortium**

Figure shows results of meta-analysis of seven studies. HRs for mortality for 5-min/day (eg, the HR for a 5-min/day increase from 1 min/day to 6 min/day [red arrow]; A) and 10-min/day (eg, the HR for a 10-min/day increase from 1 min/day to 11 min/day [red arrow]; B) increases in MVPA from observed level. Percentage PIF for 5-min/day (eg, a 5/min/day increase in MVPA in those who accumulated ≤2 min/day of MVPA was associated with 3·6% of preventable deaths [red arrow], and a 5-min increase among those accumulating 2–4 min of MVPA per day was associated with 1·4% of preventable deaths [red arrow]; C) and 10-min/day increase in MVPA from observed level (D). Bar charts show distribution and percentages of participants. All results are based on fully adjusted models (age, sex, accelerometer wear-time, BMI, smoking, education, cardiovascular disease, cancer, and diabetes). HR=hazard ratio. MVPA=moderate-to-vigorous-intensity physical activity. PIF=population impact fraction.

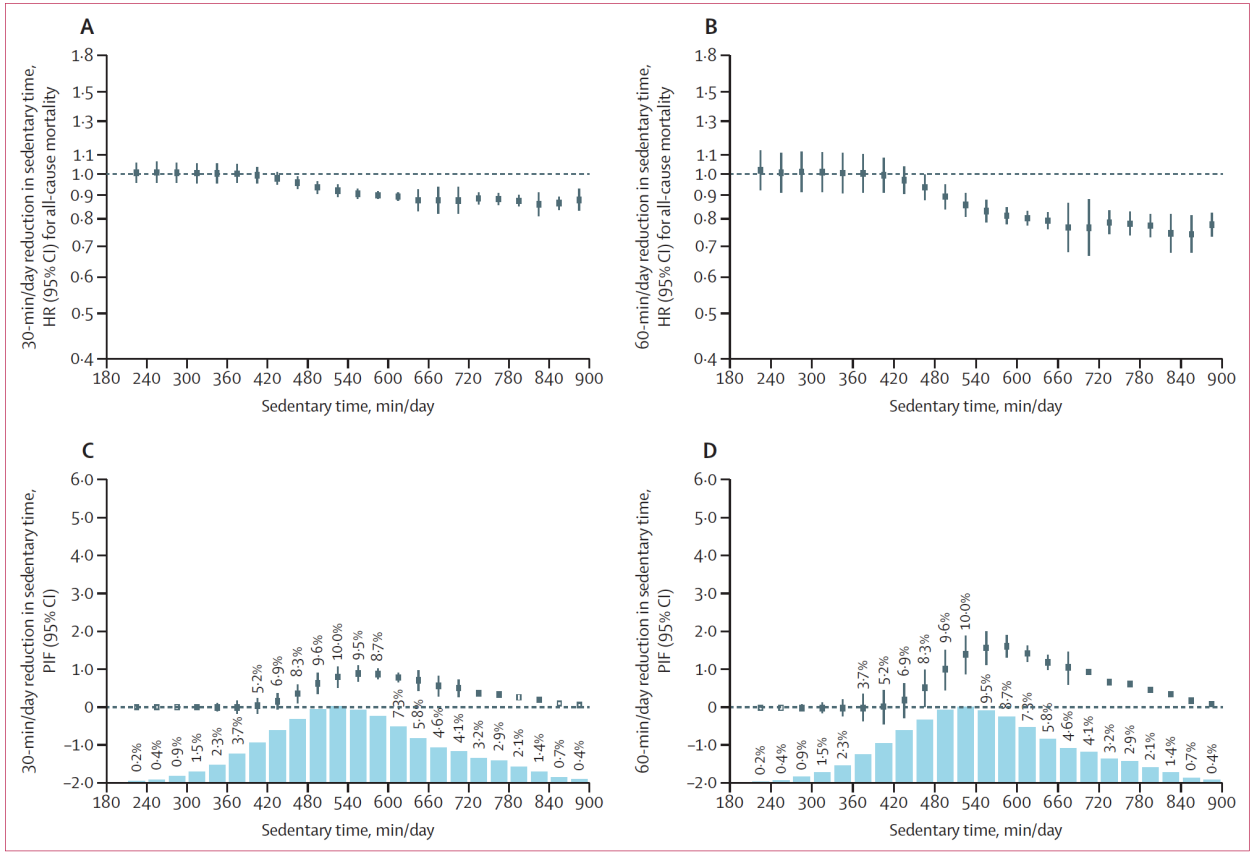


Figure 2: **Sedentary time and mortality risk in the accelerometer consortium**

Figure shows results of meta-analysis of six studies. HRs for mortality for 30-min/day (A) and 60-min/day (B) decrease in sedentary time from observed level. Percentage PIF for 30-min/day (C) and 60 min/day (D) decrease in sedentary time from observed level. Bar charts show distribution and percentages of participants. All results are based on fully adjusted models (age, sex, accelerometer wear-time, BMI, smoking, education, cardiovascular disease, cancer, and diabetes). HR=hazard ratio. MVPA=moderate-to-vigorous-intensity physical activity. PIF=population impact fraction.

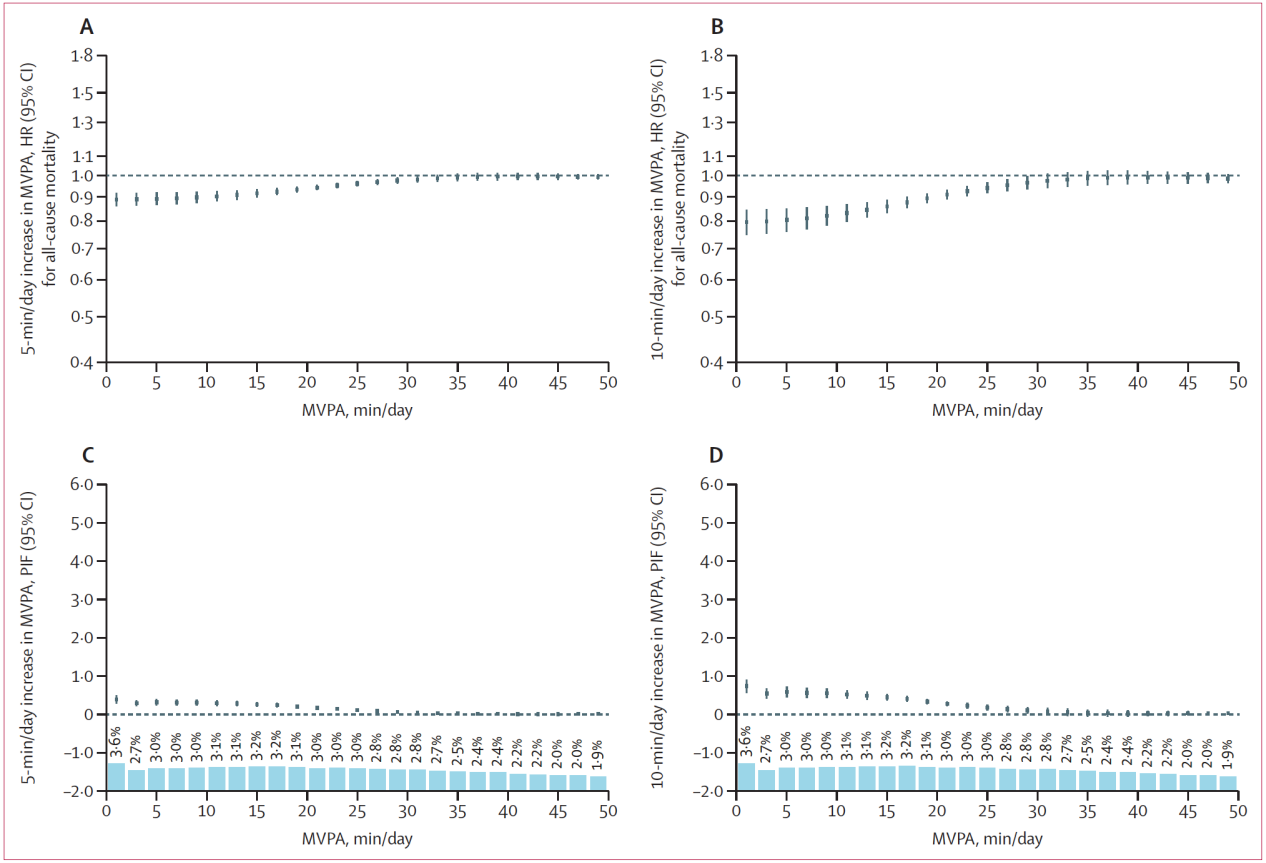


Figure 3: **MVPA and mortality risk in the UK Biobank Study**

HRs for mortality for 5-min/day (A) and 10-min/day (B) increase in MVPA from observed level. Percentage PIF for 5-min/day (C) and 10-min/day (D) increase in MVPA from observed level. Bar charts show distribution and percentages of participants. All results are based on fully adjusted models (age, sex, accelerometer wear-time, BMI, smoking, education, cardiovascular disease, cancer, and diabetes). HR=hazard ratio. MVPA=moderate-to-vigorous-intensity physical activity. PIF=population impact fraction.

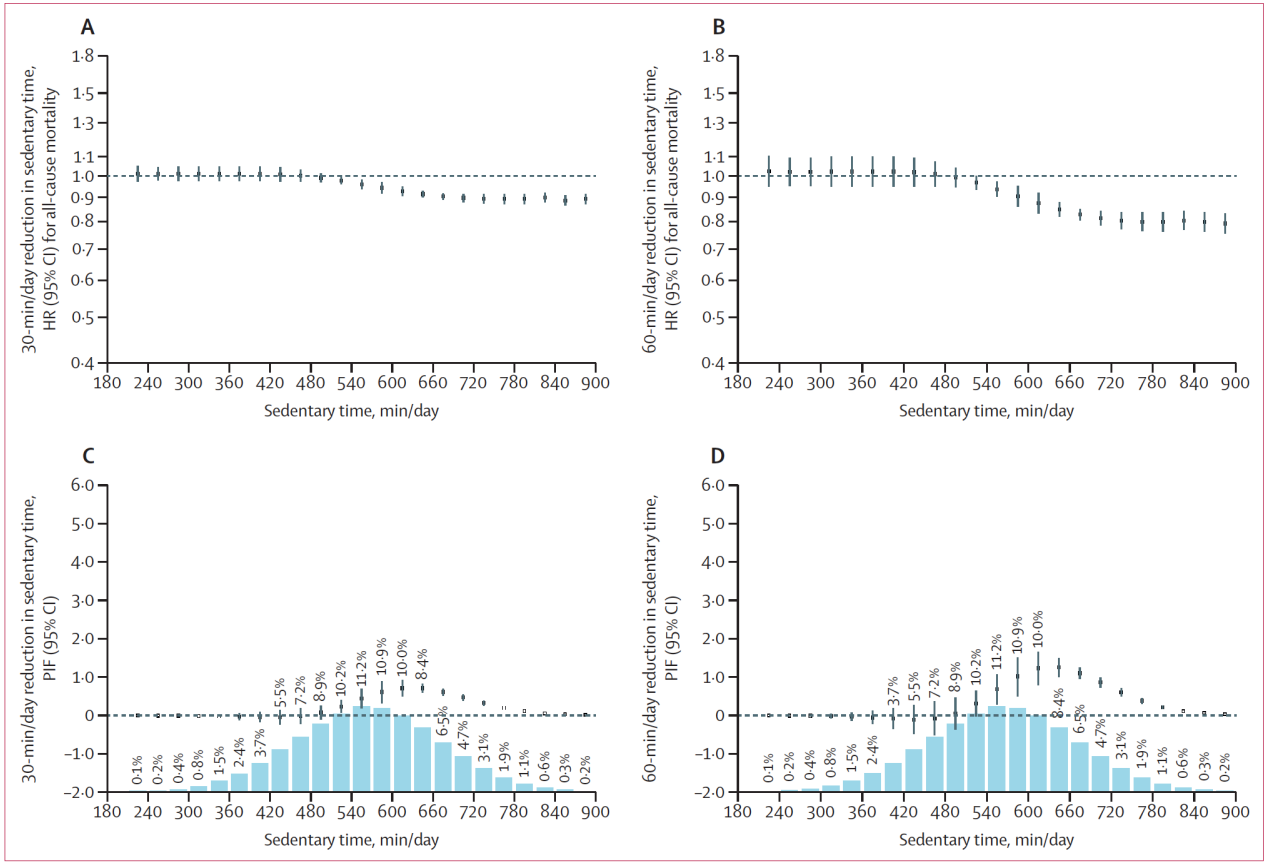


Figure 4: **Sedentary time and mortality risk in the UK Biobank Study**

HRs for mortality for 30-min/day (A) and 60-min/day (B) decrease in sedentary time from observed level. Percentage PIF for 30-min/day (C) and 60-min/day (D) decrease in sedentary time from observed level. Bar charts show distribution and percentages of participants. All results are based on fully adjusted models (age, sex, accelerometer wear-time, BMI, smoking, education, cardiovascular disease, cancer, and diabetes). HR=hazard ratio. PIF=population impact fraction.

	High-risk approach*	Population approach†
Moderate-to-vigorous intensity physical activity, 5-min/day increase		
Accelerometer consortium	6·0% (4·3–7·4)	10·0% (6·3–13·4)
UK Biobank Study	2·2% (1·6–2·7)	3·6% (2·4–4·8)
Moderate-to-vigorous intensity physical activity, 10-min/day increase		
Accelerometer consortium	8·8% (7·0–10·4)	14·9% (9·7–19·3)
UK Biobank Study	3·9% (3·0–4·7)	6·2% (4·0–8·2)
Light-intensity physical activity, 30-min/day increase		
Accelerometer consortium	3·3% (2·4–4·1)	5·4% (2·2–8·3)
UK Biobank Study	2·8% (2·3–3·2)	4·0% (2·2–5·7)
Light-intensity physical activity, 60-min/day increase		
Accelerometer consortium	5·5% (4·0–6·7)	8·9% (3·1–13·8)
UK Biobank Study	4·7% (3·9–5·3)	6·0% (2·7–9·2)
Sedentary time, 30-min/day decrease		
Accelerometer consortium	3·0% (2·0–4·1)	7·3% (4·8–9·6)
UK Biobank Study	2·5% (2·1–2·9)	4·5% (2·8–6·1)
Sedentary time, 60-min/day decrease		
Accelerometer consortium	5·5% (3·9–6·9)	12·6% (8·4–16·4)
UK Biobank Study	4·6% (3·8–5·3)	7·6% (4·4–10·6)
Total physical activity, 30-min/day increase		
Accelerometer consortium	3·4% (2·5–4·2)	6·1% (3·1–8·9)
UK Biobank Study	2·5% (2·2–2·9)	4·5% (2·8–6·1)
Total physical activity, 60-min/day increase		
Accelerometer consortium	5·5% (4·1–6·8)	10·6% (5·7–14·9)
UK Biobank Study	4·4% (3·8–5·0)	7·2% (4·0–10·1)

Results are based on meta-analysis of seven (or six; the REGARDS study is only included in the meta-analysis for moderate-to-vigorous intensity physical activity) studies in the accelerometer consortium and a separate analysis of the UK Biobank Study. PIF=potential impact fraction. REGARDS=Reasons for Geographical and Racial Differences in Stroke. *Cumulative PIF calculated for the approximately 20% least active participants. †Cumulative PIF calculated for all participants except the approximately 20% most active participants.

***Table 3*: Cumulative PIF (95% CI) for changes in moderate and vigorous physical activity, light physical activity, sedentary time, and total physical activity**

Research in context

Evidence before this study

Estimates of the population attributable fraction, which represent the theoretical number of deaths averted if all individuals currently not meeting WHO's physical activity recommendations became active by meeting recommendations, have several major methodological limitations. These include overlooking the health benefits that can be achieved by increasing physical activity even below the WHO-recommended level, and relying on self-reported physical activity data, which are prone to biases. We searched PubMed and Google Scholar from database inception to Aug 15, 2024, using the terms "physical activity", "mortality", and "population attributable fraction" and found two articles estimating the number of deaths that are potentially averted by increasing levels of device-measured physical activity. One study was restricted to individuals with prevalent cardiovascular diseases, and the other used a small sample from a single US cohort. Therefore, it remains uncertain how minor, yet potentially more achievable, population-level increases in physical activity or decreases in sedentary time might affect the proportion of preventable deaths.

Added value of this study

Our results are derived from the observed physical activity levels and the non-linear dose–response associations between physical activity and sedentary time with risk of mortality. This approach extends previous observations that were based on a theoretical elimination of physical inactivity estimated from self-reported data. Access to individual participant data allowed us to use continuous minute-by-minute, device-measured physical activity and sedentary time data, harmonising exposures, covariates, and statistical analyses across cohorts, using consistent inclusion criteria, and minimised loss of information and power.

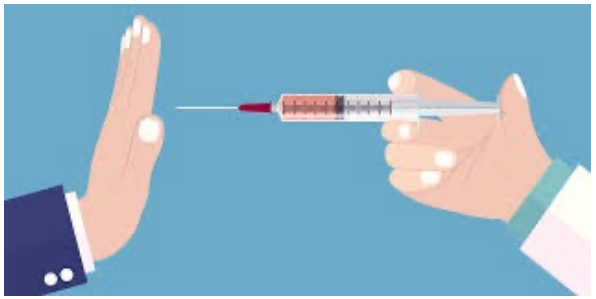
Implications of all the available evidence

Considering that it is unlikely for all individuals to achieve the WHO physical activity recommendation of 150 min of moderate-to-vigorous-intensity physical activity (MVPA) weekly, our data underscore the large impact of realistic and achievable behaviour changes on population health. If the least active 80% of participants had increased MVPA by 5 min/day or reduced sedentary time by 30 min/day, 10% and 7% of all deaths, respectively, might have been avoided during the follow-up period.

Vaccine hesitancy is defined by the World Health Organization (WHO) as a **delay in acceptance or refusal of vaccines** despite the availability of vaccination services. It is recognized as one of the top 10 threats to global health.

Key Influencing Factors

- **Misinformation and Social Media:** The rapid spread of debunked claims—such as the false link between the MMR vaccine and autism—is amplified by digital platforms, creating an "infodemic" that fuels skepticism.
- **Demographics:** As of 2026, research shows that **younger individuals (18–34)** often express higher hesitancy, partly due to lower perceived risk of severe illness. Women have also reported higher concern regarding side effects like fertility, which have been scientifically disproven.
- **Socioeconomic Status:** While higher education often promotes vaccine acceptance, it can also lead to increased "calculation" or questioning of medical authority. Conversely, economic deprivation is a consistent predictor of lower uptake due to limited access and lower trust in institutions.
- **Historical and Cultural Context:** Historical medical injustices (e.g., the Tuskegee Syphilis Study) and religious beliefs regarding vaccine ingredients (e.g., porcine gelatin) significantly impact specific communities.



Profiling vaccine attitudes and subsequent uptake in 1·1 million people in England: a nationwide cohort study

Summary

Background Despite highly effective vaccines against SARS-CoV-2, COVID-19 vaccine hesitancy persisted in some populations in England during the pandemic, with rates and motivations for hesitancy varying by demographic group. Addressing the drivers of vaccine hesitancy through targeted interventions in hesitant groups is a public health priority for better and more rapid control of disease spread. We aimed to characterise the determinants and subtypes of vaccine hesitancy and identify more persistent forms of hesitancy via analysis of vaccine uptake in a large cross-sectional cohort with linked National Health Service (NHS) data.

Methods We conducted an initial cross-sectional analysis of vaccine hesitancy at baseline, followed by a longitudinal analysis of vaccine uptake in the hesitant cohort. We analysed survey data from the Real-time Assessment of Community Transmission (REACT) studies, which monitored the prevalence of SARS-CoV-2 in England during the COVID-19 pandemic at regular intervals from May 1, 2020, to March 31, 2022, in random samples of the population. Participants self-reported detailed sociodemographic information, vaccination status, and attitudes towards vaccination. Participants were classified as hesitant if they reported that they had refused, planned to refuse, or had not yet decided whether to receive the COVID-19 vaccine. Participants who said they were unvaccinated when NHS records showed that they had been vaccinated were excluded from further analysis. The primary outcome of the cross-sectional analysis was vaccine hesitancy. Longitudinal analysis of vaccine uptake was done in participants in the hesitant cohort who consented to the use of linked NHS vaccination records to track their vaccination history after the survey, with post-survey vaccination as the outcome. Consensus clustering was used to categorise reasons for vaccine hesitancy, and cross-sectional and longitudinal analyses used logistic regression models to identify demographic predictors of vaccine hesitancy and subsequent vaccination.

Findings Our analyses included 1 137 927 adults (aged 18 years and older) surveyed between Jan 6, 2021, and March 31, 2022. Across the whole study period, 37 982 (3·3%) participants indicated some form of vaccine hesitancy. Hesitancy rates peaked at 8·0% in early 2021, subsequently decreasing to a low of 1·1% at the start of 2022, and increasing to 2·2% in early 2022. Of the 24 229 participants who indicated hesitancy and consented to NHS data linkage, 15 744 (65·0%) went on to receive one or more vaccinations. Cluster analysis identified eight stable categories of vaccine hesitancy, including concerns about effectiveness and side-effects, perception of low risk from COVID-19 and mistrust of vaccine developers, and fear of vaccines and reactions. The most prevalent categories of hesitancy, related to effectiveness and health concerns, declined substantially over the roll-out period and were not strongly associated with the likelihood of later vaccination. Some forms of hesitancy, primarily related to low trust, low risk perception, and general anti-vaccine sentiment, were more resistant, rebounded in 2022, and were strongly associated with a lower likelihood of subsequent vaccination.

Interpretation Our findings suggest that most COVID-19 vaccine hesitancy was rooted in concrete concerns that can be addressed and successfully overcome with time and increasing availability of information. These findings should help future vaccination roll-outs to encourage vaccine acceptance.

Funding UK National Institute for Health and Care Research, UK Research and Innovation, and the UK Department of Health and Social Care.

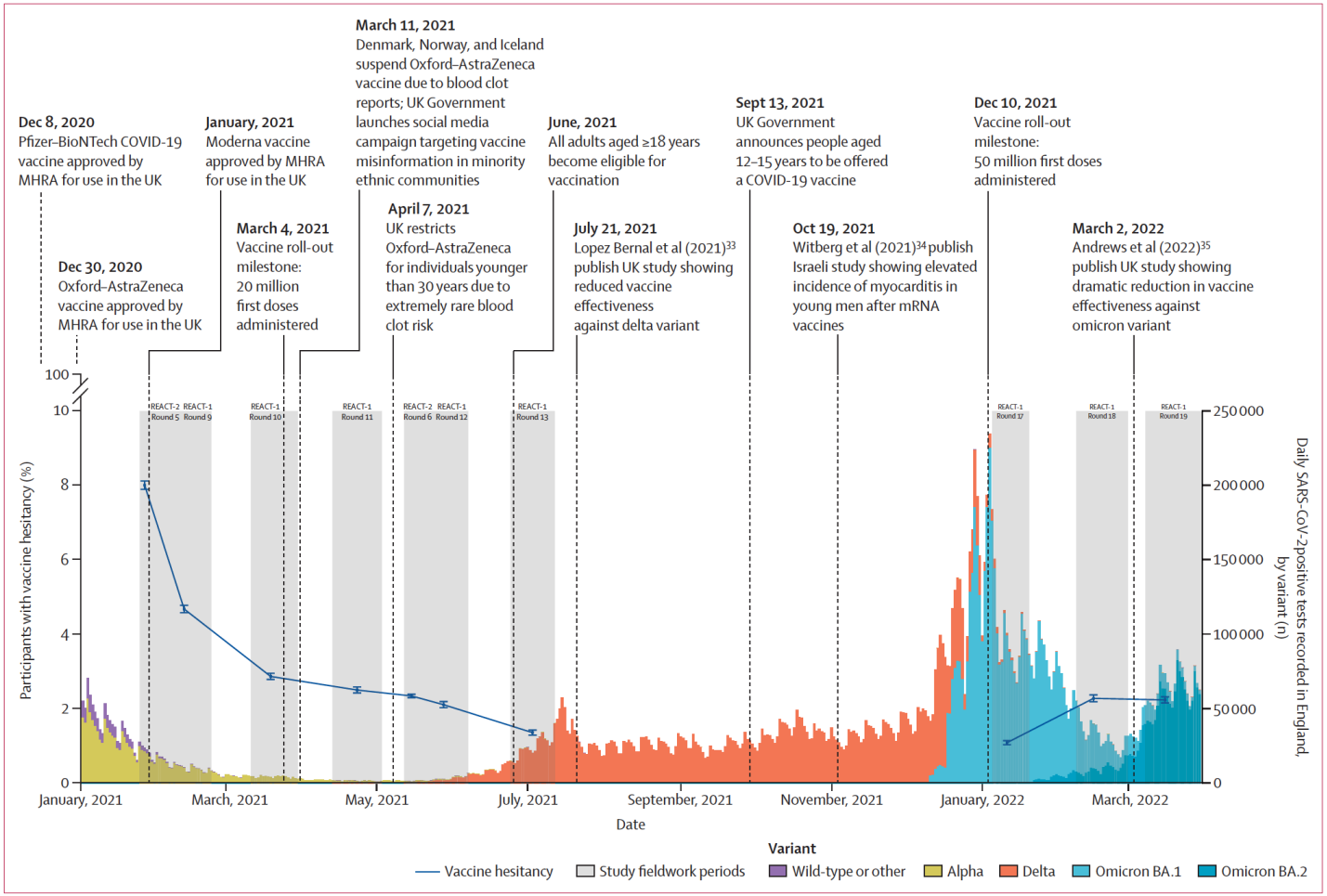
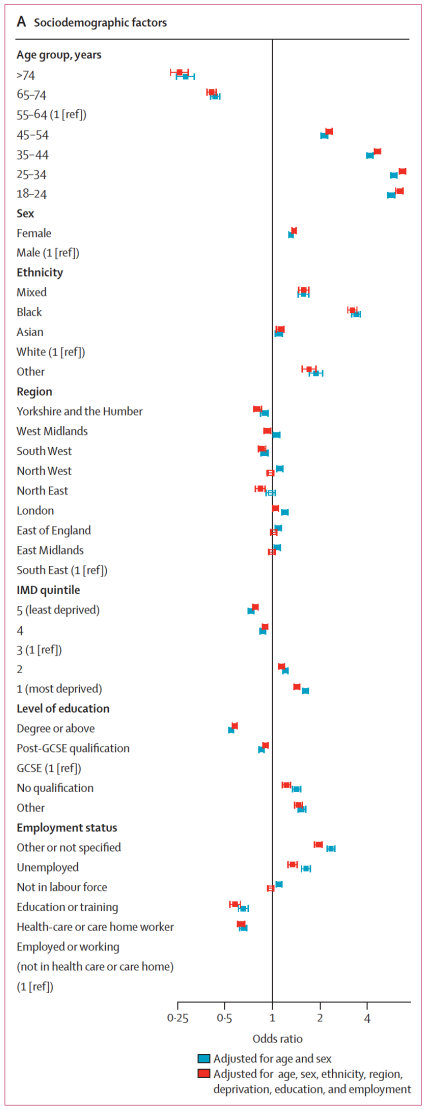


***Figure 1*: Daily SARS-CoV-2 positive tests recorded in England from Jan 1, 2021, to March 31, 2022, and percentage of study population reporting vaccine hesitancy**

The plot shows the numbers of SARS-CoV-2 positive tests by variant (right-hand y-axis; shaded and colour-coded plot area; data from the UK Health Security Agency[31] and GISAID via covariants.org,[32] with major processing by Our World in Data) and percentage of study participants reporting hesitancy (right y axis; black error bars and dotted joining lines); error bars denote 95% CIs. REACT-1[25] and REACT-2[26] fieldwork periods are denoted by shaded grey areas. Milestones in the UK vaccine roll-out and notable publications and events relating to vaccine safety and effectiveness are shown in annotations.[33–35] MHRA=UK Medicines and Healthcare products Regulatory Agency.



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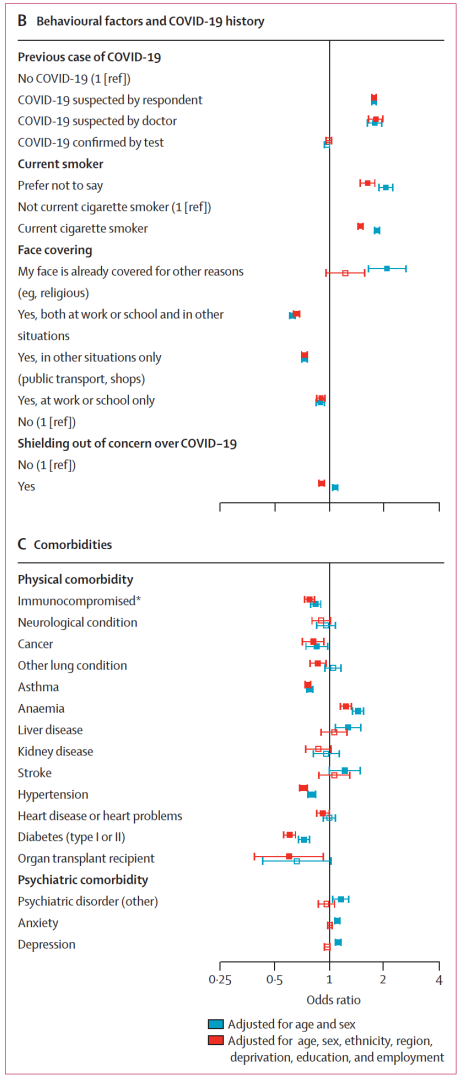


Figure 2: **Odds ratios for vaccine hesitancy or refusal versus intention to vaccinate or previous vaccination in 1 137 927 participants in the REACT study**

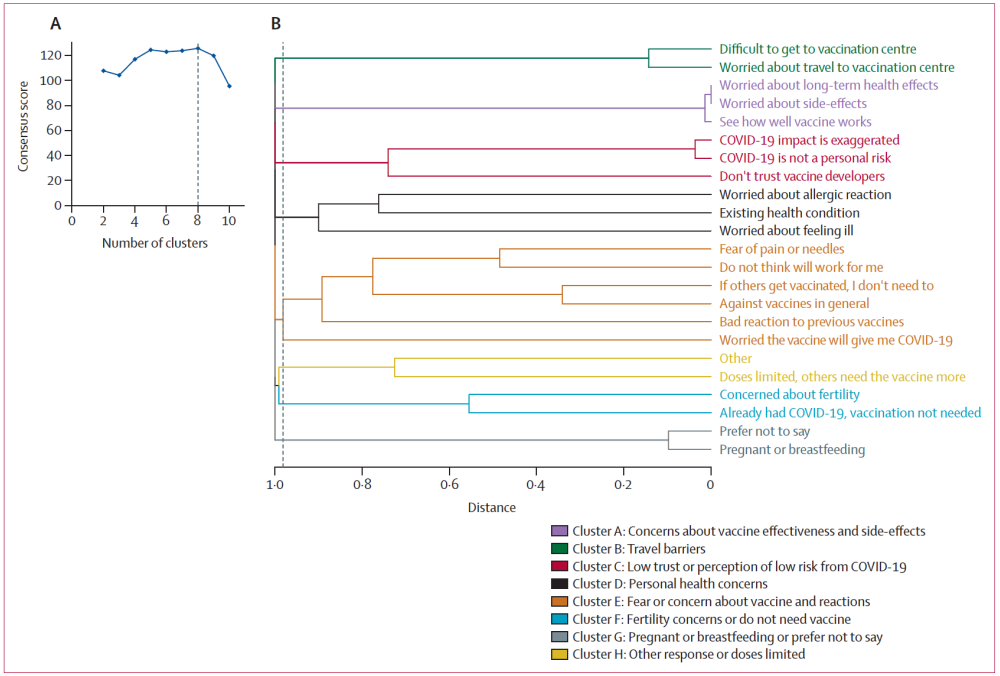


Figure 3: **Consensus clustering of vaccine hesitancy reasons in 30 701 participants**

(A) Optimisation plot with consensus clustering as a function of the number of clusters, showing that eight clusters optimised the consensus score. (B) Dendrogram showing the clustering of hesitancy reasons. Dashed line on dendrogram indicates optimal split point according to the consensus score.

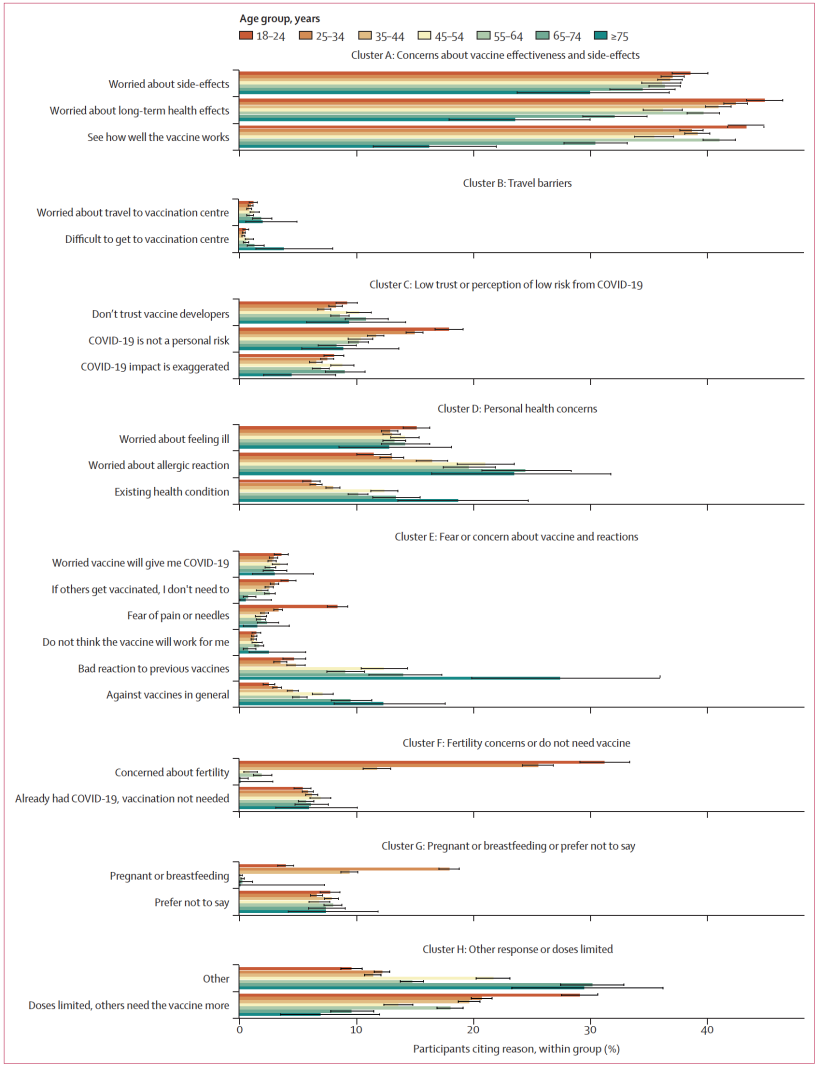


Figure 4: **Prevalence of reasons for vaccine hesitancy in 30 701 participants, by age group**
The percentages of respondents with hesitancy were calculated using the numbers of individuals who selected a particular reason for hesitancy divided by the number of those who were given this reason as an option (further details are in the appendix [p 5]). Whiskers indicate 95% CIs.

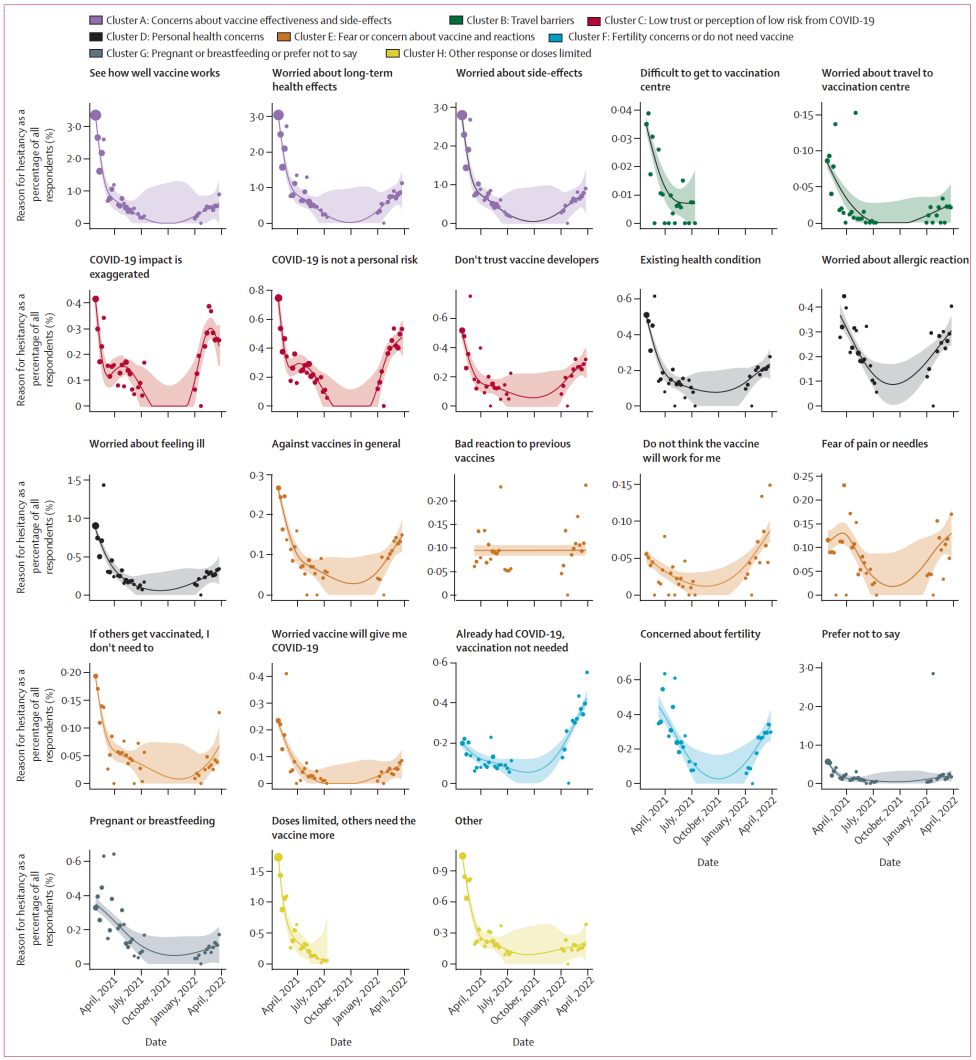
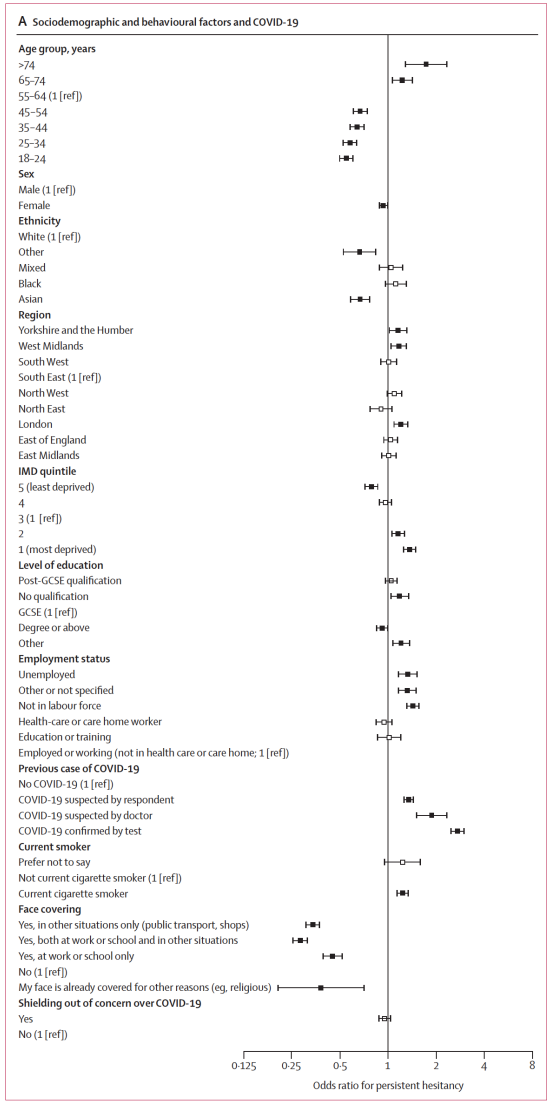


Figure 5: **Change in prevalence of reasons for hesitancy over time in all 1 137 927 participants**
Reported reasons for hesitancy are shown as a percentage of all respondents, by survey week, grouped by hesitancy reason cluster. Weighted generalised additive models were fitted to show trends (model specifications are provided in the appendix [p 6]). Shaded areas show 95% CIs. Point size indicates the number of people reporting each reason for hesitancy each week (from 0 to 5072). Variable scales have been used in the y-axes to facilitate visualisation of trajectories at different hesitancy prevalences.



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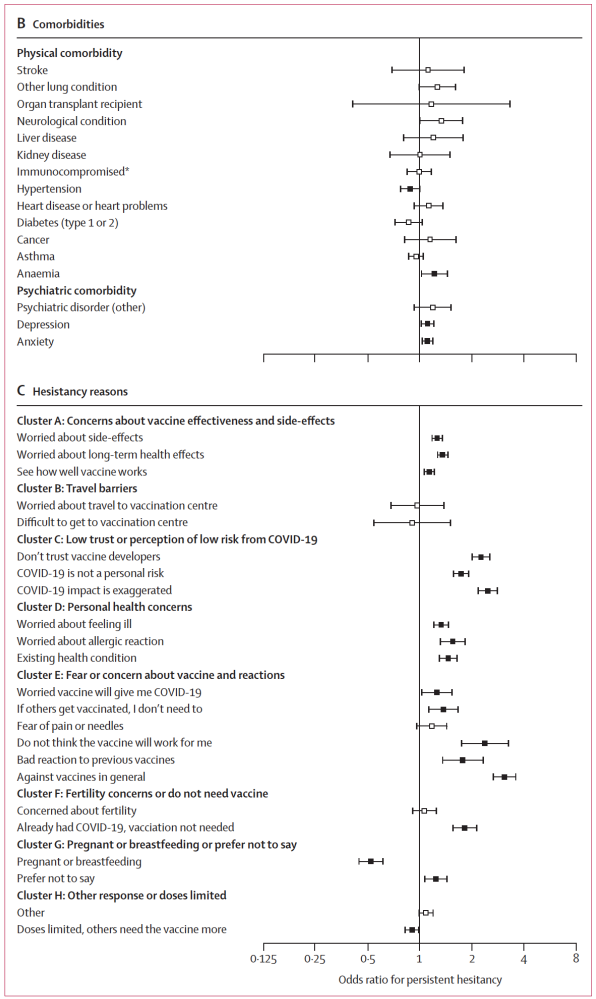


Figure 6: **Odds ratios for persistent hesitancy (ie, no subsequent vaccination recorded) in 24 229 vaccine-hesitant participants who consented to UK National Health Service data linkage**

Logistic regression modelling was done against demographic covariates (A), comorbidities (B), and reasons for hesitancy (C). In models (A) and (B), odds ratios were adjusted for age, sex, ethnicity, region, deprivation, education, and employment; in model (C), odds ratios were adjusted for age and sex. Solid boxes indicate significant odds ratios; hollow boxes indicate non-significant odds ratios. Whiskers indicate 95% CIs. GCSE=General Certificate of Secondary Education. IMD=Index of Multiple Deprivation. *Weakened immune system or reduced ability to deal with infections.

Research in context

Evidence before this study

A PubMed search for ("vaccine"[Title] OR "vaccination"[Title]) AND ("hesitancy"[Title] OR "attitude"[Title]) OR "Vaccine hesitancy"[MeSH Terms] OR "Vaccine acceptance"[MeSH Terms] from database inception to June 16, 2025, without language restrictions, returned 3689 papers. Of these, 2044 mentioned COVID-19 or SARS-CoV-2 in the title. Estimates showed that the prevalence of COVID-19 vaccine hesitancy in the UK changed over time from as high as 31% in March, 2020, to as low as 4% in early 2022. Established psychological predicates of COVID-19 vaccine hesitancy include low trust in institutions and experts, concerns over side-effects, perception of COVID-19 as being low risk, and lack of information.

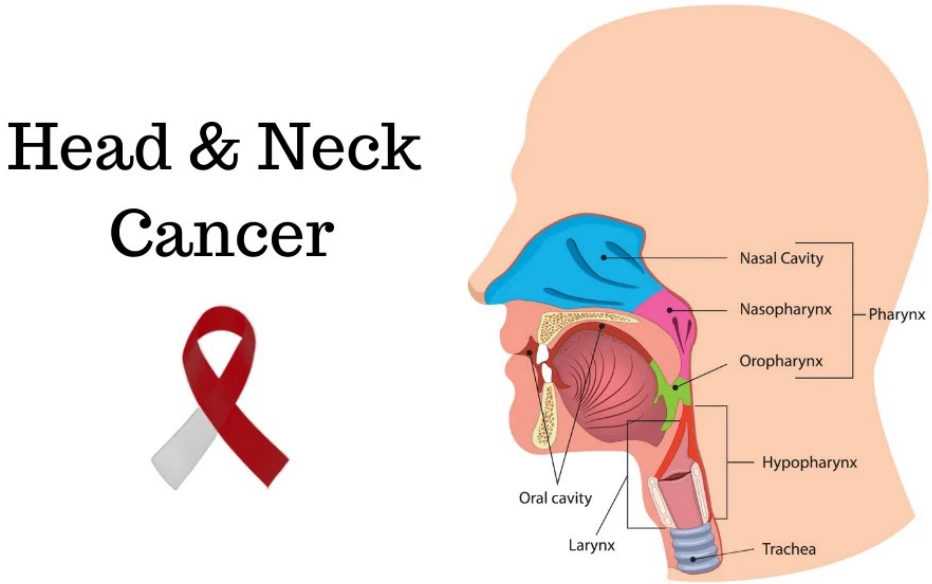
Added value of this study

To the best of our knowledge, no previous research has linked COVID-19 vaccine attitudes before vaccination with subsequent vaccination behaviour. Our analyses leveraged longitudinal survey data from participants in the Real-time Assessment of Community Transmission studies, in whom vaccine sentiment at enrolment could be compared with subsequent vaccination history from linkage data. Our results show that specific types of hesitancy, generally relating to concerns over vaccine effectiveness and health consequences, were more prevalent in the early phase of the vaccine roll-out. Individuals expressing these types of hesitancy were more likely to go on to be vaccinated than those expressing hesitancy stemming from low trust, perception of COVID-19 as being low risk, or general anti-vaccine sentiment.

Implications of all the available evidence

Our results provide a data-driven characterisation of the main types of vaccine hesitancy and a first quantitative exploration of their potential for reversibility. The findings will help inform the targeting and messaging for future vaccination roll-outs.

Head and neck cancer refers to a group of malignancies that usually begin in the squamous cells lining the moist mucosal surfaces of the head and neck, such as the mouth, throat, and voice box. It is estimated that more than **71,000 individuals** in the US were diagnosed with these cancers in 2024.



Nivolumab added to cisplatin and radiotherapy versus cisplatin and radiotherapy alone after surgery for people with squamous cell carcinoma of the head and neck at a high risk of relapse (GORTEC 2018-01 NIVOPOST-OP): a randomised, open-label, phase 3 trial

Summary

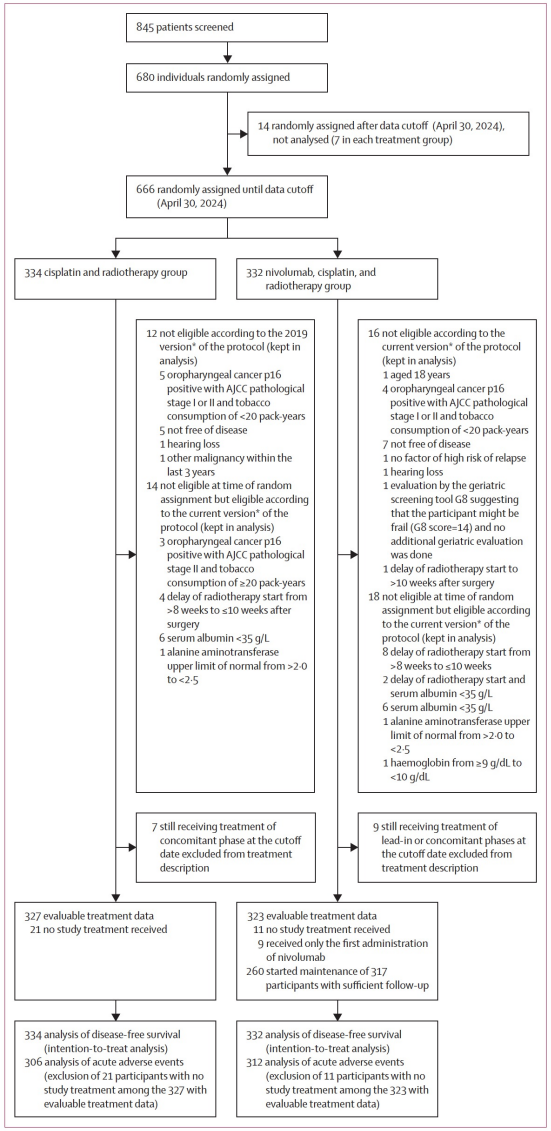
Background Postoperative cisplatin and radiotherapy is the standard of care for high-risk resected locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN). The NIVOPOST-OP trial aimed to assess the efficacy and safety of programmed death 1 blockade by nivolumab added to cisplatin and radiotherapy in this setting.

Methods This open-label, phase 3 trial evaluated adding nivolumab to cisplatin and radiotherapy after surgery for LA-SCCHN with high-risk pathological features. The main inclusion criteria were age 19–74 years, an Eastern Cooperative Oncology Group performance status 0–1, squamous cell carcinoma of the oral cavity, oropharynx, larynx, or hypopharynx resected with macroscopic complete resection, and at least one high-risk pathological feature: nodal extracapsular extension, microscopically positive margins, four or more cervical nodal involvements without extracapsular extension, and multiple perineural invasions. 680 participants recruited in 82 sites across six countries (France, Spain, Poland, Belgium, Greece, and Switzerland) were randomly assigned 1:1 to receive cisplatin and radiotherapy (66 Gy, cisplatin 100 mg/m^2 intravenously once every 3 weeks, for three cycles); or nivolumab 240 mg intravenously, followed by cisplatin and radiotherapy with three cycles of concomitant nivolumab 360 mg once every 3 weeks, and six cycles of adjuvant nivolumab 480 mg once every 4 weeks. The primary endpoint was disease-free survival as per investigator assessment in the intention-to-treat population. 230 disease-free survival events (relapses or deaths) were required to detect a hazard ratio of 0·65 with 0·05 two-sided α error, with 90% power. The trial is registered at ClinicalTrials.gov (NCT03576417) and is active, but not recruiting.

Findings The 680 patients were recruited from Oct 15, 2018, to July 3, 2024. The analysis was based on 666 participants randomly assigned until the cutoff date (April 30, 2024), at which point the required number of events was reached (median follow-up 30·3 months). Disease-free survival was significantly improved with nivolumab, cisplatin, and radiotherapy versus cisplatin and radiotherapy alone, irrespective of programmed death ligand 1 expression (HR 0·76; 95% CI 0·60–0·98; stratified log-rank test p value=0·034). There was an increase in the rate of participants with treatment-related grade 4 adverse events with nivolumab, cisplatin, and radiotherapy compared with cisplatin and radiotherapy (30 [10%] of 312 *vs* 16 [5%] of 306). Treatment-related deaths occurred in two participants in each group.

Interpretation Nivolumab added to cisplatin and radiotherapy in high-risk resected LA-SCCHN improves disease-free survival with moderate toxic effect increase, and can be proposed as a new standard treatment.

Funding Groupe Oncologie Radiotherapie Tete Et Cou (GORTEC) and Bristol Myers Squibb.



	Cisplatin and radiotherapy (n=334)	Nivolumab, cisplatin, and radiotherapy (n=332)
Age, years		
Median, IQR	59 (53–64)	59 (53–65)
Range	22–74	18–74
Sex		
Female	77 (23%)	82 (25%)
Male	257 (77%)	250 (75%)
Eastern Cooperative Oncology Group performance status		
0	168 (50%)	169 (51%)
1	166 (50%)	163 (49%)
Smoking status		
Never smoked	64 (19%)	45 (14%)
Former smoker	109 (33%)	108 (33%)
Current smoker	161 (48%)	179 (54%)
Number of pack-years in former or current smokers		
Median, IQR	40 (25–45)	40 (25–50)
Range	1–150	1–150
Site of cancer and p16 status		
Oral cavity	193 (58%)	192 (58%)
Hypopharynx	40 (12%)	43 (13%)
Larynx	41 (12%)	40 (12%)
Oropharyngeal cancer p16 negative	43 (13%)	41 (12%)
Oropharyngeal cancer p16 positive	17 (5%)	16 (5%)
Pathological stage		
I	3 (1%)	3 (1%)
II	8 (2%)	9 (3%)
III	46 (14%)	44 (13%)
IVa	117 (35%)	128 (39%)
IVb	160 (48%)	148 (45%)
Pathological factors of a high risk of relapse*		
Node with extracapsular extension†	213 (64%)	205 (62%)
Positive margins	183 (55%)	203 (61%)
Multiple perineural invasion‡	188 (56%)	182 (55%)
Four or more involved nodes without extracapsular extension	44 (13%)	42 (13%)
Combination of factors of a high risk of relapse		
Extracapsular extension and positive margins	100 (30%)	109 (33%)
Extracapsular extension or positive margins	196 (59%)	190 (57%)
No extracapsular extension, no positive margins, but multiple perineural invasion or four or more involved nodes	38 (11%)	32 (10%)
No factor of high risk of relapse	0	1
PD-L1 combined positive score§		
Negative	34/308 (11%)	44/313 (14%)
1–19	141/308 (46%)	157/313 (50%)
≥20	133/308 (43%)	113/313 (36%)

Data are median (IQR), range, or n (%). PD-L1=programmed death ligand 1. *One participant in the nivolumab plus cisplatin plus radiotherapy group had no pathological factors of a high risk of relapse (eligibility criteria violation). †Missing in one participant of the cisplatin plus radiotherapy group. This participant had positive margins. ‡Missing in three participants: one in the cisplatin plus radiotherapy group (positive margins, nodal extracapsular extension, and more than four involved nodes) and two in the nivolumab plus cisplatin plus radiotherapy group (one had positive margins, nodal extracapsular extension, and more than four involved nodes and the other had four involved nodes, no extracapsular extension, and negative margins). §PD-L1 combined positive score was not evaluated in 44 (7%) participants: 26 (8%) in the cisplatin plus radiotherapy group and 18 (5%) in the nivolumab plus cisplatin plus radiotherapy group.

Table 1: **Characteristics of the participants at baseline**

	Cisplatin and radiotherapy (n=334)	Nivolumab, cisplatin, and radiotherapy (n=332)
Number of participants with disease-free survival event	140	112
Type of first event		
Local relapse alone	30	15
Regional relapse alone	20	12
Locoregional relapse	11	12
Distant relapse alone	40	37
Combined locoregional and distant relapse	22	16
Death as first event	17	20
Disease-free survival		
3-year rate	52·5% (46·2–58·4)	63·1% (57·0–68·7)
Stratified* HR of disease-free survival event	1	0·76 (0·60–0·98)
Cumulative incidence of locoregional relapse alone		
3-year rate	19·8% (15·3–24·6)	12·9% (9·3–17·2)
Stratified* subdistribution HR of locoregional relapse alone	1	0·63 (0·42–0·94)
Cumulative incidence of distant relapse alone		
3-year rate	13·2% (9·6–17·5)	12·6% (9·0–16·8)
Stratified* subdistribution HR of distant relapse alone	1	0·95 (0·61–1·48)
Cumulative incidence of combined locoregional and distant relapse		
3-year rate	7·6% (4·9–11·1)	5·7% (3·4–8·8)
Stratified* subdistribution HR of locoregional and distant relapse	1	0·74 (0·39–1·41)
Cumulative incidence of death as first event		
3-year rate	6·9% (4·1–10·7)	5·7% (3·3–9·0)
Stratified* subdistribution HR of death as first event	1	1·20 (0·63–2·28)

Data are n, rate (95% CI), or HR (95% CI). HR=hazard ratio. *Stratified for p16 status (oropharyngeal cancer p16 positive vs oropharyngeal cancer p16 negative and non-oropharyngeal cancer).

Table 2: **Disease-free survival analysis**

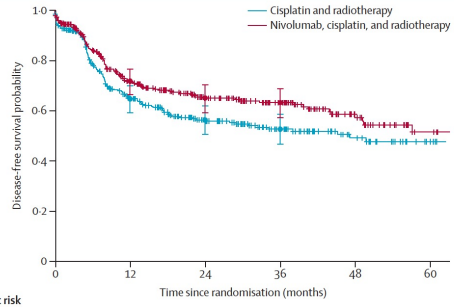
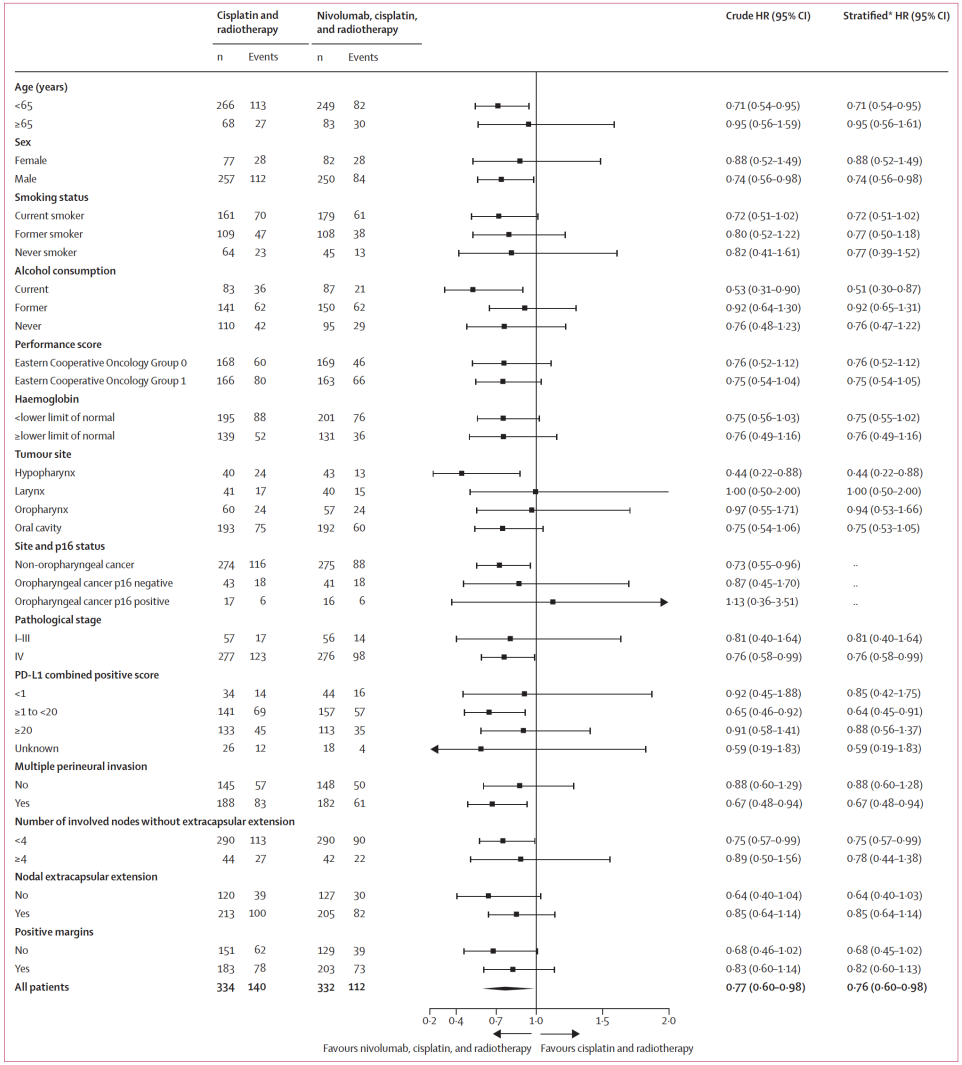


Figure 2: **Kaplan–Meier estimates of disease-free survival according to treatment group**



	Cisplatin and radiotherapy		Nivolumab, cisplatin, and radiotherapy		Crude HR (95% CI)	Stratified* HR (95% CI)
	n	Events	n	Events		
Age (years)						
<65	266	113	249	82	0·71 (0·54–0·95)	0·71 (0·54–0·95)
≥65	68	27	83	30	0·95 (0·56–1·59)	0·95 (0·56–1·61)
Sex						
Female	77	28	82	28	0·88 (0·52–1·49)	0·88 (0·52–1·49)
Male	257	112	250	84	0·74 (0·56–0·98)	0·74 (0·56–0·98)
Smoking status						
Current smoker	161	70	179	61	0·72 (0·51–1·02)	0·72 (0·51–1·02)
Former smoker	109	47	108	38	0·80 (0·52–1·22)	0·77 (0·50–1·18)
Never smoker	64	23	45	13	0·82 (0·41–1·61)	0·77 (0·39–1·52)
Alcohol consumption						
Current	83	36	87	21	0·53 (0·31–0·90)	0·51 (0·30–0·87)
Former	141	62	150	62	0·92 (0·64–1·30)	0·92 (0·65–1·31)
Never	110	42	95	29	0·76 (0·48–1·23)	0·76 (0·47–1·22)
Performance score						
Eastern Cooperative Oncology Group 0	168	60	169	46	0·76 (0·52–1·12)	0·76 (0·52–1·12)
Eastern Cooperative Oncology Group 1	166	80	163	66	0·75 (0·54–1·04)	0·75 (0·54–1·05)
Haemoglobin						
<lower limit of normal	195	88	201	76	0·75 (0·56–1·03)	0·75 (0·55–1·02)
≥lower limit of normal	139	52	131	36	0·76 (0·49–1·16)	0·76 (0·49–1·16)
Tumour site						
Hypopharynx	40	24	43	13	0·44 (0·22–0·88)	0·44 (0·22–0·88)
Larynx	41	17	40	15	1·00 (0·50–2·00)	1·00 (0·50–2·00)
Oropharynx	60	24	57	24	0·97 (0·55–1·71)	0·94 (0·53–1·66)
Oral cavity	193	75	192	60	0·75 (0·54–1·06)	0·75 (0·53–1·05)
Site and p16 status						
Non-oropharyngeal cancer	274	116	275	88	0·73 (0·55–0·96)	..
Oropharyngeal cancer p16 negative	43	18	41	18	0·87 (0·45–1·70)	..
Oropharyngeal cancer p16 positive	17	6	16	6	1·13 (0·36–3·51)	..
Pathological stage						
I–III	57	17	56	14	0·81 (0·40–1·64)	0·81 (0·40–1·64)
IV	277	123	276	98	0·76 (0·58–0·99)	0·76 (0·58–0·99)
PD-L1 combined positive score						
<1	34	14	44	16	0·92 (0·45–1·88)	0·85 (0·42–1·75)
≥1 to <20	141	69	157	57	0·65 (0·46–0·92)	0·64 (0·45–0·91)
≥20	133	45	113	35	0·91 (0·58–1·41)	0·88 (0·56–1·37)
Unknown	26	12	18	4	0·59 (0·19–1·83)	0·59 (0·19–1·83)
Multiple perineural invasion						
No	145	57	148	50	0·88 (0·60–1·29)	0·88 (0·60–1·28)
Yes	188	83	182	61	0·67 (0·48–0·94)	0·67 (0·48–0·94)
Number of involved nodes without extracapsular extension						
<4	290	113	290	90	0·75 (0·57–0·99)	0·75 (0·57–0·99)
≥4	44	27	42	22	0·89 (0·50–1·56)	0·78 (0·44–1·38)
Nodal extracapsular extension						
No	120	39	127	30	0·64 (0·40–1·04)	0·64 (0·40–1·03)
Yes	213	100	205	82	0·85 (0·64–1·14)	0·85 (0·64–1·14)
Positive margins						
No	151	62	129	39	0·68 (0·46–1·02)	0·68 (0·45–1·02)
Yes	183	78	203	73	0·83 (0·60–1·14)	0·82 (0·60–1·13)
All patients	**334**	**140**	**332**	**112**	**0·77 (0·60–0·98)**	**0·76 (0·60–0·98)**

0·2 0·4 0·7 1·0 1·5 2·0

Figure 3: **Subgroup analysis of disease-free survival**
Crude HRs are represented in the forest plot. *HRs are stratified for p16 status (p16-positive oropharyngeal cancer vs p16-negative oropharyngeal cancer and non-oropharyngeal cancer). HR=hazard ratio. PD-L1=programmed death ligand 1.

	Cisplatin and radiotherapy (n=306)					Nivolumab, cisplatin, and radiotherapy (n=312)				
	Any grade	Grade 3–5	Grade 3	Grade 4	Grade 5	Any grade	Grade 3–5	Grade 3	Grade 4	Grade 5
Treatment-related adverse events										
Any	304 (99%)	211 (69%)	209 (68%)	16 (5%)	2 (1%)	301 (96%)	230 (74%)	227 (73%)	30 (10%)	2 (1%)
Serious	59 (19%)	48 (16%)	45 (15%)	4 (1%)	2 (1%)	104 (33%)	91 (29%)	84 (27%)	14 (4%)	2 (1%)
Nivolumab-related adverse events										
Any	NA	NA	NA	NA	NA	213 (68%)	64 (21%)	58 (19%)	6 (2%)	2 (1%)
Leading to nivolumab discontinuation	NA	NA	NA	NA	NA	25 (8%)	14 (4%)	12 (4%)	2 (1%)	0
Serious	NA	NA	NA	NA	NA	32 (10%)	25 (8%)	21 (7%)	3 (1%)	2 (1%)
Cisplatin-related adverse events										
Any	291 (95%)	157 (51%)	154 (50%)	16 (5%)	2 (1%)	286 (92%)	176 (56%)	168 (54%)	27 (9%)	1 (<1%)
Leading to cisplatin discontinuation	54 (18%)	37 (12%)	34 (11%)	4 (1%)	0	65 (21%)	49 (16%)	41 (13%)	10 (3%)	0
Serious	54 (18%)	44 (14%)	41 (13%)	4 (1%)	2 (1%)	75 (24%)	68 (22%)	58 (19%)	13 (4%)	1 (<1%)
Radiotherapy-related adverse events										
Any	297 (97%)	156 (51%)	156 (51%)	2 (1%)	0	294 (94%)	161 (52%)	159 (51%)	9 (3%)	0
Serious	18 (6%)	12 (4%)	12 (4%)	1 (<1%)	0	39 (13%)	30 (10%)	28 (9%)	4 (1%)	0

Since the same adverse events can be related to several treatments (nivolumab, cisplatin, and radiotherapy), the number of participants with treatment-related adverse events is not the sum of participants with adverse events related to nivolumab, cisplatin, and radiotherapy. N/A=not applicable.

Table 3: **Number of participants with adverse events and serious adverse events (all periods together)**

Research in context

Evidence before this study

To identify evidence before the NIVOPOST-OP trial (initiated 2018), we searched PubMed, and American Society of Clinical Oncology and European Society For Medical Oncology abstracts published between Jan 1, 2015, and June 1, 2025, in English, for randomised trials on immunotherapy and radiotherapy in locally advanced head and neck squamous cell carcinoma (LA-SCCHN). Search terms used were "head and neck squamous cell carcinoma," "locally advanced," "immunotherapy," "radiotherapy," "PD-1/PD-L1 inhibitors," and "randomized trial".

Head and neck cancers are the 6th most common type of cancer worldwide, consisting mostly of LA-SCCHN. A large proportion of LA-SCCHN are treated by surgery and the standard postoperative treatment for high-risk resected LA-SCCHN was established in 2004 with postoperative cisplatin-based chemoradiotherapy. The magnitude of the benefit due to the addition of concomitant chemotherapy to postoperative radiotherapy is illustrated in the meta-analysis MACH-NC based on updated individual patient data, with a 9% improvement in 3-year disease-free survival. However, despite this combination of surgery followed by postoperative cisplatin-based chemotherapy, recurrence still occurs in 40–45% of people, showing an unmet clinical need.

Programmed death 1 (PD-1) inhibitors are effective treatments in SCCHN and have been established as the standard-of-care in the recurrent or metastatic setting (eg, in the CheckMate 141 and KEYNOTE-048 studies), but randomised phase 2–3 trials have not reached their efficacy endpoint in the locally advanced setting (eg, in the GORTEC 2015–01 PembroRad, NRG-HN004, JAVELIN Head and Neck 100, GORTEC 2017–01 REACH, KEYNOTE-412, and IMvoke010 studies).

In 2018, when NIVOPOST-OP (NCT03576417) was initiated, a randomised phase 3 trial evaluating the addition of both neoadjuvant and adjuvant pembrolizumab to standard-of-care for people with resectable LA-SCCHN (KEYNOTE-689, NCT03765918) began concurrently with our study.

Added value of this study

To our knowledge, NIVOPOST-OP is the first large-scale randomised, phase 3 trial, evaluating the addition of anti-PD-1 nivolumab (concomitant and adjuvant) to the standard-of-care postoperative radiotherapy and concomitant cisplatin-based chemotherapy in high-risk resected LA-SCCHN. The benefit of adding nivolumab to cisplatin-based chemotherapy (HR of disease-free survival events 0·76; an increase of 10·6% in the 3-year disease-free survival rate) is similar to that of concomitant chemotherapy added to postoperative radiotherapy (hazard ratio 0·78; an increase of 9% in the 3-year event-free survival rate). The benefit of adding nivolumab was obtained along with a moderate increase in toxicity, with no increase in toxic deaths, indicating a favourable risk to benefit ratio.

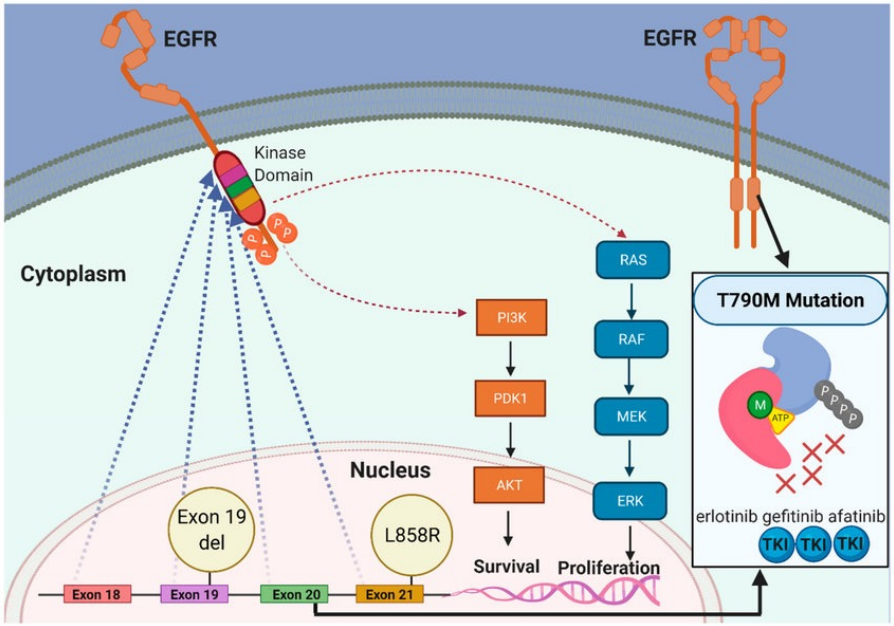
Implications of all the available evidence

NIVOPOST-OP provides strong evidence that adding nivolumab to postoperative radiotherapy and concomitant cisplatin-based chemotherapy significantly improves disease-free survival in high-risk resected LA-SCCHN, addressing a 20-year therapeutic gap since radiotherapy and concomitant cisplatin-based chemotherapy became standard. Unlike previous LA-SCCHN trials with negative results, NIVOPOST-OP highlights the efficacy of PD-1 inhibition in the postoperative setting. Its favorable risk–benefit profile supports adopting nivolumab plus radiotherapy and concomitant cisplatin-based chemotherapy as a new standard of care, offering a strategy to reduce recurrence.

In der Behandlung des **EGFR-mutierten nicht-kleinzelligen Lungenkarzinoms (NSCLC)** wurden bis zum Jahr **2026** bedeutende Fortschritte erzielt. Die Therapie hat sich von einer reinen Monotherapie hin zu personalisierten Kombinationsansätzen entwickelt, die das Überleben signifikant verlängern.

1. Diagnostik und Mutationen
Die molekulare Testung ist der Standard für alle NSCLC-Stadien (I–IV).

- **Häufige Mutationen:** Rund 90 % der Fälle entfallen auf die „klassischen“ aktivierenden Mutationen: **Exon-19-Deletionen** und die **L858R-Punktmutation** (Exon 21).
- **Prävalenz:** In Europa tragen etwa 10–14 % der NSCLC-Patienten diese Mutationen, in asiatischen Populationen bis zu 50 %.
- **Methoden:** Neben der Gewebebiopsie hat die **Liquid Biopsy** (ctDNA) an Bedeutung gewonnen, insbesondere zur Überwachung von Resistenzen und bei Patienten mit unzureichendem Tumorgewebe.



Savolitinib plus osimertinib versus chemotherapy for advanced, *EGFR* mutation-positive, *MET*-amplified non-small-cell lung cancer in China (SACHI): interim analysis of a multicentre, open-label, phase 3 randomised controlled trial

Summary

Background Savolitinib combined with osimertinib is a potential novel therapy for patients with *EGFR* mutation-positive non-small-cell lung cancer (NSCLC) harbouring *MET* amplification after progression on EGFR tyrosine kinase inhibitor (TKI) therapy. We aimed to evaluate the efficacy and safety of savolitinib–osimertinib versus standard of care platinum-based doublet chemotherapy in this patient population.

Methods SACHI was a multicentre, randomised, active-controlled, open-label, phase 3 trial conducted across 68 Chinese hospitals. Eligible adults with locally advanced or metastatic *EGFR* mutation-positive NSCLC and *MET* amplification after EGFR TKI failure were randomly assigned (1:1) to once daily oral savolitinib–osimertinib or intravenous chemotherapy (pemetrexed plus either cisplatin or carboplatin), both in 21-day cycles. Central randomisation was implemented through an interactive web-response system with stratification based on the presence of brain metastases, previous exposure to third-generation EGFR TKIs, and *EGFR* mutation subtype, using a mixed block-size methodology. The primary endpoint, investigator-assessed progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumours version 1.1, was tested using a hierarchical procedure: first in the third-generation EGFR TKI-naive population, and if positive, the intention-to-treat (ITT) population. Safety analysis was performed in all patients who received at least one dose of the study treatment. Interim analysis data cutoff was Aug 30, 2024. This study is registered with ClinicalTrials.gov (NCT05015608) and is complete.

Findings Between Oct 15, 2021, and Aug 30, 2024, 211 patients were enrolled, 106 were randomly assigned to savolitinib–osimertinib and 105 were randomly assigned to chemotherapy, including 137 (65%) of 211 who were third-generation EGFR TKI-naive (69 in the savolitinib–osimertinib group; 68 in the chemotherapy group). In 106 patients in the savolitinib–osimertinib group, the median age was 59·4 years (IQR 54·3–65·8), 62 (58%) were female, and 44 (42%) were male. In 105 patients in the chemotherapy group, the median age was 61·9 years (IQR 56·3–69·1), 55 (52%) were female, and 50 (48%) were male. All participants were Asian. Median PFS was significantly prolonged with savolitinib–osimertinib versus chemotherapy in the third-generation EGFR TKI-naive (9·8 months [95% CI 6·9–12·5] *vs* 5·4 months [4·2–6·0]; hazard ratio 0·34 [0·21–0·56]; p<0·0001) and ITT populations (8·2 months [6·9–11·2] *vs* 4·5 months [3·0–5·4]; 0·34 [0·23–0·49]; p<0·0001). Grade 3 or worse treatment-emergent adverse events occurred in the same proportion of patients in both groups who received the study drugs (60 [57%] of 106 patients in the savolitinib–osimertinib group and 55 [57%] of 96 patients in the chemotherapy group).

Interpretation The savolitinib–osimertinib combination improved PFS versus chemotherapy in patients with *EGFR* mutation-positive, *MET*-amplified NSCLC that had progressed on EGFR TKI therapy, while maintaining a favourable tolerability profile. This regimen offers a potential oral treatment option for this biomarker-selected population.

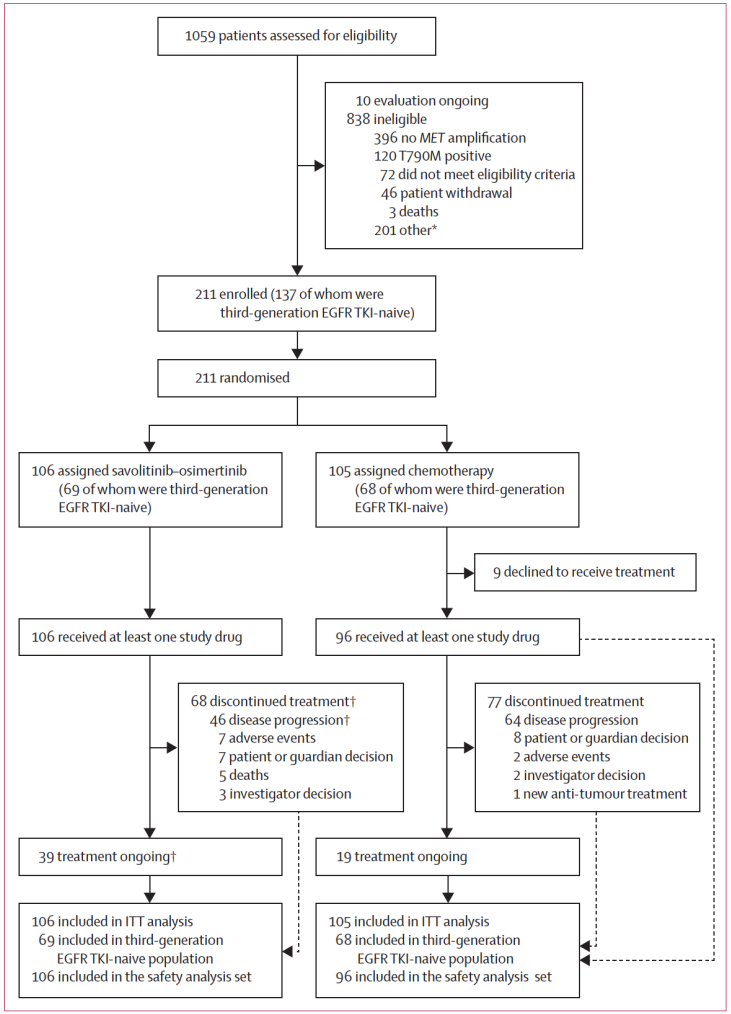


Figure 1: **Study profile**
ITT=intention-to-treat. TKI=tyrosine kinase inhibitor. *No tissue samples or samples disqualified for testing (n=95); *MET* copy number of at least 5 and less than 10 for third-generation EGFR TKI-treated population (n=54); and patient did not fulfil all inclusion and exclusion criteria (n=52). †One patient discontinued savolitinib only so is included in discontinued treatment (savolitinib) and treatment ongoing (osimertinib).

	Savolitinib–osimertinib (n=106)	Chemotherapy (n=105)
Age, years	59·4 (54·3–65·8)	61·9 (56·3–69·1)
Sex		
Male	44 (42%)	50 (48%)
Female	62 (58%)	55 (52%)
Race		
Asian	106 (100%)	105 (100%)
Bodyweight, kg	60·0 (52·0–67·0)	60·0 (55·0–68·1)
<50	19 (18%)	8 (8%)
≥50	87 (82%)	97 (92%)
ECOG performance score		
0	28 (26%)	27 (26%)
1	78 (74%)	78 (74%)
Pathological diagnosis		
Adenocarcinoma	105 (99%)	105 (100%)
Other	1 (1%)*	0
Time from diagnosis to randomisation, months	17·2 (10·4–30·9)	14·7 (9·9–24·5)
Type of *EGFR* mutation		
Exon 19 deletion	40 (38%)	40 (38%)
L858R	55 (52%)	53 (50%)
Other†	11 (10%)	12 (11%)
MET amplification detected by central laboratory	106 (100%)	105 (100%)
Brain metastasis		
Yes	39 (37%)	41 (39%)
No	67 (63%)	64 (61%)
Liver metastasis		
Yes	11 (10%)	15 (14%)
No	95 (90%)	90 (86%)
Previous first-line EGFR TKI	106 (100%)	105 (100%)
First generation or second generation	69 (65%)	68 (65%)
Icotinib	28/69 (41%)	33/68 (49%)
Gefitinib	20/69 (29%)	17/68 (25%)
Afatinib	14/69 (20%)	11/68 (16%)
Dacomitinib	5/69 (7%)	7/68 (10%)
Erlotinib	3/69 (4%)	0
Third generation	37 (35%)	37 (35%)
Osimertinib	23/37 (62%)	29/37 (78%)
Aumolertinib	9/37 (24%)	5/37 (14%)
Furmonertinib	2/37 (5%)	3/37 (8%)
Rezivertinib	3/37 (8%)	0

Data are median (IQR), n (%), or n/N (%). ECOG=Eastern Cooperative Oncology Group. TKI=tyrosine kinase inhibitor. NSCLC=non-small-cell lung cancer. *This patient was diagnosed with NSCLC without a specific pathological type, which was recorded as a major protocol deviation. †Other *EGFR* mutations included G719X (four patients in the savolitinib–osimertinib group *vs* four patients in the chemotherapy group), L861Q (two patients *vs* four patients), G719X and S768I (one patient *vs* two patients), L833V and H835L (two patients *vs* zero patients), S768I (one patient *vs* zero patients), G719X and L833V (one patient *vs* zero patients), G719X and L861Q (zero patients *vs* one patient), and G719X and S768I (zero patients *vs* one patient).

Table 1: **Summary of patient baseline demographic and disease characteristics in the intention-to-treat population**

	Third-generation EGFR TKI-naive population					Intention-to-treat population				
	Savolitinib–osimertinib (n=69)	Chemotherapy (n=68)	HR (95% CI)	OR (95% CI)	p value	Savolitinib–osimertinib (n=106)	Chemotherapy (n=105)	HR (95% CI)	OR (95% CI)	p value
Primary endpoint										
Progression-free survival (INV), months	9·8 (6·9–12·5)	5·4 (4·2–6·0)	0·34 (0·21–0·56)	..	<0·0001	8·2 (6·9–11·2)	4·5 (3·0–5·4)	0·34 (0·23–0·49)	..	<0·0001
Progression-free survival rate at 6 months	71% (58–81)	40% (27–54)	..	..	..	67% (56–76)	32% (22–42)	..	..	..
Secondary endpoints										
Progression-free survival (IRC), months	8·2 (6·8–11·1)	5·7 (4·2–7·0)	0·47 (0·29–0·76)	..	0·0017	7·2 (5·7–11·1)	4·2 (4·0–5·7)	0·40 (0·28–0·59)	..	<0·0001
Progression-free survival rate at 6 months	65% (51–76)	48% (33–61)	..	..	..	60% (49–69)	35% (24–46)	..	..	..
Objective response rate (INV)	39 (57%, 44–68)	26 (38%, 27–51)	..	2·15 (1·02–4·53)	0·030	62 (58%, 49–68)	36 (34%, 25–44)	..	2·74 (1·50–4·98)	0·0004
Objective response rate (IRC)	46 (67%, 54–78)	26 (38%, 27–51)	..	3·24 (1·52–6·88)	0·0009	67 (63%, 53–72)	38 (36%, 27–46)	..	3·05 (1·66–5·48)	<0·0001
Disease control rate (INV)	63 (91%, 82–97)	46 (68%, 55–78)	..	5·03 (1·76–16·02)	0·0006	94 (89%, 81–94)	70 (67%, 57–76)	..	4·00 (1·81–8·82)	0·0001
Disease control rate (IRC)	60 (87%, 77–94)	52 (76%, 65–86)	..	2·04 (0·77–5·66)	0·11	91 (86%, 78–92)	76 (72%, 63–81)	..	2·35 (1·11–5·06)	0·015
Duration of response (INV), months	8·8 (5·9–11·9)	4·1 (2·8–5·5)	..	..	..	8·4 (5·9–11·1)	3·2 (2·8–4·2)	..	..	..
Duration of response (IRC), months	8·2 (5·6–11·9)	4·3 (2·8–5·3)	..	..	..	9·7 (5·8–12·4)	4·3 (2·8–5·1)	..	..	..
Time to response (INV), months	1·4 (1·4–1·4)	2·1 (1·4–2·9)	..	..	..	1·4 (1·4–1·4)	1·5 (1·4–2·8)	..	..	..
Time to response (IRC), months	1·4 (1·4–1·4)	1·6 (1·4–2·8)	..	..	..	1·4 (1·4–1·4)	1·5 (1·4–1·6)	..	..	..

Data are median (95% CI), % (95% CI), or n (%, 95% CI), unless otherwise stated. The widths of the CIs have not been adjusted for multiplicity and should not be used to infer definitive treatment effects. HR=hazard ratio. INV=investigator assessed. IRC=independent review committee assessed. OR=odds ratio. TKI=tyrosine kinase inhibitor.

Table 2: **Summary of primary and secondary efficacy findings in the third-generation EGFR TKI-naive and intention-to-treat populations**

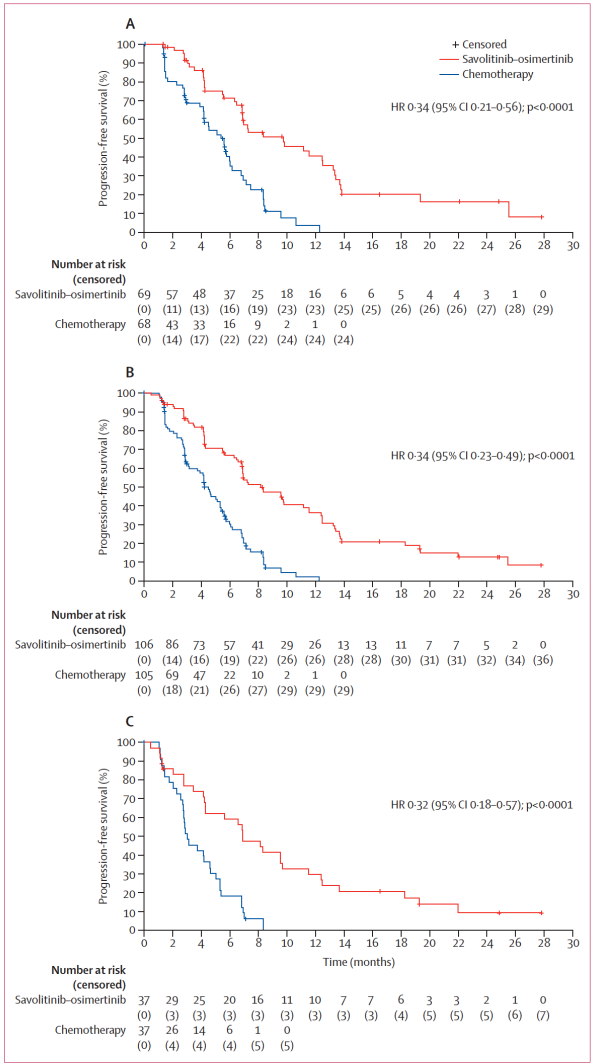
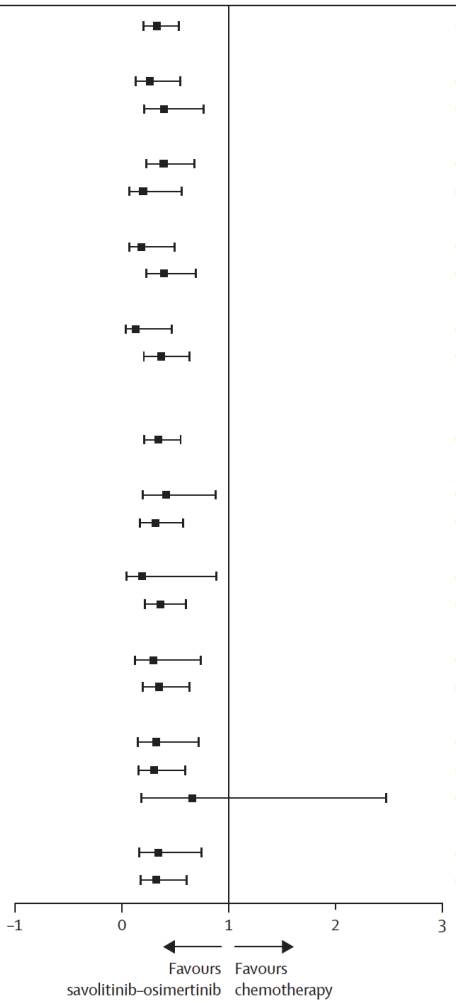


Figure 2: **Kaplan–Meier plots of investigator-assessed progression-free survival**
(A) Third-generation EGFR TKI-naive population. (B) Intention-to-treat population. (C) Third-generation EGFR TKI-treated population. HR=hazard ratio. TKI=tyrosine kinase inhibitor.

A	Savolitinib–osimertinib	Chemotherapy	HR (95% CI)
	Number of events/at risk	Number of events/at risk	
Overall	**40/69**	**44/68**	**0·32 (0·20–0·53)**
Sex			
Male	14/30	25/33	0·25 (0·12–0·54)
Female	26/39	19/35	0·39 (0·20–0·76)
Age at randomisation			
<65 years	31/48	29/40	0·39 (0·22–0·68)
≥65 years	9/21	15/28	0·19 (0·07–0·56)
Baseline ECOG performance score			
0	12/19	12/19	0·18 (0·06–0·49)
1	28/50	32/49	0·39 (0·22–0·69)
Smoking status			
Current or previous smoker	8/18	13/17	0·13 (0·03–0·46)
Non-smoker (never)	32/51	31/51	0·36 (0·21–0·63)
Current tumour stage			
IIIB or IIIC	0/1	3/6	
IV, IVA, or IVB	40/68	41/62	0·34 (0·21–0·55)
Brain metastases			
Yes	16/24	18/24	0·41 (0·19–0·88)
No	24/45	26/44	0·31 (0·16–0·57)
Liver metastases			
Yes	6/8	8/8	0·18 (0·04–0·88)
No	34/61	36/60	0·35 (0·21–0·60)
Number of metastasis sites			
<3	9/21	15/21	0·29 (0·11–0·73)
≥3	31/47	26/41	0·34 (0·19–0·63)
Type of *EGFR* mutations			
Exon 19 deletion	12/24	20/25	0·32 (0·14–0·71)
L858R	21/34	19/32	0·30 (0·15–0·59)
Other	7/11	5/11	0·66 (0·18–2·47)
***MET* copy number**			
>5 and <10	15/26	21/35	0·34 (0·16–0·74)
≥10	25/43	23/33	0·32 (0·17–0·60)



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	Assessed by investigator					Assessed by independent review committee				
	Savolitinib–osimertinib (n=37)	Chemotherapy (n=37)	HR (95% CI)	OR (95% CI)	p value	Savolitinib–osimertinib (n=37)	Chemotherapy (n=37)	HR (95% CI)	OR (95% CI)	p value
Progression-free survival, months	6·9 (4·2–9·7)	3·0 (2·7–4·6)	0·32 (0·18–0·57)	..	<0·0001	6·9 (4·3–11·1)	3·0 (2·7–4·1)	0·32 (0·18–0·58)	..	<0·0001
Progression-free survival rate at 6 months	59% (41–74)	18% (7–33)	..	..	..	52% (34–67)	15% (5–29)	..	..	..
Objective response rate	23 (62%, 45–78)	10 (27%, 14–44)	..	4·46 (1·50–13·31)	0·0025	21 (57%, 39–73)	12 (32%, 18–50)	..	2·73 (0·95–7·74)	0·0390
Disease control rate	31 (84%, 68–94)	24 (65%, 47–80)	..	2·86 (0·84–10·36)	0·062	31 (84%, 68–94)	24 (65%, 47–80)	..	2·91 (0·85–10·81)	0·058
Duration of response, months	8·2 (5·3–12·4)	3·0 (0·9–4·1)	..	..	..	9·7 (4·2–14·8)	3·4 (1·3–5·7)	..	..	..
Time to response, months	1·4 (1·4–1·4)	1·4 (1·2–1·5)	..	..	..	1·4 (1·4–1·4)	1·4 (1·3–1·5)	..	..	..

Data are median (95% CI), % (95% CI), or n (%, 95% CI). The widths of the CIs have not been adjusted for multiplicity and should not be used to infer definitive treatment effects. Subgroup analyses were not stratified. HR=hazard ratio. OR=odds ratio. TKI=tyrosine kinase inhibitor.

Table 3: **Efficacy summary in third-generation EGFR TKI-treated population**

	Savolitinib–osimertinib (n=106)		Chemotherapy (n=96)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any treatment-emergent adverse event	104 (98%)	60 (57%)	92 (96%)	55 (57%)
Any serious adverse event	40 (38%)	..	27 (28%)	..
Leading to discontinuation of any study drug	9 (8%)	..	8 (8%)	..
Leading to discontinuation of two study drugs	5 (5%)	..	1 (1%)	..
Leading to interruption of any study drug	54 (51%)	..	40 (42%)	..
Leading to dose reduction of any study drug	38 (36%)	..	25 (26%)	..
Death within treatment cycles	11 (10%)*	..	7 (7%)	..
Treatment-emergent adverse events by preferred term†				
White blood cell count decreased	52 (49%)	7 (7%)	51 (53%)	12 (13%)
Nausea	51 (48%)	0	36 (38%)	2 (2%)
Vomiting	47 (44%)	1 (1%)	18 (19%)	2 (2%)
Anaemia	43 (41%)	4 (4%)	70 (73%)	22 (23%)
Neutrophil count decreased	43 (41%)	15 (14%)	57 (59%)	25 (26%)
Hypoalbuminaemia	40 (38%)	0	16 (17%)	0
Decreased appetite	39 (37%)	1 (1%)	27 (28%)	1 (1%)
Oedema peripheral	38 (36%)	0	1 (1%)	0
Platelet count decreased	35 (33%)	4 (4%)	29 (30%)	8 (8%)
Alanine aminotransferase increased	30 (28%)	7 (7%)	36 (38%)	3 (3%)
Aspartate aminotransferase increased	30 (28%)	6 (6%)	35 (36%)	0
Blood creatinine increased	26 (25%)	0	9 (9%)	1 (1%)
Pyrexia	25 (24%)	1 (1%)	6 (6%)	0
Weight decreased	24 (23%)	0	13 (14%)	0
Hypocalcaemia	23 (22%)	1 (1%)	4 (4%)	0
Diarrhoea	22 (21%)	1 (1%)	5 (5%)	0
Hypokalaemia	22 (21%)	3 (3%)	15 (16%)	3 (3%)
Amylase increased	20 (19%)	0	2 (2%)	0
Constipation	20 (19%)	0	23 (24%)	1 (1%)
Lymphocyte count decreased	20 (19%)	4 (4%)	8 (8%)	3 (3%)
Blood lactate dehydrogenase increased	19 (18%)	0	9 (9%)	0
Rash	19 (18%)	2 (2%)	2 (2%)	0
Urinary tract infection	19 (18%)	0	6 (6%)	1 (1%)
COVID-19	18 (17%)	2 (2%)	11 (11%)	0
Blood creatine phosphokinase increased	17 (16%)	3 (3%)	1 (1%)	0
Dizziness	14 (13%)	0	11 (11%)	1 (1%)
Headache	14 (13%)	0	7 (7%)	0
Upper respiratory tract infection	14 (13%)	1 (1%)	4 (4%)	0
Hyperuricaemia	13 (12%)	0	3 (3%)	0
Mouth ulceration	13 (12%)	0	2 (2%)	0
Electrocardiogram QT prolonged	12 (11%)	2 (2%)	1 (1%)	0
Hyponatraemia	12 (11%)	4 (4%)	9 (9%)	0
Paronychia	12 (11%)	0	0	0
Pneumonia	12 (11%)	6 (6%)	10 (10%)	6 (6%)
Asthenia	11 (10%)	1 (1%)	13 (14%)	2 (2%)
Arthralgia	11 (10%)	0	5 (5%)	0
Fatigue	11 (10%)	0	7 (7%)	2 (2%)
Hyperglycaemia	11 (10%)	1 (1%)	8 (8%)	0
Hypoesthesia	11 (10%)	0	9 (9%)	0
Cough	10 (9%)	0	10 (10%)	0
Malaise	10 (9%)	0	10 (10%)	0
Gamma glutamyltransferase increased	9 (8%)	0	11 (11%)	2 (2%)
Leukopenia	7 (7%)	1 (1%)	11 (11%)	1 (1%)

(Table 4 continues on next page)

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Patients with more than one treatment-emergent adverse event within a particular preferred term were counted only once for that preferred term. *Two deaths were considered by the investigator to be related to the study treatment. †Reported in ≥10% of patients in either group.

Table 4: **Overview of treatment-emergent adverse events in the safety analysis set**

Research in context

Evidence before this study

PubMed was searched from database inception to April 21, 2025, using the search terms "((lung cancer) AND (EGFR)) AND (MET)", filtered for clinical trials and then sorted to capture articles reporting on EGFR tyrosine kinase inhibitor (TKI) MET combination treatments for patients with advanced, *MET*-amplified, *EGFR* mutation-positive non-small-cell lung cancer (NSCLC) with progression after EGFR TKI therapy. An additional search of the American Society of Clinical Oncology (ASCO) abstracts database was conducted using the same search terms and time frame. These searches yielded a total of 12 relevant articles and eight ASCO abstracts describing findings from 13 distinct clinical trials, all published since 2013. All clinical trials were early phase (1, 1b, or 2), and predominantly single-arm, open-label, and global studies; three were randomised. The patient populations of the studies were highly heterogeneous with respect to the previous EGFR TKI treatment and line of therapy associated with treatment failure, the method of identifying MET expression status (ie, gene dysregulation *vs* immunohistochemistry-based tumour cell MET protein expression), and requirement for *MET* mutation as a study entry criterion. Patients with *MET* amplification or MET tumour tissue overexpression with progression after first-line EGFR TKI were the focus of just three studies (NCT02099058, NCT03940703 [INSIGHT 2], and NCT03778229 [SAVANNAH]). Of the three randomised trials, one compared erlotinib with or without emibetuzumab in patients with acquired resistance to erlotinib (any line of therapy) and tumour MET overexpression. A second compared erlotinib with or without onartuzumab in patients with recurrent NSCLC who had two or three previous lines of therapy. Although neither *EGFR* nor *MET* dysregulation were required at baseline, findings were analysed separately according to MET immunohistochemistry expression and *EGFR* mutation status. The third trial was a randomised subset of the SAVANNAH trial that evaluated outcomes with savolitinib with or without osimertinib, overall and according to the presence of brain metastases. The absence of evidence comparing study drug combinations with standard of care in this field highlights the need for efficacious and well-tolerated options to address resistance to EGFR TKI therapy, which invariably develops in patients with *EGFR* mutation-positive NSCLC.

Added value of this study

The protocol-specified interim analysis of the SACHI study met its primary endpoint of statistically significant prolongation of investigator-assessed progression-free survival (PFS) with savolitinib in combination with osimertinib versus chemotherapy in Chinese patients with *EGFR* mutation-positive NSCLC and *MET* amplification after failure of first-line EGFR TKI, in both the third-generation EGFR TKI-naive and intention-to-treat populations. As a result, an independent data monitoring committee recommended termination of study enrolment for superior efficacy. Savolitinib plus osimertinib also showed improvements in independent review committee-assessed PFS and tumour response versus chemotherapy in both analysis populations, and conferred efficacy benefits in patients with previous first-line third-generation EGFR TKI exposure. The safety profile of savolitinib plus osimertinib was well tolerated and similar to that reported in early-phase studies and with proportionately fewer haematological adverse events than observed with chemotherapy.

Implications of all the available evidence

SACHI is the first randomised phase 3 trial to support the efficacy of MET inhibition in patients with acquired *MET* amplification after progression on previous EGFR TKIs. Savolitinib plus osimertinib has potential to provide an oral treatment option that directly targets *MET* amplification-mediated resistance, which occurs in about a fifth of patients with *EGFR* mutation-positive NSCLC treated with EGFR TKIs.

In 2026, healthcare in India is a massive, multi-tiered system undergoing rapid digital and structural transformation to achieve universal coverage. It is characterized by a significant divide between public and private sectors, as well as between urban and rural access.

Healthcare Structure & Delivery

- **Public Sector:** Primarily tax-funded and free for all residents at government facilities. It follows a three-tier model:
  - **Primary:** Over 200,000 **Ayushman Arogya Mandirs** (formerly Health & Wellness Centres) provide localized screening and basic care.
  - **Secondary:** Community Health Centres (CHCs) and Sub-District Hospitals.
  - **Tertiary:** Medical Colleges and AIIMS institutions providing specialized care.
- **Private Sector:** Dominates the market, providing roughly 70% of outpatient and 58% of inpatient care. Major corporate chains include Apollo, Fortis, Manipal, and Max Healthcare.

2. Major Government Schemes

- **Ayushman Bharat (PM-JAY):** The world's largest government-funded health insurance scheme, providing up to ₹5 lakh ($6,000) per family annually for secondary and tertiary care to over 550 million vulnerable citizens.

The *Lancet* Commission on a citizen-centred health system for India

Executive summary

India stands at a pivotal moment in its journey towards universal health coverage—a crucial component of the government's Viksit Bharat vision to elevate it to the status of a developed country by 2047, 100 years since its formation as an independent nation. At this juncture, there is unprecedented political will for reform and sustained economic growth, creating a window of opportunity to advance transformative change and for India to leapfrog to a new health-care paradigm: a universal, citizen-centred, and technology-driven system that dissociates affluence from access to high-quality, comprehensive health care. The *Lancet* Commission on a citizen-centred health system for India was established in December, 2020, to identify the reforms needed to realise this vision. Our analyses are rooted in the lived experiences, expectations, and preferences of the people of India and guided by the principle that they enjoy a universal, fundamental, and inalienable Right to Health, and that the government must be accountable for financing and operating the public sector and stewarding both the public and private sectors. To this end, the Commission engaged a diverse spectrum of expertise and drew systematically upon existing and new research to arrive at our recommendations.

A citizen-centred health system

Reform action 1: enable meaningful citizen engagement by firmly building the health system upon people's participation

The existing platforms of local government and civil society collectives must be strengthened with financial investments and capacity strengthening. Citizen participation should include access to adequate and timely information about entitlements, their health system's performance, how and where to seek care, and available recourse when rights are denied. It should also enable citizens to engage in health-promoting behaviours; share care experiences in ways that meaningfully inform priority-setting, governance, and purchasing decisions; and access to robust grievance redressal mechanisms, including a citizen-led complaints ombudsman. The health system must commit to addressing inequities arising from social determinants of health by prioritising the most vulnerable, integrating social services within health-care settings, and implementing regulations and grievance mechanisms against discriminatory practices.

Progress and challenges on the road to universal health coverage

Recognising achievements while confronting inequities and emerging challenges

India has achieved remarkable improvements in life expectancy, maternal and child survival, and the control of infectious diseases. At the same time, progress has been uneven across States and districts, income groups, geographies, marginalised castes, tribes, and genders. Additionally, the rapid rise of non-communicable diseases accompanying population ageing, mental health conditions, antimicrobial resistance, and climate change present formidable health system challenges.

Expanding access while strengthening quality

Large-scale government initiatives, such as the Ayushman Bharat Pradhan Mantri Jan Arogya Yojana (AB-PMJAY), Ayushman Arogya Mandirs, the Ayushman Bharat Digital Mission, the e-Sanjeevani telemedicine platform, deployment of multiple cadres of medical and allied health professionals, and the establishment of new tertiary hospitals and medical colleges across the country, together with a vibrant private sector, have expanded coverage and are reshaping the delivery of care. India has achieved self-sufficiency in essential medicines and diagnostics through both public and private sector manufacturing and delivery, while nurturing a growing domestic biotech and medical technology industry. Yet, uneven care quality limits the value of expanded access and has resulted in low-value care. The conceptualisation and implementation of comprehensive primary health care have fallen short of meeting people's needs. Without care coordination, citizens are left to fend for themselves and obtain discontinuous care of uncertain quality from a myriad of providers, often at expensive hospitals rather than primary health-care facilities, undermining continuity, equity, and efficiency.

Increasing spending bolstered by the need for greater efficiency

Government spending on health has risen in absolute terms and is increasing in several States, with particularly strong growth during the COVID-19 pandemic. However, health expenditure, as a share of gross domestic product, remains low and has not grown in line with India's overall economic growth. Fragmented budgets, their suboptimal allocation, inefficient utilisation, and rigid financing mechanisms have constrained system responsiveness and weakened institutional capacities, especially at decentralised levels. The predominance of line-item budgets (in the public sector) and fee-for-service (in the private sector) as payment methods has limited the health system's flexibility to tailor services to population needs and promote rational care.

Enhancing financial protection

Financial risk protection has improved over the past decade, with expansions in affordable care and insurance coverage through the AB-PMJAY (covering 600 million people) and its State-level counterparts. However, insurance schemes are focused on hospitalisation, overlooking outpatient and chronic care. Consequently, out-of-pocket expenditure, driven by the costs of medication and diagnostics, remains a leading cause of financial hardship, especially for lower-income groups.

Building on citizen engagement and community action for health

India has pioneered models of community engagement. The National Health Mission (2013) and the National Health Policy (2017) have emphasised people's participation in universal health coverage through ongoing initiatives such as the Accredited Social Health Activist programme and Community Action for Health. The success of these initiatives can be reinforced by continued efforts to address information asymmetries and power imbalances and enhance accountability through citizens' engagement in governing health.

Effecting better regulations and responsive governance

The government's digital e-governance tools and digital public infrastructure offer opportunities to strengthen accountability and trust, but require scaling-up and alignment with citizen priorities. Despite an array of health regulations covering payers, providers, and patients' rights, limited State capacity for oversight and enforcement, regulatory capture, and misaligned incentives have reduced their effectiveness. Shortfalls in timely and reliable health system data and weak health research networks are barriers to responsive governance.

Guiding principles of this Commission

Several guiding principles underscore our reimagination of the health system:

- A transition from a facility-centric, reactive, and fragmented delivery system focused on specific diseases towards a comprehensive, coordinated, citizen-centred health system
- A transition from citizens being passive recipients of services to becoming active agents with rights who are engaged in the health system
- A transition from focusing merely on physical access to health-care services to ensuring high-quality health care that treats everybody with respect and dignity
- A transition from centralised governance to decentralised, citizen-centric governance informed by robust, comprehensive, and timely data that report local population-level outcomes
- A transition from providing weight to only professional qualifications to emphasising provider competencies, values, and motivations, and empowering frontline workers and practitioners of Indian systems of medicine (eg, Ayurveda, Yoga, Unani, Siddha, and Homeopathy)
- To responsibly and ethically leverage the power of innovative technology to support the reimagined health system and deliver citizen-centred care
- To explicitly acknowledge rights and health equity as a core value of universal health coverage and the reduction of inequities as a measure of progress across universal health coverage goals

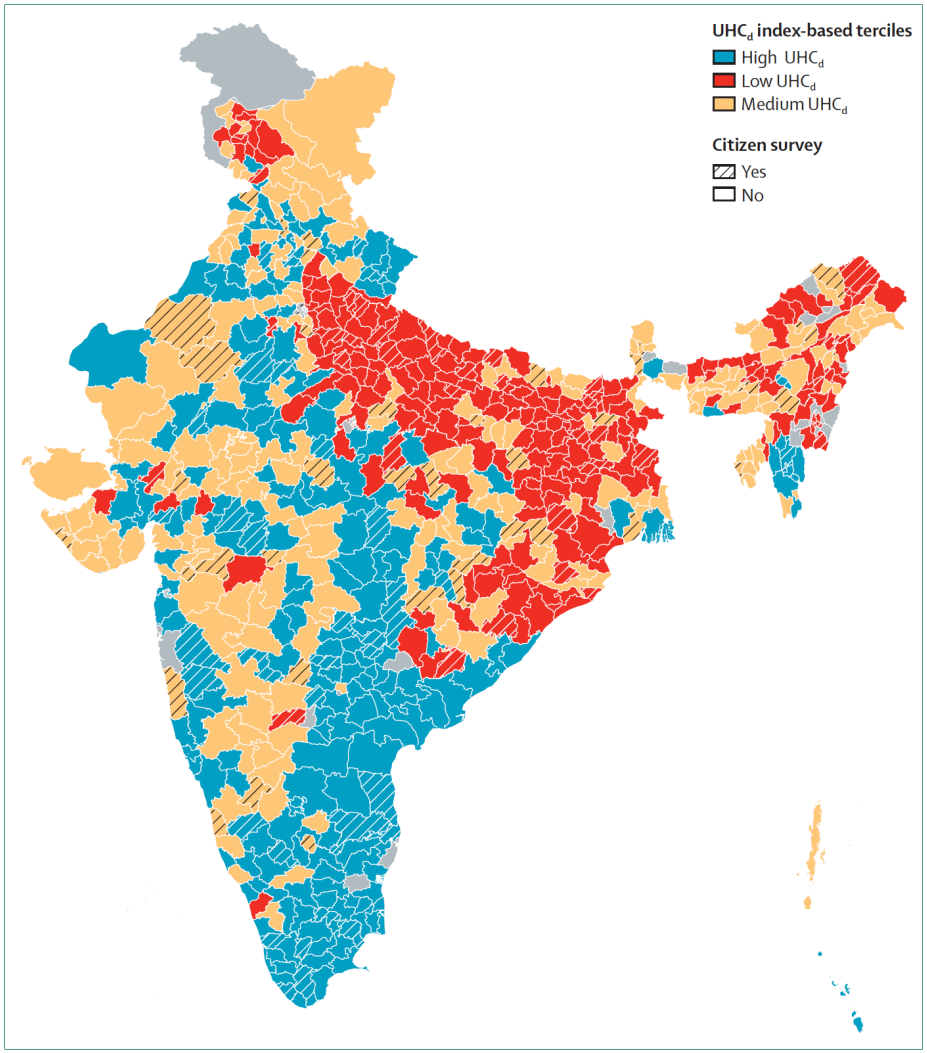


Figure 1: **UHC$_d$ index-based terciles in India and districts sampled in the Citizens' Survey (2023)**
UHC$_d$=universal health coverage performance at the district level.

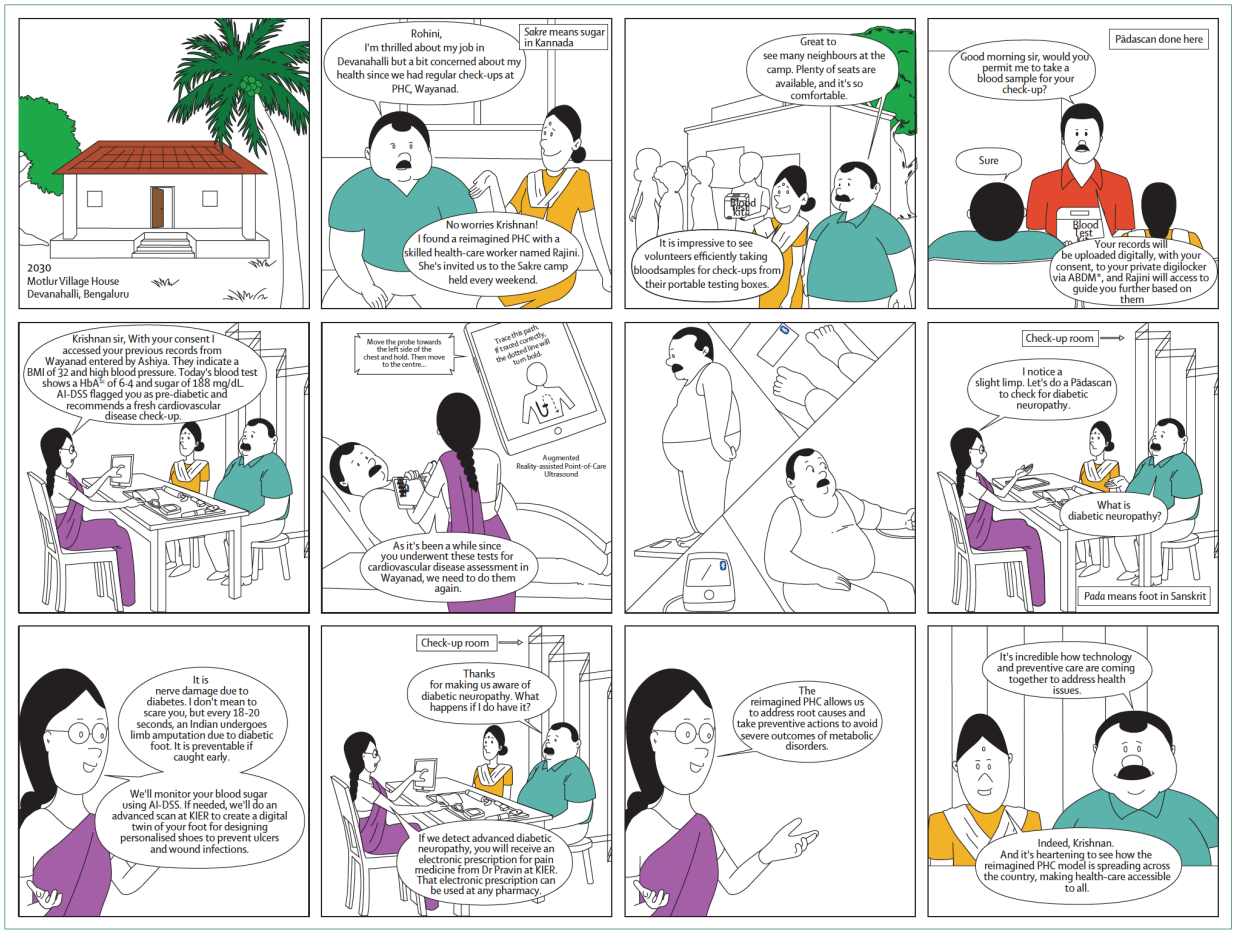
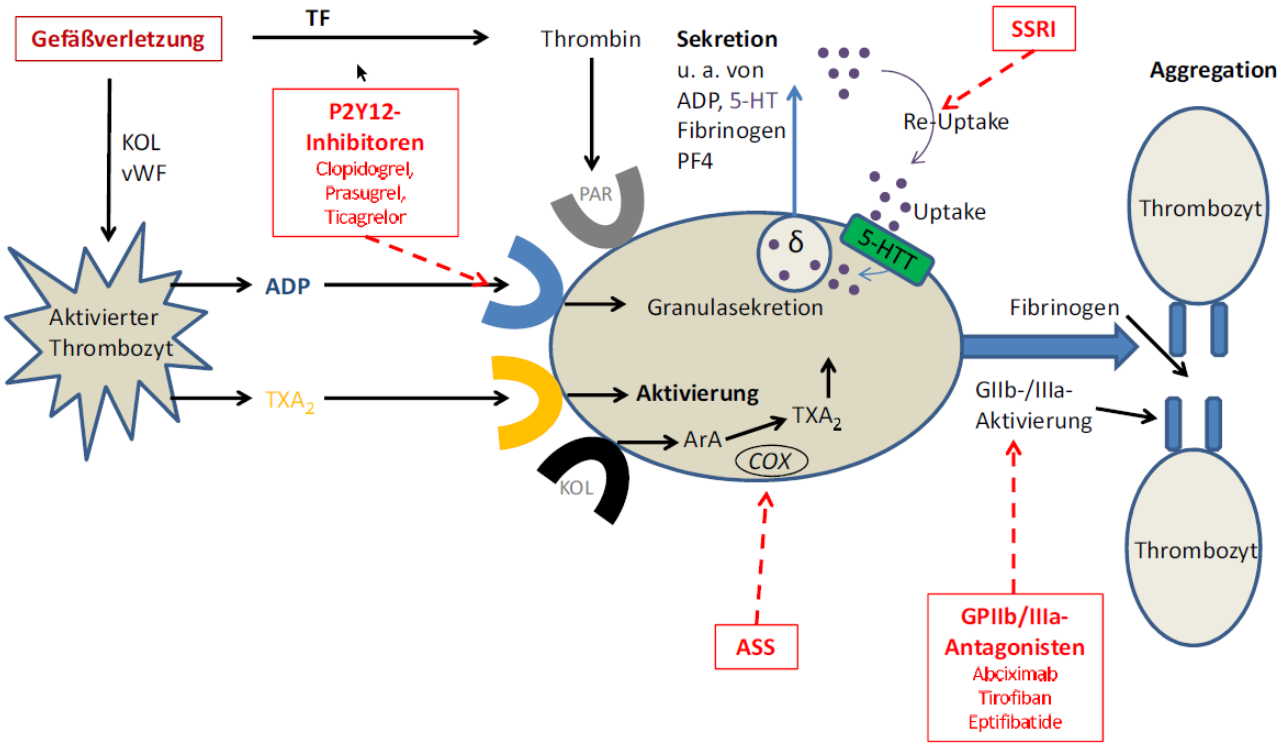


Figure 21: **A patient's journey in a reimagined primary health care-focused system**

This cartoon is the third in a series of three cartoons created as part of the Commission's deliberations to show how different kinds of technologies might provide a more citizen-centred approach to health care. It is based on an experiment in progress with a team of interdisciplinary stakeholders to build a replicable and reimagined primary health centre in a rural village in north Bengaluru, India. Each cartoon in the series reflects a different condition or disease and different actors. These cartoons are not designed to be an ideal or a recommendation; they are prototypes that aim to elicit more concrete and useful reflections and reactions that can envision what a patient's journey might look like in the future. The cartoons are suggestive of the potential of certain types of innovation. Some of these innovations are already available, some can be developed relatively easily, and others are more complex. The target audience for these cartoons is the same as that for the report—stakeholders and decision makers in the health system who are mostly English readers. However, if it is useful, these resources can be translated into multiple languages. The first two cartoons are available at https://www.artpark.in/reimagine-health. PHC=primary health centre. ABDM=Ayushman Bharat Digital Mission. HbA_{1c}=glycated haemoglobin. AI-DSS=artificial intelligence decision-support system. KIER=Karnataka Institute for Endocrinology Research. *ABDM provides key digital public infrastructure for India's health systems.

Many of our proposed reform actions have already been initiated by Central or State government policies, and their inclusion herein is an endorsement of these policies and an acknowledgment that the challenge lies in their effective implementation. However, some of our reform actions are potentially more transformative. Thus, we expect that some of our reforms might not be palatable or even feasible for specific jurisdictions at this moment in time. We recognise that vested interests, conflicting ideologies, political considerations, and governance and implementation capacities are considerable barriers to successful reforms. Thus, high-level political commitment is indispensable to the successful realisation of the goal of UHC. Moreover, major public policy decisions should be (even if often not so) the result of iterative processes of discourse with the relevant stakeholders[423] and through a continuing learning process resulting from pilots of innovative actions and the scaling-up of these actions. In the spirit of positioning this report as the final output of a Commission focused on citizen-centred care, our recommendations will require extensive consultations with civil society and health system actors across the country to assess their feasibility, acceptability, scalability, and risks, followed by iterative cycles of implementation and evaluation. With determined political leadership leveraging broad-based support from diverse stakeholders, India can transform its health system to better serve all its citizens, setting the stage for a sustainable and resilient future.

Thrombozyten (Blutplättchen) sind kleine Zellfragmente im Blut, die für die Blutstillung unerlässlich sind, indem sie sich bei Gefäßverletzungen anlagern, verklumpen und ein Gerinnsel bilden, um Blutungen zu stoppen. Sie entstehen im Knochenmark und werden im kleinen Blutbild bestimmt; sowohl zu wenige (Thrombozytopenie, erhöhtes Blutungsrisiko) als auch zu viele (Thrombozytose, erhöhtes Thromboserisiko) können zu Problemen führen.



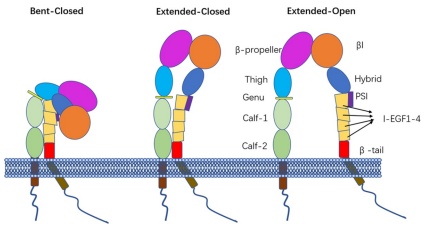
Tethered platelets in severe infection

Platelets are cell fragments that plug leaks in blood vessels, preventing bleeding. However, they also form clots that impede blood flow (thrombosis) and increase inflammation. Activated platelets, which can bind to each other, and hyporesponsive platelets, which do not form clots, are detected in patients with acute severe infections, such as COVID-19 and sepsis. How to uncouple the protective and harmful proinflammatory functions of platelets is a therapeutic dilemma. Kusch et al. report the formation of platelet-derived integrin and tetraspanin-enriched tethers (PITTs) in patients with severe infections. PITTs, which are enriched in specific platelet proteins, remain anchored to the blood vessel wall (endothelium) and promote neutrophil recruitment, inflammation, and tissue damage, whereas the main platelet body shears off and reenters circulation in a hyporesponsive state. PITTs may contribute to blood clotting, immune dysregulation, and bleeding complications that characterize severe infections.

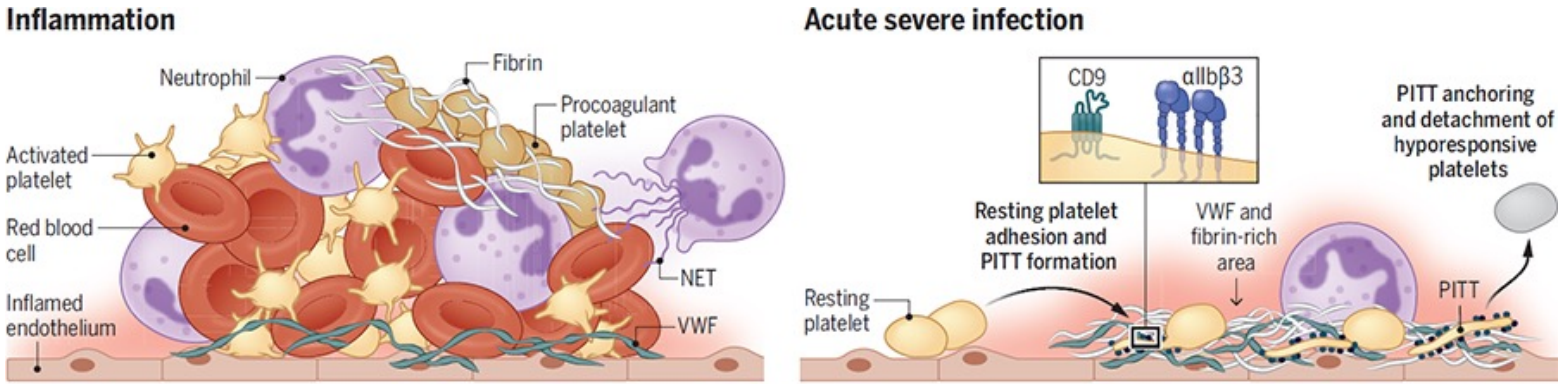
At sites of vascular injury, expression of thrombotic and inflammatory molecules drives platelet recruitment. Platelets switch from a sentinel to an effector (activated) function through their rolling on exposed subendothelium, firm adhesion and activation, secretion of thromboxane A2 and adenosine diphosphate (which activate and recruit more platelets), release of granule contents, exposure of phosphatidylserine on their surface (which supports coagulation), and aggregation. This latter step is driven by switching integrin αIIbb3, the most abundant platelet surface receptor protein, from a resting to an activated state.
Neutrophil extracellular traps—weblike structures composed of DNA, histones, and antimicrobial proteins that trap and kill harmful bacteria—provide a scaffold for platelets and coagulation factors in pathogenic clots, exacerbating clotting and amplifying inflammation. Besides forming clots, activated and procoagulant platelets bind to immune cells and modulate their functions—including recruitment, activation, and extracellular trap formation—in animal models and in patients with inflammatory diseases and severe infections such as COVID-19 and sepsis.

In severe infection, platelet activation can be driven by stimuli such as thrombotic agonists, endotoxins, cytokines, damage-associated molecular patterns, and immune complexes that are produced as part of the host response to pathogens. Platelets from patients with COVID-19 are often hyporesponsive, with reduced αIIbβ3 expression and decreased reactivity to thrombotic stimuli in ex vivo assays, characteristics that are associated with worse disease outcomes. This phenotype is often attributed to exhaustion (when repeatedly stimulated platelets lose their capacity to respond), receptor desensitization (when receptors at the surface of the platelet become hyporesponsive) after sustained activation, or receptor shedding.

αIIbβ3
(Alpha-IIb Beta-3), auch bekannt als Glykoprotein IIb/IIIa (GpIIb/IIIa), ist ein Rezeptor für Fibrinogen und den von-Willebrand-Faktor, der auf der Oberfläche von Blutplättchen (Thrombozyten) vorkommt.



Platelet-derived integrin and tetraspanin-enriched tethers (PITTs)



NET, neutrophil extracellular trap; PITT, platelet-derived integrin- and tetraspanin-enriched tether; VWF, von Willebrand factor.

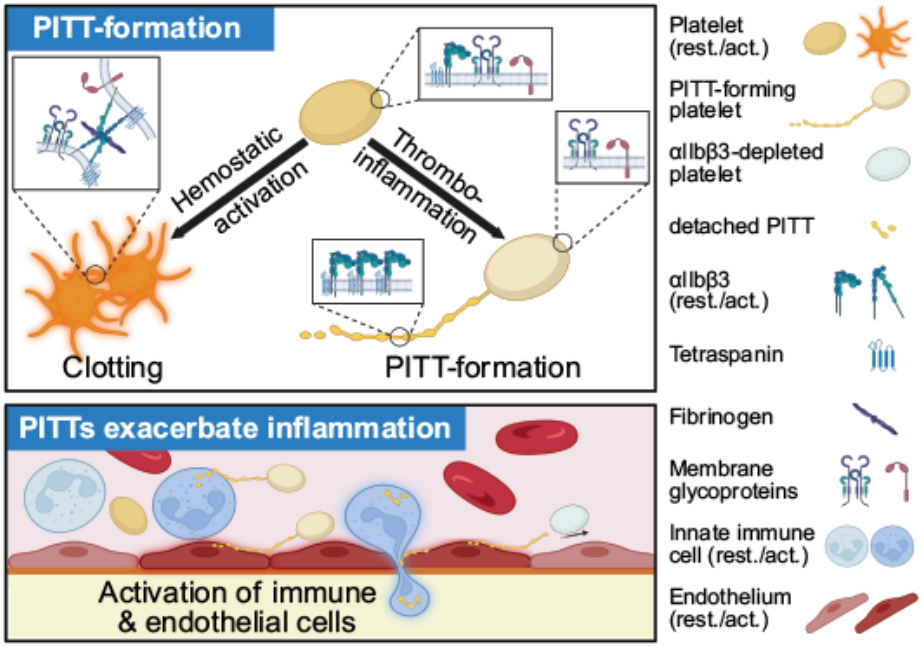
PITTs in infection

Heterogeneous blood clots rich in activated and procoagulant platelets, fibrin, and red blood cells form on the endothelium of blood vessels at sites of inflammation and infection. Activated platelets support neutrophil recruitment and activation, and the formation of NETs, which are webs of DNA, histones, and antimicrobial proteins that trap and kill harmful bacteria. In acute severe infection, platelets can also adhere to VWF and fibrin at sites of inflammation, in a process that is blood-flow dependent. Two platelet proteins, the integrin αIIβ3 and the tetraspanin CD9, cluster on tethers called PITTs on the endothelium and on neutrophils. The main body of the platelet detaches and reenters the circulation in a hyporesponsive state, which might increase bleeding risk.

Kusch *et al*. observed that blood smears from patients with COVID-19 and sepsis, but not those from patients with uncomplicated infection and healthy controls, contained platelet-derived elongated structures that they called PITTs. Using a microfluidic flow chamber approach in which human blood flow on a substrate mimics how platelets are recruited in blood vessels, as well as mice treated with an antibody that promotes platelet depletion, the authors observed that PITT formation was blood-flow dependent and that it required platelet adhesion and tethering but not classic activation. PITT formation occurred upon platelet adhesion to specific immobilized substrates, von Willebrand factor (VWF) and fibrin, which are abundant at sites of vascular injury and inflammation. PITTs lacked classic platelet receptors and activation markers and were enriched in integrin αIIbβ3 in its resting state and in tetraspanin CD9, a small membrane protein linked to the organization and regulation of integrin-dependent platelet activation. This concentration of αIIbβ3 and CD9 in PITTs decreases their abundance on the surface of the parent platelet body, which reenters the circulation with reduced reactivity. This effect potentially contributes to the bleeding complications that are associated with severe infection.

In hemostasis, platelets seem to be a homogeneous cell population with a fairly uniform behavior, but this assumption is less tenable for inflammation, especially during severe infection, when platelets and their progenitors, megakaryocytes, undergo reprogramming and diversification. Whether all platelets generate PITTs or whether PITTs arise from specific subpopulations is unclear. Furthermore, do PITTs aid pathogen clearance while also promoting thromboinflammation and organ dysfunction in severe infection and, if so, by which mechanism? The frequency of PITT formation in vivo is also unknown. Because inhibition or deficiency in VWF, fibrin, or αIIbβ3 has effects on both thrombosis and inflammation, the importance of PITTs in thromboinflammation remains unclear. Answering these questions will require defining the molecular machinery that governs the formation of PITTs and their inflammatory activity. This will reveal whether PITTs are realistic candidates for new anti-inflammatory therapies and whether they can be targeted to restore platelet dysfunction in severe infections, which often cause both thrombotic and bleeding complications.

Nonactivated platelets release integrin-and tetraspanin-enriched tethers (PITTS) to promote thrombo-inflammation. Circulating platelets can use their principal adhesion receptor, integrin αIIbβ3, to switch between hemostatic and thrombo-inflammatory programs. At sites of vascular injury, classical activation triggers inside-out signaling of αIIbβ3, promoting fibrinogen binding, platelet adhesion, and thrombus formation. Under thromboinflammatory conditions, nonactivated platelets generate PITTs that can attach to leukocytes and endothelial cells, exacerbating inflammation, whereas the platelet body detaches in a state partially depleted of αIIbβ3. Rest., resting; act., activated.



(abscheuliche)

The abhorrent power of the photograph of a 5-year-old held by ICE

A viral image of 5-year-old Liam Conejo Ramos shows the boy in a blue knit hat with white bunny ears and pompoms, standing with a blank look on his face, staring at the back of a truck. Liam and his father were captured by Immigration and Customs Enforcement officers in Minnesota on Tuesday, and both are now detained in San Antonio, more than 1,200 miles from Liam's home, his school, his friends and most of his family.

School officials in Minnesota say that the prekindergarten student was used "as bait" by ICE, in an apparent attempt to gain access to the adults inside the private house where he once lived. That act, the use of a boy too young to understand the political game in which he became a pawn, mirrors in a perverse and deeply disturbing way the power of the photograph. The photograph stirs empathy and compassion, the same emotions that ICE agents apparently used to entice adults into making themselves vulnerable to capture.