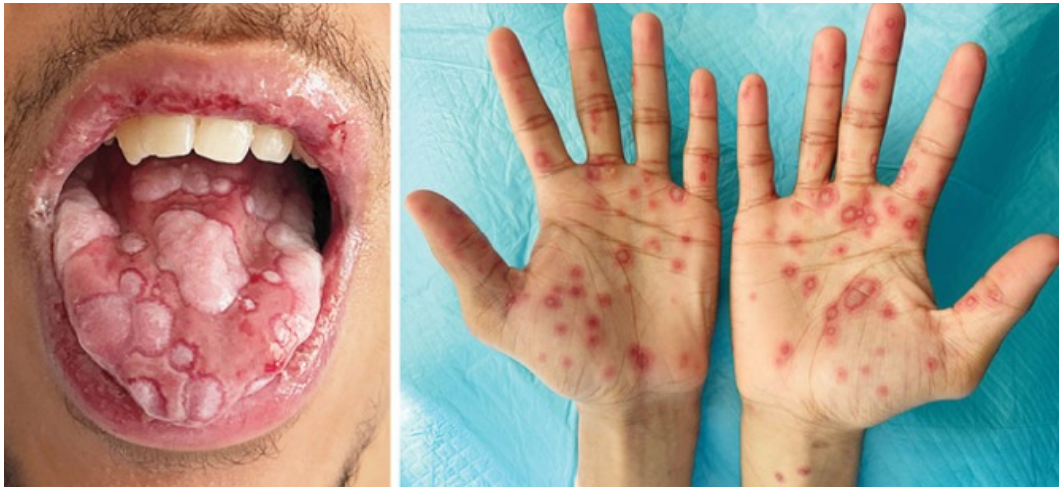
https://www.mdc-berlin.de/de/veroeffentlichungstypen/clinical-journal-club

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!



Erythema multiforme is an acute, immune-mediated mucocutaneous reaction that is most commonly triggered by infection. It may also be idiopathic or associated with medication. It can be accompanied by systemic symptoms in severe cases and may have a recurring course, as in this patient.

A 22-year-old man presented to the emergency department with a 5-day history of painful lesions on his hands, feet, and mouth, with accompanying fever and malaise. Two months earlier, he had had a similar episode. PCR testing from a swab sample of the lip ulceration was positive for herpes simplex virus (HSV) type 1. Which of the following diagnoses best explains the lesions on the tongue and palm?

Bullous pemphigoid

Disseminated herpes infection

● Erythema multiforme

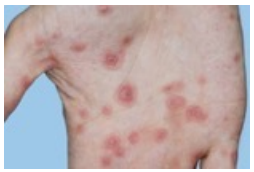
Sweet syndrome

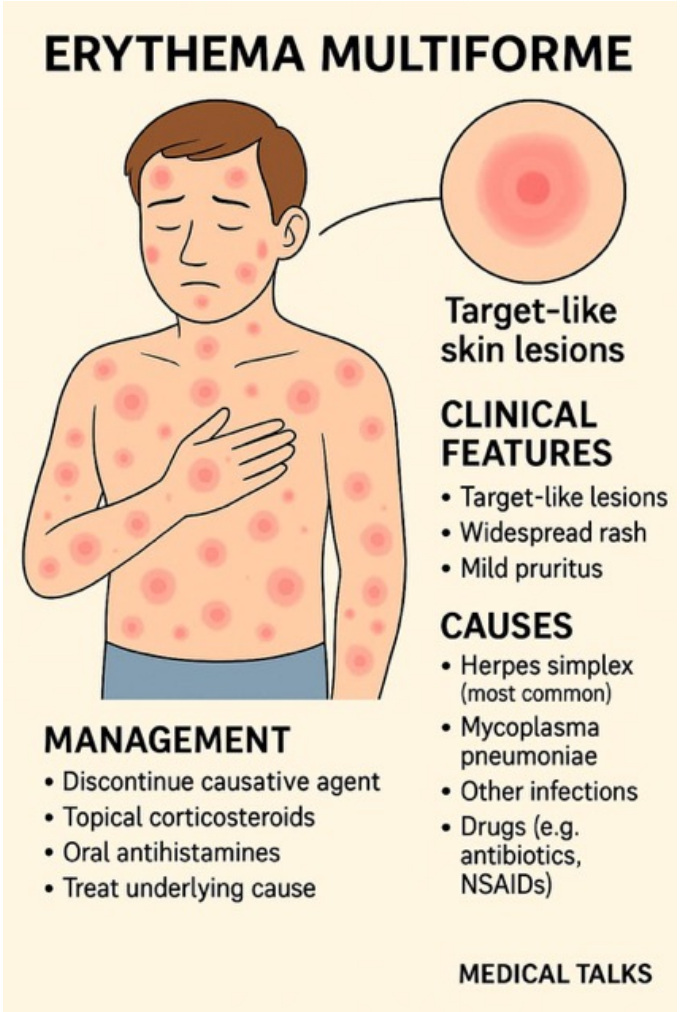
Urticaria

Das **Erythema exsudativum multiforme** (EEM) ist eine akute, immunvermittelte Entzündung der Haut und Schleimhäute, oft ausgelöst durch Herpes-simplex-Viren oder Medikamente. Typisch sind schießscheibenartige Hauterscheinungen (Kokarden) an Extremitäten, Händen und Lippen. Die meist harmlose Hauterkrankung heilt oft von selbst, erfordert aber bei schweren Formen eine gezielte Behandlung.

Symptome und Erscheinungsbild

- **Kokarden-Läsionen:** Charakteristische, zielscheibenförmige rote Flecken mit dunklem, oft blasigem Zentrum, einem blassen Ring und rotem Rand.
- **Lokalisation:** Meist symmetrisch an Handrücken, Unterarmen, Füßen und Knien, seltener im Gesicht
.
- **Schleimhautbeteiligung:** Besonders bei der **Major-Form** schmerzhafte Blasen und Blutungen im Mund, an den Lippen oder im Genitalbereich.
- **Allgemeinsymptome:** Fieber, Juckreiz oder Gelenkschmerzen können auftreten.





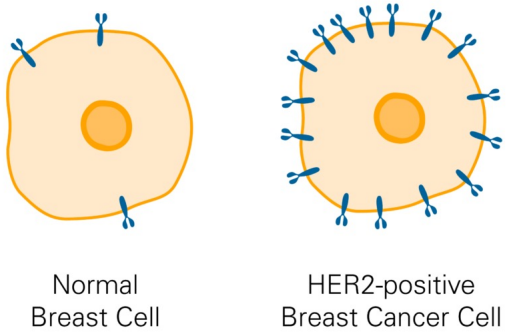
HER is also HIS

HER2 (Human Epidermal Growth Factor Receptor 2) ist ein Eiweißstoff auf der Oberfläche von Zellen, der das Zellwachstum steuert. Bei ca. 15–20 % der Brustkrebspatientinnen ist das HER2-Gen verändert, was zu einer Überexpression (HER2-positiv) führt. Dieser Typ wächst schneller, ist aber gut mit zielgerichteten Therapien wie Trastuzumab behandelbar.

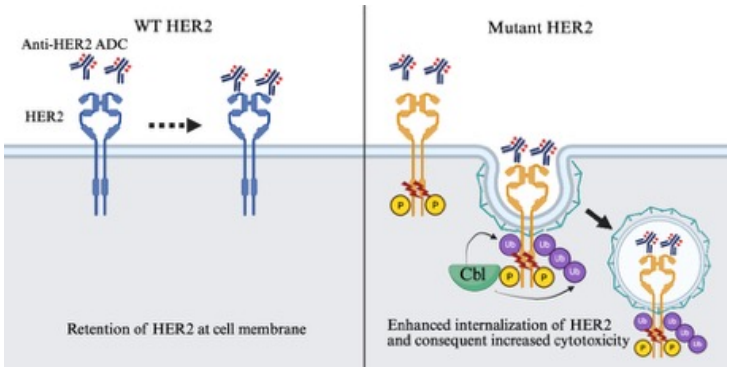
Wichtige Aspekte zu HER2:

- **HER2-Status:** Wird durch einen Pathologen mittels Immunhistochemie (IHC) bestimmt. Der Score reicht von 0 bis 3+.
- **HER2-positiv (3+ oder 2+ mit ISH-Nachweis):** Der Tumor spricht gut auf HER2-gezielte Therapien (Antikörper) an.
- **HER2-low (1+ oder 2+ ohne ISH-Nachweis):** Tumore mit geringer HER2-Expression, die zunehmend durch spezifische Antikörper-Wirkstoff-Konjugate behandelbar sind.
- **Therapie:** Der Standard umfasst oft eine zielgerichtete Therapie (z.B. Trastuzumab, Pertuzumab) in Kombination mit Chemotherapie.
- **Diagnostik:** Der Status kann sich im Verlauf oder bei einem Rezidiv ändern.

Increased expression



Mutated form

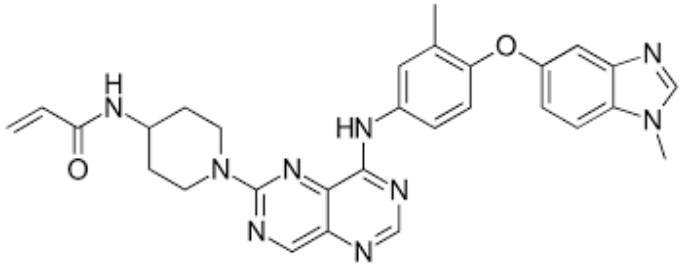


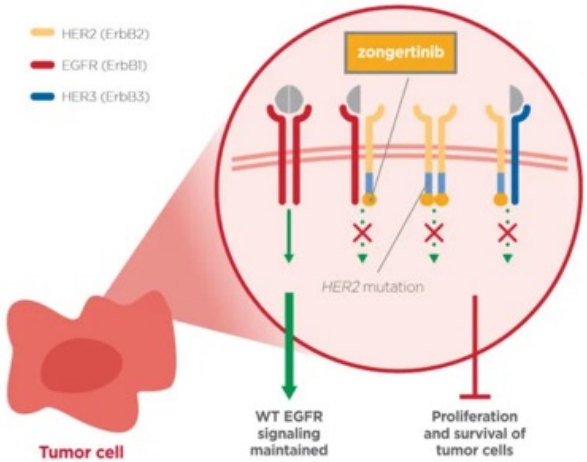
2 to 4% of non–small-cell lung cancers (NSCLCs).

Zongertinib (Handelsname **Hernexeos**) ist ein neuartiges Krebsmedikament zur gezielten Behandlung von fortgeschrittenem Lungenkrebs.

Wirkmechanismus
Zongertinib wurde entwickelt, um selektiv an mutierte Formen des HER2-Rezeptors zu binden.

- **Präzision**: Es blockiert gezielt den HER2-Rezeptor, schont aber weitgehend den Wildtyp-EGFR (epidermaler Wachstumsfaktor-Rezeptor).
- **Vorteil**: Durch diese Selektivität werden typische Nebenwirkungen herkömmlicher Therapien (wie schwerer Hautausschlag oder Durchfall) reduziert.
- **Effekt**: Es stoppt das unkontrollierte Wachstum der Krebszellen und kann den Tumor verkleinern.

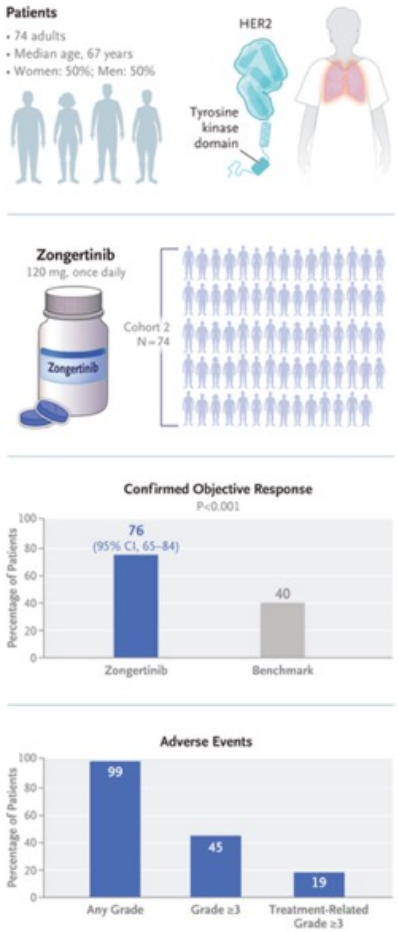




First-Line Zongertinib in Advanced HER2-Mutant Non–Small-Cell Lung Cancer

Until recently, no first-line targeted treatment options were available for patients with human epidermal growth factor receptor 2 (*HER2*)–mutant non–small-cell lung cancer (NSCLC). Zongertinib is an oral, irreversible tyrosine kinase inhibitor that selectively inhibits HER2 while sparing wild-type epidermal growth factor receptor (EGFR), thereby minimizing associated toxic effects.

We conducted a phase 1a–1b, multicohort trial to assess zongertinib in patients with advanced or metastatic nonsquamous *HER2*-mutant NSCLC. Here, we evaluated zongertinib at a dose of 120 mg once daily in patients who had not previously received treatment (cohort 2). The primary end point was objective response as assessed by blinded independent central review. Secondary end points included duration of response and progression-free survival. In addition, zongertinib was evaluated in patients with active brain metastases (exploratory cohort 4).



Lung cancer remains the leading cause of cancer-related death worldwide. Mutations within human epidermal growth factor receptor 2 (*HER2*; also known as ErbB-2 receptor tyrosine kinase 2 [*ERBB2*]) occur in approximately 2 to 4% of non–small-cell lung cancers (NSCLCs). *HER2* mutations most commonly occur within the tyrosine kinase domain and are distinct from other HER2 alterations. *HER2*-mutant NSCLC is a highly aggressive disease, characterized by poor prognosis and a high incidence of brain metastases. Despite advances in targeted treatments for NSCLC, *HER2*-mutant NSCLC has not yet shown the same therapeutic improvements as other oncogene-driven tumors, such as epidermal growth factor receptor (*EGFR*)–driven and anaplastic lymphoma kinase (*ALK*)–driven disease, especially in the context of first-line treatment. Until recently, the only approved HER2-directed agent was trastuzumab deruxtecan (T-DXd) for previously treated patients. This intravenous antibody–drug conjugate showed encouraging efficacy in this context; however, it can be associated with serious toxic effects. Zongertinib is an oral, irreversible tyrosine kinase inhibitor that selectively inhibits HER2 while sparing wild-type EGFR, thereby minimizing associated toxic effects.

Methods

Trial Design and Patients

Eligible patients were at least 18 years of age, with histologically or cytologically confirmed advanced or metastatic NSCLC, a documented *HER2* mutation in the tyrosine kinase domain, at least one measurable non–central nervous system lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, and an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (scores range from 0 to 5, with higher scores indicating greater disability).

End Points

The primary end point in cohort 2 was a systemic objective response (best overall response of complete or partial response), as assessed by blinded independent central review, according to RECIST, version 1.1. Secondary end points included duration of response (time from the first complete or partial response until disease progression or death); progression-free survival according to RECIST, version 1.1; and objective response according to Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria for patients with central nervous system lesions at baseline.

Characteristic	Cohort 2 (N=74)†
Median age (range) — yr	67 (35–88)
Age group — no. (%)	
18 to <65 yr	31 (42)
65 to <75 yr	30 (41)
≥75 yr	13 (18)
Sex — no. (%)	
Female	37 (50)
Male	37 (50)
Race — no. (%)‡	
Asian	34 (46)
White	32 (43)
Black	1 (1)
Missing§	7 (9)
ECOG performance-status score — no. (%)¶	
0	34 (46)
1	40 (54)
Tobacco use — no. (%)	
Never	47 (64)
Former	25 (34)
Current	1 (1)
Missing	1 (1)
Site of metastases at screening — no. (%)	
Brain‖	22 (30)
Liver	12 (16)
HER2 tyrosine kinase domain mutation — no. (%)	
A775_G776insYVMA**	50 (68)
Other	24 (32)

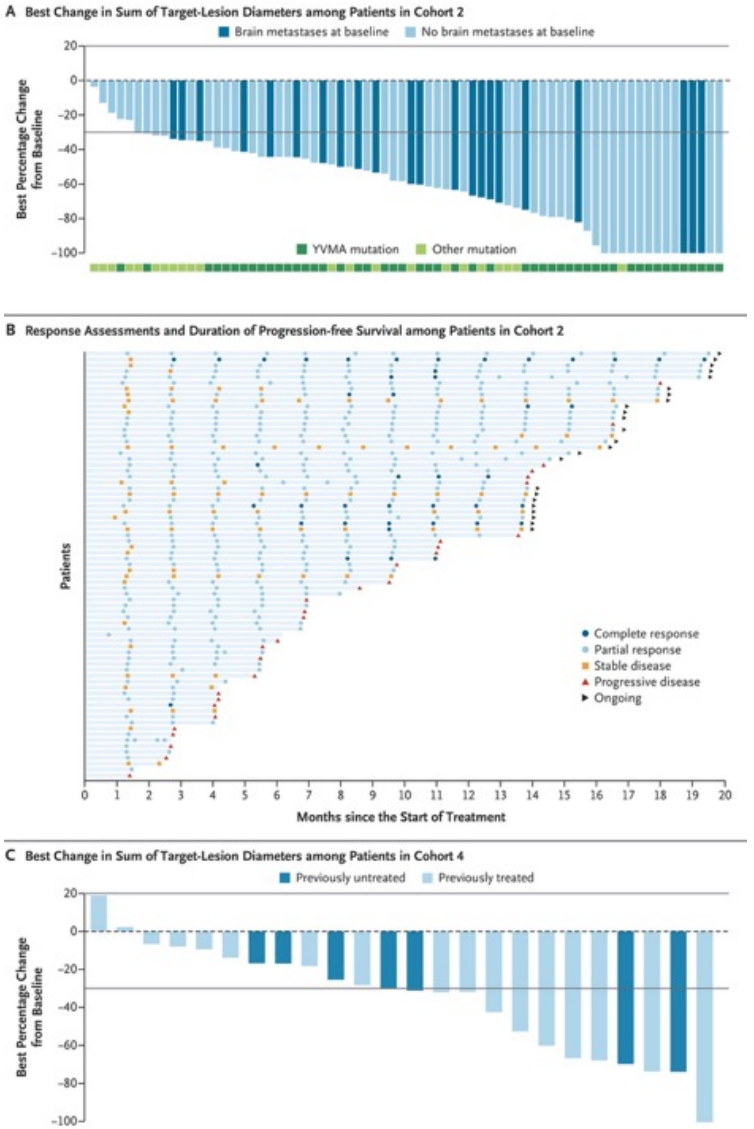
Confirmed Systemic Response in Patients in Cohort 2 Who Received First-Line Zongertinib at a Dose of 120 mg.

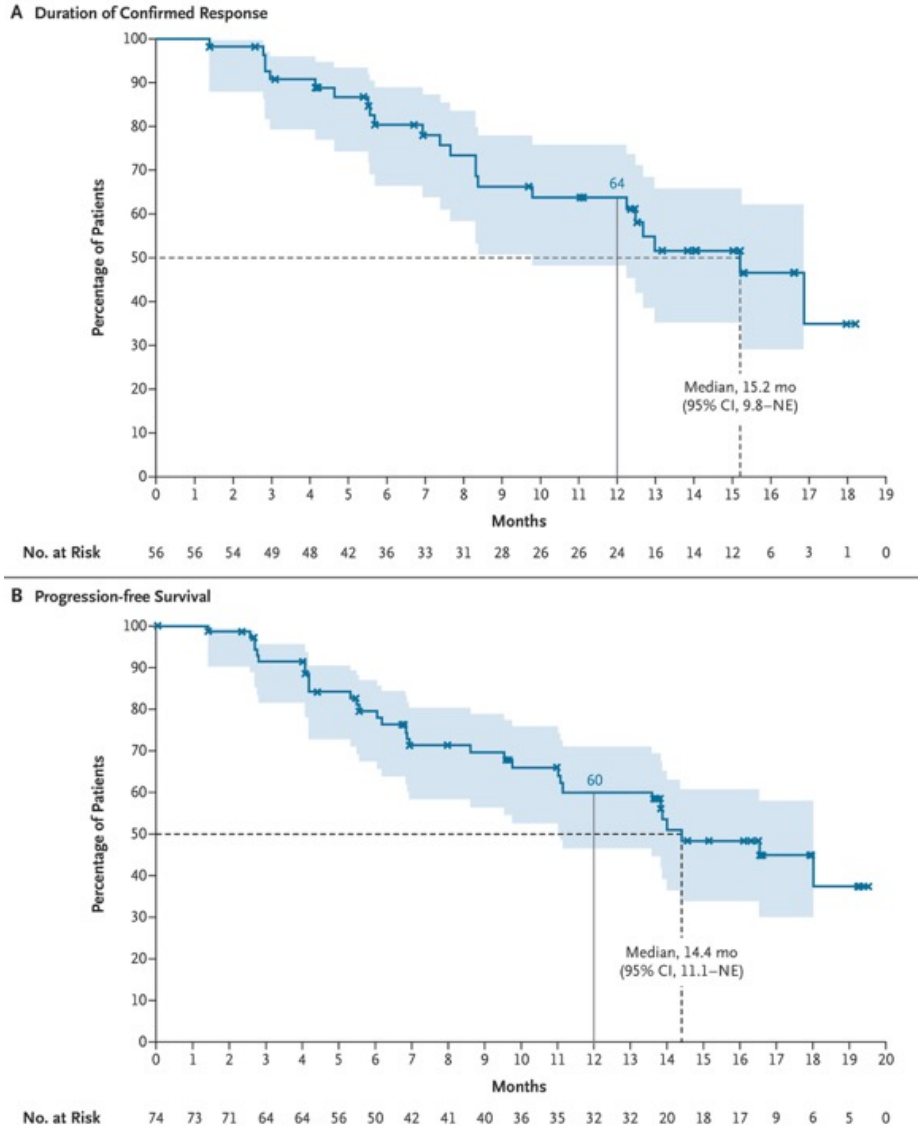
Variable	Cohort 2 (N=74)
Objective response	
Total no. of patients	56†
Percent (95% CI)	76 (65–84)
Complete response — no. (%)	8 (11)
Partial response — no. (%)	48 (65)
Stable disease — no. (%)	15 (20)
Progressive disease — no. (%)	1 (1)
Not evaluable — no. (%)	2 (3)

Zongertinib is a HER2-targeted therapy primarily causing common adverse reactions including diarrhea (up to 53%), rash (up to 32%), fatigue, nausea, and increased liver enzymes (hepatotoxicity). Serious side effects include hepatotoxicity (27%), severe diarrhea, dyspnea (shortness of breath), and potential heart failure, often managed with dose interruptions or reductions

Safety Summary in the 74 Patients in Cohort 2 Who Received First-Line Zongertinib at a Dose of 120 mg.

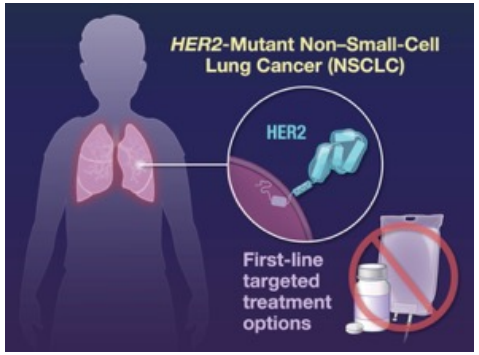
Event	Any Grade	Grade ≥3
	no. of patients (%)	
Adverse events during the treatment period		
Any	73 (99)	33 (45)
Led to dose reduction†	12 (16)	5 (7)
Led to treatment discontinuation‡	7 (9)	3 (4)
Treatment-related adverse events§		
Any	67 (91)	14 (19)
Diarrhea	41 (55)	2 (3)
Rash¶	18 (24)	0
Increased alanine aminotransferase	13 (18)	3 (4)
Dysgeusia	13 (18)	0
Nausea	13 (18)	0
Increased aspartate aminotransferase	12 (16)	2 (3)
Paronychia	10 (14)	1 (1)
Dry skin	10 (14)	0
Pruritus	10 (14)	0
Fatigue	9 (12)	0
Anemia	8 (11)	2 (3)
Stomatitis	8 (11)	0
Serious treatment-related adverse event	8 (11)	6 (8)

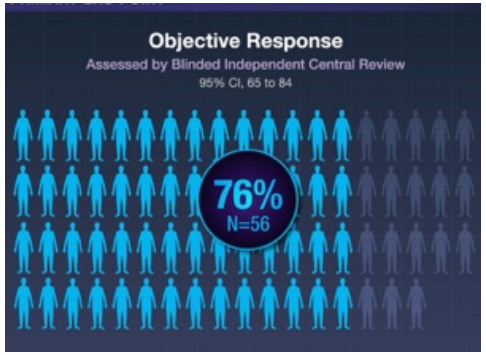


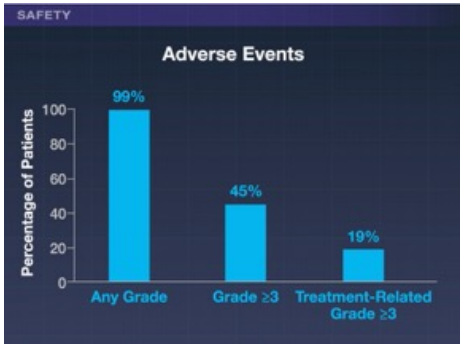


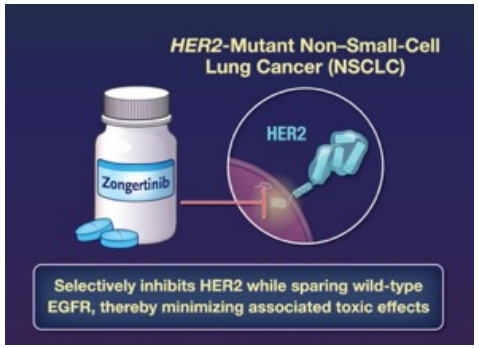
Durability of Systemic Responses in Patients in Cohort 2 Who Received First-Line Zongertinib at a Dose of 120 mg.

Panel A shows the duration of confirmed response and Panel B the progression-free survival among patients in cohort 2 who received zongertinib at a dose of 120 mg. Response was assessed by blinded independent central review according to RECIST, version 1.1. Shaded areas denote 95% confidence intervals. The confidence intervals were calculated without adjustment for multiplicity; therefore, their widths should be interpreted descriptively and not used for formal hypothesis testing. The date of data cutoff was August 21, 2025. NE denotes not evaluable.

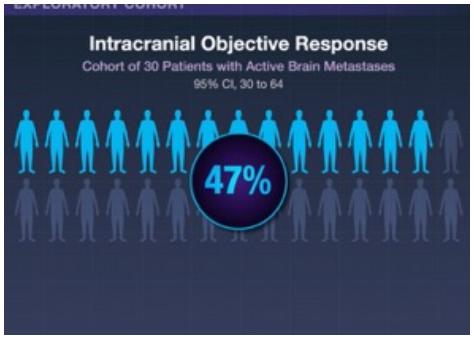

HER2-Mutant Non–Small-Cell Lung Cancer (NSCLC)
HER2
First-line targeted treatment options

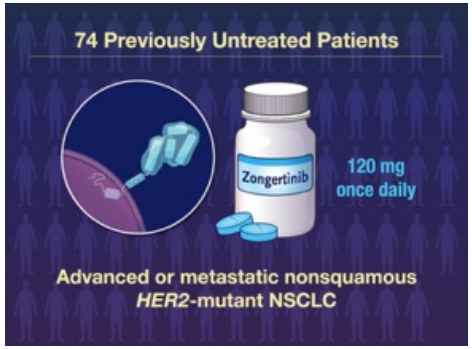

Objective Response
Assessed by Blinded Independent Central Review
95% CI, 65 to 84
76%
N=56


SAFETY
Adverse Events
Percentage of Patients
100
80
60
40
20
0
99%
45%
19%
Any Grade
Grade ≥3
Treatment-Related Grade ≥3

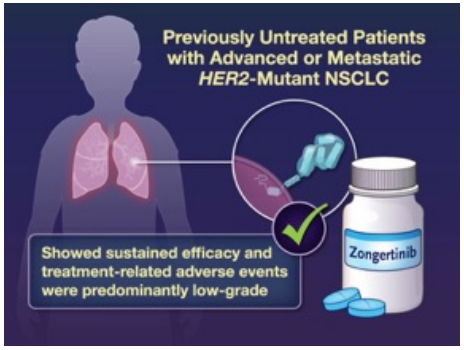

HER2-Mutant Non–Small-Cell Lung Cancer (NSCLC)
HER2
Zongertinib
Selectively inhibits HER2 while sparing wild-type EGFR, thereby minimizing associated toxic effects


PRIMARY END POINT
Confirmed Objective Response
Median Duration
Percentage of Patients
100
80
60
40
20
0
15.2 mo
0
2
4
6
8
10
12
14
16
18
Months


Intracranial Objective Response
Cohort of 30 Patients with Active Brain Metastases
95% CI, 30 to 64
47%


74 Previously Untreated Patients
Zongertinib
120 mg once daily
Advanced or metastatic nonsquamous *HER2*-mutant NSCLC


PRIMARY END POINT
Progression-free Survival
Median Duration
Percentage of Patients
100
80
60
40
20
0
14.4 mo
0
2
4
6
8
10
12
14
16
18
Months


Previously Untreated Patients with Advanced or Metastatic *HER2*-Mutant NSCLC
Showed sustained efficacy and treatment-related adverse events were predominantly low-grade
Zongertinib

Das **APT-Sepsis Programm** (*Active Prevention and Treatment of Maternal Sepsis*) ist ein klinisch erprobtes, kostengünstiges Programm zur Senkung der Müttersterblichkeit durch schwere Infektionen.

APT-Sepsis is as follows:

Kernziele und Ergebnisse

Das Programm wurde speziell für Regionen mit begrenzten Ressourcen entwickelt. Eine großangelegte Studie in 59 Krankenhäusern in **Malawi und Uganda** mit über 430.000 Frauen zeigte beeindruckende Resultate:

- **32 % Reduktion** von mütterlichen Todesfällen und schweren Infektionen.
- **47 % Reduktion** am Ende der 12-monatigen Einführungsphase.
- **Verbesserte Früherkennung** durch geschulte "Champions" und strukturierte Überwachung.

Die drei Säulen des Programms

Die Initiative basiert auf drei zentralen, evidenzbasierten Bereichen:

1.Händehygiene: Konsequente Einhaltung der "WHO 5 Momente der Händehygiene".

2.Infektionsprävention: Einsatz bewährter Praktiken wie Antibiotikaprophylaxe bei Hochrisikogeburten und verbesserte chirurgische Standards.

3.Sepsis-Management (FAST-M): Schnelle Behandlung bei Verdachtsfällen durch das FAST-M Bundle:

•**Sepsis-Management (FAST-M):** Schnelle Behandlung bei Verdachtsfällen durch das

FAST-M Bundle:

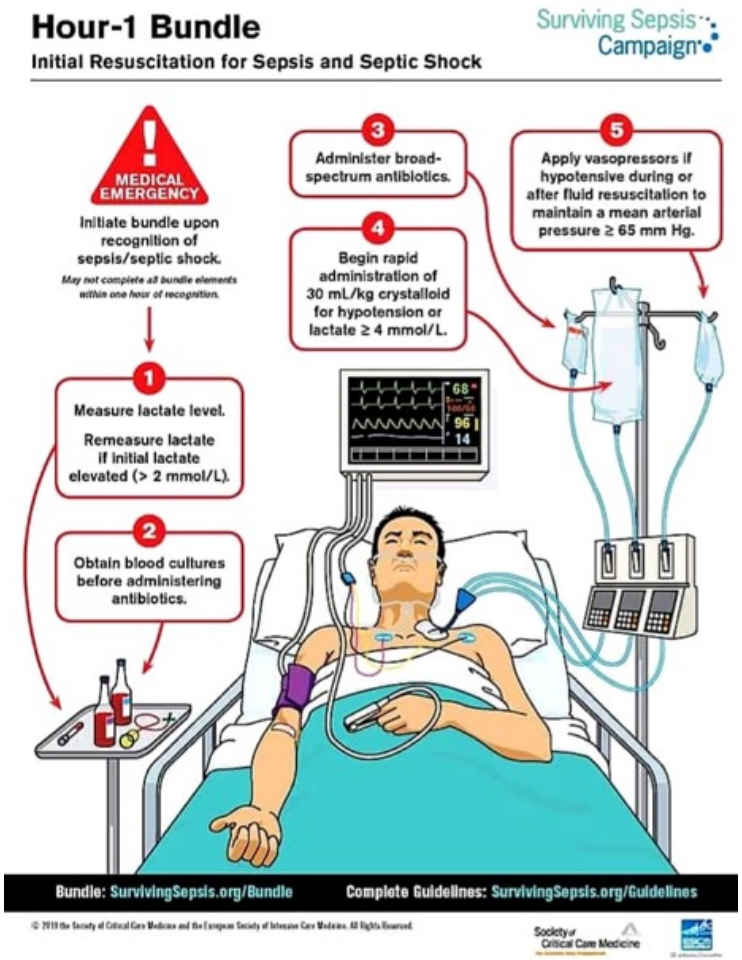
•**F**luids (Flüssigkeit)

•**A**ntibiotics (Antibiotika)

•**S**ource control (Infektionsherd finden/beseitigen)

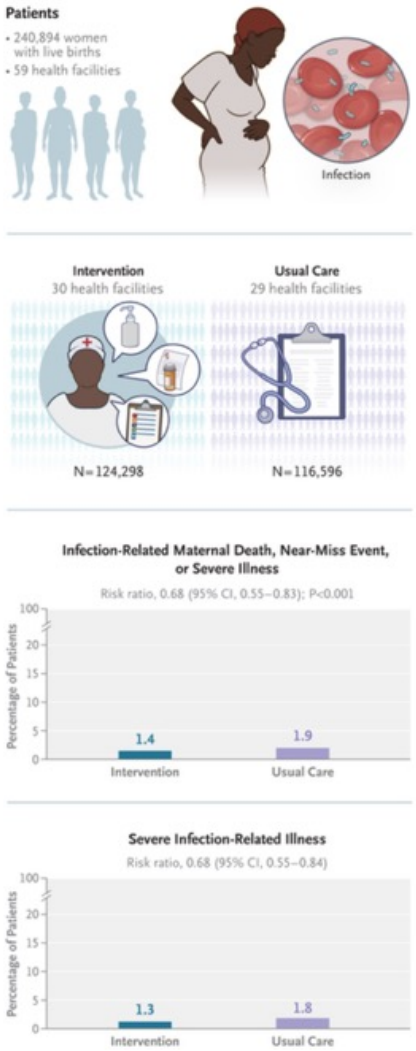
•**T**ransport/Transfer (Verlegung in spezialisierte Zentren)

•**M**onitoring (Stetige Überwachung von Mutter und Kind)



A Multicomponent Intervention to Improve Maternal Infection Outcomes

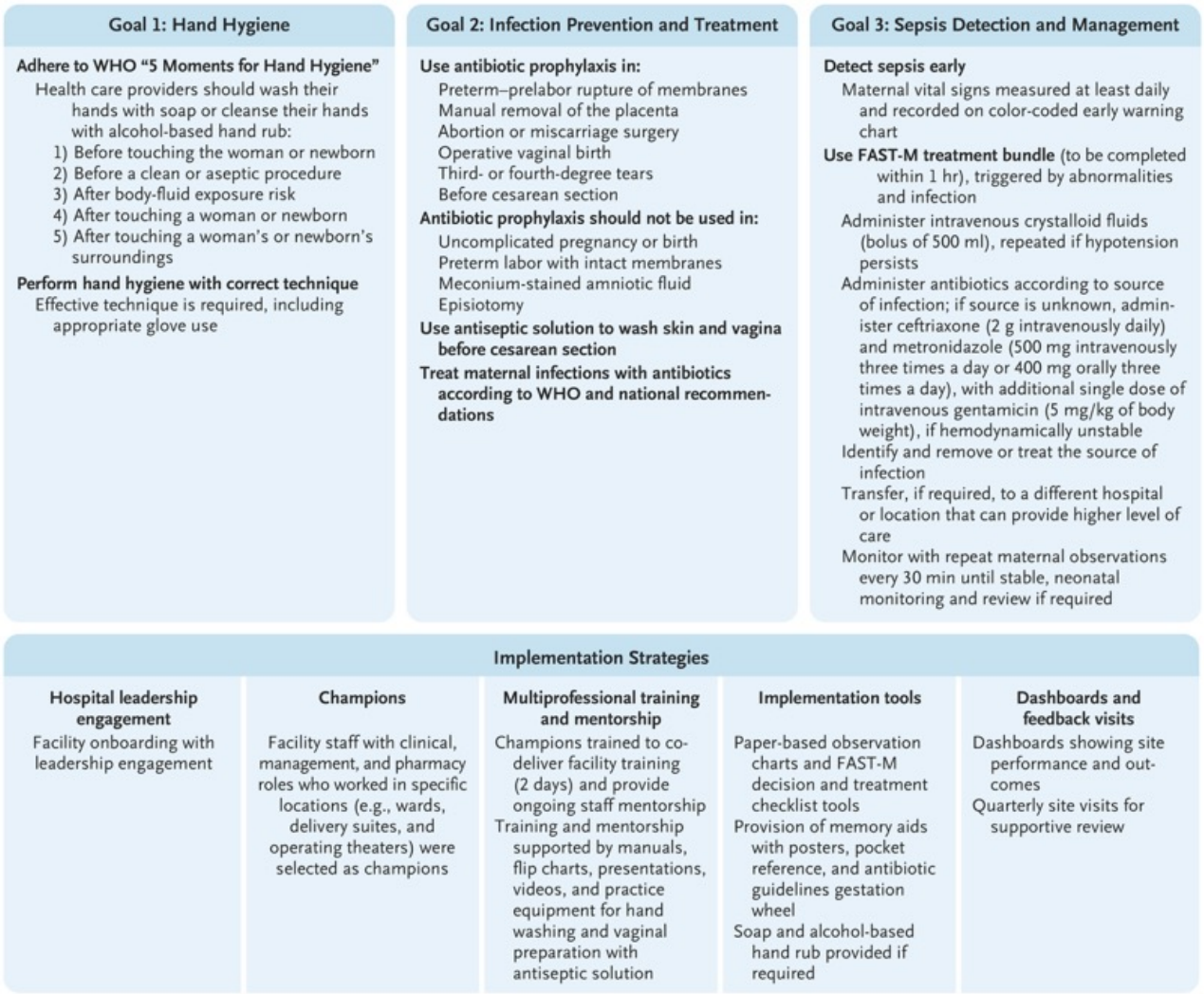
Maternal infection and sepsis are major causes of maternal death and severe illness worldwide, particularly in low- and middle-income countries. Inconsistent implementation of evidence-based recommendations for infection prevention and management and delays in detection and treatment of maternal sepsis contribute to the number of preventable deaths.
We conducted a cluster-randomized trial to assess a multicomponent intervention, the Active Prevention and Treatment of Maternal Sepsis (APT-Sepsis) program. This program was designed to support health care providers in achieving three goals: adherence to World Health Organization (WHO) hand-hygiene standards; adoption of evidence-based practices for maternal infection prevention and management; and early detection of sepsis and use of the FAST-M (fluids, antibiotics, source control, transfer if required, and monitoring) treatment bundle. Usual care was provided in the control group, along with dissemination of guidelines. The primary outcome was a composite of infection-related maternal death, infection-related near-miss event (events in which women survived a life-threatening complication), or severe infection-related illness (deep surgical-site, deep perineal, or body-cavity infection) among women who were pregnant or had recently been pregnant.



The World Health Organization (WHO) has issued recommendations on adherence to hand-hygiene standards and evidence-based practices to prevent and treat maternal infection. However, adherence to these recommendations is suboptimal. The use of structured tools and bundles of care have been shown to improve recognition and timely treatment of other obstetrical emergencies, such as postpartum hemorrhage, and have been associated with better outcomes, even in health facilities with limited resources. Moreover, sepsis treatment bundles are widely used in high-income countries, particularly in the nonmaternity population. A maternal sepsis treatment bundle has been developed specifically for low-resource settings, but its effect on maternal outcomes has not been established.

The Active Prevention and Treatment of Maternal Sepsis (APT-Sepsis) program was designed to address these deficiencies through an integrated, multicomponent intervention delivered at the facility level. The program seeks to help health care providers achieve three goals: (1) to improve hand-hygiene adherence, (2) to improve prevention and management of maternal infection, and (3) to increase early recognition and bundled treatment of sepsis.

We conducted a large cluster-randomized trial in Malawi and Uganda to evaluate whether implementation of the APT-Sepsis program in health facilities would reduce the risk of a composite of infection-related maternal death, infection-related near-miss event, or severe infection-related illness.



Active Prevention and Treatment of Maternal Sepsis (APT-Sepsis) Intervention.

This multicomponent intervention enabled health care providers to meet three goals related to hand hygiene, infection prevention and treatment, and sepsis detection and management, with support from an implementation strategy designed to promote behavioral change. FAST-M denotes fluids, antibiotics, source identification and control, assessment of the need for transfer to a higher level of care, and monitoring of the woman and baby, and WHO World Health Organization.

Methods

Trial Design and Oversight

The APT-Sepsis trial was a multicountry, cluster-randomized trial with a baseline control phase. We designed the intervention to be delivered at the health facility level (cluster) to target the behaviors of health care providers and systems within the facilities.

The trial included a baseline phase for all participating facilities of at least 6 months, during which usual care was provided. On completion of the baseline phase, facilities were randomly assigned in a 1:1 ratio to either continue providing usual care or receive the trial intervention for 12 months. A transition period of 3 months was used to implement and embed the intervention into hospital systems; data from this period were not included in the effectiveness analysis. Participating sites underwent randomization in Malawi from November 6, 2023, to January 8, 2024, and in Uganda from January 8, 2024, to March 4, 2024.

Outcome Measures

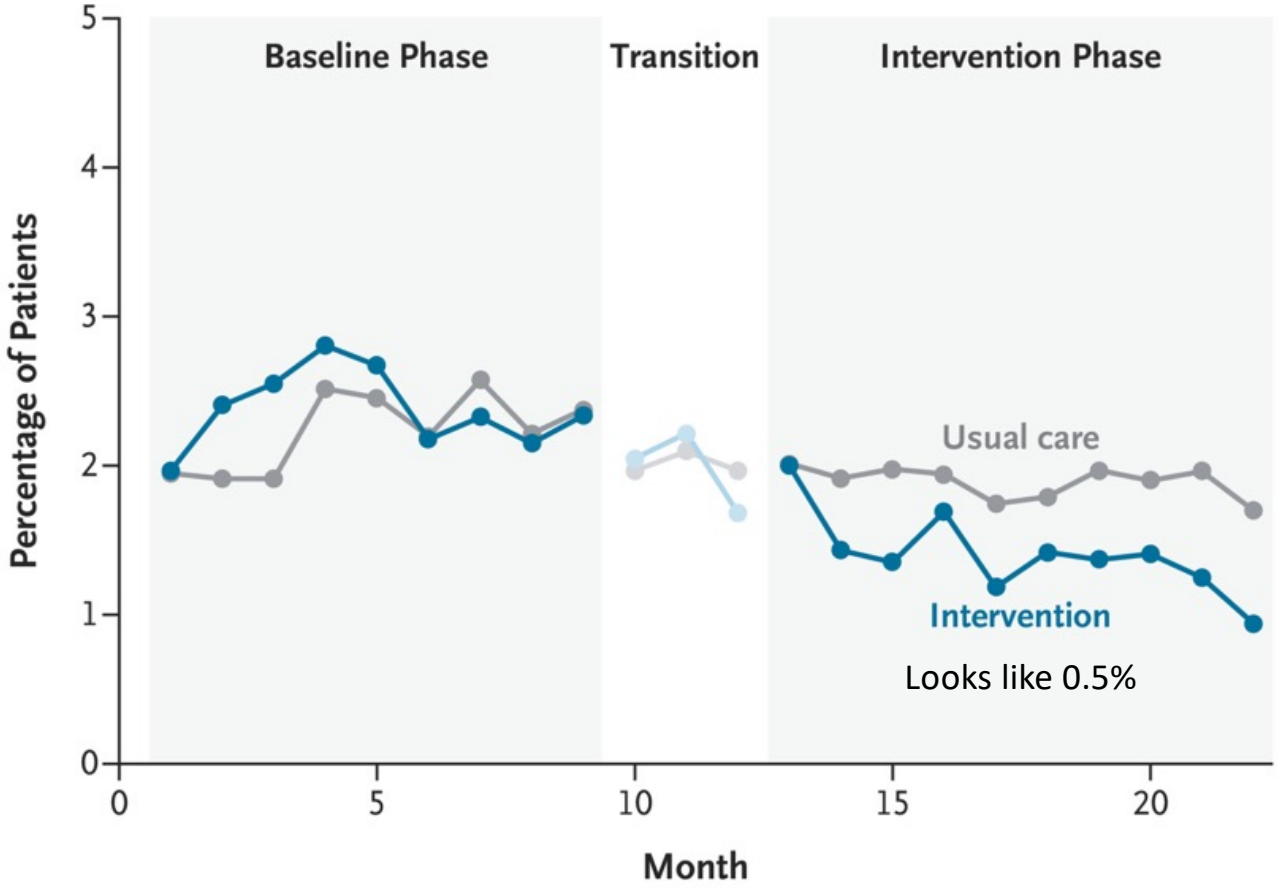
The primary outcome was a composite of infection-related maternal death, infection-related maternal near-miss event (defined as events in which women survived a life-threatening complication), or severe infection-related illness (defined as a deep surgical-site, deep perineal, or body-cavity infection) during pregnancy, childbirth, or within 42 days after pregnancy had ended or at any time up to 28 days after discharge (whichever occurred first), irrespective of birth outcome.

Characteristics of Participating Health Facilities and Resource Availability at Baseline.

Characteristic	Intervention	Usual Care
No. of live births	94,730	95,770
No. of early pregnancy losses	9,656	9,358
No. of stillbirths	2,267	2,054
Neonatal death — no./total no. (%)	2,334/94,730 (2.5)	2,456/95,770 (2.6)
Vaginal birth — no./total no. (%)	67,343/94,730 (71.1)	70,512/95,770 (73.6)
Forceps or vacuum birth — no./total no. (%)	1,346/94,730 (1.4)	1,564/95,770 (1.6)
Cesarean section birth — no./total no. (%)	24,154/94,730 (25.5)	21,205/95,770 (22.1)
Vaginal breech delivery birth — no./total no. (%)	1,346/94,730 (1.4)	1,564/95,770 (1.6)
Born before arrival — no./total no. (%)	1,259/94,730 (1.3)	1,575/95,770 (1.6)
Postpartum hemorrhage (>1 liter) — no./total no. (%)	1,680/94,730 (1.8)	1,355/95,770 (1.4)
Severe preeclampsia or eclampsia — no./total no. (%)	1,201/94,730 (1.3)	1,262/95,770 (1.3)
Median availability of key resources (IQR) — % of weeks available†		
Functioning autoclave	100 (97.1–100)	100 (96.0–100)
Running water	83.7 (8.8–97.1)	85.4 (35.3–96.9)
Thermometers	44.4 (4.0–80.5)	19.5 (5.6–71.9)
Blood-pressure devices	6.8 (0–16.7)	2.6 (0–19.5)
Soap	80.9 (43.8–96.9)	71.9 (38.2–94.1)
Alcohol-based hand rub	66.1 (31.7–88.9)	68.8 (36.1–92.7)
Oxygen concentrators	54.6 (7.3–83.3)	44.4 (2.6–84.4)
Bottle or piped oxygen	9.9 (0–46.9)	0 (0–25.0)
Intravenous crystalloid fluid	84.7 (61.0–95.1)	81.6 (50.0–96.9)
Intravenous cephalosporin	66.6 (33.3–92.7)	75.6 (58.8–87.5)
Intravenous metronidazole	60.6 (36.6–82.4)	63.2 (44.1–81.3)
Intravenous gentamicin	72.1 (50.0–82.9)	65.9 (55.6–93.8)

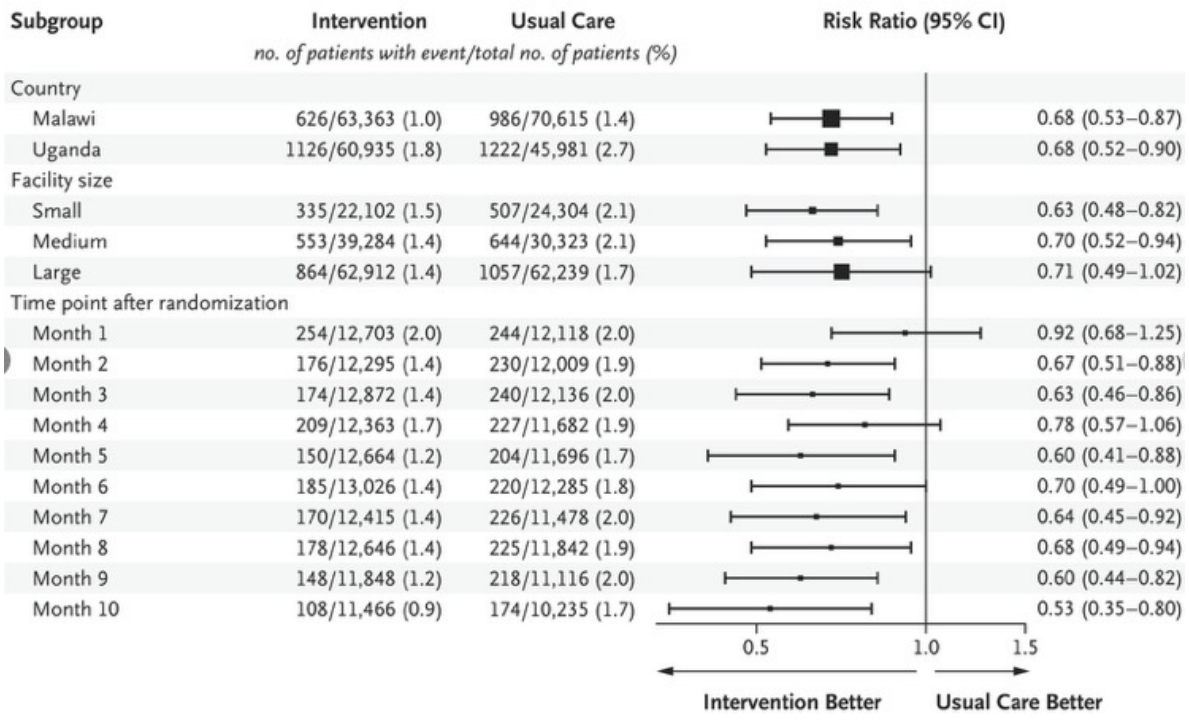
Primary and Secondary Outcomes.

Outcome	Intervention (N=124,298)	Usual Care (N=116,596)	Risk Ratio or Mean Difference (95% CI)†
Primary outcome			
Composite of infection-related maternal death; infection-related near-miss event; or severe infection-related illness — no. (%)‡	1752 (1.4)	2208 (1.9)	0.68 (0.55 to 0.83)
Components of the primary outcome§			
Infection-related maternal death — no. (%)	90 (0.1)	77 (0.1)	0.96 (0.69 to 1.32)
Infection-related near-miss event — no. (%)	119 (0.1)	141 (0.1)	0.82 (0.54 to 1.25)
Deep surgical-site, deep perineal, or body-cavity infection — no. (%)	1672 (1.3)	2102 (1.8)	0.68 (0.55 to 0.84)
Secondary outcomes			
Stillbirth — no./total no. (%)¶	2708/127,006 (2.1)	2314/118,910 (1.9)	0.90 (0.73 to 1.10)
Neonatal death — no. (%)‖	2691 (2.2)	2761 (2.4)	0.88 (0.73 to 1.04)
Neonatal death (infection-related) — no. (%)	819 (0.7)	622 (0.5)	0.86 (0.57 to 1.30)
Maternal death (any cause) — no. (%)	288 (0.2)	235 (0.2)	0.96 (0.74 to 1.24)
Maternal near-miss event (any cause) — no. (%)	771 (0.6)	609 (0.5)	0.90 (0.73 to 1.10)
Maternal severe acute respiratory infection — no. (%)**	10 (<0.1)	7 (<0.1)	1.04 (0.45 to 2.39)
Implementation outcomes††			
Adherence to hand hygiene — %	32.9±19.3	15.1±10.5	14.48 (10.1 to 18.9)
Appropriate cesarean section antibiotic prophylaxis — %	73.7±32.5	57.7±36.4	15.0 (4.0 to 26.0)
Complete vital signs recorded at admission — %	48±29	14.5±19.5	32.4 (24.5 to 40.4)
Patients with suspected sepsis with complete vital signs recorded — %	59.9±32.6	33.9±39.0	27.7 (15.2 to 40.2)
Patients with suspected sepsis given intravenous fluids within 1 hr — %	32.9±33.6	21.9±24.5	13.4 (4.8 to 22.0)
Patients with suspected sepsis given antibiotics within 1 hr — %	43.6±37.5	38.4±37.7	8.2 (−2.7 to 19.0)



Patients with Primary-Outcome Event during the Baseline, Transition, and Intervention Phases.

The primary outcome was a composite of infection-related maternal death, infection-related maternal near-miss event (events in which women survived a life-threatening complication, according to adapted World Health Organization criteria), or severe infection-related illness (defined as deep surgical-site, perineal, or body-cavity infection; adapted from Centers for Disease Control and Prevention definition of deep surgical-site infection or body-cavity infection) during pregnancy, childbirth, or within 42 days of pregnancy ending or at any time up to 28 days of discharge (whichever occurred first).

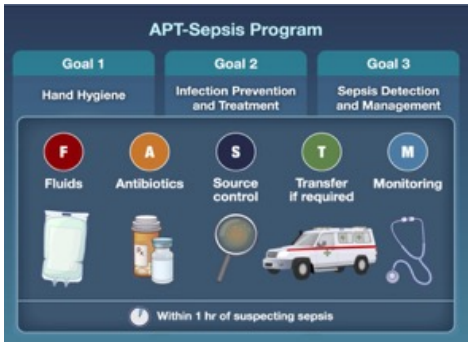


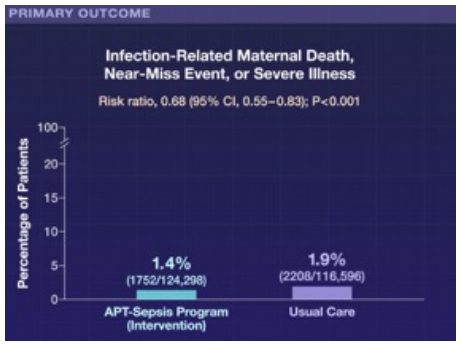
Prespecified Subgroup Analyses of the Primary Outcome.

The forest plot shows the primary outcome (a composite of infection-related maternal death, infection-related maternal near-miss event, or severe infection-related illness, assessed among women who were pregnant or had recently been pregnant) in prespecified subgroups based on country, facility size (defined according to small, medium, or large facilities within each country at the point of randomization), and time point after randomization (in months). The size of each square is proportional to the number of patients in each subgroup. The I bars indicate 95% confidence intervals. The widths of the confidence intervals for these analyses have not been adjusted for multiplicity and should not be used to infer definitive effects of the intervention.

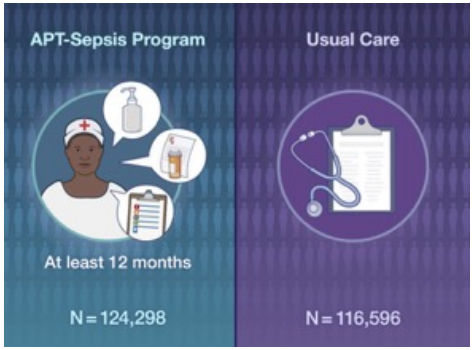

Infection
(including sepsis)
Up to half of in-hospital maternal deaths
Greatest burden seen in low- and middle-income countries


APT-Sepsis Trial
• Cluster-randomized
• 59 Sites in Malawi and Uganda

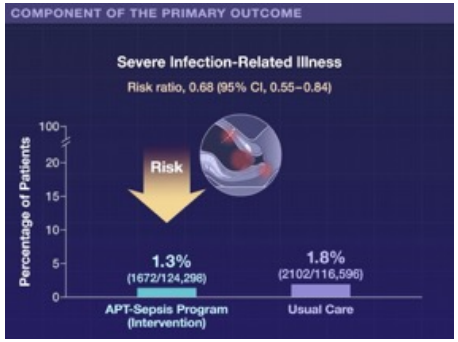

APT-Sepsis Program
Goal 1
Hand Hygiene
Goal 2
Infection Prevention and Treatment
Goal 3
Sepsis Detection and Management
F
Fluids
A
Antibiotics
S
Source control
T
Transfer if required
M
Monitoring
Within 1 hr of suspecting sepsis


PRIMARY OUTCOME
Infection-Related Maternal Death, Near-Miss Event, or Severe Illness
Risk ratio, 0.68 (95% CI, 0.55–0.83); P<0.001
Percentage of Patients
100
20
15
10
5
0
1.4%
(1752/124,298)
1.9%
(2208/116,596)
APT-Sepsis Program (Intervention)
Usual Care

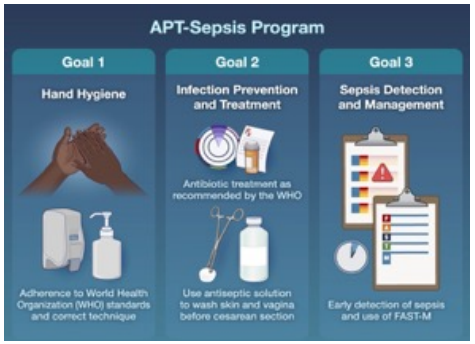

Numerous Deficiencies in Care
Inconsistent adherence to infection-prevention practices
Lack of early recognition and adequate management of sepsis
Maternal death and severe illness

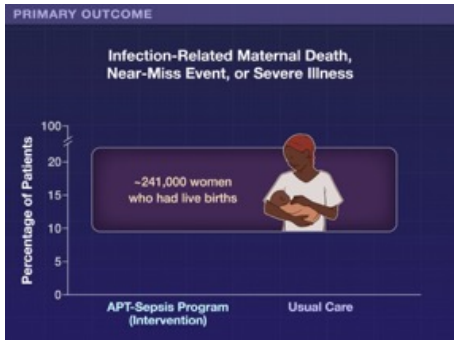

APT-Sepsis Program
Usual Care
At least 12 months
N = 124,298
N = 116,596

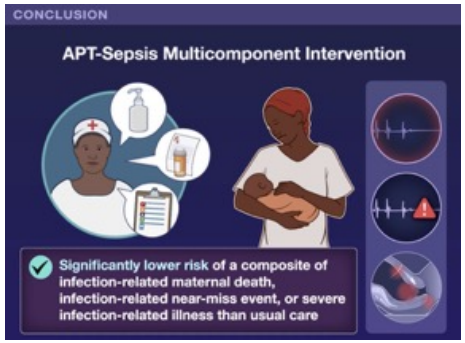

PRIMARY OUTCOME
Composite of
Infection-Related Maternal Death
Infection-Related Maternal Near-Miss Event
Events in which women survived a life-threatening complication
Severe Infection-Related Illness


COMPONENT OF THE PRIMARY OUTCOME
Severe Infection-Related Illness
Risk ratio, 0.68 (95% CI, 0.55–0.84)
Risk
Percentage of Patients
100
20
15
10
5
0
1.3%
(1672/124,298)
1.8%
(2102/116,596)
APT-Sepsis Program (Intervention)
Usual Care


NEW TRIAL
Multicomponent Intervention
Implementation strategies to promote behavior change
(e.g., leadership engagement, training materials, performance dashboards, and feedback visits)
Risk of poor outcomes related to maternal infection


APT-Sepsis Program
Goal 1
Hand Hygiene
Adherence to World Health Organization (WHO) standards and correct technique
Goal 2
Infection Prevention and Treatment
Antibiotic treatment as recommended by the WHO
Use antiseptic solution to wash skin and vagina before cesarean section
Goal 3
Sepsis Detection and Management
Early detection of sepsis and use of FAST-M

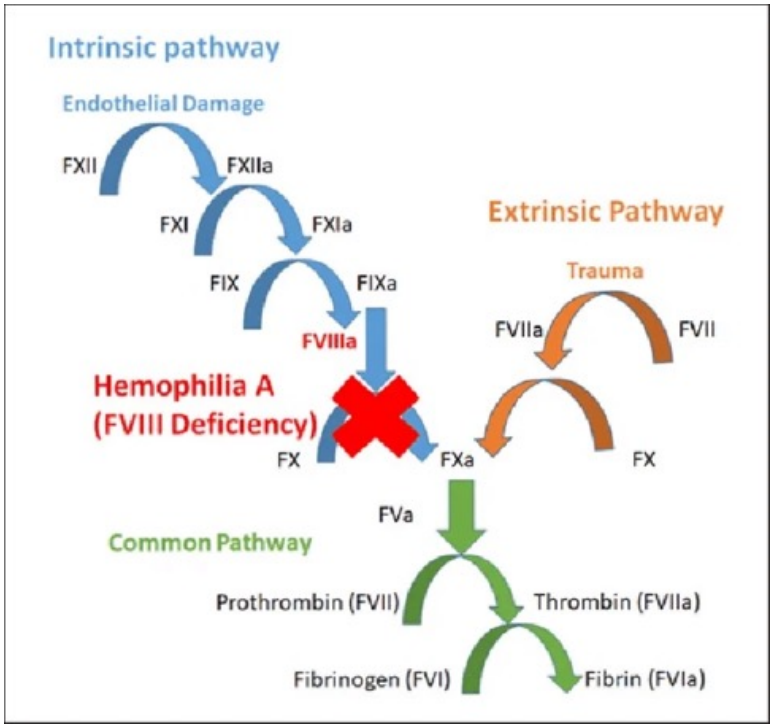

PRIMARY OUTCOME
Infection-Related Maternal Death, Near-Miss Event, or Severe Illness
Percentage of Patients
100
20
15
10
5
0
~241,000 women who had live births
APT-Sepsis Program (Intervention)
Usual Care


CONCLUSION
APT-Sepsis Multicomponent Intervention
Significantly lower risk of a composite of infection-related maternal death, infection-related near-miss event, or severe infection-related illness than usual care

Hämophilie A (auch „klassische Hämophilie“ genannt) ist eine erbliche **Blutgerinnungsstörung**, die durch einen Mangel an **Gerinnungsfaktor VIII** verursacht wird. Ohne diesen Faktor kann das Blut nicht stabil gerinnen, was zu verlängerten Blutungen nach Verletzungen oder sogar zu spontanen inneren Blutungen führt.

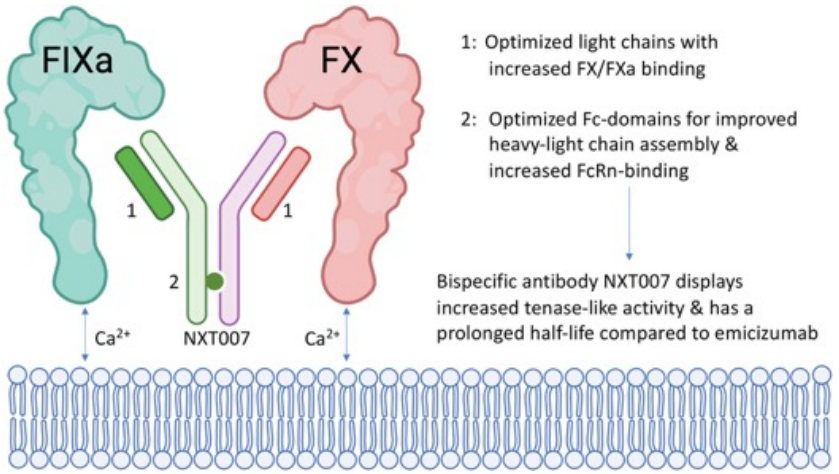
Ursachen und Vererbung

- **Genetischer Defekt**: Mutationen im F8-Gen auf dem X-Chromosom verhindern die Produktion von funktionsfähigem Faktor VIII.
- **X-chromosomal-rezessiv**: Da Männer nur ein X-Chromosom besitzen, erkranken sie fast ausschließlich (ca. 1 von 5.000 Männern).
- **Überträgerinnen (Konduktorinnen)**: Frauen mit einem defekten Gen sind meist symptomfreie Trägerinnen, da ihr zweites X-Chromosom den Defekt ausgleicht.
- **Spontanmutationen**: In etwa 30 % der Fälle tritt die Krankheit ohne familiäre Vorbelastung auf.



Antikörper bindet Faktor Xia an Faktor X und so umgeht Faktor VIII

Mim8 (Denecimig) ist ein neuartiger **bispezifischer Antikörper** von Novo Nordisk , der zur vorbeugenden Behandlung (Prophylaxe) von **Hämophilie A** entwickelt wurde.



So funktioniert Mim8

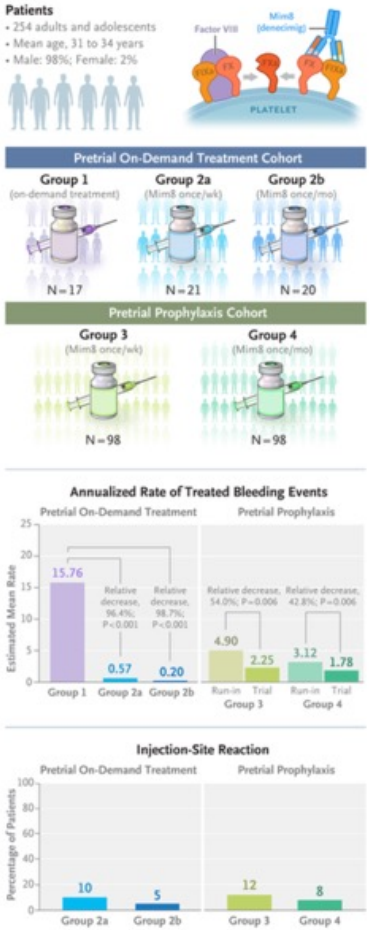
Normalerweise dient Faktor VIII in unserem Blut als eine Art „Brücke“. Er bringt zwei andere Faktoren (IXa und X) zusammen, damit eine Kettenreaktion ausgelöst wird, die das Blut gerinnen lässt.

- **Die Brückenfunktion:** Mim8 ist ein „bispezifischer Antikörper“. Das bedeutet, er hat zwei Bindungsstellen: Eine greift sich den Faktor IXa, die andere den Faktor X.
- **Faktor-VIII-Ersatz:** Indem Mim8 diese beiden Faktoren physisch zusammenführt, übernimmt es die Rolle des fehlenden Faktors VIII und ermöglicht so eine normale Blutgerinnung.

Mim8 Bispecific Antibody Prophylaxis in Hemophilia A with or without Inhibitors

Mim8 (denecimig), a bispecific antibody mimicking activated factor VIII, was developed for bleeding prophylaxis in patients with hemophilia A with or without factor VIII inhibitors.

In this phase 3, randomized trial, we assigned patients 12 years of age or older with hemophilia A with or without inhibitors to receive subcutaneous Mim8 once weekly or once monthly at a dose tiered according to body weight and given in a fixed injection volume (0.8 ml). Patients who had been receiving on-demand treatment before the trial were assigned in a 1:1:1 ratio to continue on-demand treatment (group 1) or receive Mim8 once weekly (group 2a) or once monthly (group 2b). Patients who had been receiving clotting factor concentrates during a run-in phase were assigned in a 1:1 ratio to receive Mim8 once weekly (group 3) or once monthly (group 4). The first primary end point was the annualized rate of treated bleeding events (those treated with a coagulation factor product) in an evaluation of Mim8 in group 2a and Mim8 in group 2b as compared with on-demand treatment in group 1. The second was the annualized rate of treated bleeding events in an intrapatient evaluation of Mim8 in group 3 and Mim8 in group 4 as compared with clotting factor concentrate prophylaxis during the run-in phase.



Mim8 (denecimig) is a factor VIIIa–mimetic bispecific antibody. Mim8 has distinct binding epitopes that are optimized for high cofactor activity and low binding affinity for factor X and factor IXa — features that minimize the risk of nonspecific binding while effectively activating factor X. Mim8 has a thrombin-generation potency that is approximately 15 times as high as that of the factor VIIIa mimetic emicizumab ex vivo and that of a sequence-identical analogue of emicizumab in vitro. Because of this increased thrombin-generation potency, Mim8 can be given as a one-time loading dose and a fixed, low-volume injection for all dose-administration frequencies. Mim8 can be administered by means of a prefilled device to minimize administration errors and drug waste. A new, tiered-dosing approach was implemented in phase 3 trials, with Mim8 administered in a fixed injection volume of 0.8 ml at a dose based on body-weight ranges and the patient's preferred frequency of administration. This tiered approach was designed to remove the need for dose calculations, reduce the burden of treatment administration, and avoid drug wastage. Here, we report week 26 results of FRONTIER2, a phase 3a trial that investigated the efficacy and safety of subcutaneous Mim8 prophylaxis, administered once weekly or once monthly, in patients with hemophilia A of any severity with or without factor VIII inhibitors.

Methods

Trial Oversight

This phase 3a, prospective, open-label, randomized, controlled trial was designed by Novo Nordisk.

Trial Design and Patients

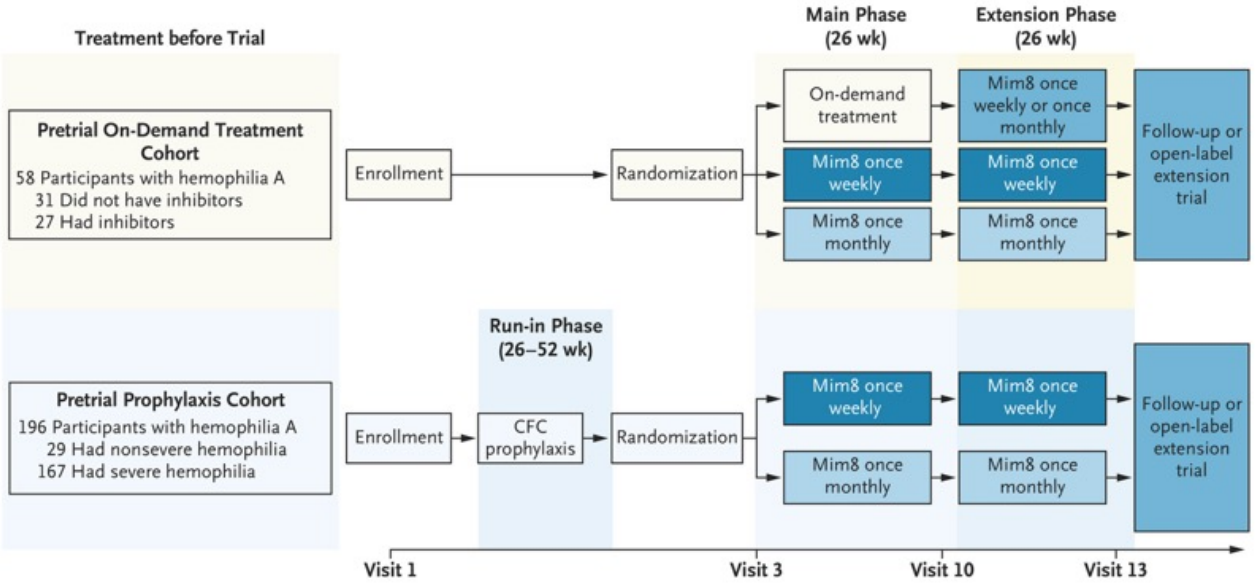
Patients with hemophilia A with or without inhibitors were assigned to one of five groups during the 26-week main phase of the trial. Patients who had been receiving on-demand treatment before enrollment (pretrial on-demand treatment cohort) were randomly assigned in a 1:1:1 ratio to continue on-demand treatment (group 1) or to receive Mim8 once weekly (group 2a) or once monthly (group 2b).

Treatment

Mim8 was administered subcutaneously once weekly or once monthly in a fixed volume of 0.8 ml. The Mim8 dose was tiered according to body weight (30 to <45 kg or ≥45 kg). To rapidly achieve steady-state plasma levels of Mim8, patients weighing 30 to less than 45 kg were given a one-time loading dose of 24 mg if receiving Mim8 once weekly or 40 mg if receiving Mim8 once monthly and those weighing at least 45 kg were given a one-time loading of 55 mg if receiving Mim8 once weekly or 92 mg if receiving Mim8 once monthly.

Objectives and End Points

The primary objective was to assess the efficacy of Mim8 in preventing bleeding. The first primary end point was the annualized rate of treated bleeding events in a comparison of Mim8 once-weekly prophylaxis (group 2a) and Mim8 once-monthly prophylaxis (group 2b) with on-demand treatment (group 1).



Trial Design.

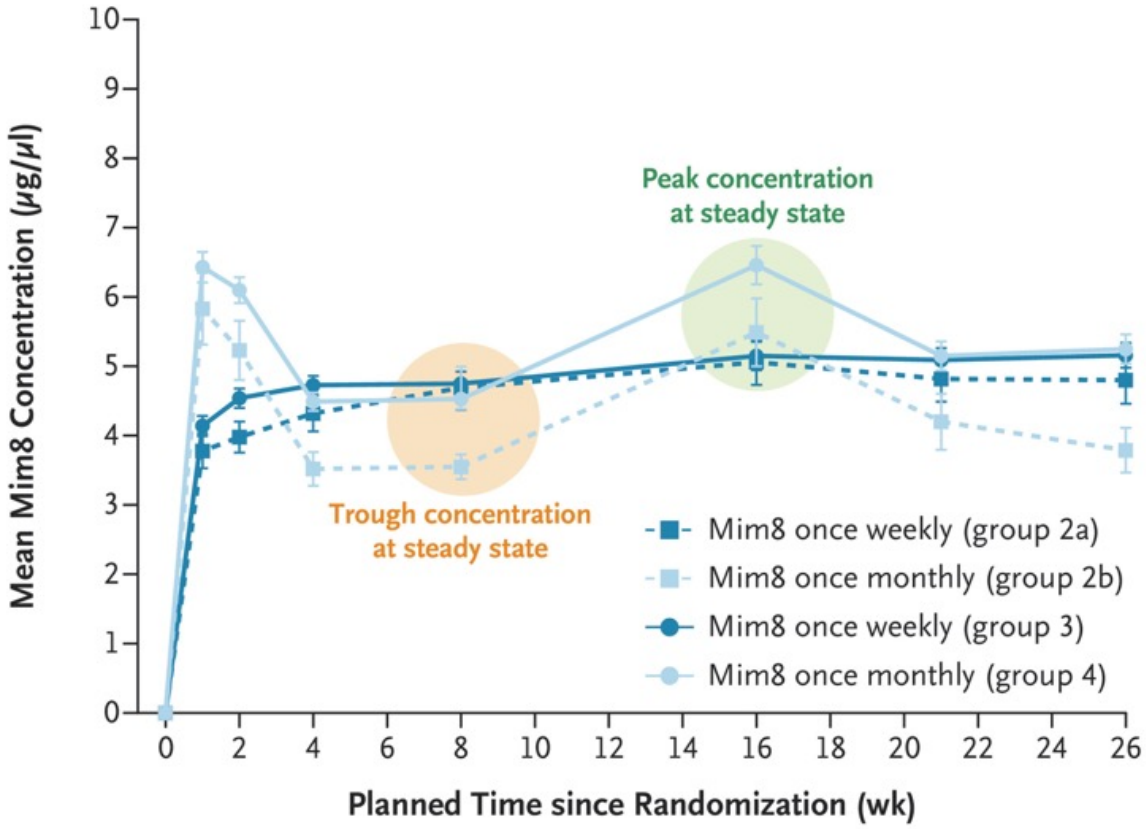
Patients with hemophilia A with or without factor VIII inhibitors were assigned to one of five groups during the 26-week main phase of the trial. Patients who had been receiving on-demand treatment before enrollment (pretrial on-demand treatment cohort) were randomly assigned in a 1:1:1 ratio to continue on-demand treatment (group 1) or to receive Mim8 prophylaxis once weekly (group 2a) or once monthly (group 2b). Randomization was stratified according to the historical annualized rate of bleeding events during the 12 months before screening (≥18 events per year vs. <18 events per year) and factor VIII inhibitor status (with inhibitors vs. without inhibitors, with the presence of inhibitors defined by use or prescription of bypassing treatment during the 6 months before screening). Patients needed to have had at least five treated bleeding events during the 26 weeks before screening. Patients who had been receiving clotting factor concentrate (CFC) as prophylaxis before enrollment and then continued clotting factor concentrate prophylaxis during a run-in phase lasting 26 to 52 weeks before the trial (pretrial prophylaxis cohort) were randomly assigned in a 1:1 ratio to receive Mim8 prophylaxis once weekly (group 3) or once monthly (group 4). Randomization was stratified according to hemophilia severity (severe vs. nonsevere, defined by endogenous factor VIII activity of <1% and ≥1%, respectively) at diagnosis. Patients with a factor VIII activity of at least 1% needed to have had at least one treated bleeding event during the 26 weeks before screening.

Baseline Characteristics of the Patients.

Characteristic	Pretrial On-Demand Treatment			Pretrial Prophylaxis	
	On-Demand Treatment (N=17)	Mim8 Once Weekly (N=21)	Mim8 Once Monthly (N=20)	Mim8 Once Weekly (N=98)	Mim8 Once Monthly (N=98)
Age					
Mean (range) — yr	31 (13–52)	32 (13–64)	34 (13–64)	33 (12–68)	32 (12–69)
Distribution — no. (%)					
12–17 yr	5 (29)	5 (24)	4 (20)	26 (27)	26 (27)
≥18 yr	12 (71)	16 (76)	16 (80)	72 (73)	72 (73)
Sex — no. (%)					
Female	1 (6)	0	2 (10)	0	1 (1)
Male	16 (94)	21 (100)	18 (90)	98 (100)	97 (99)
Race or ethnic group — no. (%)†					
Asian	11 (65)	11 (52)	11 (55)	12 (12)	17 (17)
Black	1 (6)	1 (5)	2 (10)	1 (1)	2 (2)
Native Hawaiian or other Pacific Islander	0	0	0	1 (1)	0
White	4 (24)	9 (43)	7 (35)	72 (73)	68 (69)
Other	1 (6)	0	0	7 (7)	7 (7)
Body weight					
Overall — kg	63.3±16.1	72.0±20.9	69.5±18.9	76.7±20.3	78.2±19.7
Distribution — no. (%)					
30 to <45 kg	1 (6)	2 (10)	4 (20)	5 (5)	0
≥45 kg	16 (94)	19 (90)	16 (80)	93 (95)	98 (100)
Severity of hemophilia — no. (%)					
Mild	2 (12)	2 (10)	1 (5)	0	1 (1)
Moderate	2 (12)	5 (24)	1 (5)	14 (14)	14 (14)
Severe	13 (76)	14 (67)	18 (90)	84 (86)	83 (85)
Current inhibitor status — no. (%)					
Positive	8 (47)	10 (48)	9 (45)	2 (2)	2 (2)
Negative	9 (53)	11 (52)	11 (55)	96 (98)	96 (98)

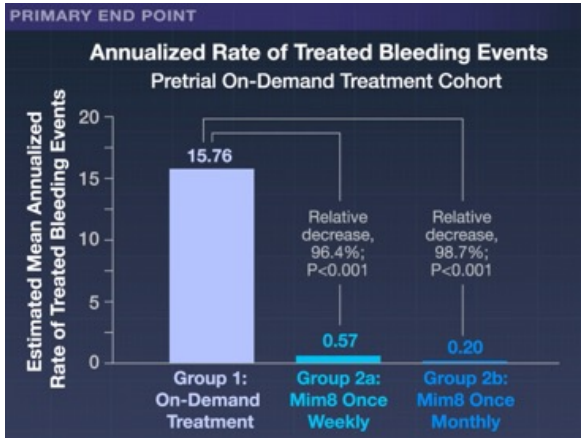
Treated Bleeding Events (Intention-to-Treat Analysis).

Variable	Pretrial On-Demand Treatment			Pretrial Prophylaxis			
	On-Demand Treatment (N=17)	Mim8 Once Weekly (N=21)	Mim8 Once Monthly (N=20)	Mim8 Once Weekly (N=98)		Mim8 Once Monthly (N=98)	
				Run-in Phase	Main Phase	Run-in Phase	Main Phase
Mean exposure time — wk	25.7	25.6	25.8	40.9	25.3	39.1	26.0
Treated bleeding events — no.	146	8	3	383	103	233	88
Mean estimated ABR (95% CI)†	15.76 (10.70–23.20)	0.57 (0.25–1.30)	0.20 (0.06–0.71)	4.90 (3.65–6.56)	2.25 (1.37–3.71)	3.12 (2.25–4.32)	1.78 (1.18–2.71)
Ratio of mean estimated ABRs (95% CI)†‡	—	0.04 (0.01–0.09)	0.01 (<0.01–0.05)	—	0.46 (0.26–0.80)	—	0.57 (0.38–0.85)
Percentage reduction in mean estimated ABR (95% CI)†§	—	96.4 (91.0–98.6)	98.7 (95.2–99.7)	—	54.0 (19.6–73.6)	—	42.8 (14.7–61.6)
P value¶		<0.001	<0.001		0.006		0.006
Median estimated ABR (IQR)†	12.24 (8.03–18.06)	0 (0–0)	0 (0–0)	2.11 (0.00–5.72)	0 (0–2.01)	1.49 (0–3.87)	0 (0–2.01)
Distribution of treated bleeding events — no. (%)							
0 events	0	17 (81)	19 (95)	32 (33)	65 (66)	36 (37)	63 (64)
1 or 2 events	2 (12)	3 (14)	0	26 (27)	21 (21)	34 (35)	25 (26)
≥3 events	15 (88)	1 (5)	1 (5)	40 (41)	12 (12)	28 (29)	10 (10)
Severe bleeding — no./total no. of bleeding events (%)‖	7/146 (4.8)	1/8 (12.5)	0/3	0/383	1/103 (1.0)	2/233 (0.9)	1/88 (1.1)
Treated bleeding events according to type							
No./total no. of bleeding events (%)**							
Spontaneous bleeding	108/146 (74.0)	2/8 (25.0)	3/3 (100)	221/383 (57.7)	59/103 (57.3)	136/233 (58.4)	40/88 (45.5)
Traumatic bleeding	35/146 (24.0)	6/8 (75.0)	0/3	156/383 (40.7)	42/103 (40.8)	96/233 (41.2)	43/88 (48.9)
Surgical bleeding	3/146 (2.1)	0/8	0/3	3/383 (0.8)	2/103 (1.9)	1/233 (0.4)	5/88 (5.7)
Mean estimated ABR (95% CI)†							
Spontaneous bleeding	11.77 (7.48–18.53)	0.17 (0.04–0.74)	0.24 (0.07–0.84)	2.75 (1.96–3.85)	1.26 (0.61–2.63)	1.83 (1.10–3.03)	0.76 (0.43–1.34)
Traumatic bleeding	1.86 (0.87–4.00)	0.22 (0.07–0.70)	0	2.02 (1.45–2.83)	0.89 (0.58–1.37)	1.30 (0.94–1.80)	0.87 (0.56–1.35)
Bleeding into joints	10.57 (6.34–17.63)	0.53 (0.21–1.34)	0	3.68 (2.70–5.02)	1.62 (0.90–2.93)	2.07 (1.44–2.97)	1.10 (0.61–1.99)
Recurrent bleeding into joints	3.85 (1.99–7.47)	0.30 (0.09–1.01)	0	1.12 (0.62–2.02)	0.38 (0.13–1.06)	0.48 (0.21–1.10)	0.34 (0.11–1.08)
Treated bleeding events according to location — no./total no. of bleeding events (%)							
Joints							
Overall	97/146 (66.4)	7/8 (87.5)	0/3	294/383 (76.8)	75/103 (72.8)	155/233 (66.5)	55/88 (62.5)
Spontaneous bleeding	81/97 (83.5)	2/7 (28.6)	0/3	178/294 (60.5)	50/75 (66.7)	102/155 (65.8)	29/55 (52.7)
Other	49/146 (33.6)	1/8 (12.5)	3/3 (100)	89/383 (23.2)	28/103 (27.2)	78/233 (33.5)	33/88 (37.5)



Arithmetic Plasma Concentration of Mim8.

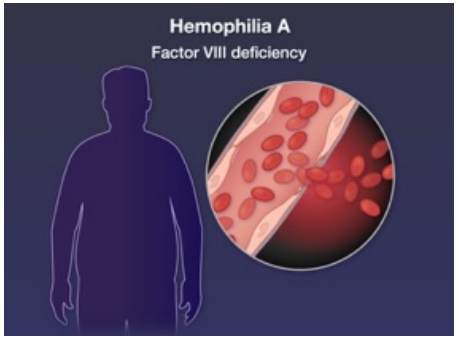
As prespecified in the protocol, the trough concentration of Mim8 at steady state was defined as the estimated plasma concentration at week 8 and the peak concentration of Mim8 at steady state as the estimated plasma concentration at week 16. Concentrations are shown on a linear scale. The planned time since randomization indicates the time of the planned follow-up visit; some visits may not have occurred on the planned day. The I bars indicate standard errors.

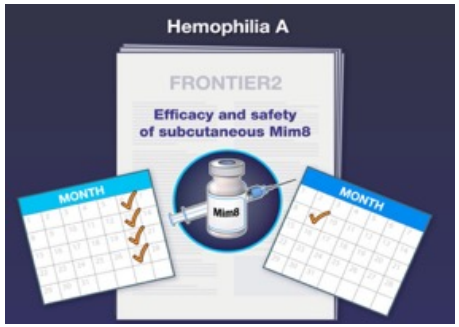


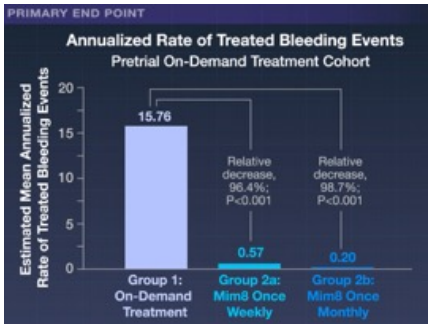
Mostly injection site reactions

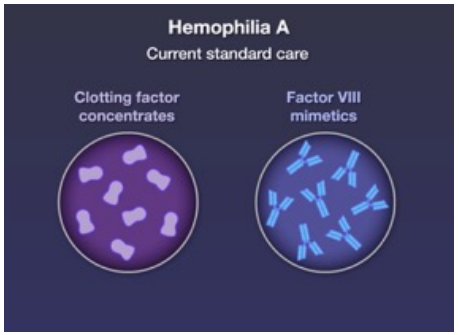
Adverse Events.

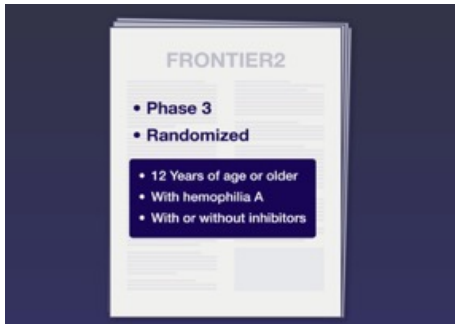
Variable	Pretrial On-Demand Treatment			Pretrial Prophylaxis†			
	On-Demand Treatment (N=17)	Mim8 Once Weekly (N=21)	Mim8 Once Monthly (N=20)	Mim8 Once Weekly (N=98)		Mim8 Once Monthly (N=98)	
				Run-in Phase	Main Phase	Run-in Phase	Main Phase
Total exposure time — yr	8.4	9.9	9.9	77.1	46.6	73.8	48.7
Any adverse event‡							
No. of patients (%)	5 (29)	10 (48)	6 (30)	58 (59)	71 (72)	51 (52)	65 (66)
No. of events per total exposure time	1.31	1.51	1.91	1.58	5.28	1.57	4.23
Serious adverse event							
No. of patients (%)	1 (6)	1 (5)	0	6 (6)	4 (4)	2 (2)	4 (4)
No. of events per total exposure time	0.12	0.10	0	0.10	0.09	0.03	0.10
Adverse event of special interest							
Thromboembolic event — no. (%)	0	0	0	0	0	0	0
Severity of adverse event							
Mild							
No. of patients (%)	3 (18)	7 (33)	6 (30)	49 (50)	67 (68)	48 (49)	61 (62)
No. of events per total exposure time	0.59	1.11	1.91	1.14	4.44	1.23	3.39
Moderate							
No. of patients (%)	2 (12)	2 (10)	0	20 (20)	24 (24)	17 (17)	21 (21)
No. of events per total exposure time	0.59	0.20	0	0.42	0.79	0.31]	0.78
Severe							
No. of patients (%)	1 (6)	2 (10)	0	1 (1)	2 (2)	2 (2)	3 (3)
No. of events per total exposure time	0.12	0.20	0	0.03	0.04	0.03	0.06
Adverse event considered by the investigator as related to Mim8§							
No. of patients (%)	NA	4 (19)	1 (5)	NA	20 (20)	NA	17 (17)
No. of events per total exposure time	NA	0.40	0.20	NA	2.06	NA	0.62
Adverse event considered by the investigator as leading to permanent discontinuation of Mim8§¶							
No. of patients (%)	NA	1 (5)	0	NA	2 (2)	NA	0
No. of events per total exposure time	NA	0.10	0	NA	0.06	NA	0
Adverse event considered by the investigator as probably or possibly causally related to Mim8§							
Injection-site reaction							
No. of patients (%)	NA	2 (10)	1 (5)	NA	12 (12)	NA	8 (8)
No. of events per total exposure time	NA	0.20	0.20	NA	1.67	NA	0.27
Hypersensitivity reaction — no. (%)	NA	0	0	NA	0	NA	0
Adverse event due to medication error or misuse or abuse of Mim8 — no. (%)							
No. of patients (%)	NA	0	0	NA	1 (1)	NA	0
No. of events per total exposure time	NA	0	0	NA	0.02	NA	0

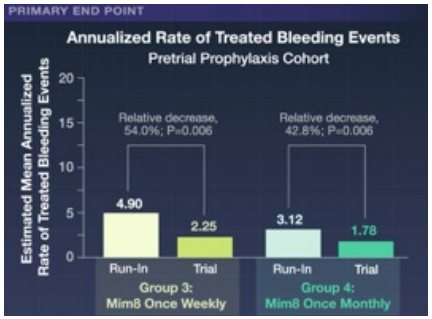

Hemophilia A
Factor VIII deficiency

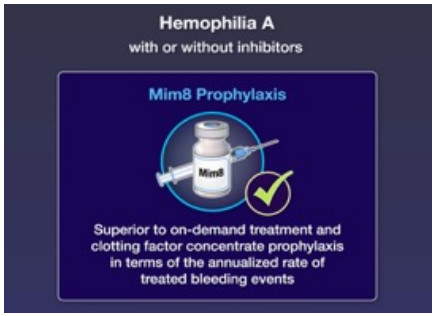

Hemophilia A
FRONTIER2
Efficacy and safety of subcutaneous Mim8
MONTH
Mim8
MONTH

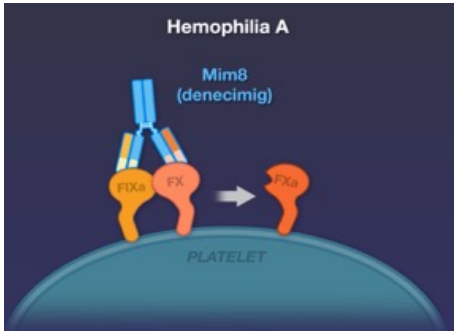

PRIMARY END POINT
Annualized Rate of Treated Bleeding Events
Pretrial On-Demand Treatment Cohort
Estimated Mean Annualized Rate of Treated Bleeding Events
20
15
10
5
0
15.76
Relative decrease, 96.4%; P<0.001
Relative decrease, 98.7%; P<0.001
0.57
0.20
Group 1: On-Demand Treatment
Group 2a: Mim8 Once Weekly
Group 2b: Mim8 Once Monthly

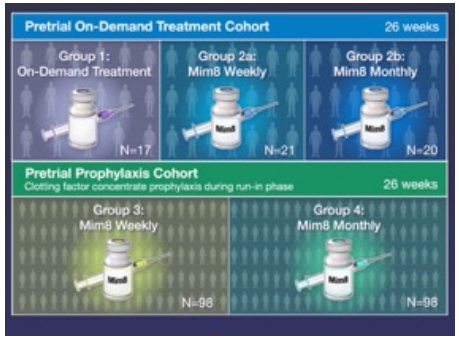

Hemophilia A
Current standard care
Clotting factor concentrates
Factor VIII mimetics

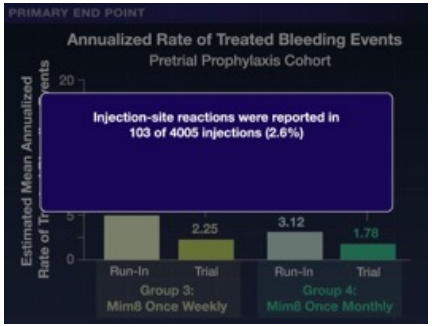

FRONTIER2
• Phase 3
• Randomized
• 12 Years of age or older
• With hemophilia A
• With or without inhibitors


PRIMARY END POINT
Annualized Rate of Treated Bleeding Events
Pretrial Prophylaxis Cohort
Estimated Mean Annualized Rate of Treated Bleeding Events
20
15
10
5
0
Relative decrease, 54.0%; P=0.006
Relative decrease, 42.8%; P=0.006
4.90
2.25
3.12
1.78
Run-In
Trial
Run-In
Trial
Group 3: Mim8 Once Weekly
Group 4: Mim8 Once Monthly


Hemophilia A
with or without inhibitors
Mim8 Prophylaxis
Mim8
Superior to on-demand treatment and clotting factor concentrate prophylaxis in terms of the annualized rate of treated bleeding events


Hemophilia A
Mim8 (denecimig)
FIXa
FX
FXa
PLATELET

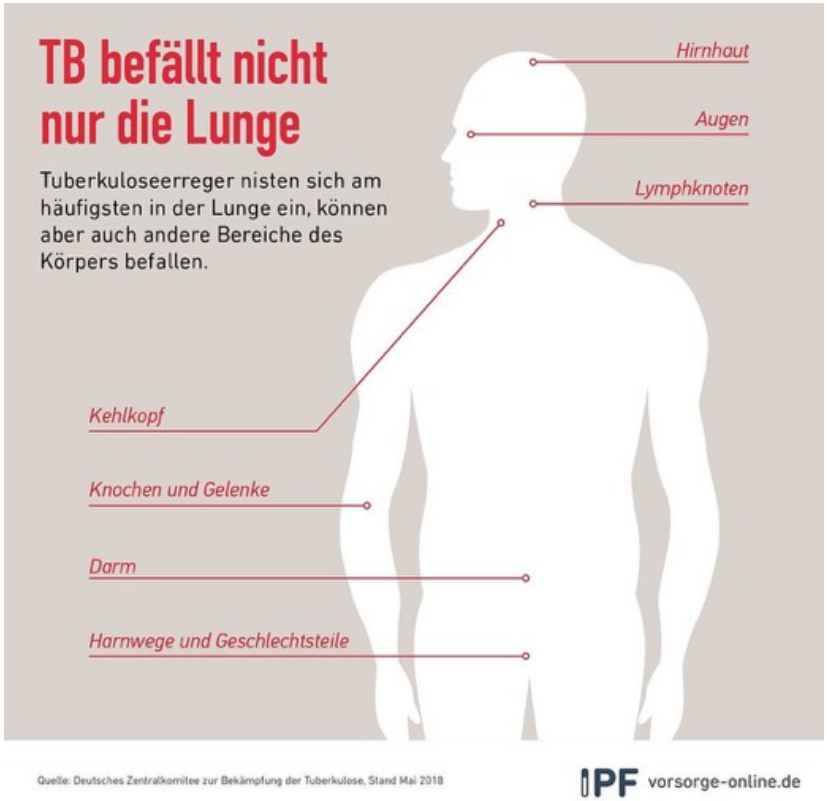

Pretrial On-Demand Treatment Cohort
26 weeks
Group 1: On-Demand Treatment
Group 2a: Mim8 Weekly
Group 2b: Mim8 Monthly
N=17
N=21
N=20
Pretrial Prophylaxis Cohort
Clotting factor concentrate prophylaxis during run-in phase
26 weeks
Group 3: Mim8 Weekly
Group 4: Mim8 Monthly
N=98
N=98


PRIMARY END POINT
Annualized Rate of Treated Bleeding Events
Pretrial Prophylaxis Cohort
Injection-site reactions were reported in 103 of 4005 injections (2.6%)
2.25
3.12
1.78
Run-In
Trial
Run-In
Trial
Group 3: Mim8 Once Weekly
Group 4: Mim8 Once Monthly

Die Diagnose einer Tuberkulose (Tbc oder TB) erfolgt durch eine Kombination aus Anamnesegespräch, bildgebenden Verfahren (Röntgen) und spezifischen Laboruntersuchungen zum Erregernachweis. Man unterscheidet dabei zwischen dem Nachweis einer Infektion (latente TB) und dem Nachweis der aktiven Erkrankung.

Wichtige diagnostische Schritte:

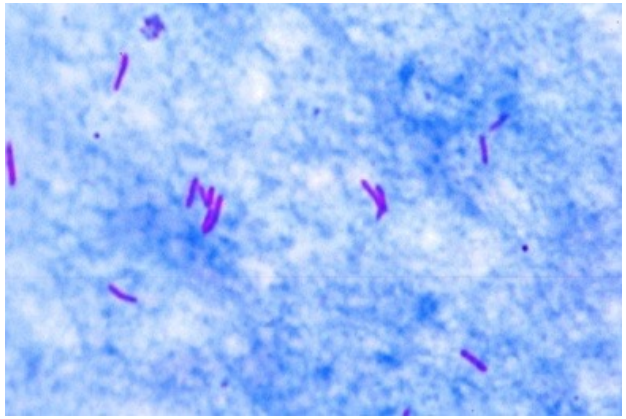
- **Anamnese:** Abfrage von Symptomen wie länger anhaltendem Husten, Fieber, Nachtschweiß und Gewichtsverlust sowie Kontakt zu Erkrankten.
- **Immunologische Tests (TB-Test):**
  - **IGRA (Interferon-Gamma-Release-Assay):** Ein Bluttest, der nach Anzeichen einer Infektion sucht. Er ist der neue Standard bei Erwachsenen/Jugendlichen, da er genauer ist als Hauttests und nicht durch BCG-Impfungen beeinflusst wird.
  - **Tuberkulin-Hauttest (Mendel-Mantoux):** Wird heute hauptsächlich noch bei Kleinkindern eingesetzt.
  - *Hinweis:* Beide Tests zeigen eine Infektion an, können aber nicht zwischen latenter (inaktiver) und aktiver TB unterscheiden.



Die Diagnose von Tuberkulose (Tbc) basiert auf einer Kombination aus schnellen mikroskopischen Verfahren wie der **Ziehl-Neelsen-Färbung** und dem Goldstandard, der **Tbc-Kultur** (Anzucht), um Mykobakterien sicher nachzuweisen.

1. Ziehl-Neelsen-Färbung (Mikroskopie)

- **Zweck:** Schnellnachweis von säurefesten Stäbchen (Mykobakterien) im Sputum oder anderen Proben.
- **Funktionsweise:** Die Proben werden mit Karbolfuchsin gefärbt. Mykobakterien sind "säurefest", das heißt, sie behalten den roten Farbstoff auch nach Behandlung mit saurem Alkohol, während andere Bakterien entfärbt werden.
- **Vorteile:** Sehr schnell (Ergebnis oft am selben Tag), essenziell zur schnellen Einschätzung der Infektiosität.
- **Nachteile:**
    - Benötigt eine hohe Keimzahl >10^4 Keime/ml Sputum).
    - Unterscheidet nicht zwischen lebenden und toten Bakterien.
    - Kann nicht zwischen verschiedenen Mykobakterien-Arten unterscheiden.



Das MiniDock MTB Testsystem

Das vom Unternehmen **Pluslife** entwickelte System ist ein tragbares Molekulardiagnose-Gerät (Point-of-Care), das Tuberkulose-DNA in weniger als 30 Minuten nachweisen kann.

- **Probenflexibilität:** Erkennt Erreger sowohl in Sputum (Auswurf) als auch in einfachen Zungenabstrichen.
- **Einfachheit:** Ermöglicht Tests direkt vor Ort (z. B. in ländlichen Kliniken), ohne dass ein großes Labor nötig ist.
- **Zielgruppe:** Besonders wertvoll für Kinder oder HIV-Patienten, die oft Schwierigkeiten haben, Sputum-Proben abzugeben.
- **Kosten:** Das Gerät ist mit ca. 155 deutlich günstiger als herkömmliche PCR-Maschinen; ein einzelner Test kostet etwa 4 $

Pulmonary Tuberculosis Detection with MiniDock MTB Using Swab Samples

Improved diagnostic tools for tuberculosis that are suitable for use in peripheral health centers are essential for reducing the persistent gap between estimated and notified cases. The diagnostic accuracy and usability of the MiniDock MTB test for detecting pulmonary tuberculosis is unknown. We conducted a prospective, cross-sectional study at outpatient centers in India, Nigeria, the Philippines, South Africa, Uganda, Vietnam, and Zambia. Patients 12 years of age or older with presumptive pulmonary tuberculosis were enrolled between September 12, 2024, and March 31, 2025. Assessment with MiniDock MTB was performed with sputum swabs and tongue swabs. Diagnostic accuracy was evaluated against a sputum-culture–based reference and as compared with sputum-smear microscopy and Xpert MTB/RIF Ultra assay. Usability was assessed with a system usability scale and direct observation.

Conclusions

MiniDock MTB met WHO targets for diagnostic accuracy and usability for tuberculosis detection across diverse clinical settings. (Funded by the National Institutes of Health and others; Rapid Research in Diagnostics Development for TB Network and Assessing Diagnostics at Point-of-Care for Tuberculosis

MTB Nucleic Acid Test Card (MiniDock MTB, Guangzhou Pluslife Biotech) is a qualitative molecular test designed for detecting *Mycobacterium tuberculosis* complex with the Pluslife Integrated Nucleic Acid Testing Device (MiniDock PM001 Ultra), a low-cost, portable, battery-operable isothermal platform. The test uses RNase hybridization–assisted amplification, which combines loop-mediated isothermal amplification with RNase HII–mediated signal detection in a single reaction that produces visible results in 12 to 25 minutes. It targets conserved regions of the insertion sequence IS*6110* and the gene *gyrB* and includes an internal control to verify sample adequacy and amplification integrity. Sample preparation is performed with Pluslife Thermolyse, which combines automated bead-beating–based mechanical lysis (3000 rpm) and thermal lysis (75°C for 5 minutes) to process sputum (from a swab swirled in sputum) or tongue-swab samples. In a multicenter pilot study, a prototype test showed sensitivity of 89.9% (95% confidence interval [CI], 80.2 to 95.8) with sputum and 85.7% (95% CI, 75.3 to 92.9) with tongue swabs, with greater than 98% specificity for both. These results exceeded World Health Organization (WHO) target product profile criteria for minimum accuracy with respect to near-point-of-care tuberculosis diagnostics, which require at least 85% sensitivity for sputum samples and 75% for nonsputum samples and 98% specificity for both.

Methods

Study Design and Setting

This prospective, cross-sectional, diagnostic accuracy study was conducted in outpatient clinics in India, Nigeria, the Philippines, South Africa, Uganda, Vietnam, and Zambia as part of the Rapid Research in Diagnostics Development for TB Network study and the Assessing Diagnostics at Point-of-care for Tuberculosis study.

Study Procedures

Participants' data were managed with Research Electronic Data Capture (REDCap) software hosted by the University of California, San Francisco. Blood was collected for HIV testing and diabetes screening, and tongue swabs plus up to three spot sputum samples were collected for tuberculosis testing. If participants were unable to expectorate spontaneously, sputum induction was performed. Tongue swabs were collected before sputum samples, in accordance with MiniDock MTB test instructions.

Comparator Tests

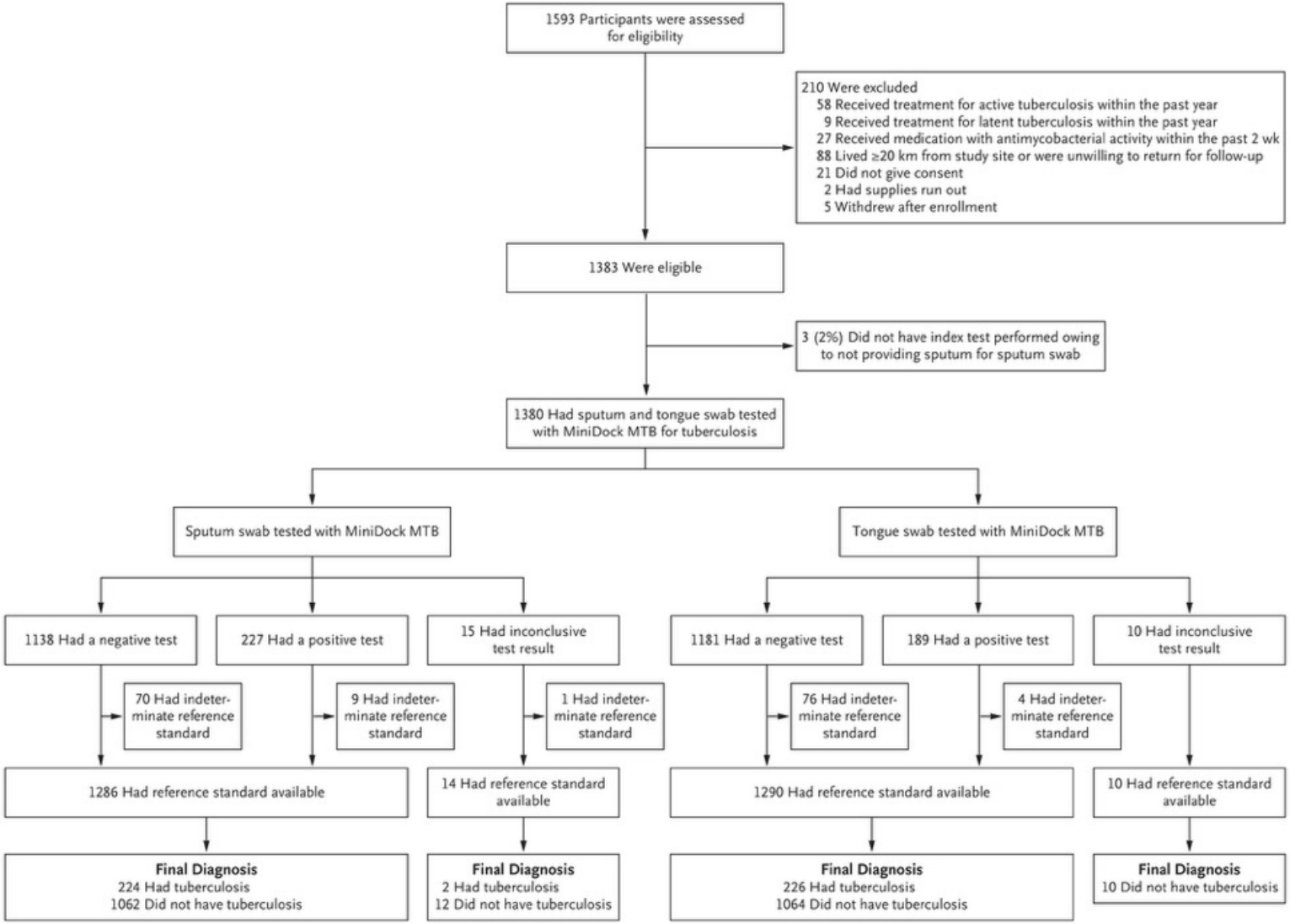
Light-emitting diode fluorescence microscopy was performed on smears of decontaminated sputum in accordance with WHO-recommended protocols.[7] Xpert Ultra testing was performed on the remaining portion of the first sputum sample. If the initial Xpert Ultra result yielded a result of invalid or error or indicated a trace semiquantitative result, testing was repeated.

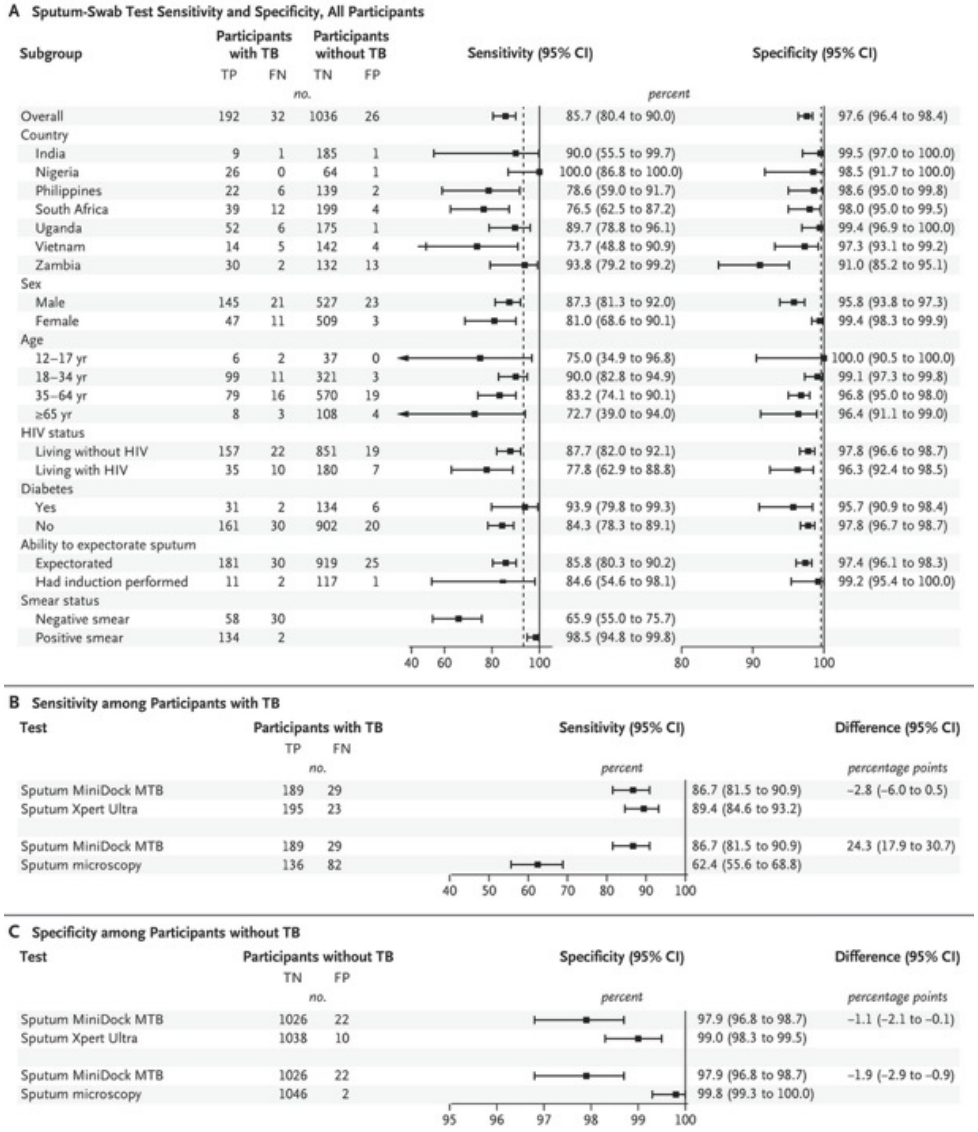
Reference Standard

The primary reference standard was the microbiologic reference standard, which is based on mycobaterial liquid culture by Mycobacterial Growth Indicator Tube, as described in the WHO Technical Specifications.

Characteristics of the Participants.

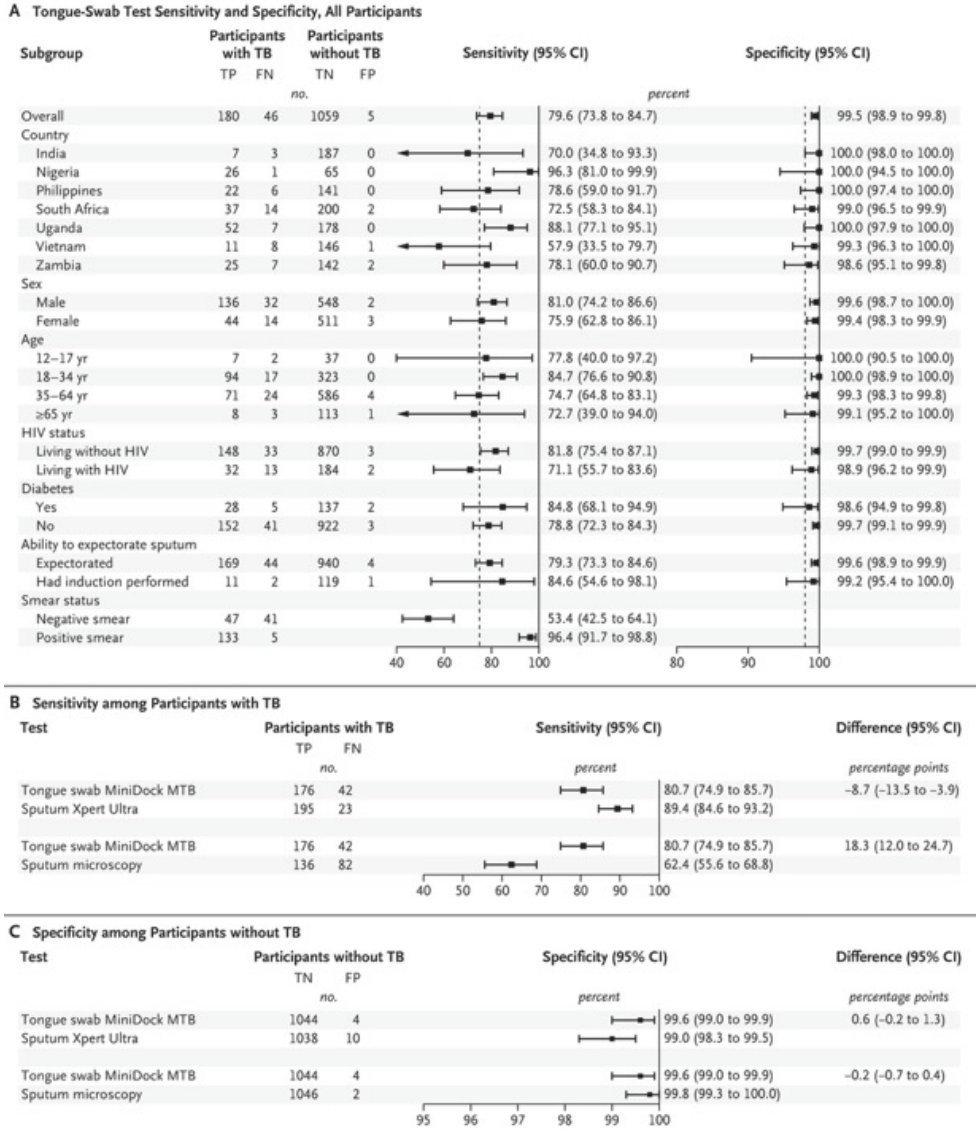
Variable	Total (N=1380)	India (N=210)	Nigeria (N=96)	Philippines (N=182)	South Africa (N=270)	Uganda (N=262)	Vietnam (N=180)	Zambia (N=180)
Percentage of total study population	100	15.2	7.0	13.2	19.6	19.0	13.0	13.0
Sex — no. (%)								
Female	603 (43.7)	91 (43.3)	41 (42.7)	91 (50.0)	137 (50.7)	102 (38.9)	81 (45.0)	60 (33.3)
Male	777 (56.3)	119 (56.7)	55 (57.3)	91 (50.0)	133 (49.3)	160 (61.1)	99 (55.0)	120 (66.7)
Median age (IQR) — yr	41 (29–54)	51 (36–61)	35 (26–45)	50 (33–61)	37 (28–46)	34 (23–45)	53 (40–64)	37 (29–46)
Symptomatic — no. (%)†	1342 (97.2)	207 (98.6)	96 (100)	179 (98.4)	258 (95.6)	243 (92.7)	180 (100)	179 (99.4)
Cough ≥2 weeks — no. (%)	1313 (95.1)	207 (98.6)	96 (100)	175 (96.2)	247 (91.5)	236 (90.1)	180 (100)	172 (95.6)
History of tuberculosis — no. (%)	236 (17.1)	19 (9.0)	6 (6.2)	42 (23.1)	69 (25.6)	26 (9.9)	38 (21.1)	36 (20.0)
Postive test or assay — no. (%)								
HIV‡	255 (18.5)	1 (0.5)	6 (6.2)	2 (1.1)	96 (35.6)	76 (29.0)	5 (2.8)	69 (38.3)
Diabetes§	187 (13.6)	57 (27.1)	6 (6.2)	23 (12.6)	27 (10.0)	33 (12.6)	18 (10.0)	23 (12.8)
Sputum smear	144 (10.4)	6 (2.9)	29 (30.2)	19 (10.4)	18 (6.7)	47 (17.9)	7 (3.9)	18 (10.0)
Sputum Xpert Ultra¶	213 (15.4)	11 (5.2)	30 (31.2)	28 (15.4)	41 (15.2)	55 (21.0)	18 (10.0)	30 (16.7)
Microbiologic reference standard	226 (16.4)	10 (4.8)	27 (28.1)	28 (15.4)	51 (18.9)	59 (22.5)	19 (10.6)	32 (17.8)


1593 Participants were assessed for eligibility
210 Were excluded
58 Received treatment for active tuberculosis within the past year
9 Received treatment for latent tuberculosis within the past year
27 Received medication with antimycobacterial activity within the past 2 wk
88 Lived ≥20 km from study site or were unwilling to return for follow-up
21 Did not give consent
2 Had supplies run out
5 Withdrew after enrollment
1383 Were eligible
3 (2%) Did not have index test performed owing to not providing sputum for sputum swab
1380 Had sputum and tongue swab tested with MiniDock MTB for tuberculosis
Sputum swab tested with MiniDock MTB
Tongue swab tested with MiniDock MTB
1138 Had a negative test
227 Had a positive test
15 Had inconclusive test result
1181 Had a negative test
189 Had a positive test
10 Had inconclusive test result
70 Had indeterminate reference standard
9 Had indeterminate reference standard
1 Had indeterminate reference standard
76 Had indeterminate reference standard
4 Had indeterminate reference standard
1286 Had reference standard available
14 Had reference standard available
1290 Had reference standard available
10 Had reference standard available
Final Diagnosis
224 Had tuberculosis
1062 Did not have tuberculosis
Final Diagnosis
2 Had tuberculosis
12 Did not have tuberculosis
Final Diagnosis
226 Had tuberculosis
1064 Did not have tuberculosis
Final Diagnosis
10 Did not have tuberculosis



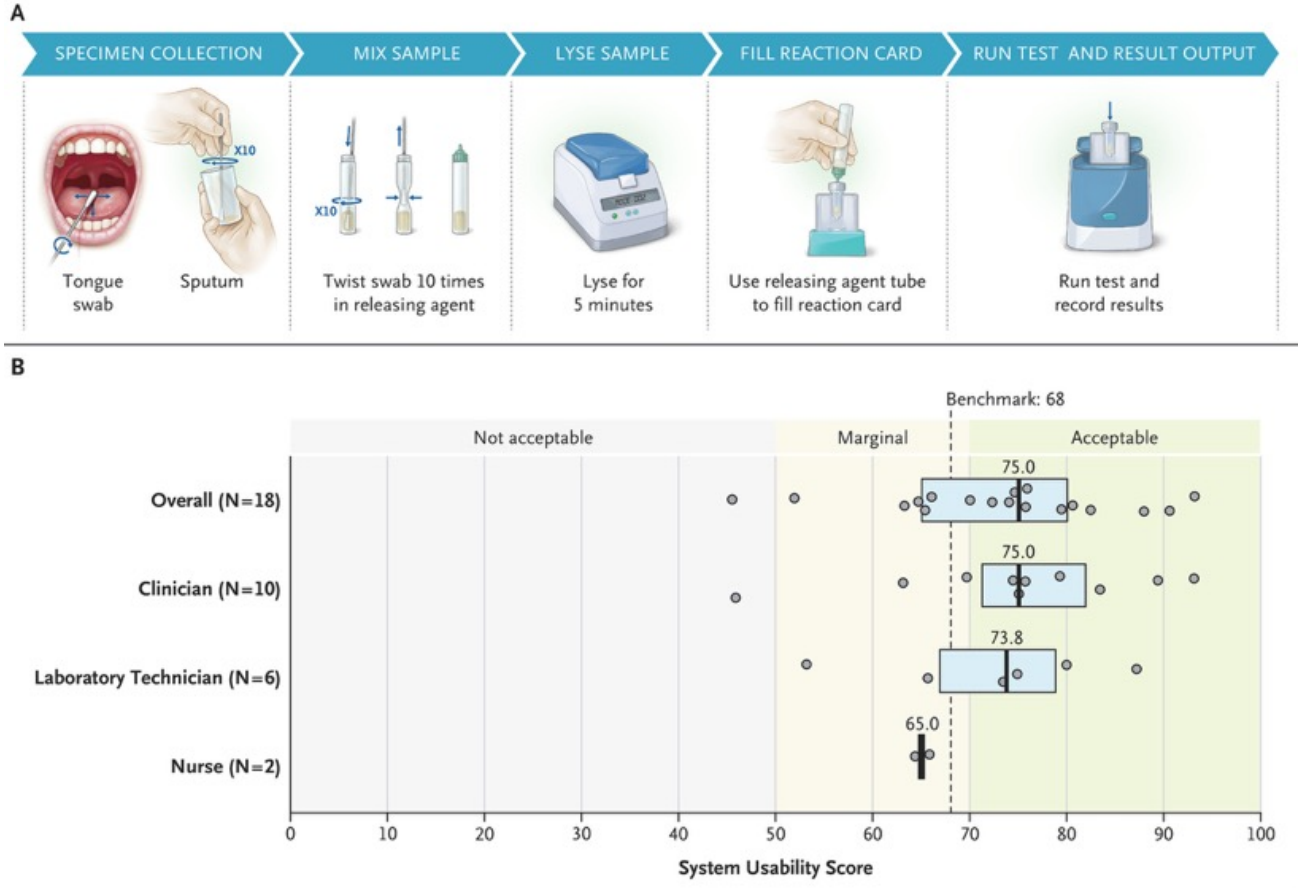
Sensitivity and Specificity for Analysis of Sputum Swabs as Compared with Microbiologic Reference Standard.

Diagnostic accuracy of MiniDock MTB and Xpert Ultra overall and according to subgroup are shown in Panel A. The dashed line represents World Health Organization target product profile performance targets for a sputum-based near-point-of-care tuberculosis test (sensitivity, ≥85%; specificity, ≥98%). Panel B shows head-to-head sensitivity comparisons with conventional sputum-based tests, and Panel C shows head-to-head specificity comparisons with other sputum-based test tests. Data shown in Panel B and Panel C exclude participants without valid MiniDock MTB, smear microscopy, and Xpert Ultra results and participants with trace results on Xpert Ultra. FN denotes false negative, FP false positive, HIV human immunodeficiency virus, TB tuberculosis, TN true negative, and TP true positive.



Sensitivity and Specificity of Tongue-Swab Analysis.

Diagnostic accuracy of MiniDock MTB and Xpert Ultra overall and according to subgroup are shown in Panel A. The dashed line represents World Health Organization target product profile performance targets for a non–sputum-based near-point-of-care tuberculosis test (sensitivity, ≥75%; specificity, ≥98%). Panel B shows head-to-head sensitivity comparisons with conventional sputum-based tests, and Panel C shows head-to-head specificity comparisons with other sputum-based tests. Data shown in Panel B and Panel C exclude participants without valid MiniDock MTB, smear microscopy, and Xpert Ultra results and participants with trace results on Xpert Ultra.



Usability Assessment.

Health care workers who were included in the usability assessment followed the MiniDock MTB instructions for collection and processing of tongue swabs and sputum samples (Panel A). They then rated the workflow by responding to 10 statements on a 5-point Likert scale. The responses were converted to an overall score on the system usability scale (scores range from 0 to 100, with higher scores indicating better perceived usability) (Panel B).

Discussion

In this multinational study, the MiniDock MTB test showed diagnostic accuracy that was consistent with the WHO target product profile for near-point-of-care tuberculosis diagnostics that use sputum and tongue-swab specimens. In addition to showing robust performance, the test was rated as being easy to use, with high usability scores that indicate it can be operated with minimal training. These findings support the feasibility of implementing MiniDock MTB as a flexible, user-friendly diagnostic option that performs similarly to or better than established tuberculosis diagnostic tests, allows for noninvasive sampling, and facilitates universal access to molecular tuberculosis testing.

MiniDock MTB using sputum swabs and tongue swabs showed diagnostic accuracy and usability that met WHO targets for tuberculosis detection across diverse clinical settings. Its near-point-of-care design and minimal training requirements could expand access to timely diagnosis, particularly in peripheral health centers in areas with a high tuberculosis burden that continue to rely on smear microscopy or do not currently offer tuberculosis testing.

Norman Rupert Barrett (* 16. Mai 1903 in Adelaide; † 8. Januar 1979 in London) war ein australisch-britischer Chirurg. Nach ihm wurden unter anderem das Barret-Ulkus (Barrett-Syndrom) bzw. die Barrett-Metaplasie und der Barrett-Ösophagus benannt.
Barrett wurde in Australien geboren, kam aber als Zehnjähriger ins Vereinigte Königreich, wo er studierte und zeitlebens arbeitete. Er erhielt seine Ausbildung im Eton College und am Trinity College der Universität Cambridge. 1928 graduierte er am St Thomas' Hospital (London).
Am 7. März 1947 operierte er als Erster erfolgreich eine spontane Ösophagusruptur (Boerhaave-Syndrom). Barrett beschrieb die refluxbedingte Umwandlung des Plattenepithels der distalen Speiseröhre in ein Zylinder-Epithel, was als Barrett-Ösophagus bezeichnet wird, häufig mit einem Zwerchfellbruch verbunden ist und in bis zu 14 % zu einem Adenokarzinom führt.
1962 wurde er Präsident der Thoraxchirurgen von Großbritannien und Irland. Von 1946 bis 1971 war er Herausgeber der Fachzeitschrift Thorax.

CLINICAL PRACTICE

Barrett's Esophagus

Summary

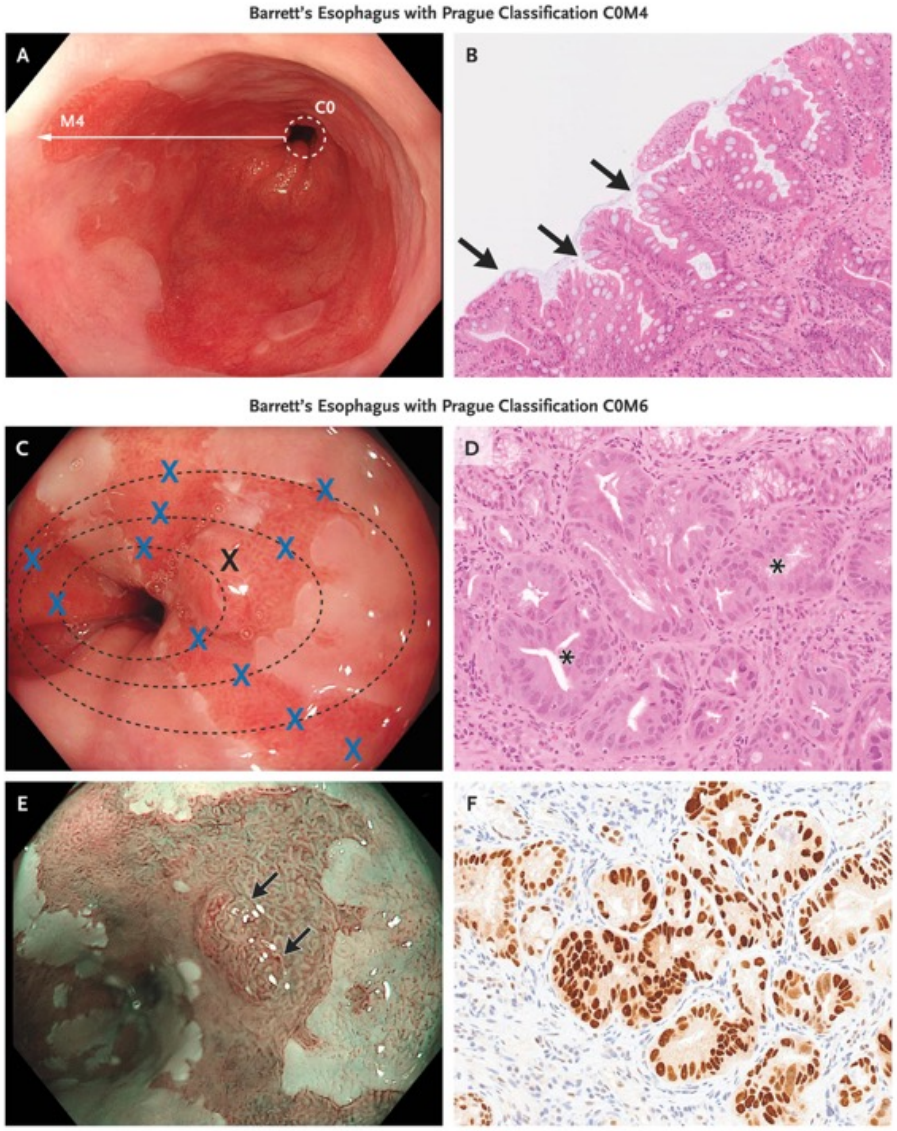
Barrett's esophagus develops as a result of chronic acid and bile reflux and carries an increased risk of esophageal adenocarcinoma. Because it has no specific symptoms, many patients do not receive a diagnosis or they present with symptoms of gastroesophageal reflux disease and other related risk factors or complications. Diagnosis relies on endoscopic and histopathological findings, including a visible columnar-cell–lined segment measuring at least 1 cm long that contains intestinal metaplasia with goblet cells. Ongoing surveillance focuses on early detection of malignant progression, particularly high-grade dysplasia and early-stage cancer, which allows curative endoscopic treatment and avoids the adverse effects associated with chemotherapy or esophagectomy. Participation in clinical trials is encouraged to improve detection, risk stratification, and management strategies.

A 61-year-old man presents with a 10-year history of occasional use of antacids for heartburn. However, the symptoms have worsened during the past 6 months despite regular administration of acid-suppressant medication and are affecting his sleep. He has overweight, and he used to smoke cigarettes but stopped several years ago. He is worried about the risk of cancer. How would you treat this patient?

KEY POINTS

Barrett's Esophagus

- Barrett's esophagus occurs in response to damage from acid and bile reflux and is associated with an increased risk of adenocarcinoma.
- No specific symptom is associated with Barrett's esophagus; therefore, most patients do not receive a diagnosis, or they present with symptoms of gastroesophageal reflux disease and other associated risk factors or complications.
- The diagnosis is based on endoscopic and histopathological features, including a visible columnar-cell–lined segment measuring at least 1 cm long that contains a mosaic of gastric and intestinal cells that must include goblet cells.
- Ongoing monitoring focuses on identifying and stopping malignant progression through early detection of lesions (such as high-grade dysplasia and early-stage cancer) for curative endoscopic therapy without the adverse effects associated with chemotherapy or esophagectomy.
- Participation in clinical trials to inform better case ascertainment and risk stratification should be encouraged.



Key Endoscopic and Histopathological Features of Barrett's Esophagus.

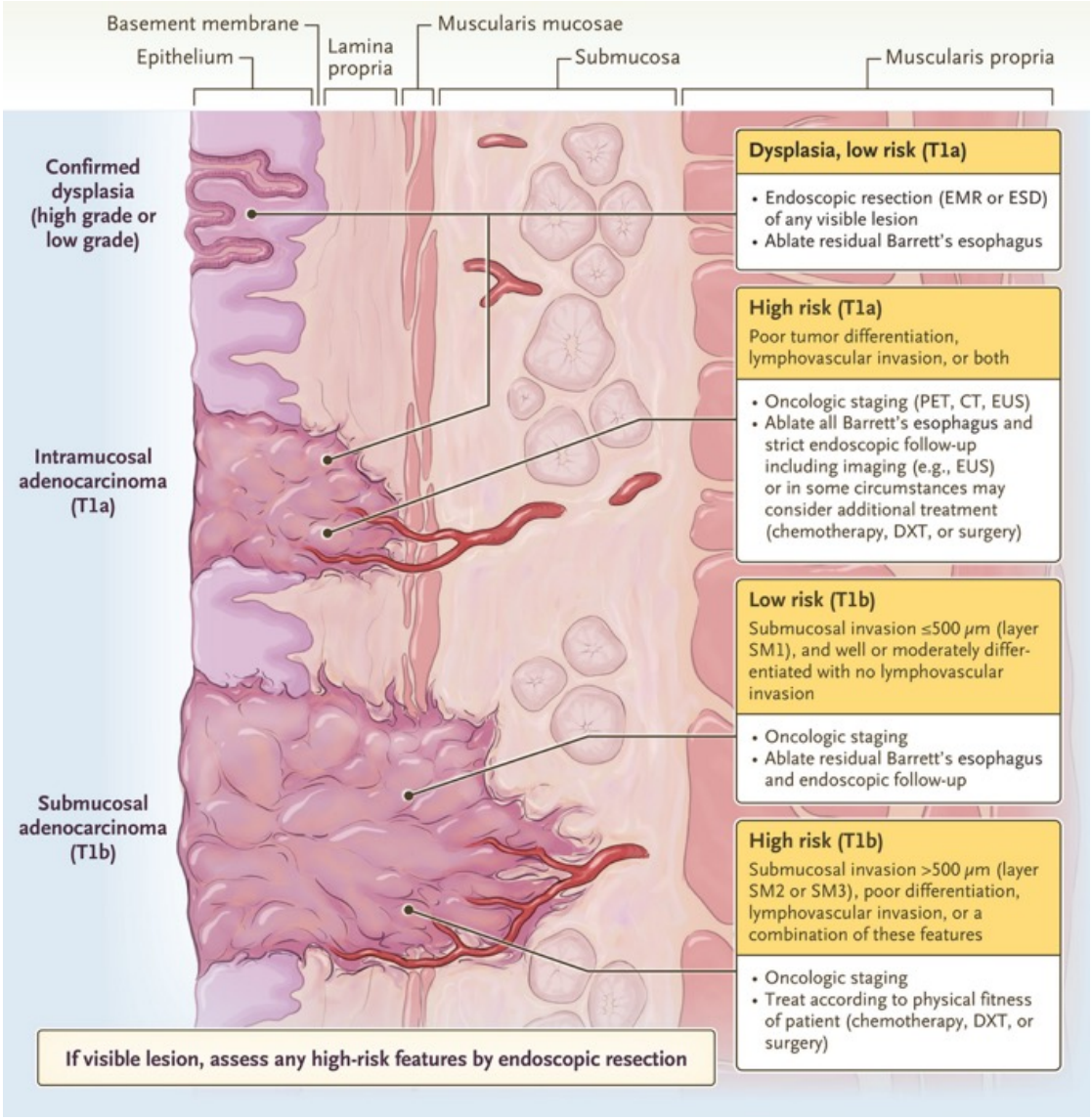
Panel A shows a high-definition, white-light endoscopic image of a columnar-lined mucosa looking down toward the gastroesophageal junction in a patient with Barrett's esophagus. This case has extensive tongues (i.e., noncircumferential areas of Barrett's esophagus) extending 4 cm (arrow) above the gastroesophageal junction but no circumferential component (circle) and is therefore scored as Prague classification C0M4. Panel B shows the corresponding histopathological hematoxylin and eosin stain of a biopsy sample taken from the segment of Barrett's esophagus; the image shows a high number of goblet cells (arrows), which indicates florid intestinal metaplasia. Panels C and E show a visible lesion on a white-light endoscopic image (black X, Panel C) and on the corresponding narrow-band image (arrows, Panel E) in a patient with Barrett's esophagus with Prague classification C0M6. Biopsy samples should be taken from the visible lesion, and systematic biopsies should be performed in accordance with the Seattle protocol, which states that a biopsy sample should be obtained for every 2 cm of Barrett's esophagus–affected epithelium in each quadrant; the ellipses in Panel C show each level where biopsy samples are taken, and the blue Xs show the biopsy site. At the most proximal extent of the affected tissue in this case, only one biopsy sample would be taken. Panel D shows the corresponding histopathological hematoxylin and eosin stain, which shows nuclear enlargement and disruption of glandular atypia (asterisks), indicating high-grade dysplasia. Panel F shows the corresponding immunohistochemical stain; the image shows aberrant overexpression of p53 in the affected tissue as compared with the wild-type glands, which confirms the genomic basis for this phenotypic change.

Steps in the Clinical Pathway of Barrett's Esophagus.

Steps in Clinical Pathway	Description	Quality Indicators
Risk factors	A history of reflux symptoms and three of the following: White race, male sex, age of >50 yr, central obesity, tobacco use, or first-degree relative with Barrett's esophagus or esophageal adenocarcinoma	Barrett's esophagus and rate of detection of dysplasia or esophageal adenocarcinoma (neoplasia detection rate is inversely correlated with subsequent missed cancer)[11]
Diagnostic method	Triage with a nonendoscopic test in an office setting to increase access and uptake of the screening or diagnostic test; endoscopy and biopsy to determine endoscopic location and extent	Minimum inspection time of 1 min per cm of Barrett's esophagus Photographic documentation of landmarks Eight biopsies for initial diagnosis
Endoscopic dysplasia assessment	High-dose PPI used to heal any esophagitis High-definition white-light endoscopy with access to enhanced imaging (virtual or chromoendoscopy) to delineate focal changes and biopsies, including systematic biopsies Biopsy of all visible lesions and random four-quadrant biopsies for every 2 cm of Barrett's esophagus (Seattle protocol)	Prague criteria Paris classification for any visible lesions Adherence to Seattle protocol Audit of postendoscopy Barrett's neoplasia within 3 yr
Histopathological assessment	Assessment of intestinal metaplasia and any dysplasia (low grade, high grade, or indefinite) or cancer at each biopsy; consensus diagnosis of dysplasia by two independent pathologists Use of immunohistochemical staining for TP53 to confirm inflammatory or malignant changes if any dysplasia is suspected	Intestinal metaplasia and dysplasia status reported for each level (recorded in centimeters) of Barrett's esophagus biopsied Audit of postendoscopy Barrett's neoplasia within 3 yr

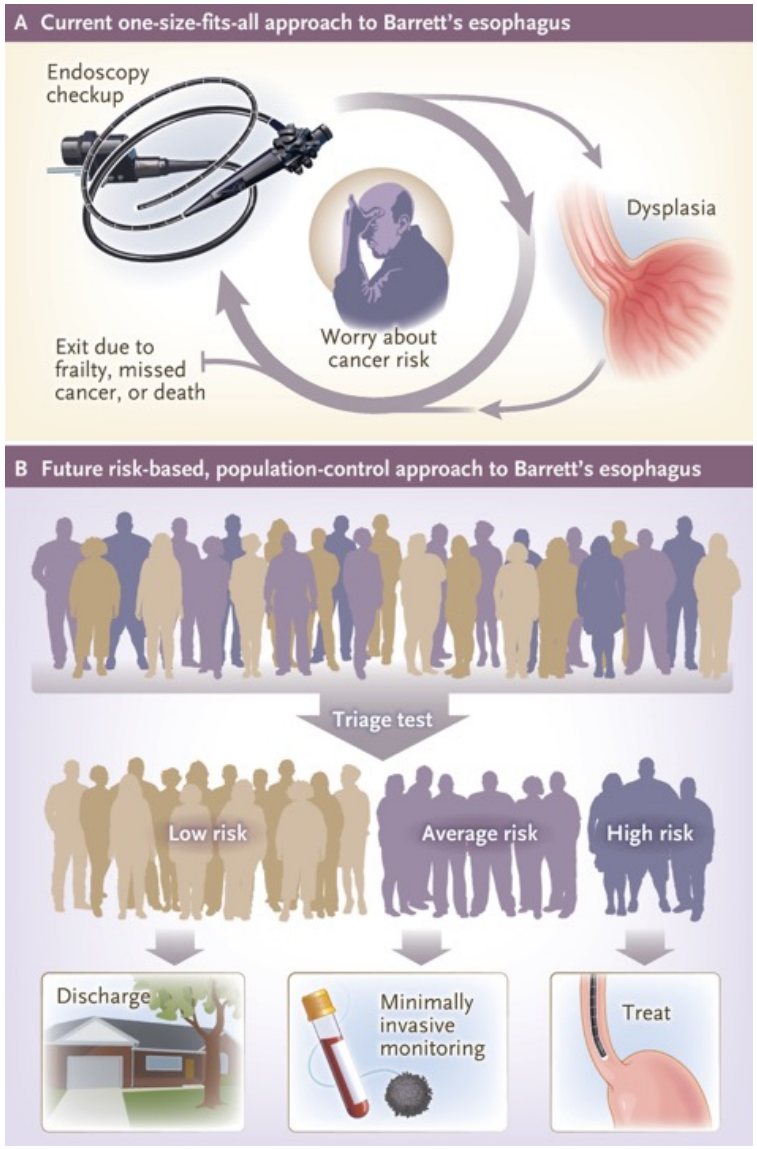
Progression of Barrett's Esophagus According to Study Type and Baseline Criteria for Inclusion.

Study	Context	Follow-up	Baseline	End Points	Percent Progressed per Year†
		yr			
Population studies with case ascertainment dependent on real-world coding					
Hvid-Jensen et al.[12]	Danish pathological registry (11,028 patients)	Median, 5.2	Pathologic intestinal metaplasia	Esophageal adenocarcinoma	0.12
Krishnamoorthi et al.[20]	United Kingdom General Practice Research Database (9660 patients)	Mean, 4.8	Diagnostic code for Barrett's esophagus	Esophageal adenocarcinoma	0.223
Bhat et al.[14]	Northern Ireland Barrett's Esophagus Register (8522 patients)	Mean, 7	Nondysplastic disease or low-grade dysplasia	High-grade dysplasia or esophageal adenocarcinoma	0.38
Randomized trial comparing surveillance and endoscopy as needed in real world					
Old et al.[15]	Multicenter trial in the United Kingdom (3453 patients)	Median, 12.8	Nondysplastic disease or low-grade dysplasia	High-grade dysplasia or esophageal adenocarcinoma	0.164
Historical cohort study					
Wani et al.[16]	Multicenter, retrospective study in the United States (1204 patients)	Mean, 5.5	Nondysplastic Barrett's esophagus	High-grade dysplasia or esophageal adenocarcinoma	0.63
Contemporary, single-center, longitudinal study					
Honing et al.[17]	Involved endoscopists trained on enhanced imaging and biopsy review by expert pathologists (969 patients)	Median, 5.8	Nondysplastic Barrett's esophagus or low-grade dysplasia	High-grade dysplasia or esophageal adenocarcinoma	1.63
Retrospective analysis of randomized trial					
Duits et al.[18]	Patients screened for SURF trial (255 patients)	Median, 3.5	Low-grade dysplasia detected at baseline	High-grade dysplasia or esophageal adenocarcinoma	
Low-grade dysplasia confirmed by one pathologist					2.4
Low-grade dysplasia confirmed by two endoscopies					9.28
Randomized trial of radiofrequency ablation efficacy					
Phoa et al.[19]‡	European multicenter trial (68 patients)	3	Low-grade dysplasia	High-grade dysplasia or esophageal adenocarcinoma	11.8
Shaheen et al.[21]‡	United States (43 patients)	1	Low- or high-grade dysplasia	Esophageal adenocarcinoma	9.3
Meta-analysis of four previously published studies					
Rastogi et al.[40]	Previously diagnosed high-grade dysplasia (236 patients)	Mean, 5.3	High-grade dysplasia	Esophageal adenocarcinoma	5.57



Disease Extent, Features, and Therapy Recommendations in Barrett's Esophagus.

The diagram shows the criteria for assessing the extent of disease and any high-risk features in Barrett's esophagus, as well as subsequent therapy recommendations. The endoscopic resection may entail cap-assisted mucosal resection for lesions less than 20 mm deep that are confined to the mucosal layer or submucosal dissection for deeper lesions (>20 mm) and those suspicious for submucosal invasion (type 0–Is [polypoid or sessile and broad-based] or 0–IIc [superficially depressed] according to the Paris classification) or in fibrotic areas. Pathological information cannot be obtained after ablation therapy; therefore, close follow-up with biopsies is warranted. Additional oncologic treatment should be considered after endoscopic resection in cases of a tumor-positive deep (vertical) resection margin. All treatment decisions should be discussed among members of a multidisciplinary team and will be influenced by patient physical fitness and choice. CT denotes computed tomography, DXT external beam radiation therapy, EMR endoscopic mucosal resection, ESD endoscopic submucosal dissection, EUS endoscopic ultrasonography, and PET positron-emission tomography.



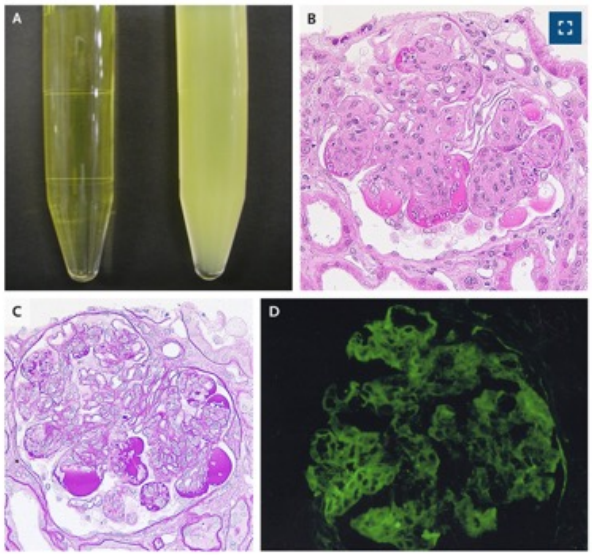
Current and Future Management of Barrett's Esophagus.

Panel A shows the current approach to managing Barrett's esophagus. The disease is diagnosed on a case-by-case basis, with patients entering a vicious circle of lifetime endoscopy checkups and treatment if dysplasia or early cancer is detected. Patients exit the circle if they become too frail for further checkups, have a missed cancer (i.e., an interval cancer diagnosed before the next cycle of surveillance) warranting systemic treatment, or die from another cause. Panel B shows a future risk-based, population-control approach to managing Barrett's esophagus. The population to be offered screening is enriched on the basis of risk factors. A triage test determines whether the patients in this population have a low, average, or high lifetime risk of cancer. The approach to management is tailored to each patient to minimize harm and maximize detection of dysplasia or stage I cancer.

Conclusions and Recommendations

Because the patient in the vignette has GERD and several other risk factors for Barrett's esophagus — such as male sex, older age, history of smoking, overweight, and heartburn — I would recommend a diagnostic test with either direct endoscopy or a nonendoscopic triage test, depending on the patient's preference and the resources available. His symptoms are interfering with his quality of life; therefore, a review of behaviors and medications would be useful to address causes of reflux that can be modified. Potent and continuous antireflux medication could ensure adequate control of symptoms; if medication is unsuccessful, then surgical antireflux options could be considered. If a diagnosis of Barrett's esophagus is made, a careful explanation of the disease should be given with a recommendation to undergo surveillance at intervals determined by the length of the affected segment (3 years for a segment of ≥3 cm and 5 years for a short segment of 1 to <3 cm) or treatment if dysplasia is identified and confirmed. Decision making should be based on the low lifetime risk for cancer and the effectiveness of treatment for early disease identified during surveillance. Apart from PPIs, there is no evidence that treatment with aspirin or statins will reduce the risk of cancer and obviate the need for monitoring.

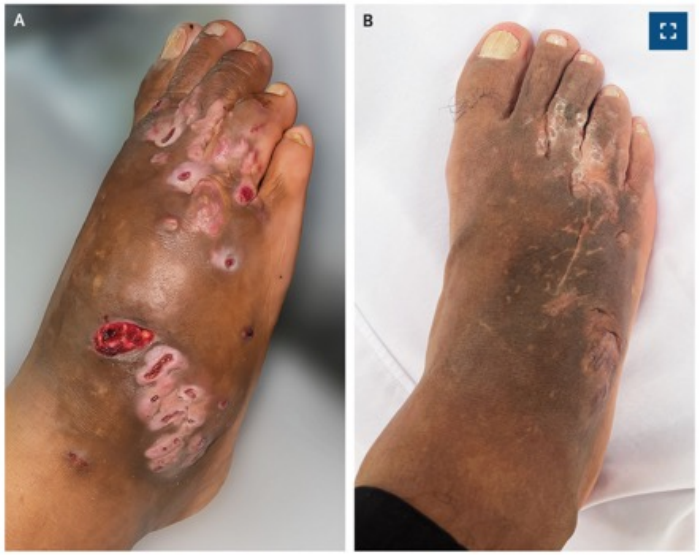
Membranoproliferative Glomerulonephritis Due to Cryoglobulinemia



A 60-year-old woman with stage II follicular lymphoma, for which she was undergoing monitoring for disease progression but was not receiving active treatment, was referred to the hospital for evaluation of leg swelling and proteinuria that had persisted for 2 weeks. She also had a rash on her lower legs that was provoked by cold temperatures. Physical examination was notable for edema in both legs with overlying livedo reticularis. Laboratory studies showed a rapid rise in the urea nitrogen and creatinine levels and nephrotic-range proteinuria. An IgG kappa monoclonal protein was also detected. Blood complement levels and the results of antibody testing for hepatitis C virus were normal. The patient's plasma was clear at 37°C but turbid at 4°C (Panel A) — a sign of temperature-dependent precipitation of cryoglobulins. A semiquantitative cryocrit was 25% (normal result, undetectable). A kidney biopsy revealed endocapillary proliferative glomerulonephritis (Panel B, hematoxylin and eosin stain) with intraglomerular hyaline pseudothrombi created by cryoglobulin deposits (Panel C, periodic acid–Schiff stain). Immunofluorescence staining showed diffuse granular IgG deposits (Panel D). A diagnosis of type I (i.e., monoclonal immunoglobulin-related) cryoglobulinemia resulting in membranoproliferative glomerulonephritis was made. The patient began treatment with glucocorticoids for cryoglobulinemia-associated glomerulonephritis and rituximab-based therapy for lymphoma. Three months after initiation of treatment, the patient's kidney function improved, and her condition remained in remission at 12 months.

IMAGES IN CLINICAL MEDICINE

Mycetoma



An otherwise healthy 30-year-old man was referred to the infectious diseases clinic for a 2-year history of skin lesions on his right foot. The patient worked as an agricultural laborer and had sustained injuries to his feet over the years, including a puncture wound to the skin between the fourth and fifth toes of his right foot. Physical examination was notable for swelling of the right foot with overlying ulcerated nodules (Panel A). Histopathological examination of a skin-biopsy specimen revealed a suppurative and granulomatous inflammatory process. Filamentous, branching structures were observed on modified Ziehl–Neelsen staining, a finding consistent with the presence of nocardia species. Polymerase-chain-reaction testing of the tissue identified *Nocardia brasiliensis*. A diagnosis of mycetoma (also known as Madura foot) was made. Mycetoma is a chronic infection of the skin and underlying tissues that manifests with swelling, sinus tracks, and purulent discharge. The infection may be caused by bacteria (actinomycetoma) or fungi (eumycetoma) and most commonly occurs in persons residing in tropical and subtropical climates who are frequently exposed to soil. Imaging of the foot showed concurrent osteomyelitis and septic arthritis, and surgical débridement was performed. The patient received a 6-month course of trimethoprim–sulfamethoxazole, and at follow-up 6 months after starting treatment, the condition of his foot had improved (Panel B).

Die Kryoglobulinämie ist eine seltene Gefäßentzündung (Vaskulitis), verursacht durch abnormal verklumpende Eiweiße (Kryoglobuline) im Blut bei Kälte. Dies führt zu Durchblutungsstörungen, Hautveränderungen (Purpura), Gelenkschmerzen und Organschäden (Niere, Nerven). Häufigste Ursachen sind chronische Infektionen (insb. Hepatitis C) oder Autoimmunerkrankungen.

Hauptmerkmale und Symptome

•**Kryoglobuline:** Antikörper, die bei Temperaturen unter 37°C ausfallen und bei Erwärmung wieder gelöst werden.

•**Vaskulitis:** Entzündung kleiner Gefäße durch Ablagerung dieser Komplexe.

•**Symptomtrias (Meltzersche Trias):** Purpura (tastbare, rote Hautflecken), Schwäche (Asthenie) und Gelenkschmerzen (Arthralgie)

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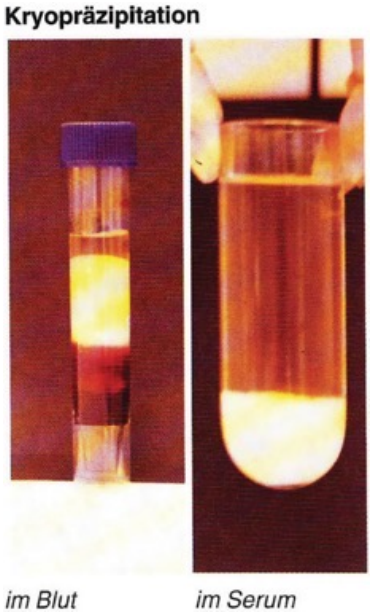
•**Organsysteme:** Nierenschäden (Glomerulonephritis), periphere Neuropathie (Nervenschäden) und Durchblutungsstörungen der Haut (Nekrosen).



Diese Präzipitate können im Patienten (in vivo) als auch nach Blutentnahme (in vitro) auftreten. Das Präzipitationsverhalten dieser Eiweiße ist von Patient zu Patient und auch beim Patienten selbst über die Zeit unterschiedlich, abhängig u.a. von Konzentration, Immunglobulinklasse, Aminosäuresequenz, Körpertemperatur, Außentemperatur und pH-Wert.

Case 13-2026: A 76-Year-Old Woman with Fatigue, Rash, and Kidney Failure

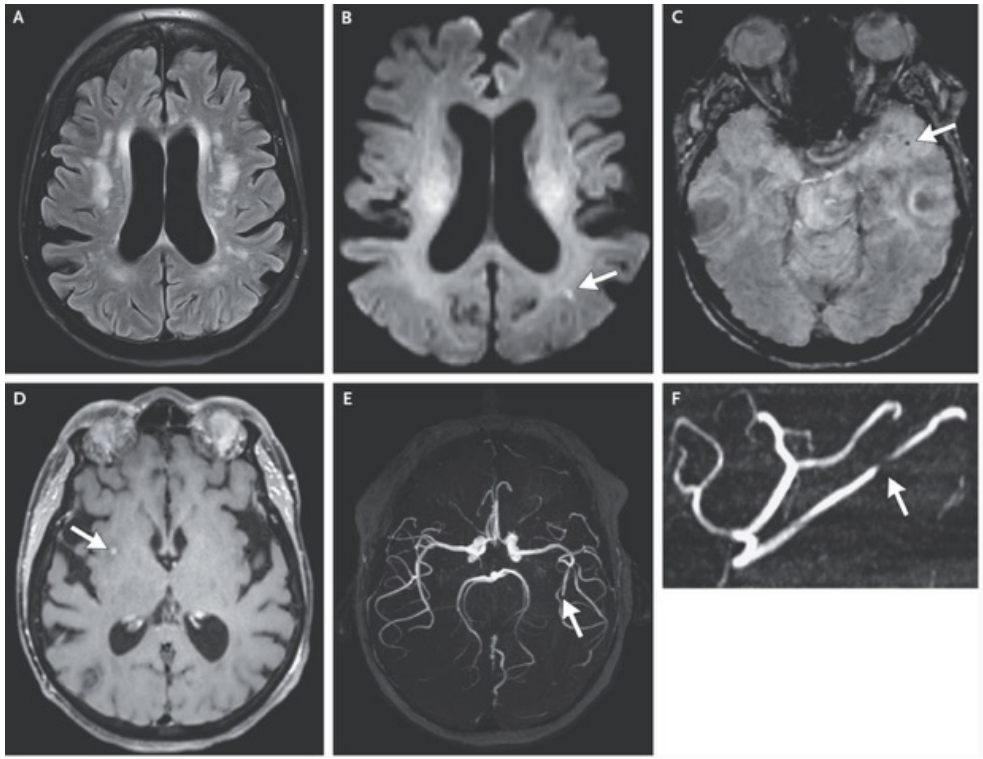
A 76-year-old woman was transferred to the medical service of this hospital because of rapidly progressive kidney failure.

The patient had been in her usual state of health until 1 year before the current presentation, when a painless purpuric rash on the lower legs developed. The rash waxed and waned. There was no joint pain, edema, weakness, or weight loss. The patient was seen by a dermatologist at another hospital, and the results of a skin biopsy were reportedly consistent with leukocytoclastic vasculitis. The results of urinalysis and kidney-function tests were normal. Her symptoms were attributed to a history of hepatitis C virus (HCV) infection; topical glucocorticoid treatment was initiated, and the rash resolved.

Four weeks before the current presentation, the patient had persistent sinonasal congestion, drainage, and pain, and she received amoxicillin as treatment for presumptive bacterial sinusitis. The sinonasal symptoms resolved, but after she completed the course of amoxicillin, the purpuric rash on the lower legs recurred and was accompanied by arthralgias, ankle edema, and fatigue.

The patient was evaluated in the rheumatology clinic of the other hospital. Physical examination was notable for pitting edema extending from the ankles to the shins and palpable purpura on the lower legs and thighs, without synovitis or motor weakness. Glucocorticoid treatment was deferred, and additional laboratory evaluation was planned.

Urinalysis showed 3+ blood (reference value, negative), more than 180 red cells per high-power field (reference range, 0 to 2), and 3+ protein (reference value, negative). Quantification of protein in a 24-hour urine collection showed 4.4 g of total protein per day.



MRI and MRA of the Head.

MRI of the head was performed on admission. An axial fluid-attenuated inversion recovery image (Panel A) shows moderate, nonspecific hyperintensities that are compatible with chronic small-vessel disease. An axial diffusion-weighted image (Panel B) shows a punctate focus of acute or early subacute infarction in the left parieto-occipital parenchyma (arrow). An axial susceptibility-weighted image (Panel C) shows a nonspecific microhemorrhage in the left temporal lobe (arrow). An axial contrast-enhanced T1-weighted black-blood image (Panel D) shows a punctate focus of enhancement in the right putamen (arrow) without corresponding restricted diffusion, a finding suggestive of late subacute infarction. No abnormal vascular-wall enhancement is shown in the visualized arteries. Magnetic resonance angiography (MRA) was also performed. Axial and sagittal images (Panels E and F, respectively) show focal critical stenosis or occlusion of the middle portion of the M2 segment of the left middle cerebral artery (arrows), along with focal stenoses of the proximal portion of the M2 segment of the left middle cerebral artery and the P3 segment of the left posterior cerebral artery.

Differential Diagnosis

This 76-year-old woman with a history of treated HCV infection first reported a purpuric rash 1 year before the current presentation. A skin biopsy revealed leukocytoclastic vasculitis, a histopathological finding that is commonly seen with most types of cutaneous small-vessel vasculitis. At that time, there was no evidence of extracutaneous involvement, and the purpura resolved with the administration of topical glucocorticoids.

Within a month before the current presentation, the patient had recurrent purpura that was accompanied by arthralgias, proteinuria, an active urinary sediment, and deteriorating kidney function. The urinary profile, coupled with the rapid decline in kidney function, is consistent with the clinical syndrome of rapidly progressive glomerulonephritis (RPGN). This patient's clinical problem can best be represented as a systemic small-vessel vasculitis with severe kidney involvement.

Variable	Reference Range, Adults, This Hospital†	2 Wk before Current Presentation, Other Hospital	3 Days before Current Presentation, Other Hospital	On Current Presentation, This Hospital
Hemoglobin (g/dl)	12.0–16.0	—	8.4	9.6
Hematocrit (%)	41.0–53.0	—	26.4	29.2
White-cell count (per μl)	4500–11,000	—	5600	14,690
Differential count (per μl)				
Neutrophils	1800–7700	—	4370	13,530
Lymphocytes	1000–4800	—	680	700
Monocytes	200–1200	—	380	310
Eosinophils	0–900	—	100	0
Basophils	0–300	—	30	10
Immature granulocytes	0–100	—	0	140
Platelet count (per μl)	150,000–400,000	—	284	260
Sodium (mmol/liter)	135–145	139	137	137
Potassium (mmol/liter)	3.4–5.0	4.3	4.8	4.4
Chloride (mmol/liter)	98–108	108	100	103
Carbon dioxide (mmol/liter)	23–32	20	20	25
Urea nitrogen (mg/dl)	8–25	39	49	34
Creatinine (mg/dl)	0.6–1.5	2.6	4.2	2.6
Calcium (mg/dl)	8.5–10.5	9.2	9.0	8.8
Glucose (mg/dl)	70–110	99	100	103
Aspartate aminotransferase (U/liter)	9–32	—	—	25
Alanine aminotransferase (U/liter)	7–33	—	—	17
Alkaline phosphatase (U/liter)	30–100	—	—	68
Total bilirubin (mg/dl)	0.0–1.0	—	—	0.2
Albumin (g/dl)	3.3–5.0	—	—	3.0
Globulin (g/dl)	1.9–4.1	—	—	2.4
C3 (mg/dl)	81–157	—	73	41
C4 (mg/dl)	12–39	—	<6	<6
IgG (mg/dl)	614–1295	—	—	78
IgA (mg/dl)	69–309	—	—	109
IgM (mg/dl)	53–334	—	—	466
Free kappa light chain (mg/liter)	3.3–19.4	—	—	356.3
Free lambda light chain (mg/liter)	5.7–26.3	—	—	18.1
Kappa:lambda ratio	0.30–1.70	—	—	19.69
Serum protein electrophoresis	Negative for monoclonal component	—	—	IgM kappa M component detected (0.12 g/dl)

Rheumatoid factor was positive

Conceptual Framework for Systemic Small-Vessel Vasculitis

The pathogenesis of small-vessel vasculitis with glomerular involvement can be conceptualized in terms of the three immunofluorescence patterns that can be seen on kidney biopsy: linear, pauci-immune, and immune-complex.

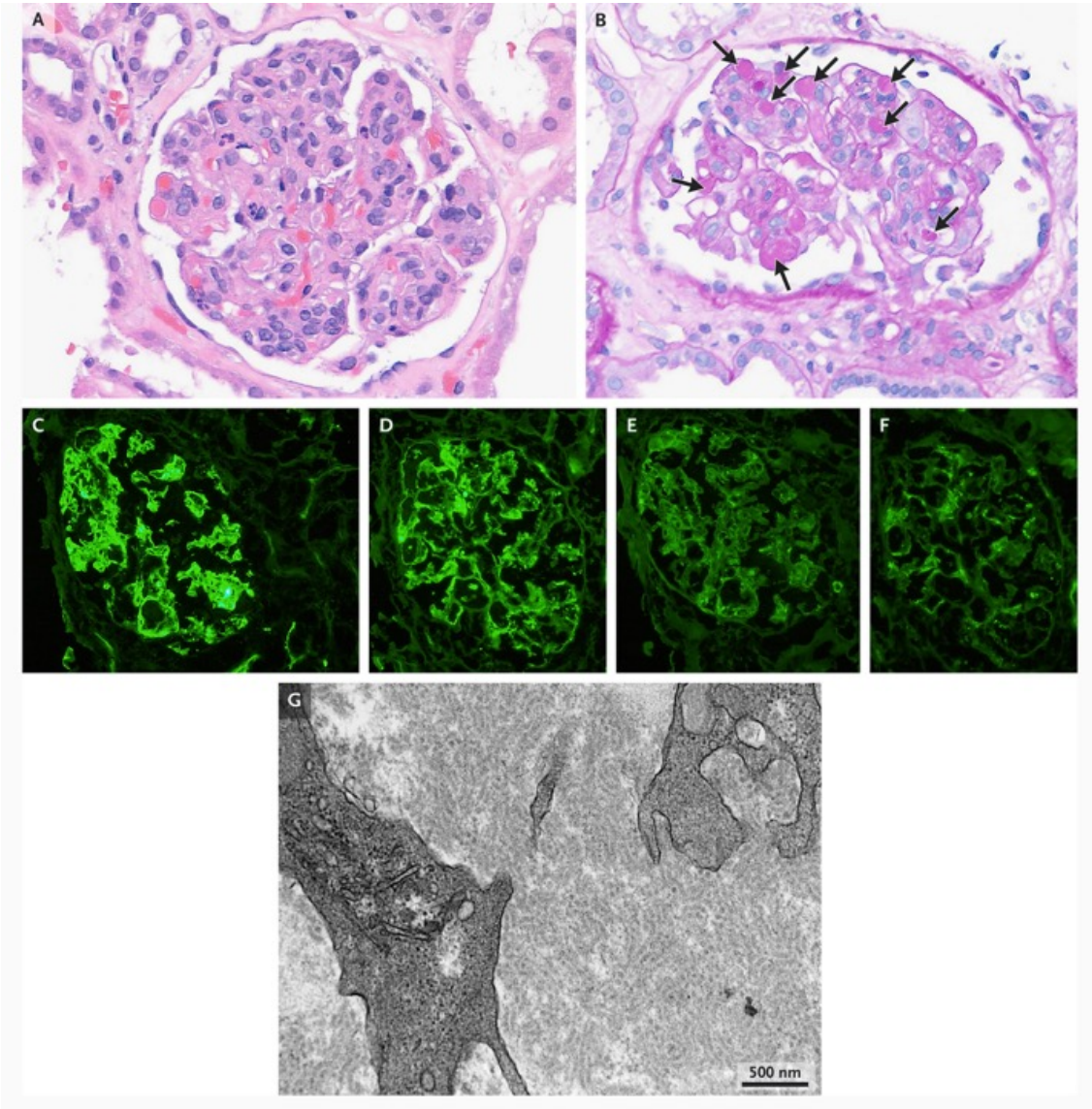
Serum Complement Levels in the Evaluation of Glomerulonephritis

In a patient with glomerulonephritis, obtaining serum levels of C3 and C4 is a useful first step. This patient has an undetectable C4 level and a mildly low C3 level. Given that patients with ANCA-associated vasculitis, anti-GBM disease, or IgA vasculitis typically present with normal serum complement levels, these diagnoses can be ruled out on the basis of the patient's complement profile.

Cryoglobulinemic Vasculitis

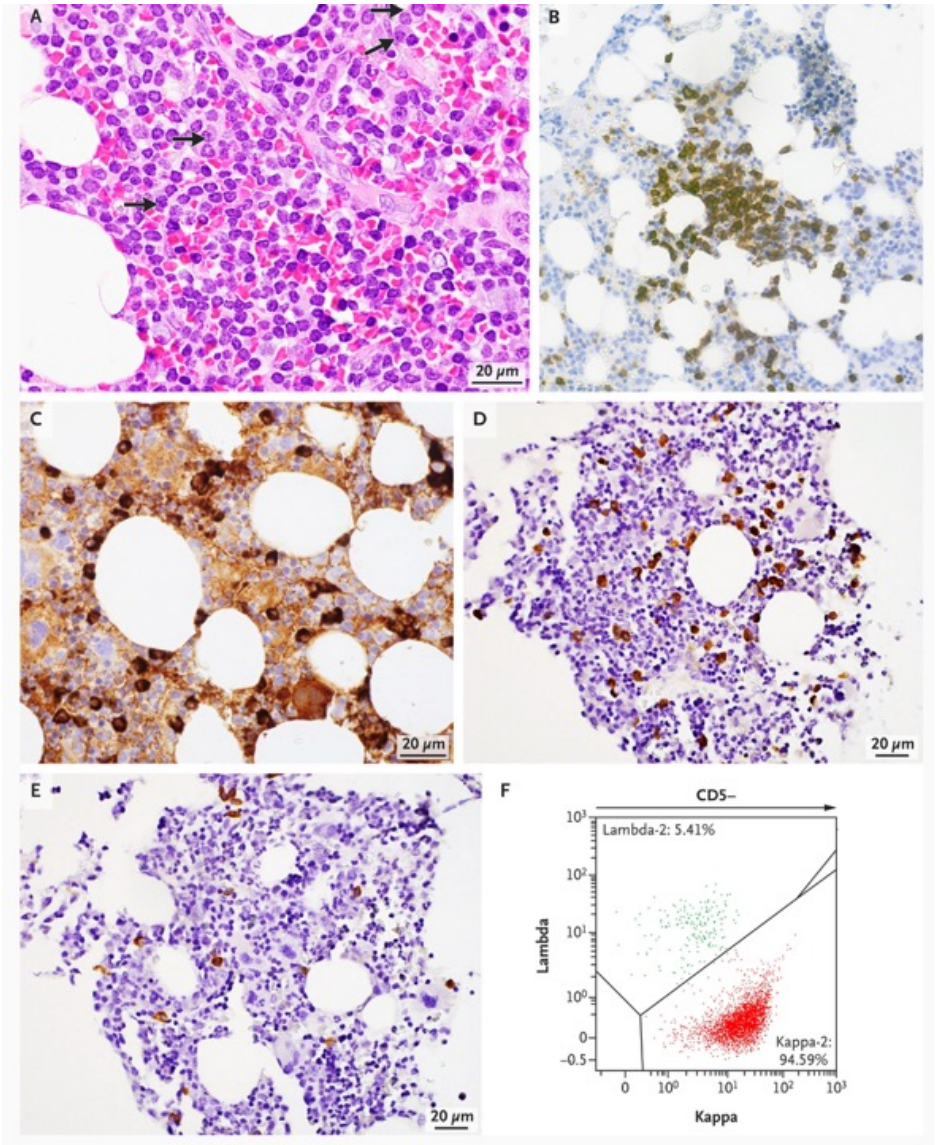
Cryoglobulins are immunoglobulins that precipitate from serum in vitro at temperatures below 37°C and redissolve upon rewarming. When cryoglobulins are detected, their composition should be determined to guide additional evaluation. Type I cryoglobulins consist of a single monoclonal immunoglobulin, typically IgG or IgM. Type II and type III cryoglobulins are mixed cryoglobulins that usually consist of IgM with rheumatoid factor activity and polyclonal IgG. In type II cryoglobulins, the IgM component is monoclonal (typically IgM kappa), whereas in type III cryoglobulins, the IgM component is polyclonal.

This patient had a positive test for rheumatoid factor and had a spike in IgM kappa, findings that are most consistent with type II cryoglobulins. Whereas type I cryoglobulins typically cause tissue injury through precipitation in small vessels, which leads to mechanical obstruction, mixed cryoglobulins are potent activators of the classical complement cascade and cause overt vasculitis. This patient has documented cutaneous vasculitis and would be expected to have a membranoproliferative pattern of injury on kidney biopsy, which is the histopathological finding typically observed with cryoglobulinemic glomerulonephritis.



Kidney-Biopsy Specimens.

Hematoxylin and eosin staining (Panel A) shows a glomerulus with a membranoproliferative pattern of injury, including endocapillary hypercellularity with polymorphonuclear neutrophils and intracapillary eosinophilic material that is suggestive of pseudothrombi. Periodic acid–Schiff staining (Panel B) is positive in intracapillary material (arrows), a finding typical of pseudothrombi; negative staining would be typical of fibrin thrombi. Immunofluorescence staining (Panels C through F) shows deposits along the glomerular basement membranes, in the mesangium, and in the capillary lumens that are reactive for IgM (3+) and kappa (3+) (Panels C and D, respectively) and for C3 (2+) (not shown), with lesser reactivity for IgG (1+) and lambda (1+) (Panels E and F, respectively) and with no reactivity for C1q and IgA (not shown). Electron microscopy (Panel G) shows mesangial deposits with microtubular organization and a curvilinear pattern.



Bone Marrow–Biopsy Specimens and Peripheral-Blood Analysis.

Hematoxylin and eosin staining (Panel A) shows a lymphoid aggregate with scattered plasma cells (arrows). Immunohistochemical staining for CD20 (Panel B) is positive in a B-cell aggregate. Immunohistochemical staining for the μ immunoglobulin heavy chain (Panel C) shows strong IgM expression in B-cell aggregates. In situ hybridization for kappa and lambda immunoglobulin light chains (Panels D and E, respectively) shows predominant kappa light-chain expression in the plasma cells. Panel F shows representative results from flow cytometric analysis of the peripheral blood. A kappa–lambda immunoglobulin light-chain dot plot of CD5– B cells shows a dominant kappa-restricted population (94.59%) and a minor lambda-restricted population (5.41%), findings consistent with a clonal B-cell process.

Pathological Diagnosis

Type II cryoglobulinemic vasculitis associated with a small mature B-cell lymphoma with plasmacytic differentiation.

Discussion of Management

Symptomatic cryoglobulinemia — whether monoclonal type I or mixed type II — is an indication for the initiation of therapy for Waldenström macroglobulinemia. Waldenström macroglobulinemia, the most common subtype of lymphoplasmacytic lymphoma, is characterized by the presence of detectable IgM monoclonal protein. Although the *MYD88* L265P mutation is found in more than 90% of patients with Waldenström macroglobulinemia, this patient appeared to have a wild-type mutation. False negative results of genetic sequencing may occur, particularly when testing is performed on unsorted bone marrow specimens with a low tumor burden. *MYD88*–wild-type Waldenström macroglobulinemia is associated with more aggressive clinical features and worse outcomes than *MYD88*-mutated disease.

Initial therapy with a proteasome inhibitor–based regimen that consisted of bortezomib, dexamethasone, and rituximab was selected because of its activity in patients with kidney dysfunction. Proteasome inhibitor–based regimens are also effective across genomic subgroups of Waldenström macroglobulinemia. Shortly after the initiation of therapy, the patient had an acute transient increase in IgM levels with worsening cryoglobulinemic manifestations, a response consistent with a rituximab-associated IgM flare.

After discharge from this hospital, the patient elected to continue oncology care at another hospital closer to her home. She continued to receive treatment with bendamustine combined with rituximab, as well as prednisone daily. Her treatment course was complicated by deep-vein thrombosis and severe hypogammaglobulinemia with recurrent infections. These complications were associated with marked functional decline, necessitating prolonged inpatient rehabilitation.

Three months after discharge from this hospital, the patient reestablished care at this hospital. The rash associated with leukocytoclastic vasculitis had resolved. Waldenström macroglobulinemia was in remission, with a very good partial response involving a reduction in IgM levels of more than 90%. Cryoglobulinemia was also in remission, with a reduction in cryoglobulin levels from 3% of the total serum volume to less than 1%. Bendamustine combined with rituximab was discontinued after four cycles, monthly therapy with intravenous immune globulin was initiated, and the dose of glucocorticoids was tapered.

Five months after discharge from this hospital, the patient received a diagnosis of metastatic Merkel-cell carcinoma. Despite remission of Waldenström macroglobulinemia and cryoglobulinemia, the carcinoma progressed, leading to multiorgan failure. The patient was transitioned to hospice care and died peacefully at home approximately 8 weeks later.

Final Diagnosis

Waldenström macroglobulinemia associated with type II cryoglobulinemic vasculitis.

Der Morbus Waldenström (Makroglobulinämie) ist ein seltenes, langsam fortschreitendes (indolentes) Non-Hodgkin-Lymphom, bei dem entartete B-Zellen das Knochenmark infiltrieren und große Mengen an Immunglobulin M (IgM) produzieren. Dies führt zu einer Verdickung des Blutes (Hyperviskosität), Anämie und Symptomen wie Fatigue, Blutungsneigung und Lymphknotenvergrößerung.

Wichtige Fakten zur Erkrankung:

•**Charakteristika:** Es handelt sich um ein lymphoplasmozytisches Lymphom, das Zellen aufweist, die zwischen B-Lymphozyten und Plasmazellen liegen.

•**Ursache & Diagnose:** Die genauen Ursachen sind unbekannt, oft liegt eine nicht vererbte Mutation im *MYD88*-Gen vor. Die Diagnose erfolgt meist über Blutuntersuchungen (Nachweis von IgM-Paraproteinen) und eine Knochenmarkbiopsie

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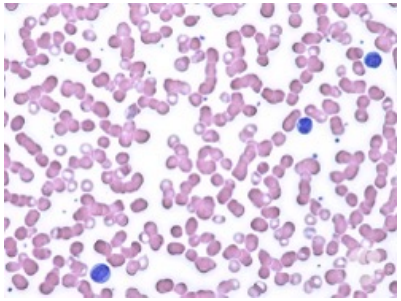
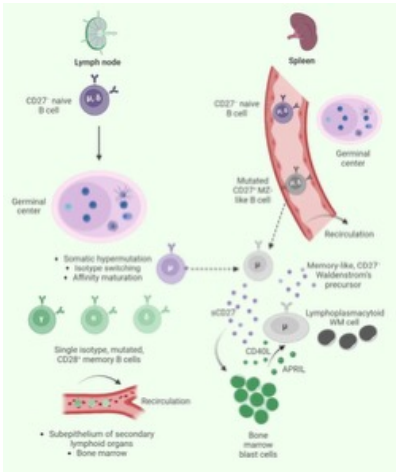


Rouleaux

•**Symptome:** Häufig verläuft die Erkrankung anfangs symptomlos. Später treten Müdigkeit (Fatigue), geschwollene Lymphknoten/Milz, Infektanfälligkeit, Blutungen (Nase/Zahnfleisch) und Sehstörungen auf.

•**Therapie:** Da die Krankheit oft langsam verläuft, wird initial oft eine "Watch and Wait"-Strategie (Beobachten statt sofort Behandeln) verfolgt. Bei Symptomen kommen Therapien wie:

- •**Plasmapherese:** Blutwäsche zur Reduzierung des IgM-Spiegels bei Hyperviskositätssyndrom.
- •**Immunchemotherapie:** Einsatz von Wirkstoffen wie Rituximab, Bendamustin oder Bortezomib.
- •**BTK-Inhibitoren:** Moderne zielgerichtete Medikamente wie Ibrutinib oder Zanubrutinib.



COMPONENTS OF THE ALCOHOL USE DISORDERS IDENTIFICATION TEST (AUDIT)

ALCOHOL CONSUMPTION

Measures drinking frequency, quantity, and binge drinking habits to identify risky patterns.

DRINKING BEHAVIORS

Assesses loss of control, increased tolerance, and impact on responsibilities to detect alcohol dependence.

ALCOHOL-RELATED HARM

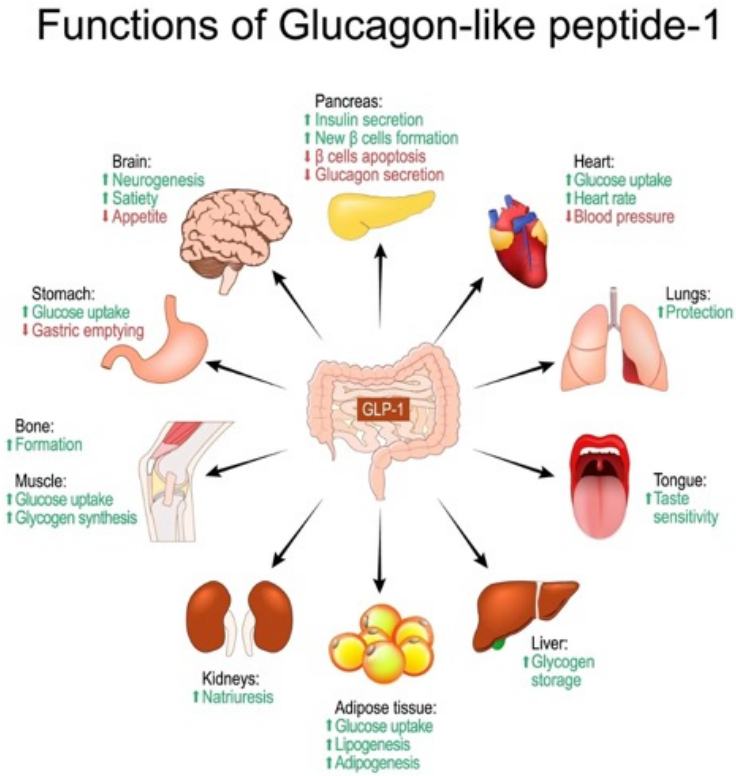
Evaluates blackouts, injuries, and negative social or legal consequences to determine the severity of alcohol misuse.

CAROLINA RECOVERY CENTER FOR

GLP-1 receptor agonists (e.g., semaglutide) show significant promise in treating alcohol use disorder (AUD) by reducing cravings and consumption, likely by modulating dopamine in the brain's reward system.

Die meisten Fragen beziehen sich auf das **letzte Jahr** und werden auf einer Skala von 0 bis 4 Punkten bewertet.

1. Wie oft trinken Sie Alkohol?
2. Wie viele Gläser trinken Sie an einem typischen Tag?
3. Wie oft trinken Sie sechs oder mehr Gläser bei einer Gelegenheit?
4. Wie oft konnten Sie im letzten Jahr nicht mit dem Trinken aufhören?
5. Wie oft haben Sie wegen des Trinkens Pflichten vernachlässigt?
6. Wie oft brauchten Sie morgens Alkohol, um „in die Gänge“ zu kommen?
7. Wie oft hatten Sie nach dem Trinken Schuldgefühle oder Gewissensbisse?
8. Wie oft hatten Sie einen Filmriss (Erinnerungslücken)?
9. Haben Sie sich oder andere durch Ihr Trinken verletzt?
10. Haben sich Freunde oder Ärzte wegen Ihres Konsums besorgt gezeigt?



Once-weekly semaglutide versus placebo in patients with alcohol use disorder and comorbid obesity: a randomised, double-blind, placebo-controlled trial

Summary

Background Alcohol use disorder accounts for 5% of deaths worldwide annually, and there is an urgent need for new therapeutic interventions. Preclinical and initial human studies indicate that the GLP-1 receptor agonist semaglutide might reduce alcohol drinking. This study evaluated the efficacy of semaglutide once-weekly in treatment-seeking patients with alcohol use disorder and comorbid obesity.

Methods In a 26-week, single-centre, randomised, double-blinded, placebo-controlled trial, treatment-seeking participants with moderate to severe alcohol use disorder and comorbid obesity were assigned (1:1) to receive once-weekly semaglutide (2·4 mg subcutaneously) or placebo (saline subcutaneously), in addition to standard cognitive behavioural therapy. The primary endpoint was a reduction in the number of heavy drinking days assessed after 26 weeks of intervention, analysed with an ANCOVA model. Analysis adhered to the intention-to-treat principle, and missing outcome data were addressed using multiple imputations. Safety was assessed in all treated patients. The trial is registered at ClinicalTrials.gov NCT05895643, and is complete.

Findings From June 10, 2023, to Feb 4, 2025, 108 participants (53 women and 55 men) were enrolled, with 54 participants in each of the semaglutide and placebo treatment groups, and all were included in the data analysis. Overall, 88 participants (81%) completed the full intervention. Semaglutide was associated with a reduction in heavy drinking days (–41·1 percentage points from baseline, 95% CI –48·7 to –33·5) compared with placebo (–26·4, –34·1 to –18·6; estimated treatment difference –13·7 percentage points, –22·0 to –5·4; p=0·0015), and had substantial effects on multiple secondary alcohol-related and somatic outcomes. Adverse events were transient, generally mild to moderate gastrointestinal effects, and occurred more frequently in the semaglutide group.

Interpretation Semaglutide showed robust therapeutic effects in treatment-seeking participants with obesity and alcohol use disorder and this trial supports previous preclinical and clinical findings suggesting GLP-1 receptor agonists as a potential novel treatment target for alcohol use disorder.

Introduction

Alcohol use disorder is a chronic, relapsing brain disorder characterised by loss of control of alcohol consumption and compulsive use.[1] Several behavioural and psychological treatments are available,[1] and cognitive behavioural therapy (CBT) is among the treatments with the highest empirical support.[2] However, despite decades of research, the US Food and Drug Administration (FDA) has approved only three medications—disulfiram, acamprosate, and naltrexone[1]—highlighting the urgent need for more effective treatments. GLP-1 receptor agonists, approved for the treatment of diabetes and obesity,[3] have gained wide attention for their effects on brain pathways involved with appetite regulation and reward, suggesting potential use for mitigating alcohol consumption.[4] Importantly, GLP-1 receptor agonists are generally well tolerated and have a favourable safety profile, with a low risk of hypoglycaemia due to their glucose-dependent mechanism.[5] The endogenous GLP-1-peptide is secreted from L-cells in the small intestine and also synthesised in brain areas implicated in reward and addiction.[6]

Several GLP-1 receptor agonists have shown significant reductions in alcohol consumption, reward-processing, and relapse-like behaviours, demonstrating robust and promising effects in preclinical models of alcohol addiction.[7,8] In humans, register-based studies have reported a lower risk of alcohol-related events or alcohol use disorder diagnosis among individuals treated with a GLP-1 receptor agonist.

Phosphatidylethanol (PEth) ist ein hochspezifischer Blutmarker (Phospholipid), der nur bei Alkoholkonsum in den Zellmembranen gebildet wird. Er eignet sich hervorragend zum Nachweis von chronischem sowie moderatem Alkoholkonsum über einen Zeitraum von bis zu 3-4 Wochen. Mit einer hohen Sensitivität (ca. 4 Tage Halbwertszeit) ist er anderen Markern wie CDT überlegen.

	Placebo (n=54)	Semaglutide (n=54)
Sex assigned at birth*		
Male	28 (52%)	27 (50·0)
Female	26 (48%)	27 (50·0)
Age		
Mean age, years	51·7 (9·8)	52·8 (9·8)
40 years and younger*	6 (11%)	5 (9%)
Older than 40 years*	48 (89%)	49 (91%)
Cohabiting or married	29 (54%)	22 (41%)
Race or ethnicity		
Asian	0	4 (7%)
Black or African American	1 (2%)	1 (2%)
White	53 (98%)	49 (91%)
Employed	40 (74%)	39 (72%)
Education		
Lower secondary school	3 (6%)	3 (6%)
Upper secondary school	2 (4%)	2 (4%)
Vocational education or short-cycle higher education	21 (39%)	14 (26%)
Medium-cycle higher education or higher education	28 (52%)	35 (65%)
Previous treatment with a glucagon-like peptide-1	8 (15%)	5 (9%)
Previous pharmacological treatment for alcohol use disorder		
Disulfiram	9 (17%)	10 (19%)
Acamprosate	5 (9%)	5 (9%)
Naltrexone	1 (2%)	1 (2%)
Nalmefene	0	0
Alcohol use disorders identification test score†	22·3 (4·5)	23·2 (4·3)
Alcohol use disorders identification test consumption score‡	9·8 (1·3)	9·7 (1·2)
ICD-10: alcohol dependence		
3 symptoms	5 (9%)	2 (4%)
4 symptoms	32 (59%)	26 (48%)
5 symptoms	13 (24%)	21 (39%)
6 symptoms	4 (7%)	5 (9%)
Diagnostic and Statistical Manual of Mental Disorders, 5th edition: alcohol use disorder		
Mild (2–3 symptoms)	0	0
Moderate (4–5 symptoms)	11 (21%)	5 (9%)
Severe (>5 symptoms)	43 (80%)	49 (91%)

(Table 1 continues in next column)

(Continued from previous column)

	Placebo (n=54)	Semaglutide (n=54)
Heavy drinking days§	17·2 (7·4)	17·1 (8·2)
Heavy drinking days randomisation strata		
6–11 days*	15 (28%)	17 (32%)
12–17 days*	14 (26%)	14 (26%)
18–23 days*	10 (19%)	7 (13%)
24–30 days*	15 (28%)	16 (30%)
Days without alcohol consumption	8·5 (7·3)	9·1 (7·5)
Total alcohol consumption, g of alcohol per 30 days§	2246·6 (1091·9)	2155·3 (1171·5)
Phosphatidyl ethanol, µmol/L	0·7 (0·6)	0·5 (0·5)
WHO risk drinking level¶		
Low	1 (1·9%)	1 (1·9%)
Medium	12 (22·6%)	16 (29·6%)
High	23 (42·6%)	19 (35·2%)
Very high	18 (33·3%)	18 (33·3%)
Fagerströms test for Nicotine Dependence score‖	4·2 (2·8)	3·5 (2·5)
Cigarettes per day	14·9 (10·1)	13·2 (9·5)
Bodyweight, kg	105·2 (15·5)	100·3 (12·0)
BMI, kg/m²	35·2 (4·4)	33·7 (3·3)
Glycated haemoglobin**	5·4 (0·4)	5·5 (0·3)

Data are n (%) or mean (SD). *Randomisation strata. †Total score ranges from 0 to 40, with higher scores reflecting higher alcohol dependence. ‡Subscale with total score ranging from 0 to 12 focusing solely on alcohol consumption patterns. §The 30 consecutive days with highest alcohol use (most heavy drinking days and greatest total intake) within the 40 days before evaluation, measured by the Timeline Followback method. ¶Low risk: 1–40 g/day for men, 1–20 g/day for women; moderate risk: 41–60 g/day for men, 21–40 g/day for women; high risk: 61–100 g/day for men, 41–60 g/day for women; very high risk: >100 g/day for men, >60 g/day for women. ‖Only individuals who reported current smoking at baseline (n=31; placebo n=15 and semaglutide n=16) were included; the number of daily cigarettes were self-reported at baseline. **To convert glycated haemoglobin from percentage to mmol/mol, subtract 2·15 and multiply by 10·929.

Table 1: **Baseline characteristics**

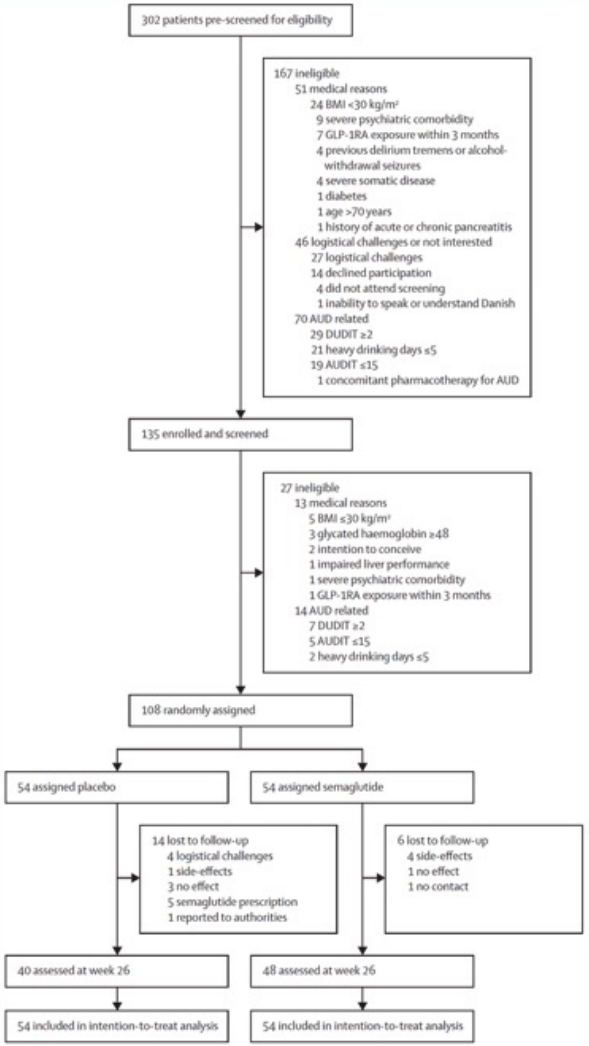


Figure 1: **Trial profile**
Pre-screenings conducted via telephone. AUD=alcohol use disorder. AUDIT=alcohol use disorders identification test. DUDIT=drug use disorders identification test. GLP-1RA=glucagon-like peptide-1 receptor agonist.

	Placebo (n=54)	Semaglutide (n=54)	Estimated treatment difference, placebo *vs* semaglutide (95% CI)	p value
Self-reported drinking and alcohol scales				
Heavy drinking days, percentage points (primary endpoint)*	−26·4 (−34·1 to −18·6)	−41·1 (−48·7 to −33·5)	−13·7 (−22·0 to −5·4)	0·0015
Total alcohol consumption, g/30 days*	−1025·9 (−1260·0 to −791·1)	−1550·2 (−1868·2 to −1232·1)	−467·5 (−739·5 to −195·4)	<0·0009
Days without alcohol consumption, percentage points*	27·6 (19·8–35·5)	38·9 (30·6–47·3)	10·1 (−0·0 to 20·2)	0·051
Change in drinks per drinking day*	−2·1 (−3·1 to −1·1)	−3·5 (−4·5 to −2·6)	−1·5 (−2·6 to −0·5)	0·0051
Reduction in WHO risk drinking levels†	−1·24 (−1·54 to −0·94)	−1·75 (−2·04 to −1·45)	−0·52 (−0·89 to −0·16)	0·0055
Alcohol craving (Penn alcohol craving scale score)‡	−6·1 (−7·6 to −4·6)	−9·2 (−10·8 to −7·6)	−3·1 (−5·1 to −1·2)	0·0020
Alcohol use disorders identification test score§	−6·3 (−7·8 to −4·7)	−9·9 (−11·6 to −8·2)	−3·3 (−5·5 to −1·1)	0·0044
Alcohol use disorders identification test consumption score¶	−2·7 (−3·4 to −1·9)	−4·2 (−5·0 to −3·5)	−1·5 (−2·6 to −0·4)	0·0071
Alcohol biomarkers				
Phosphatidyl ethanol, µmol/L	0·00 (−0·10 to 0·11)	−0·24 (−0·34 to −0·13)	−0·28 (−0·41 to −0·15)	<0·0001
Liver and pancreas parameters				
Alanine aminotransferase, U/L	−6·5 (−11·0 to −2·0)	−12·5 (−21·2 to −3·9)	−3·3 (−11·0 to 4·4)	0·40
γ-glutamyl transferase, U/L	−10·2 (−17·5 to −2·9)	−36·0 (−52·2 to −19·7)	−24·2 (−33·4 to −15·1)	<0·0001
Mean corpuscular volume, fL	0·4 (−0·6 to 1·1)	−1·3 (−1·9 to −0·6)	−1·7 (−2·6 to −0·7)	0·0007
Amylase, U/L	−0·9 (−2·7 to 1·0)	4·7 (2·8 to 6·6)	5·1 (2·5 to 7·7)	0·0002
FIB-4‖	0·0 (−0·1 to 0·1)	−1·1 (−3·2 to 1·0)	0·0 (−0·1 to 0·2)	0·67
Clinical measures				
Bodyweight, kg	−2·2 (−3·7 to −0·6)	−11·2 (−12·9 to −9·6)	−9·0 (−11·2 to −6·7)	<0·0001
Bodyweight, %	−2·0 (−3·4 to −0·5)	−11·36 (−13·0 to −9·7)	−9·0 (−11·3 to −6·8)	<0·0001
Systolic blood pressure, mm Hg	−10·6 (−16·2 to −5·0)	−14·5 (−19·8 to −9·2)	−6·8 (−13·5 to −0·1)	0·047
Diastolic blood pressure, mm Hg	−4·5 (−7·7 to −1·3)	−5·6 (−8·8 to −2·4)	−2·1 (−5·7 to 1·6)	0·26
Pulse, beat per min	2·7 (−0·8 to 6·2)	1·8 (−1·3 to 5·0)	−0·7 (−4·8 to 3·4)	0·74
Waist circumference, cm	−3·8 (−6·0 to −1·5)	−12·1 (−14·2 to −10·0)	−8·3 (−11·2 to −5·4)	<0·0001
BMI, kg/m²	−0·7 (−1·2 to −0·2)	−3·8 (−4·4 to −3·2)	−3·1 (−3·8 to −2·3)	<0·0001
Glucose metabolism				
Glycated haemoglobin**, %	0·0 (−0·0 to 0·0)	−0·3 (−0·4 to −0·2)	−0·3 (−0·4 to −0·2)	<0·0001
Other drugs				
Drug use disorders identification test score††	0·2 (−0·1 to 0·5)	0·1 (−0·1 to −0·2)	−0·1 (−0·4 to 0·3)	0·77
FTND score‡‡	−0·7 (−1·6 to 0·3)	−0·1 (−0·6 to 0·4)	0·3 (−0·9 to 1·5)	0·60
Number of cigarettes per day‡‡	−1·8 (−3·5 to −0·1)	−2·5 (−5·6 to 0·7)	−0·5 (−3·7 to 2·7)	0·75

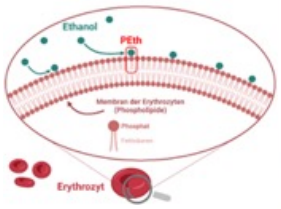
Data are mean (95% CI) unless otherwise stated. FIB-4=fibrosis-4 index. FTND=Fagerströms test for nicotine dependence. *The 30 consecutive days with highest alcohol use (most heavy drinking days and greatest total intake) within the 40 days before evaluation, measured by the Timeline Followback method. †Low risk: 1–40 g/day for men, 1–20 g/day for women; moderate risk: 41–60 g/day for men, 21–40 g/day for women; high risk: 61–100 g/day for men, 41–60 g/day for women; very high risk: >100 g/day for men, >60 g/day for women. ‡Total scores ranges from 0 to 30, with higher scores reflecting higher alcohol craving. §Total scores range from 0 to 40, with higher scores reflecting greater likelihood of alcohol-related problems. ¶Subscale with total score ranging from 0 to 12 focusing solely on alcohol consumption patterns. ‖FIB-4=(age × aspartate aminotransferase) / (platelets × √alanine aminotransferase); non-invasive liver fibrosis estimate, higher scores indicate greater risk. ** To convert glycated haemoglobin from percentage to mmol/mol, subtract 2·15 and multiply by 10·929. ††Total score ranges from 0 to 44, with higher scores indicating greater likelihood of drug-related problems. ‡‡Only individuals who reported current smoking at baseline (n=31; placebo n=15 and semaglutide n=16) were included; a lower FTND score indicates lower nicotine dependence; the number of daily cigarettes were self-reported at baseline and at week 26.

Table 2: **Change in endpoints from baseline to week 26**

30% reduction

30% reduction

Phosphatidylethanol



< 20 µg/l - kein / geringer Alkoholkonsum
20 - 200 µg/l - moderater Alkoholkonsum
> 200 µg/l - übermäßiger Alkoholkonsum

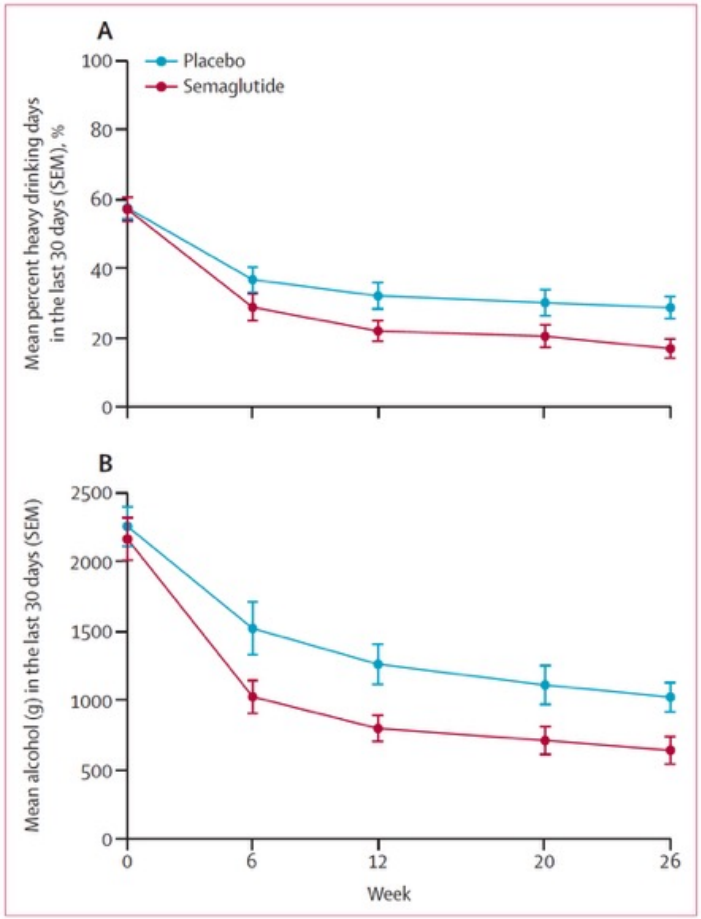


Figure 2: **Effects of once-weekly semaglutide compared with placebo on reduction in heavy drinking days and total alcohol consumption**
Changes from baseline (week 0) to follow-up (week 26) are shown for mean percent heavy drinking days in the last 30 days (A), and mean alcohol (g) consumed during the past 30 days (B), in participants randomly assigned to semaglutide 2·4 mg (n=54) or placebo (n=54). Participant level changes by treatment group are in appendix 2 (p 15). SEM=standard error of the mean.

	Placebo (n=54)	Semaglutide (n=54)
Serious adverse events		
Admitted with abdominal pain*	0	1 (2%)
Hospitalised due to withdrawal symptoms	1 (2%)	0
Posterior vitreous detachment	1 (2%)	0
Hospitalised for acute coronary syndrome observation	1 (2%)	0
Adverse events and adverse reactions		
Nausea	4 (7%)	31 (57%)
Loss of appetite	8 (15%)	19 (35%)
Food aversion	1 (2%)	13 (24%)
Vomiting	1 (2%)	8 (15%)
Abdominal pain	4 (7%)	11 (20%)
Diarrhoea	11 (20%)	15 (28%)
Constipation	9 (17%)	19 (35%)
Reflux	1 (2%)	15 (28%)
Abdominal bloating	3 (6%)	2 (4%)
Increased belching	0	2 (4%)
Fatigue	10 (19%)	17 (32%)
Generalised itching	1 (2%)	3 (6%)
Headache	10 (19%)	11 (21%)
Dizziness	4 (7%)	7 (13%)
Injection site reaction	2 (4%)	1 (2%)
Outpatient detoxification	1 (2%)	0
Elevated plasma amylase†	0	4 (7%)
Elevated liver parameters‡ (AST, ALT, and GGT)	21 (39%)	15 (28%)
Sleep disturbances	2 (4%)	4 (7%)
Depression diagnosed in primary care	1 (2%)	0
Worsening of anxiety level	0	1 (2%)
Suicidal thoughts	1 (2%)	0
Fall (no hospitalisation)	2 (4%)	3 (6%)
Miscellaneous	21 (39%)	30 (56%)

Data are n (%). ALT=alanine aminotransferase. AST=aspartate aminotransferase. GGT=γ-glutamyl transferase. *The only serious adverse event recorded in the semaglutide group was one hospital admission due to unspecific abdominal pain (semaglutide 0·25 mg), but this did not lead to trial discontinuation. †Reference range <105 U/L; highest observed level 123 U/L. ‡Total participants n=24; AST (n=8), highest observed level 125 U/L; ALT (n=12), highest observed level 121 U/L; GGT (n=16), highest observed level 209 U/L.

Table 3: **Serious adverse events, adverse events, and adverse reactions**

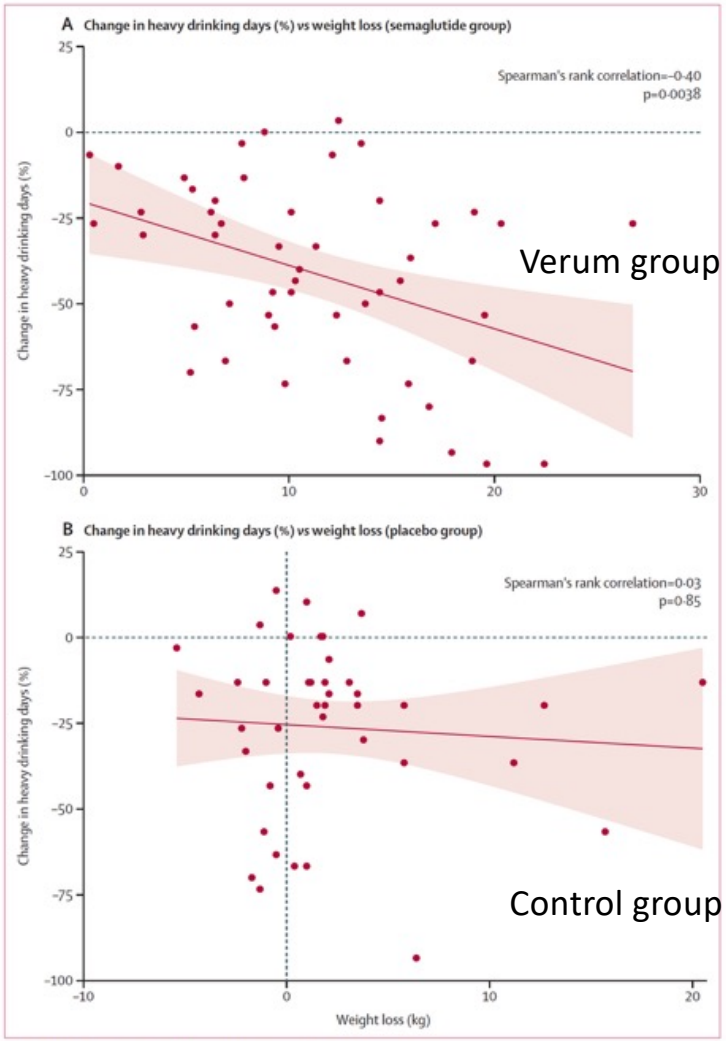


Figure 3: **Change in heavy drinking days correlated with weight loss**
(A) Changes from baseline (week 0) to follow-up (week 26) are shown for heavy drinking days versus weight loss in the semaglutide group. (B) Changes from baseline (week 0) to follow-up (week 26) are shown for heavy drinking days versus weight loss in the placebo group.

In summary, the effects of semaglutide suggest that the treatment effect was sufficiently large to be detected despite the modest sample size, and self-reported alcohol consumption was validated with the gold-standard phosphatidyl ethanol biomarker, further enhancing the validity of our findings.

To our knowledge, this RCT is the first to show that once-weekly semaglutide reduces heavy drinking days and WHO drinking-risk levels in treatment-seeking patients with alcohol use disorder and comorbid obesity. This finding adds to the growing evidence for use of GLP-1 receptor agonists in alcohol use disorder, supporting an expanded indication for semaglutide, potentially affecting millions of individuals, given the global burden of alcohol use disorder and comorbid obesity. Importantly, key limitations and safety uncertainties do persist, and additional research is needed before off-label use can be endorsed.

Research in context

Evidence before this study

No formal literature review was done before commencing this study; however, we previously published a Review on GLP-1 in addictive disorders in 2022. Alcohol use disorder is a chronic brain disorder marked by loss of control over drinking and compulsive use. Despite decades of research, only three medications are approved for alcohol use disorder, underscoring the need for novel treatments. GLP-1 receptor agonists, established therapies for diabetes and obesity, have gained wide attention for their effects on reward pathways and appetite regulation, suggesting potential use in mitigating alcohol consumption. GLP-1 receptor agonists have shown promising results in preclinical models of alcohol addiction. In humans, register-based studies have reported a lower risk of alcohol-related events or alcohol use disorder diagnosis among individuals with diabetes or obesity treated with a GLP-1 receptor agonist. At the time of study initiation, only one randomised controlled trial (RCT) of GLP-1 receptor agonists in treatment-seeking patients with alcohol use disorder showed no overall effect on heavy drinking days. However, reductions were observed among participants with a BMI greater than 30 kg/m^2, along with decreased activation to alcohol cues in reward-related brain regions, suggesting reduced incentive salience. More recently, an RCT investigating the efficacy of the GLP-1 receptor agonist semaglutide in a low dose in 48 non-treatment-seeking individuals with alcohol use disorder showed a significant reduction in alcohol intake in a laboratory self-administration task. To our knowledge to date, no other RCTs in treatment-seeking individuals have been published.

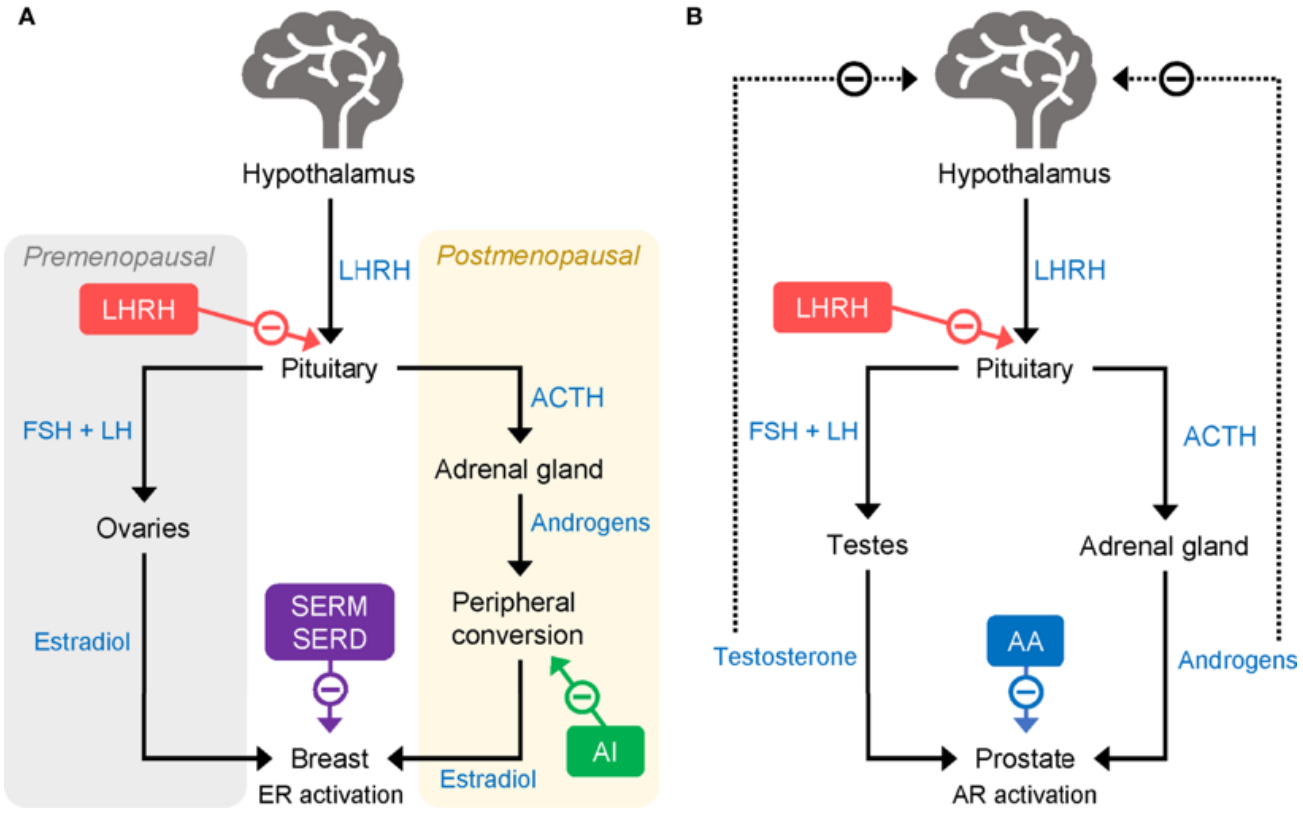
Added value of this study

This randomised, double-blind, placebo-controlled clinical trial shows, for the first time, to our knowledge, that the GLP-1 receptor agonist semaglutide at 2·4 mg once-weekly reduces alcohol consumption in treatment-seeking patients with alcohol use disorder and comorbid obesity (BMI ≥30 kg/m^2).

Implications of all the available evidence

These data, when added to the growing evidence, demonstrate the potential of GLP-1 receptor agonists as a novel treatment for alcohol use disorder. However, corroboration with larger RCTs in patients without obesity is needed to address its generalisability.

Die Ausschaltung der Eierstockfunktion (Ovarialsuppression) dient dazu, die körpereigene Produktion von Östrogen zu stoppen, da dieses Hormon das Wachstum vieler Brustkrebszellen fördert.



Effects of ovarian ablation or suppression on breast cancer recurrence and survival: patient-level meta-analysis of 15 000 women in 23 randomised trials

Summary

Background For premenopausal women with oestrogen receptor (ER)-positive early breast cancer, the additional protective effect of ovarian function suppression (OFS, by ablation or drugs) may depend on menopausal status after any chemotherapy, and tamoxifen usage. We assess the effects of OFS on breast cancer outcomes among premenopausal women and how they vary by patient or tumour characteristics and receipt of other treatments.

Methods We conducted a meta-analysis of individual participant data from the randomised trials comparing OFS versus no OFS, in women with ER-positive or ER-unknown early breast cancer who were premenopausal at randomisation and younger than 55 years. Trials were categorised by whether premenopausal status was or was not confirmed after chemotherapy (if given), and by allocation to tamoxifen. Primary outcomes were invasive breast cancer recurrence, breast cancer mortality, other mortality, and all-cause mortality. ER-weighted log-rank methods estimated event rate ratios (RRs) for ER-positive disease.

Findings Datasets were provided for 23 of 25 identified eligible trials, comprising 18 851 (98·9%) of 19 053 randomly assigned women. Among 15 075 premenopausal women with ER-positive or ER-unknown tumours, allocation to OFS significantly reduced recurrence rates (RR 0·82, 95% CI 0·77–0·87; p<0·00001), with larger reductions in women who were confirmed premenopausal after chemotherapy (or who did not receive chemotherapy) than in those with unconfirmed premenopausal status after chemotherapy; heterogeneity p=0·0004. Among confirmed premenopausal women, recurrence reductions were larger in older trials without tamoxifen (RR 0·61, 0·52–0·71; p<0·0001) than in more recent trials of OFS plus tamoxifen versus tamoxifen (RR 0·79, 0·70–0·91; p=0·0008). In these more recent trials, the additional recurrence reduction with OFS appeared larger in women younger than 45 years than in women aged 45–54 years (RR 0·73, 0·63–0·86 *vs* RR 0·95, 0·75–1·21; p=0·072); in those younger than 45 years, breast cancer mortality was similarly improved (RR 0·74, 0·58–0·94; p=0·012). There was no increase in deaths without recurrence. Findings did not differ significantly by OFS method or other recorded patient or tumour characteristics.

Interpretation For premenopausal women with ER-positive early breast cancer, even if chemotherapy or tamoxifen are given, OFS significantly reduces the 15-year risk of recurrence and death.

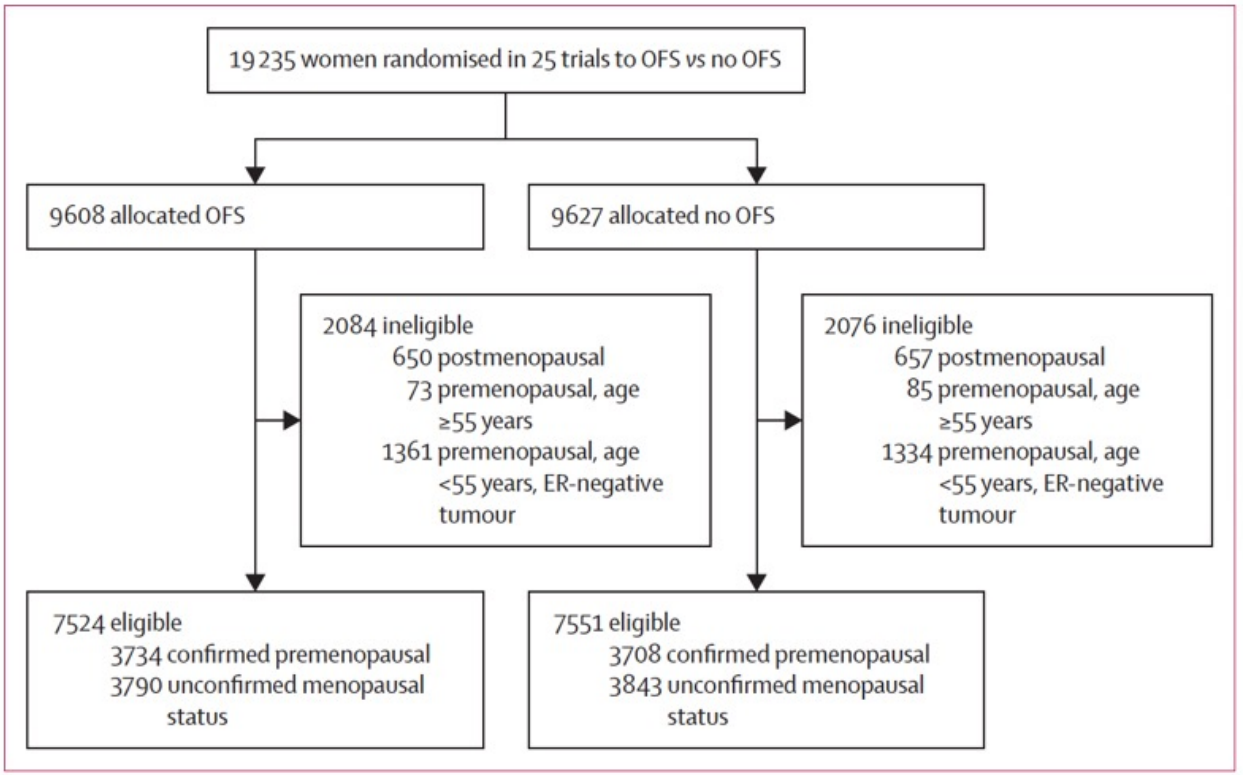


Figure 1: **Flow chart for the trials of OFS versus no OFS in early breast cancer**
OFS=ovarian function suppression. To make all comparisons evenly (1:1) balanced, 78 controls in the only three-way comparison are counted twice.

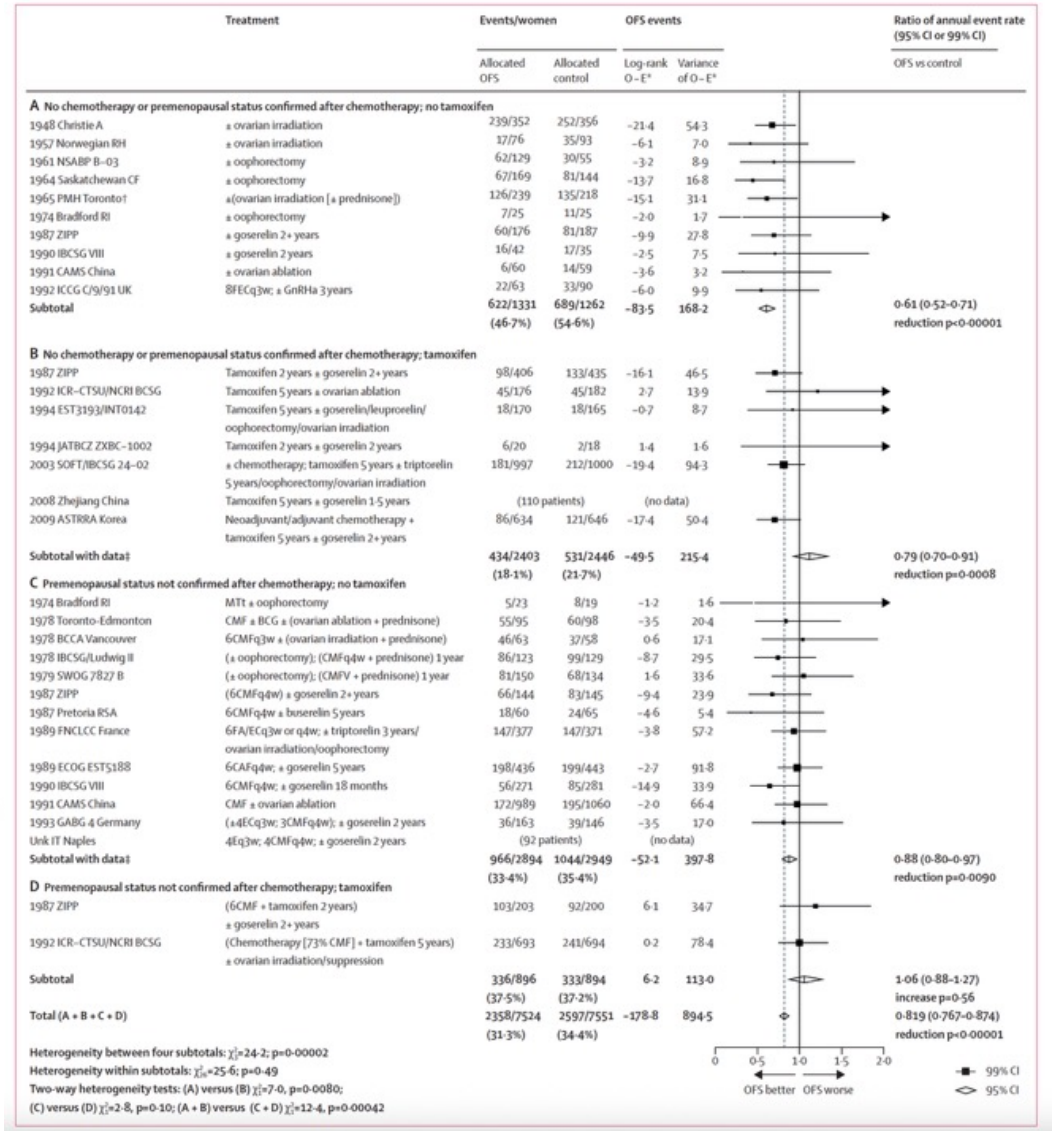
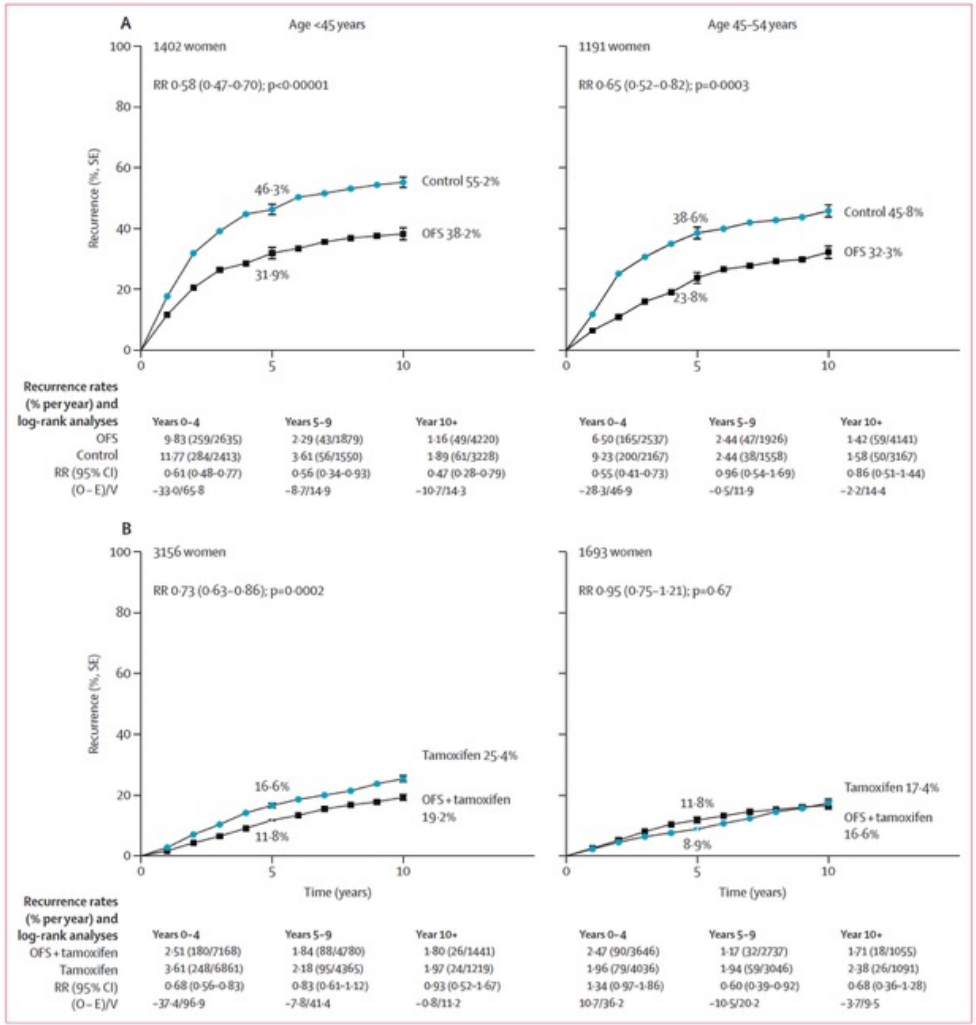


Figure 2: **Trial-specific recurrence rate ratios by allocation to OFS versus no OFS in ER-positive or ER-unknown early breast cancer, estimated from ER-weighted analyses of four types of randomised comparison**

Recurrence rate ratios (local, distant, or new contralateral invasive disease) are for ER-positive disease*. A=doxorubicin. BCG=Bacillus Calmette–Guèrin. C=cyclophosphamide. E=epirubicin. F=fluorouracil. GnRHa=gonadotrophin-releasing hormone agonist. M=methotrexate. O – E=observed minus expected. OFS=ovarian function suppression. Tt=Triethylenephosphoramide. q4w=4-weekly. q3w=3-weekly. V=vincristine. Unk=unknown. *ER weighting: the contribution to each O – E value from ER-unknown disease is 0·75 of what the unweighted contribution would have been. †To make all comparisons evenly (1:1) balanced, the 78 controls in the three-way phase of this one trial are counted twice. ‡The two trials with no data do not contribute to the subtotals or total.



Recurrence rates (% per year) and log-rank analyses	Years 0–4	Years 5–9	Year 10+	Years 0–4	Years 5–9	Year 10+
OFS	9·83 (259/2635)	2·29 (43/1879)	1·16 (49/4220)	6·50 (165/2537)	2·44 (47/1926)	1·42 (59/4141)
Control	11·77 (284/2413)	3·61 (56/1550)	1·89 (61/3228)	9·23 (200/2167)	2·44 (38/1558)	1·58 (50/3167)
RR (95% CI)	0·61 (0·48–0·77)	0·56 (0·34–0·93)	0·47 (0·28–0·79)	0·55 (0·41–0·73)	0·96 (0·54–1·69)	0·86 (0·51–1·44)
(O – E)/V	−33·0/65·8	−8·7/14·9	−10·7/14·3	−28·3/46·9	−0·5/11·9	−2·2/14·4

Recurrence rates (% per year) and log-rank analyses	Years 0–4	Years 5–9	Year 10+	Years 0–4	Years 5–9	Year 10+
OFS + tamoxifen	2·51 (180/7168)	1·84 (88/4780)	1·80 (26/1441)	2·47 (90/3646)	1·17 (32/2737)	1·71 (18/1055)
Tamoxifen	3·61 (248/6861)	2·18 (95/4365)	1·97 (24/1219)	1·96 (79/4036)	1·94 (59/3046)	2·38 (26/1091)
RR (95% CI)	0·68 (0·56–0·83)	0·83 (0·61–1·12)	0·93 (0·52–1·67)	1·34 (0·97–1·86)	0·60 (0·39–0·92)	0·68 (0·36–1·28)
(O – E)/V	−37·4/96·9	−7·8/41·4	−0·8/11·2	10·7/36·2	−10·5/20·2	−3·7/9·5

Figure 4: **Recurrence by allocation to OFS versus not OFS in confirmed premenopausal women with ER-positive or ER-unknown early breast cancer, estimated by age and by tamoxifen use**

(A) No chemotherapy (or still premenopausal after chemotherapy) and tamoxifen not given. (B) No chemotherapy (or still premenopausal after chemotherapy), but tamoxifen given (mean 4 years). RRs are from ER-weighted estimates of effect of OFS in women with ER-positive disease. ER=oestrogen receptor. O – E=observed minus expected. OFS=ovarian function suppression. RR=rate ratio. V=variance.

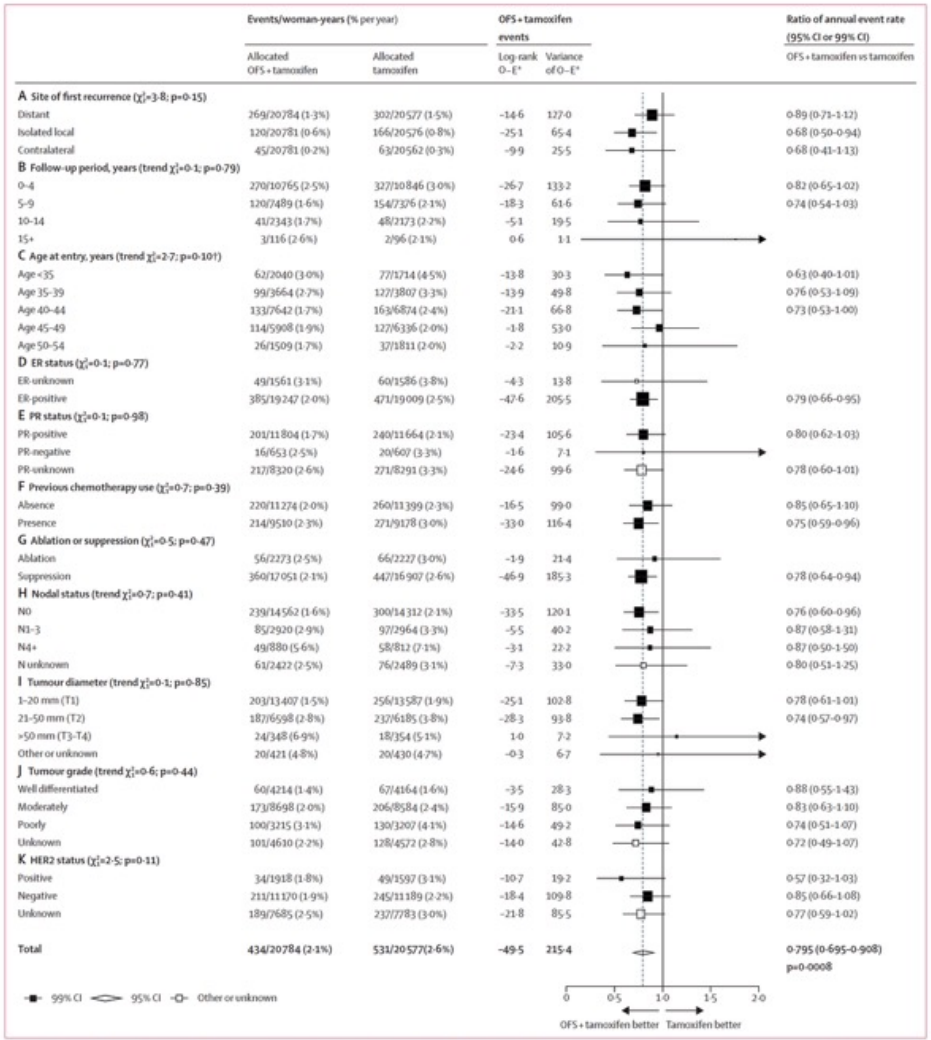
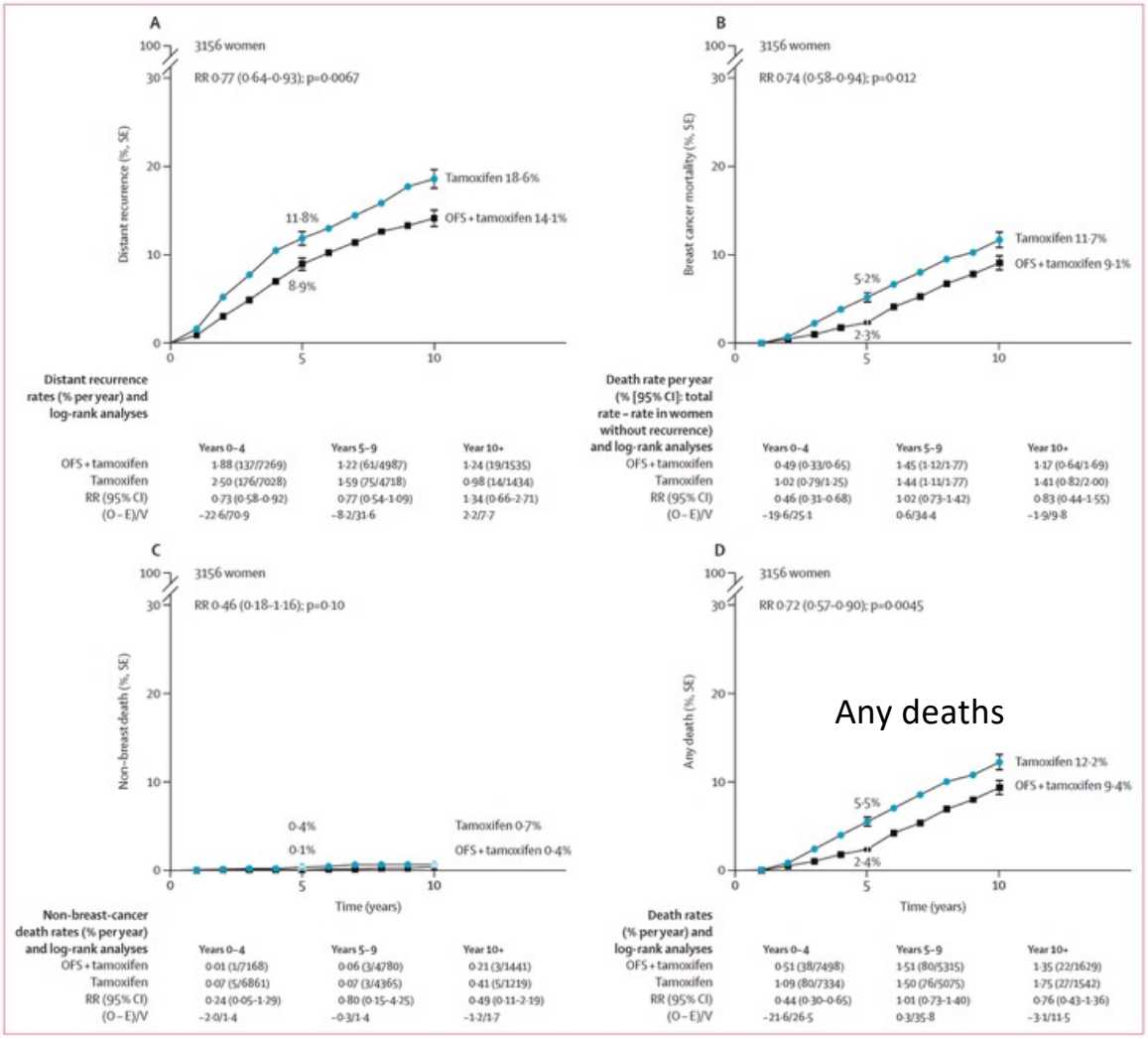


Figure 5: **Subgroup analyses of recurrence by allocation to OFS plus tamoxifen versus tamoxifen in confirmed premenopausal women with ER-positive or ER-unknown early breast cancer**
RRs are from ER-weighted estimates of effect of OFS in women with ER-positive disease. EST3193 did not provide individual patient data for method used for ovarian suppression so has been excluded from (G): 55% had oophorectomy or radiation, and 36% had GnRHa. ER=oestrogen receptor. GnRHa=gonadotrophin-releasing hormone agonist. O−E=observed minus expected. OFS=ovarian function suppression. PR=progesterone receptor. RR=rate ratio. *ER weighting: the contribution to each O−E value from ER-unknown disease is 0·75 of what the unweighted contribution would have been. †Heterogeneity between participants younger than 45 years and those aged 45 years and older, χ^2_1=3·2; p=0·072.



Distant recurrence rates (% per year) and log-rank analyses

	Years 0–4	Years 5–9	Year 10+
OFS + tamoxifen	1·88 (137/7269)	1·22 (61/4987)	1·24 (19/1535)
Tamoxifen	2·50 (176/7028)	1·59 (75/4718)	0·98 (14/1434)
RR (95% CI)	0·73 (0·58–0·92)	0·77 (0·54–1·09)	1·34 (0·66–2·71)
(O – E)/V	−22·6/70·9	−8·2/31·6	2·2/7·7

Death rate per year (% [95% CI]: total rate – rate in women without recurrence) and log-rank analyses

	Years 0–4	Years 5–9	Year 10+
OFS + tamoxifen	0·49 (0·33/0·65)	1·45 (1·12/1·77)	1·17 (0·64/1·69)
Tamoxifen	1·02 (0·79/1·25)	1·44 (1·11/1·77)	1·41 (0·82/2·00)
RR (95% CI)	0·46 (0·31–0·68)	1·02 (0·73–1·42)	0·83 (0·44–1·55)
(O – E)/V	−19·6/25·1	0·6/34·4	−1·9/9·8

Non-breast-cancer death rates (% per year) and log-rank analyses

	Years 0–4	Years 5–9	Year 10+
OFS + tamoxifen	0·01 (1/7168)	0·06 (3/4780)	0·21 (3/1441)
Tamoxifen	0·07 (5/6861)	0·07 (3/4365)	0·41 (5/1219)
RR (95% CI)	0·24 (0·05–1·29)	0·80 (0·15–4·25)	0·49 (0·11–2·19)
(O – E)/V	−2·0/1·4	−0·3/1·4	−1·2/1·7

Death rates (% per year) and log-rank analyses

	Years 0–4	Years 5–9	Year 10+
OFS + tamoxifen	0·51 (38/7498)	1·51 (80/5315)	1·35 (22/1629)
Tamoxifen	1·09 (80/7334)	1·50 (76/5075)	1·75 (27/1542)
RR (95% CI)	0·44 (0·30–0·65)	1·01 (0·73–1·40)	0·76 (0·43–1·36)
(O – E)/V	−21·6/26·5	0·3/35·8	−3·1/11·5

Figure 6: **Main outcomes by allocation to OFS plus tamoxifen versus tamoxifen for confirmed premenopausal women younger than 45 years with ER-positive or ER-unknown early breast cancer**

(A) Distant recurrence at any time. (B) Breast cancer mortality. (C) Non-breast cancer mortality. (D) All-cause mortality. RRs are from ER-weighted estimates of effect of OFS in women with ER-positive disease. ER=oestrogen receptor. O – E=observed minus expected. OFS=ovarian function suppression. RR=rate ratio. V=variance.

Research in context

Evidence before this study

A previous Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis showed that, for women with early breast cancer, ablation of ovarian function significantly reduces breast cancer recurrence and death in the absence of other systemic treatments. Subsequent trials and systematic reviews on the effects of pharmacological ovarian suppression using a gonadotrophin-releasing hormone agonist, and of ablation by irradiation, reported no clear benefit, so questions remain as to whether ovarian function suppression (OFS) by ablation or drugs can materially improve long-term outcomes beyond the effects of tamoxifen or chemotherapy. The EBCTCG's ongoing systematic searches of bibliographic databases, including MEDLINE, Embase, the Cochrane Library, and meeting abstracts, up to Sept 1, 2025, sought all randomised trials of OFS versus no OFS, with other treatments the same in both arms.

Added value of this study

This collaborative meta-analysis collated, checked, and analysed individual patient-level data from 15 075 premenopausal women with oestrogen receptor (ER)-positive or ER-unknown disease in 23 trials. Long-term follow-up of all the available randomised evidence provides unbiased estimates of the risks and benefits of OFS among premenopausal women, including those who remained premenopausal after any chemotherapy. For women with confirmed premenopausal status, the results show that OFS greatly reduces the 15-year risk of breast cancer recurrence and death among women who were not scheduled to receive any other endocrine therapy. Among women who were allocated tamoxifen (for about 4 years), the improvements were still definite, and for women younger than 45 years they were substantial, with recurrence, distant recurrence, breast cancer mortality and all-cause mortality rates during the first decade all reduced by about a quarter. There were few deaths from causes other than breast cancer, and no increase with OFS. Numbers were insufficient for reliable subgroup analyses, but there was no evidence that the proportional risk reductions differed by prognostic factors or method of OFS.

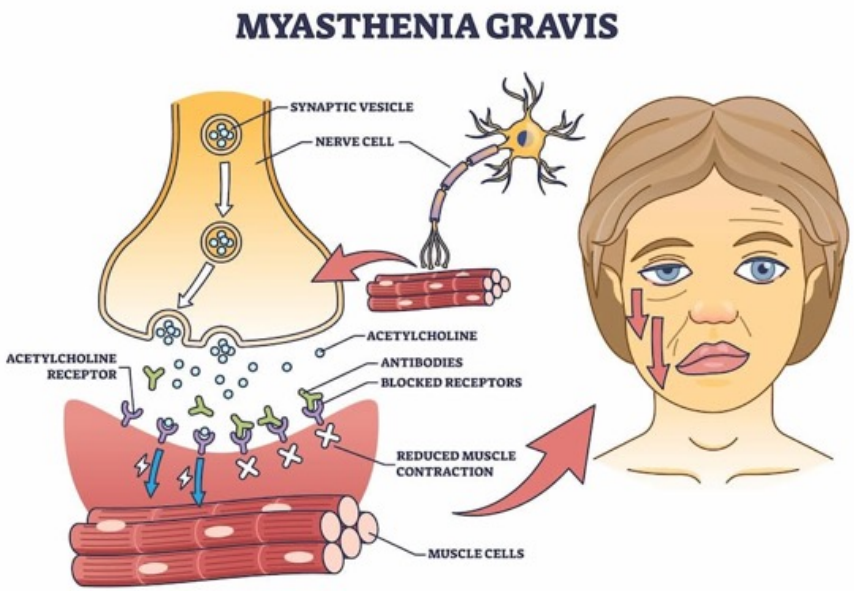
Implications of all the available evidence

For premenopausal women with early-stage, ER-positive breast cancer, including those who are still premenopausal after any chemotherapy, the additional long-term benefits of OFS over and above the established benefits of tamoxifen and of chemotherapy can reliably inform clinical guidelines as well as individual clinician and patient discussions.

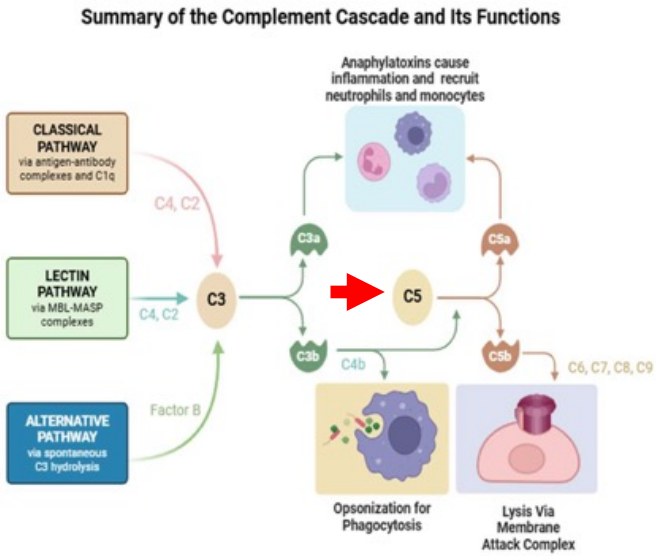
Myasthenia gravis ist eine seltene, chronische Autoimmunerkrankung, die durch belastungsabhängige Muskelschwäche gekennzeichnet ist, verursacht durch gestörte Signalübertragung zwischen Nerv und Muskel. Typische Symptome sind hängende Augenlider, Doppelbilder sowie Schluck- und Sprechstörungen. Die Behandlung erfolgt meist gut mit Medikamenten (Cholinesterasehemmern) und Immuntherapien.

Diagnose und Symptome

- **Symptome:** Muskelschwäche, die oft mit Augenproblemen (Ptosis, Diplopie) beginnt und im Tagesverlauf oder bei Belastung zunimmt. Auch Arme, Beine, Sprech- und Atemmuskulatur können betroffen sein.
- **Diagnose:** Erfolgt durch den Nachweis von Autoantikörpern (meist AChR-AK) im Blut, elektrophysiologische Untersuchungen (repetitive Stimulation), den Eis- oder Tensilon-Test (kurzwirksame Cholinesterasehemmer) und Bildgebung des Thymus (CT/MRT).
- **Verlauf:** Die Erkrankung ist nicht heilbar, aber behandelbar. Unbehandelt kann sie fortschreiten (Generalisierung).



The complement system plays a critical, central role in the pathogenesis of acetylcholine receptor (AChR) antibody-positive myasthenia gravis (MG). IgG1 and IgG3 antibodies trigger the complement cascade at the neuromuscular junction, leading to the formation of the Membrane Attack Complex (MAC), which destroys postsynaptic muscle membranes and causes muscle weakness.



•**Mechanism of Destruction:** Antibody binding triggers the classical complement pathway, resulting in MAC deposits (such as C9) at the neuromuscular junction, causing lysis and structural damage to the muscle membrane.
•**Pathogenic Driver:** While antibodies block acetylcholine receptors, complement-mediated destruction of the synaptic membrane is considered a primary, more severe mechanism of pathology.
•**Therapeutic Targets:** Inhibition of the complement system has proven effective. FDA-approved complement inhibitors, such as eculizumab and ravulizumab, target C5 to prevent MAC formation and treat generalized AChR-positive MG.
•**Disease Severity:** Studies have found complement activation products (C3a, MAC) in patients, with higher levels potentially correlating to increased disease severity

Efficacy and safety of cemdisiran siRNA in myasthenia gravis (NIMBLE): a double-blind, randomised, placebo-controlled, phase 3 trial

Summary

Background Autoantibody-mediated complement activation drives pathology in acetylcholine receptor (AChR) antibody-positive generalised myasthenia gravis. Newer targeted therapies lower overall antibody concentrations or inhibit complement activity. We aimed to evaluate an siRNA (cemdisiran) targeting complement component 5 (C5) as monotherapy and in combination with a C5 antibody (pozelimab) in generalised myasthenia gravis.

Methods NIMBLE is a randomised, double-blind, placebo-controlled, phase 3 trial conducted at 86 centres in 13 countries. We enrolled patients aged 18 years or older with a diagnosis of generalised myasthenia gravis, positive serology for anti-AChR or anti-LRP4 antibodies, and a Myasthenia Gravis-Activities of Daily Living (MG-ADL) score of 6 or greater. Patients were randomly allocated to receive cemdisiran monotherapy (600 mg every 12 weeks; cemdisiran group), pozelimab monotherapy (200 mg every 4 weeks; pozelimab group), combined cemdisiran (200 mg every 4 weeks) and pozelimab (200 mg every 4 weeks; combination group), or placebo, all administered subcutaneously, during a 24-week double-blind treatment period. The primary endpoint was change from baseline in MG-ADL scores at week 24, assessed in the modified intention-to-treat (mITT) primary analysis set (the first 245 randomly allocated patients who received any dose of study treatment and had at least one post-baseline assessment). A prespecified hierarchal statistical testing strategy was used; multiplicity was controlled for comparisons of cemdisiran versus placebo and combination versus placebo (pozelimab was not statistically tested against placebo and was used only to assess the contribution of components to the combination treatment). Safety was mainly assessed by recording of treatment-emergent adverse events in all patients who received any dose of study treatment. This study is registered with ClinicalTrials.gov (NCT05070858); the current status is active, not recruiting.

Findings Between Jan 20, 2022 and July 18, 2025, 390 participants were screened and, as of the data cut-off presented in this report (July 8, 2025), 284 were randomly allocated to the cemdisiran group (79 [28%] patients), pozelimab group (50 [18%]), combination group (80 [28%]), and placebo group (75 [26%]). Of 277 patients who received any study treatment, 263 (95%) completed the double-blind treatment period. In the mITT primary analysis set, at week 24, the least-squares mean change from baseline in MG-ADL total score was –4·5 (SE 0·4) in the cemdisiran group (n=64), –4·0 (0·4) in the combination group (n=67), and –2·2 (0·5) in the placebo group (n=59). Placebo-adjusted least-squares mean differences in MG-ADL score at week 24 were –2·3 (SE 0·7; 95% CI –3·6 to –1·0; p=0·0005) in the cemdisiran group and –1·7 (0·7; –3·0 to –0·4; p=0·0086) in the combination group. The proportion of participants with at least one adverse event during the double-blind treatment period was 54 (69%) of 78 in the cemdisiran group, 65 (81%) of 80 in the combination group, 40 (82%) of 49 in the pozelimab group, and 54 (77%) of 70 in the placebo group. The most common adverse event in the cemdisiran group was upper respiratory tract infection (nine [12%] of 78 patients), which occurred at a similar incidence in the placebo group (eight [11%] of 70). No serious or meningococcal infections occurred in the cemdisiran group. Adverse events leading to treatment discontinuation occurred in two participants (3%) in the placebo group and one participant (2%) in the pozelimab group. No deaths occurred during the double-blind treatment period. Two deaths occurred after the double-blind treatment period, one of which was assessed as treatment-related by the investigator but not treatment-related by the sponsor.

Interpretation Cemdisiran monotherapy and combination therapy were effective in the treatment of generalised myasthenia gravis, and were generally well tolerated. Subcutaneous dosing of cemdisiran, administered every 3 months, could provide a convenient treatment approach for generalised myasthenia gravis.

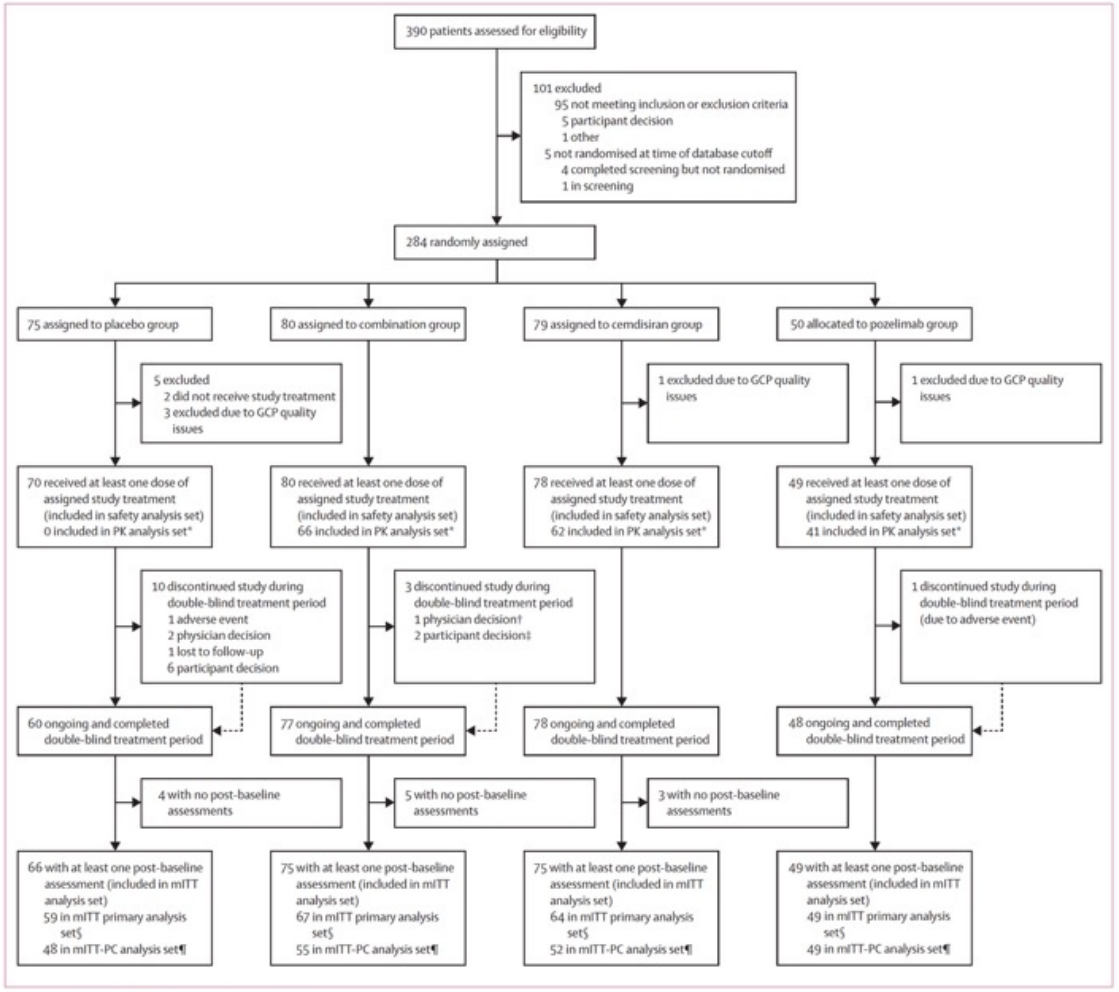


Figure 1: **Flow diagram for the double-blind treatment period**
GCP=Good Clinical Practice. mITT=modified intention-to-treat. mITT-PC=mITT pozelimab-concurrent. PK=pharmacokinetic. *The PK analysis set consisted of all patients who received at least one dose of active study drug and had at least one drug concentration result after receiving the first dose. †One participant was discontinued by physician decision in conjunction with a psychiatric consultation of the participant's suicidal ideation (expressed while hospitalised for myasthenic crisis). ‡Participants withdrew consent from the study (one due to an unspecified personal or family situation, and one due to feeling worse). §mITT primary analysis set consisted of those who received at least one dose of treatment and had at least one post-baseline assessment among the first 245 patients to be randomly allocated. ¶mITT-PC analysis set consisted of all patients who were randomly allocated on or before the date on which the 50th patient was allocated to the pozelimab group, received at least one dose of treatment, and had at least one post-baseline assessment.

	Placebo (n=59)	Combination (n=67)	Cemdisiran (n=64)	Pozelimab (n=49)
Age, years				
Mean	49·5 (15·6)	48·7 (15·1)	52·7 (15·7)	51·0 (15·6)
<35	12 (20%)	13 (19%)	10 (16%)	11 (22%)
35–64	33 (56%)	45 (67%)	34 (53%)	27 (55%)
≥65	14 (24%)	9 (13%)	20 (31%)	11 (22%)
Region				
Japan	3 (5%)	2 (3%)	3 (5%)	2 (4%)
Rest of world	56 (95%)	65 (97%)	61 (95%)	47 (96%)
Ethnicity				
Hispanic or Latino	4 (7%)	6 (9%)	8 (13%)	3 (6%)
Not Hispanic or Latino	53 (90%)	56 (84%)	54 (84%)	44 (90%)
Not reported	0	2 (3%)	0	0
Missing*	2 (3%)	3 (4%)	2 (3%)	2 (4%)
Race				
White	31 (53%)	40 (60%)	35 (55%)	29 (59%)
Black or African American	1 (2%)	5 (7%)	4 (6%)	0
Asian	24 (41%)	16 (24%)	22 (34%)	17 (35%)
American Indian or Alaska Native	0	0	0	1 (2%)
Multiple	1 (2%)	2 (3%)	1 (2%)	0
Not reported	2 (3%)	4 (6%)	2 (3%)	2 (4%)
Sex				
Female	35 (59%)	42 (63%)	36 (56%)	24 (49%)
Male	24 (41%)	25 (37%)	28 (44%)	25 (51%)
Height, cm	166·25 (10·49)	167·00 (11·47)	168·02 (9·70)	167·65 (10·69)
Weight, kg	80·11 (21·61)	80·41 (23·29)	80·86 (23·37)	82·01 (26·05)
Duration of myasthenia gravis since diagnosis, years	8·16 (9·21)	6·10 (7·14)	8·10 (8·69)	8·50 (7·56)
Number of previous myasthenic crises or impending crises				
0	39 (66%)	47 (70%)	39 (61%)	30 (61%)
1	12 (20%)	13 (19%)	14 (22%)	14 (29%)
2	5 (8%)	4 (6%)	7 (11%)	3 (6%)
3	1 (2%)	3 (4%)	2 (3%)	2 (4%)
>3	2 (3%)	0	2 (3%)	0
Time since most recent crisis, months	22·94 (23·14)	23·45 (30·92)	30·27 (51·28%)	49·94 (50·04)
Myasthenia gravis-related hospitalisation in the 2 years before randomisation				
Yes	22 (37%)	22 (33%)	24 (38%)	19 (39%)
No	37 (63%)	45 (67%)	40 (63%)	30 (61%)
Mean	1·4 (1·0)	1·8 (1·1)	1·5 (0·7)	1·3 (0·7)
History of positive serological test for anti-AChR antibodies†				
Yes	55 (93%)	63 (94%)	60 (94%)	48 (98%)
No	4 (7%)	4 (6%)	4 (6%)	1 (2%)
History of positive serological test for anti-LRP4 antibodies†				
Yes	8 (14%)	6 (9%)	5 (8%)	7 (14%)
No	51 (86%)	61 (91%)	59 (92%)	42 (86%)
History of serological test for anti-AChR antibodies and anti-LRP4 antibodies‡				
Both negative	1 (2%)	0	1 (2%)	0
Both positive	5 (8%)	2 (3%)	2 (3%)	6 (12%)
Only positive for anti-AChR antibodies	50 (85%)	61 (91%)	58 (91%)	42 (86%)
Only positive for anti-LRP4 antibodies	3 (5%)	4 (6%)	3 (5%)	1 (2%)

(Table 1 continues on next page)

	Placebo (n=59)	Combination (n=67)	Cemdisiran (n=64)	Pozelimab (n=49)
(Continued from previous page)				
MGFA classification§				
IIa	12 (20%)	18 (27%)	12 (19%)	12 (24%)
IIb	12 (20%)	10 (15%)	14 (22%)	5 (10%)
IIIa	18 (31%)	23 (34%)	23 (36%)	16 (33%)
IIIb	14 (24%)	15 (22%)	13 (20%)	13 (27%)
IVa	3 (5%)	1 (1%)	2 (3%)	3 (6%)
Number of immunosuppressive therapies used				
0	16 (27%)	14 (21%)	14 (22%)	10 (20%)
1	18 (31%)	31 (46%)	25 (39%)	22 (45%)
2	25 (42%)	21 (31%)	25 (39%)	17 (35%)
≥3	0	1 (1%)	0	0
History of complement inhibitor therapies				
Yes	4 (7%)	1 (1%)	4 (6%)	3 (6%)
No	55 (93%)	66 (99%)	60 (94%)	46 (94%)
History of FcRn inhibitor therapy				
Yes	3 (5%)	4 (6%)	3 (5%)	6 (12%)
No	56 (95%)	63 (94%)	61 (95%)	43 (88%)
MG-ADL total score	9·4 (2·6)	9·4 (2·9)	8·9 (2·4)	9·8 (3·4)
QMG total score	15·5 (6·2)	15·6 (5·5)	15·5 (4·9)	16·1 (6·1)
MGC total score	17·5 (7·2)	17·3 (6·6)	17·2 (5·8)	18·4 (8·3)
MG-QOL15r total score	16·4 (6·1)	16·3 (5·6)	15·9 (5·8)	16·0 (6·7)

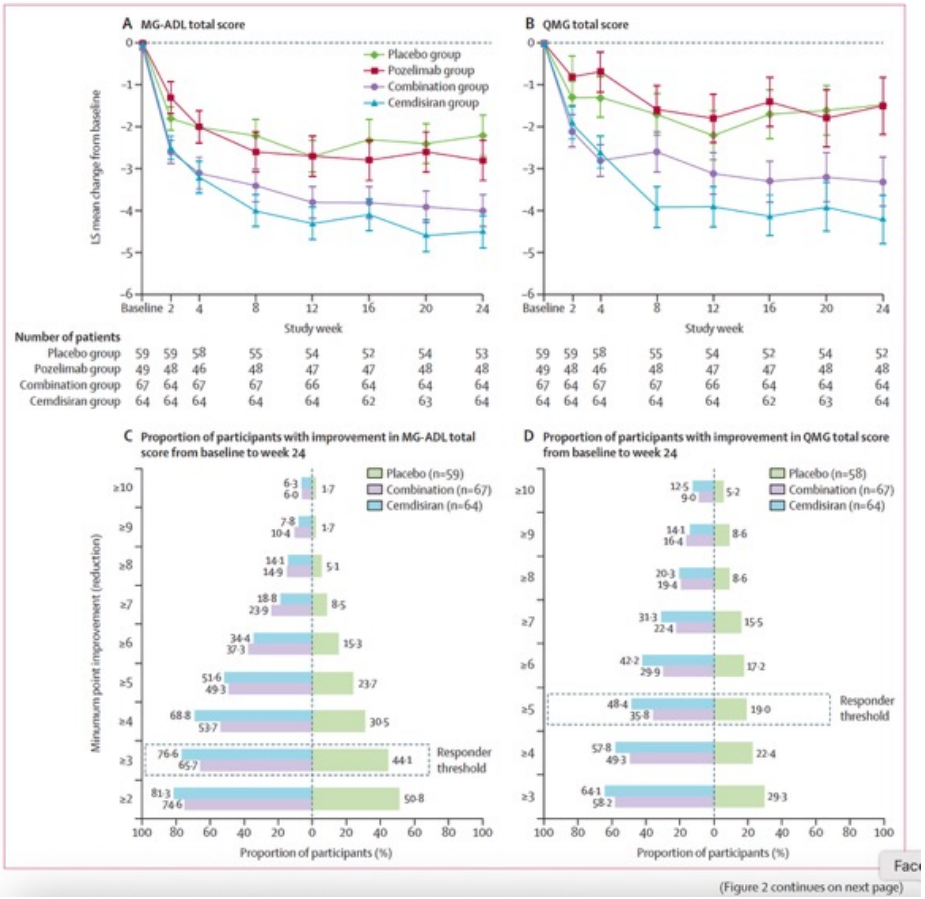
Data are mean (SD) or n (%). AChR=acetylcholine receptor. FcRN=neonatal Fc receptor. LRP4=lipoprotein receptor-related protein 4. MG-ADL=Myasthenia Gravis-Activities of Daily Living. MG-QOL15r=Myasthenia Gravis Quality of Life 15-item (revised). MGC=Myasthenia Gravis Composite. MGFA=Myasthenia Gravis Foundation of America. QMG=Quantitative Myasthenia Gravis. *Some countries did not report ethnicity. †Refers to both documented historical positivity before screening and positive result in central laboratory during screening. ‡Generated post-hoc. §MGFA classification refers to baseline classification at screening; participants were not reclassified after randomisation.

Table 1: **Demographics and baseline characteristics (modified intention-to-treat primary analysis set)**

	Placebo (n=59)	Combination (n=67)	Cemdisiran (n=64)	Pozelimab (n=49)*
Primary endpoint				
Change from baseline at week 24 in MG-ADL total score				
Mean (SD)	−2·6 (3·0)	−4·3 (3·5)	−4·3 (3·3)	−2·9 (4·0)
LS mean (SE)	−2·2 (0·5)	−4·0 (0·4)	−4·5 (0·4)	−2·8 (0·5)
Placebo-adjusted difference				
LS mean (95% CI)	–	−1·7 (−3·0 to −0·4)	−2·3 (−3·6 to −1·0)	NA
p value	–	0·0086	0·0005	NA
Key secondary endpoint				
Change from baseline at week 24 in QMG total score				
Mean (SD)	−2·0 (4·6)	−3·6 (4·3)	−4·1 (4·8)	−1·9 (4·2)
LS mean (SE)	−1·5 (0·7)	−3·3 (0·6)	−4·2 (0·6)	−1·5 (0·7)
Placebo-adjusted difference				
LS mean (95% CI)	–	−1·9 (−3·6 to −0·1)	−2·8 (−4·5 to −1·1)	NA
p value	–	0·035	0·0015	NA
Other secondary endpoints				
Proportion with MG-ADL response†				
Patients, n (%)	26 (44%)	44 (66%)	49 (77%)	24 (49%)
RR (95% CI)	–	1·514 (1·071 to 2·138)	1·843 (1·331 to 2·552)	NA
p value	–	0·014	0·0001	NA
Proportion with QMG response‡				
Patients, n (%)	11 (19%)	24 (36%)	31 (48%)	9 (18%)
RR (95% CI)	–	1·929 (1·017 to 3·657)	2·678 (1·447 to 4·958)	NA
p value	–	0·037	0·0006	NA
Change from baseline to week 24 in MGC total score				
Mean (SD)	−4·6 (7·9)	−6·4 (6·6)	−7·4 (6·4)	−3·9 (7·6)
LS mean (SE)	−3·4 (1·0)	−6·0 (0·9)	−7·8 (0·9)	−3·2 (1·0)
Placebo-adjusted difference				
LS mean (95% CI)	–	−2·6 (−5·2 to 0·0)	−4·3 (−6·9 to −1·8)	NA
p value	–	0·048§	NA¶	NA
Change from baseline to week 24 in MG-QOL15r total score				
Mean (SD)	−2·9 (5·4)	−4·3 (6·2)	−4·5 (6·6)	−1·6 (5·8)
LS mean (SE)	−2·3 (0·9)	−4·3 (0·8)	−4·7 (0·8)	−1·6 (0·9)
Placebo-adjusted difference				
LS mean (95% CI)	–	−2·0 (−4·2 to 0·3)	−2·4 (−4·7 to −0·2)	NA
p value	–	NA¶	NA¶	NA
Proportion with minimal symptom expression on MG-ADL‖				
Patients, n (%)	4 (7%)	15 (22%)	13 (20%)	7 (14%)
RR (95% CI)	–	3·676 (1·194 to 11·318)	3·390 (1·047 to 10·969)	NA
p value	–	NA¶	NA¶	NA
Proportion with consistent response on MG-ADL**				
Patients, n (%)	37 (63%)	55 (82%)	52 (81%)	31 (63%)
Estimated OR (95% CI) *vs* placebo	–	1·309 (1·041 to 1·647)	1·308 (1·041 to 1·644)	NA
p value	–	NA¶	NA¶	NA

Endpoints are presented in order of the prespecified statistical testing strategy. 95% CI widths were not adjusted for multiplicity and should not be used in place of hypothesis testing. 95% CIs were derived from the linear mixed model for repeated measures model. LS=least-squares. MG-ADL=Myasthenia Gravis—Activities of Daily Living. MG-QOL15r=Myasthenia Gravis Quality of Life 15-item (revised). MGC=Myasthenia Gravis Composite. NA=not applicable. OR=odds ratio. QMG=Quantitative Myasthenia Gravis. RR=relative risk. *Placebo-adjusted differences, RRs, and corresponding p values for pozelimab monotherapy versus placebo are not presented as this comparison was not in the scope of NIMBLE study; the pozelimab monotherapy group was included in the study to evaluate the contribution of components only. †Defined as a ≥3-point reduction (improvement) in MG-ADL total score from baseline at week 24. ‡Defined as a ≥5-point reduction (improvement) in QMG total score from baseline at week 24. §Not statistically significant at prespecified final α=0·0459; the remaining α was used in an interim analysis. ¶p values not reported as secondary endpoints were subject to hierarchical testing and the previous endpoint was not statistically significant. ‖Defined as an MG-ADL total score of 0 or 1 at week 24. **Defined as a ≥2-point reduction (improvement) in MG-ADL total score on two or more consecutive assessments spanning 4 or more weeks during the double-blind treatment period.

Table 2: **Primary and secondary efficacy endpoints (modified intention-to-treat primary analysis set)**



Improvements

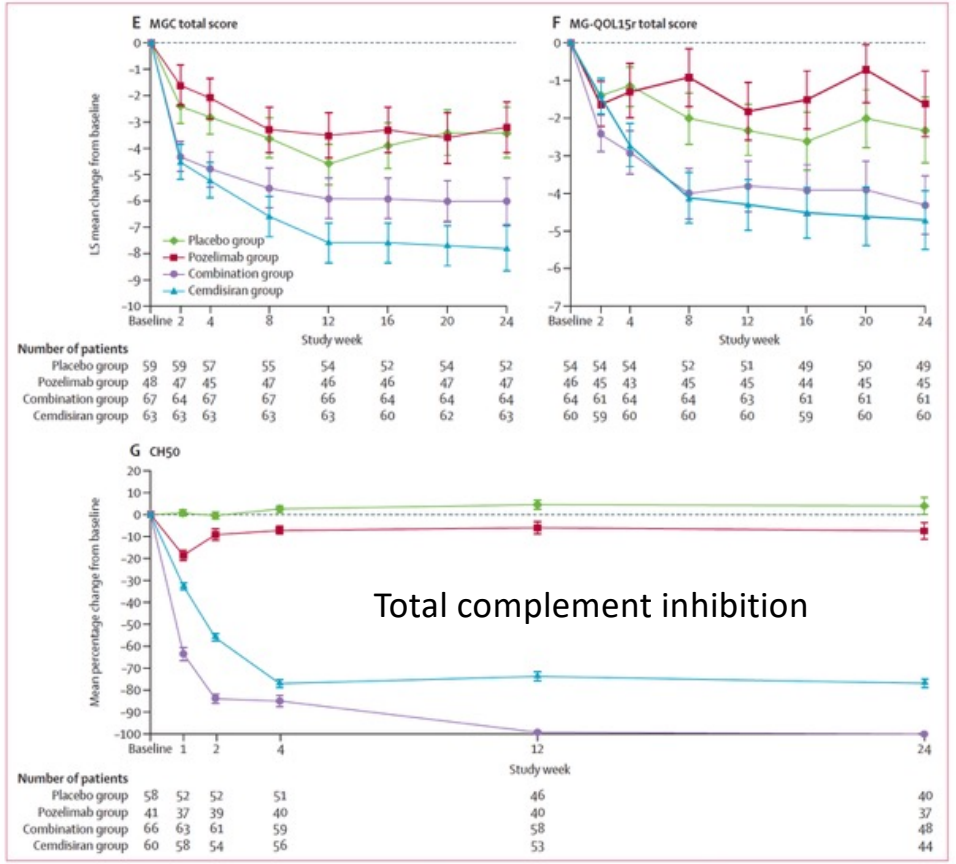


Figure 2: **Patient-reported outcomes, performance measures, and CH50 during the double-blind treatment period (modified intention-to-treat primary analysis set)**

(A, B) Change from baseline in MG-ADL total score (A) and QMG total score (B) over time; error bars are SEs. (C, D) Proportion of participants with improvement in MG-ADL total score (C) and QMG total score (D) from baseline by week 24. (E, F) Change from baseline in MGC total score (E) and MG-QOL15r total score (F) over time; error bars are SEs. (G) Percentage change from baseline in CH50 over time; error bars are 95% CIs. CH50=total complement haemolysis activity. LS=least-squares. MG-ADL=Myasthenia Gravis—Activities of Daily Living. MGC=Myasthenia Gravis Composite. MG-QOL15r=Myasthenia Gravis Quality of Life 15-item (revised). QMG=Quantitative Myasthenia Gravis.

	Placebo (n=66)	Combination (n=75)	Cemdisiran (n=75)	Pozelimab (n=49)
Participants with at least one myasthenic crisis (including impending crisis)	9/66 (14%)	6/75 (8%)	1/75 (1%)	0/49
Participants with at least one day of any hospitalisation post-randomisation*	10/66 (15%)	7/75 (9%)	2/75 (3%)	5/49 (10%)
Total days of hospitalisation post-randomisation	117	60	10	50
Participants administered rescue therapy†	6/59 (10%)	4/67 (6%)	1/64 (2%)	1/49 (2%)

Data are n/N (%) or n. *All ten participants in the placebo group had myasthenia gravis-related hospitalisations; one participant in each of the combination, cemdisiran, and pozelimab groups had myasthenia gravis-related hospitalisations. †The modified intention-to-treat primary analysis set is presented for this endpoint only as rescue therapy was considered as an intercurrent event in efficacy analyses.

***Table 3:* Exploratory endpoints during the double-blind treatment period (modified intention-to-treat analysis set)**

	Placebo (n=70)	Combination (n=80)	Cemdisiran (n=78)	Pozelimab (n=49)
Any adverse event	54 (77%)	65 (81%)	54 (69%)	40 (82%)
Mild	26 (37%)	35 (44%)	31 (40%)	12 (24%)
Moderate	21 (30%)	22 (28%)	21 (27%)	23 (47%)
Severe	7 (10%)	8 (10%)	2 (3%)	5 (10%)
Severe adverse event	7 (10%)	8 (10%)	2 (3%)	5 (10%)
Serious adverse event	10 (14%)	7 (9%)	2 (3%)	5 (10%)
Adverse event of special interest*	2 (3%)	12 (15%)	8 (10%)	1 (2%)
Treatment-related adverse event	16 (23%)	32 (40%)	23 (29%)	13 (27%)
Adverse event leading to study treatment discontinuation	2 (3%)	0	0	1 (2%)
Adverse event leading to dose interruption or reduction	3 (4%)	3 (4%)	1 (1%)	1 (2%)
Adverse events of infections and infestations by SOC†	28 (40%)	30 (38%)	21 (27%)	25 (51%)
Serious infections and infestations	3 (4%)	2 (3%)	0	2 (4%)
Adverse events occurring in ≥5% of participants in any treatment group, by preferred term				
Upper respiratory tract infection	8 (11%)	6 (8%)	9 (12%)	6 (12%)
Headache	7 (10%)	9 (11%)	4 (5%)	5 (10%)
Nasopharyngitis	3 (4%)	2 (3%)	4 (5%)	2 (4%)
Rash	1 (1%)	2 (3%)	4 (5%)	2 (4%)
Urinary tract infection	2 (3%)	5 (6%)	4 (5%)	4 (8%)
Injection-site reaction	1 (1%)	6 (8%)	3 (4%)	1 (2%)
Diarrhoea	5 (7%)	11 (14%)	2 (3%)	6 (12%)
Arthralgia	1 (1%)	5 (6%)	1 (1%)	1 (2%)
Cough	1 (1%)	4 (5%)	1 (1%)	1 (2%)
Myasthenia gravis	12 (17%)	4 (5%)	1 (1%)	4 (8%)
Pain in extremity	1 (1%)	4 (5%)	1 (1%)	0
Pruritus	0	4 (5%)	0	0

Data are n (%) of patients with at least one event. No adverse events leading to death were recorded during the double-blind treatment period. ALT=alanine aminotransferase. SOC=system order class. ULN=upper limit of normal. *Defined as any hypersensitivity reactions potentially related to study treatment, suspected *Neisseria* infection, any injection-site reactions, and any of the following abnormalities: ALT ≥3 × ULN, if baseline ALT was less than the ULN; ALT ≥2 × baseline, if baseline ALT was at or above the ULN; or total bilirubin ≥2 × ULN considered hepatic in origin by the investigator. †No cases of suspected *Neisseria* (meningococcal) infection were recorded.

***Table 4:* Adverse events during the double-blind treatment period (safety analysis set)**

Added value of this study

The phase 3 NIMBLE study evaluated the efficacy and safety of cemdisiran monotherapy administered every 3 months by subcutaneous injection, and a lower dose of cemdisiran in combination with low-dose pozelimab administered subcutaneously every month. The study included patients with AChR autoantibody-positive and LRP4 autoantibody-positive generalised myasthenia gravis, who generally require advanced therapies. The study design allowed measurement of the contribution of each component (cemdisiran and pozelimab) in the treatment of generalised myasthenia gravis. Cemdisiran monotherapy showed robust efficacy with partial inhibition of complement activity, with no meningococcal infections and no evidence of increased infective risk compared with placebo.

Implications of all the available evidence

This study showed that cemdisiran monotherapy had rapid, sustained, and clinically meaningful effects compared with placebo for the treatment of generalised myasthenia gravis, with no waning of efficacy near the end of respective 3-month dosing intervals. Cemdisiran monotherapy could provide a new approach targeting the complement C5 pathway, specifically C5 mRNA in hepatocytes. Although this regimen only led to partial complement inhibition, it could reduce treatment burden, with convenient subcutaneous dosing every 3 months. The underlying mechanisms explaining the residual complement activity while improving clinical outcomes in generalised myasthenia gravis warrant future investigations.

Die Impfung gegen Humane Papillomviren (HPV) ist die wichtigste präventive Maßnahme gegen Gebärmutterhalskrebs. Sie schützt vor den Virustypen, die für etwa 70 % bis 90 % aller Fälle von Gebärmutterhalskrebs verantwortlich sind.

💡 Kernpunkte zur HPV-Impfung

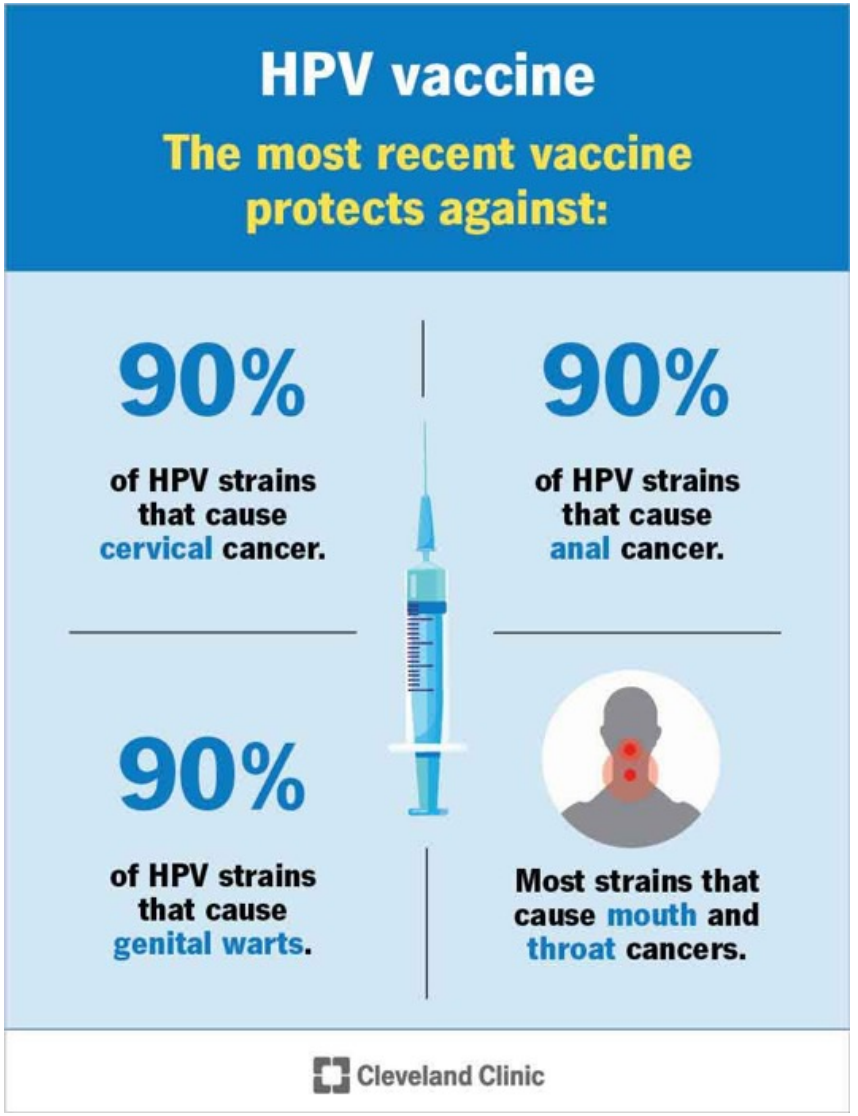
•**Wirksamkeit:** Studien zeigen, dass eine Impfung in jungem Alter (vor dem ersten sexuellen Kontakt) das Risiko für Gebärmutterhalskrebs um bis zu **90 %** senken kann.

•**Zielgruppe:** Die Impfung wird primär für Mädchen und Jungen im Alter von **9 bis 14 Jahren** empfohlen.

•**Nachholimpfung:** Eine Impfung ist oft bis zum 26. Lebensjahr (in manchen Fällen bis 45) sinnvoll, verliert jedoch an Effektivität, wenn bereits eine HPV-Infektion vorliegt.

•**Sicherheit:** Die Impfung gilt als sicher; häufigste Nebenwirkungen sind kurzzeitige Reaktionen an der Einstichstelle wie Rötungen oder Schmerzen.

The vaccine is great



Substantial increases in cervical cancer inequalities worldwide without enhanced human papillomavirus vaccination and screening efforts: a global modelling study

Summary

Background To reduce worldwide inequalities, WHO made a call for action to eliminate cervical cancer by vaccinating 90% of girls, screening 70% of women, and treating 90% of pre-cancers and cancers. Low-income countries and lower-middle-income countries (LMICs) are far from reaching the WHO elimination targets compared with high-income countries (HICs). Using mathematical modelling, we aimed to examine the following questions: (1) Are we on the path to cervical cancer elimination in LMICs and HICs? (2) What is the potential evolution of inequalities in cervical cancer between LMICs and HICs under current screening and vaccination coverage? And (3) what would be the potential impact of enhanced prevention strategies (ie, human papillomavirus [HPV] vaccination and screening) on inequalities and cervical cancer elimination?

Methods We used the HPV-ADVISE model to project the age-standardised cervical cancer incidence in 67 LMICs and 42 HICs for different HPV vaccination and screening scenarios. For the status quo scenario (of HPV vaccination and screening), we modelled the vaccine used, the start year of vaccination, vaccination coverage, and the target population for each country, and current screening coverage in LMICs and HICs. We examined five enhanced prevention strategies for LMICs: (1) status quo for all countries using the nine-valent vaccine; (2) reaching 90% vaccination coverage for girls-only routine vaccination; (3) reaching the WHO vaccination, screening, and treatment elimination targets; (4) adding routine vaccination for boys with 90% coverage (ie, universal routine vaccination) and multi-age-cohort vaccination; and (5) reaching the WHO elimination targets combined with universal routine and multi-age-cohort vaccination. Inequalities were measured as the age-standardised cervical cancer incidence (ASR) ratio between LMICs and HICs ($RR_{LMIC/HIC}=ASR_{LMICs}/ASR_{HICs}$).

Findings Under the status quo, the model projected that cervical cancer incidence in LMICs would decrease by only 23% while HICs would reach elimination by 2048 (age-standardised cervical cancer incidence <four cases per 100 000 women-years), leading to substantial increases in inequalities ($RR_{LMIC/HIC}=3$ in 2022 and 12 in 2105). Reaching 90% vaccination coverage among girls in LMICs would reduce these inequalities ($RR_{LMIC/HIC}=2$ in 2105) and lead to elimination in LMICs outside sub-Saharan Africa. To reach equality between LMICs and HICs and elimination in all LMIC regions, LMICs would need to reach the WHO elimination targets and introduce universal vaccination and multi-age-cohort vaccination.

Interpretation Worldwide inequalities in cervical cancer have been projected to increase dramatically without enhanced HPV prevention strategies. Reaching WHO vaccination and screening elimination targets or introducing universal vaccination with high coverage is necessary to eliminate cervical cancer in LMICs, which would substantially attenuate worldwide inequalities.

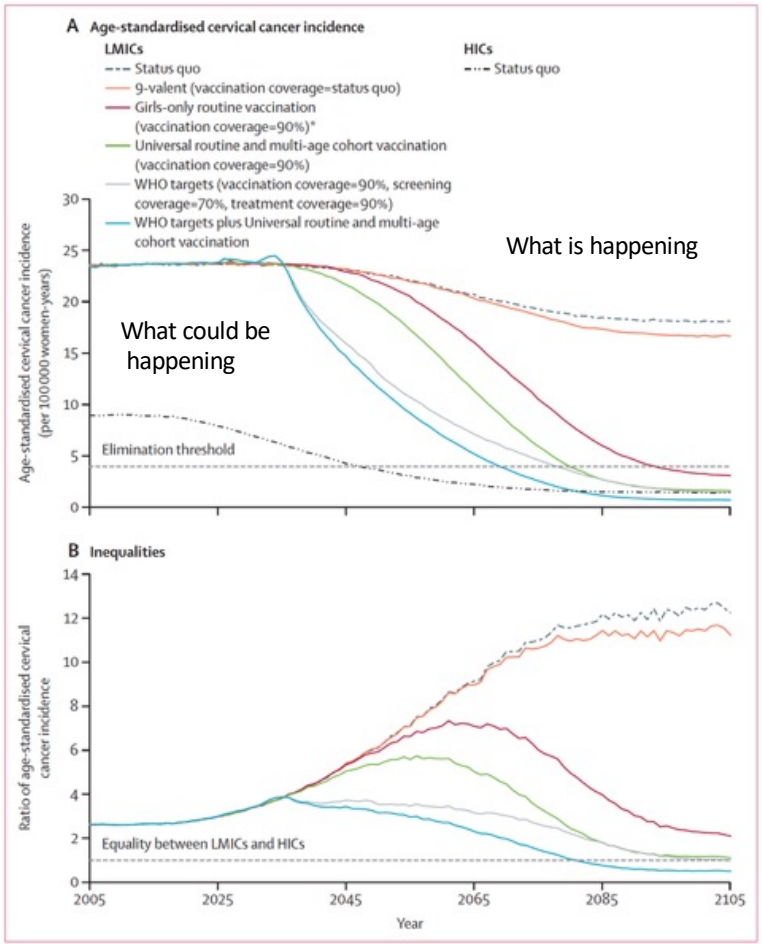


Figure 1: **Projected population-level impact of different human papillomavirus (known as HPV) vaccination and screening strategies on cervical cancer incidence (A) and inequalities (B) between HICs and LMICs over time**

The lines are the mean result of model projections using 50 parameter sets. The elimination threshold is less than four cervical cancers per 100 000 women-years. Inequality is measured as the ratio of the age-standardised cervical cancer incidence in LMICs and HICs. HIC=high-income country. LMIC=low-income and lower-middle-income countries. *Includes five LMICs (Bhutan, Bolivia, Cameroon, Cape Verde, and Mongolia) with universal vaccination in the status quo.

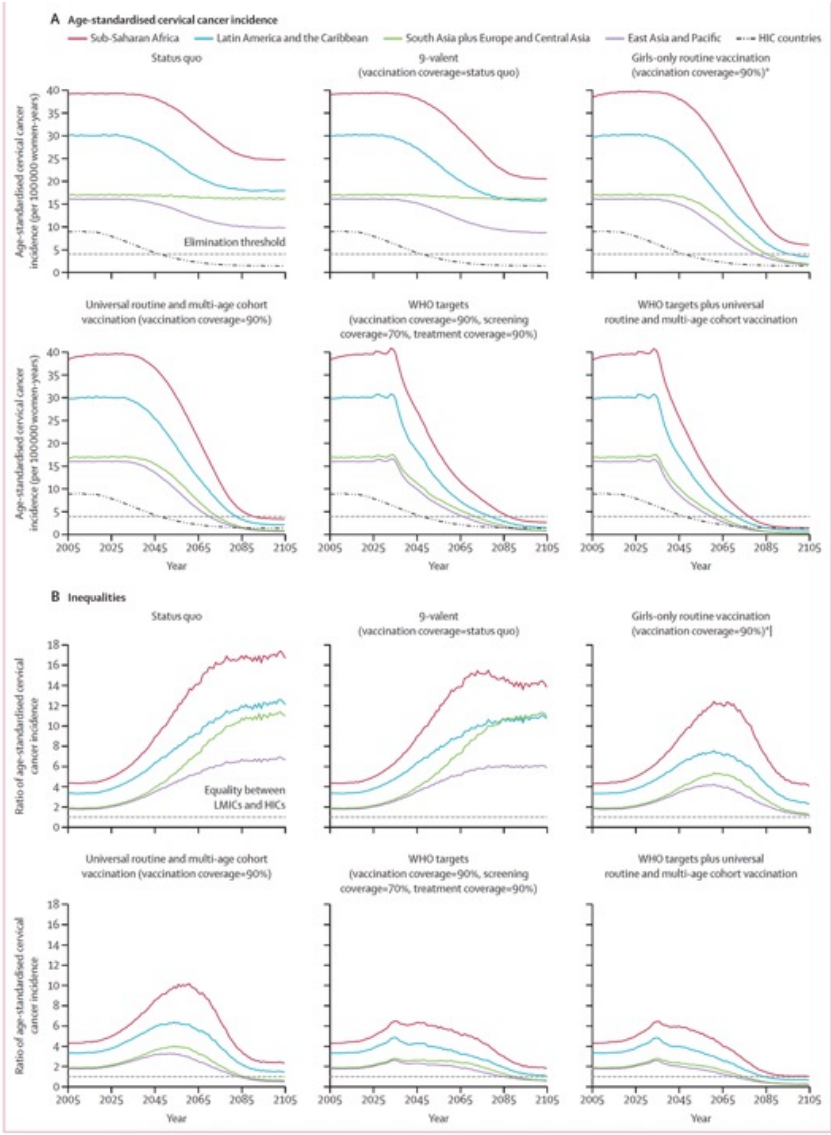


Figure 2: **Projected population-level impact of different HPV vaccination and screening strategies on cervical cancer incidence (A) and inequalities (B) between HICs and low-income and LMIC regions over time**

The lines are the mean result of model projections using 50 parameter sets. HICs are not stratified by region. The elimination threshold is less than four cervical cancers per 100 000 women-years. Inequality is measured as the ratio of the age-standardised cervical cancer incidence in LMICs and HICs. *Includes five LMICs (Bhutan, Bolivia, Cameroon, Cape Verde, and Mongolia) with universal vaccination in the status quo. HICs=high-income countries. HPV=human papillomavirus. LMIC=lower-middle-income country.

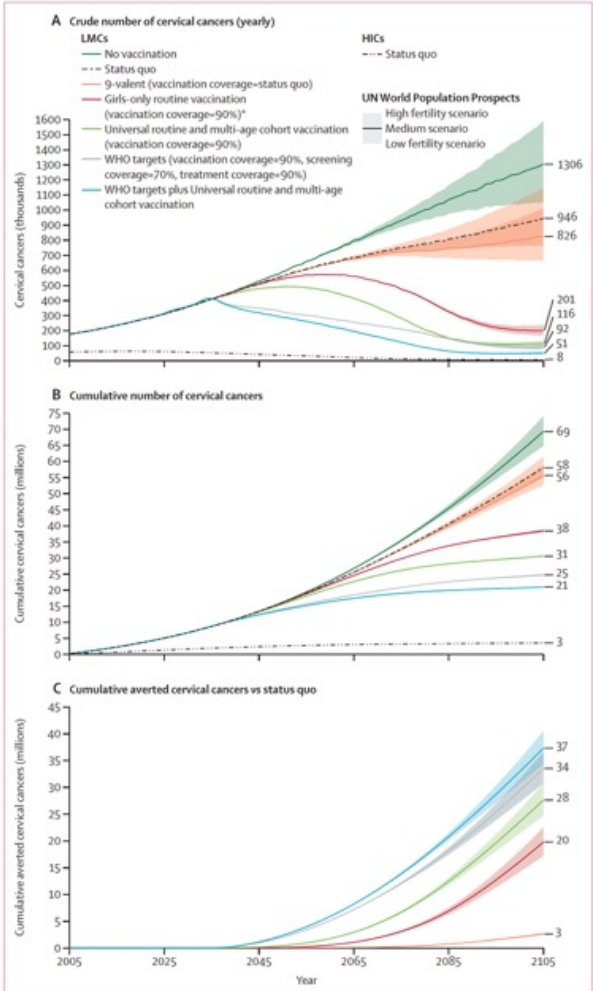
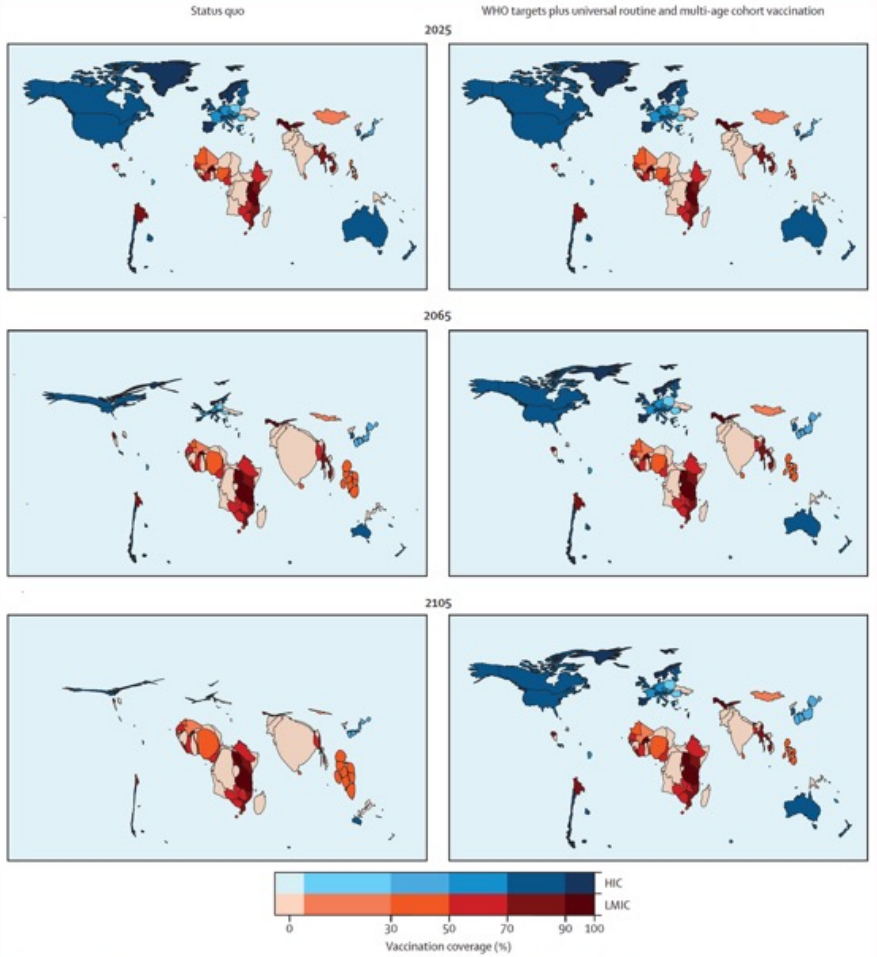


Figure 3: **Projected population-level impact of HPV vaccination and cervical screening strategies on the number of cervical cancers in HICs and LMICs over time**

(A) Crude number of cervical cancers (yearly). (B) Cumulative number of cervical cancers. (C) Cumulative number of averted cervical cancers compared to the status quo. The lines are the mean result of model projections using 50 parameter sets and the shaded area represents uncertainty in UN World Population Prospects. HICs= high-income countries. HPV=human papillomavirus. LMICs= low-income and lower-middle-income countries. *Includes five LMICs (Bhutan, Bolivia, Cameroon, Cape Verde, and Mongolia) with universal vaccination in the status quo.



Cumulated cervical cancers (since 2005) in millions

Year	Status quo		WHO targets plus universal routine and multi-age cohort vaccination
	HICs	LMICs	LMICs
2025	1	5	5
2065	3	26	17
2105	3	58	21

Yearly number of cervical cancers in thousands

Year	Status quo				WHO targets plus universal routine and multi-age cohort vaccination			
	SSA	LAC	SA+ECA	EAP	SSA	LAC	SA+ECA	EAP
2025	115	5	164	27	116	5	164	27
2065	337	9	307	37	90	3	92	12
2105	592	10	307	35	39	1	10	2

Figure 4: **Cartogram of the projected number of cervical cancers over time under the status quo (of HPV vaccination and screening) and the enhanced strategy of reaching the WHO elimination targets with universal routine and MAC vaccination in LMICs**

The figures resize geographical areas proportionally to the number of cervical cancers at a given time. The approach visually amplifies countries with a higher number of cervical cancers. Countries with a lower number of cervical cancers will shrink, whereas countries with proportionally more cervical cancers will expand. The left panel shows the status quo of human papillomavirus (HPV) vaccination and screening (as of 2023-24) and the right panel shows the enhanced strategy of reaching the WHO elimination targets (vaccination coverage=90%, screening coverage=70%, and treatement=90% of pre-cancers and cancers) with universal routine and MAC vaccination. The colour gradients in all panels reflect the 2023-24 vaccination coverage (red indicates LMICs and blue indicates HICs). EAP=east Asia and Pacific. HIC=high-income countries. LAC=Latin America and Caribbean. LMICs=low-income countries and lower-middle-income countries. MAC=multi-age cohort. SA+ECA=South Asia and Europe and central Asia. SSA=sub-Saharan Africa.

Implications of all the available evidence

5 years after the launch of the global strategy to eliminate cervical cancer, the WHO elimination targets are far from being reached in most LMICs, partly due to restrained resources, historically comparatively high cost of HPV vaccines, competing health problems, HPV vaccine supply constraints, and COVID-19. Worldwide inequalities between HICs and LMICs in cervical cancer are therefore projected to increase dramatically without enhanced HPV vaccination and screening efforts and the requisite investment in these evidence-based strategies. However, the landscape for HPV vaccination scale-up has changed substantially with WHO pre-qualified vaccines now available at low cost, the end of vaccine supply constraints, and the option to use a single dose. Our modelling study provides timely information about HPV vaccination and screening strategies that could considerably decrease worldwide inequalities and accelerate the elimination of cervical cancer in the countries with the highest burden. Implementation research to adapt these results to the specific context of countries and political will are urgently needed.

Depression

Depression is a common illness that affects people within every society around the world. It afflicts the young and the old and everyone in between, and as such poses an immense global burden. New interventions and a deeper understanding of this illness are emerging, but improving the use of existing treatments is equally important and might be a more efficient and effective strategy to addressing depression. Therefore, it is imperative that we improve the diagnosis of depression and its clinical management.

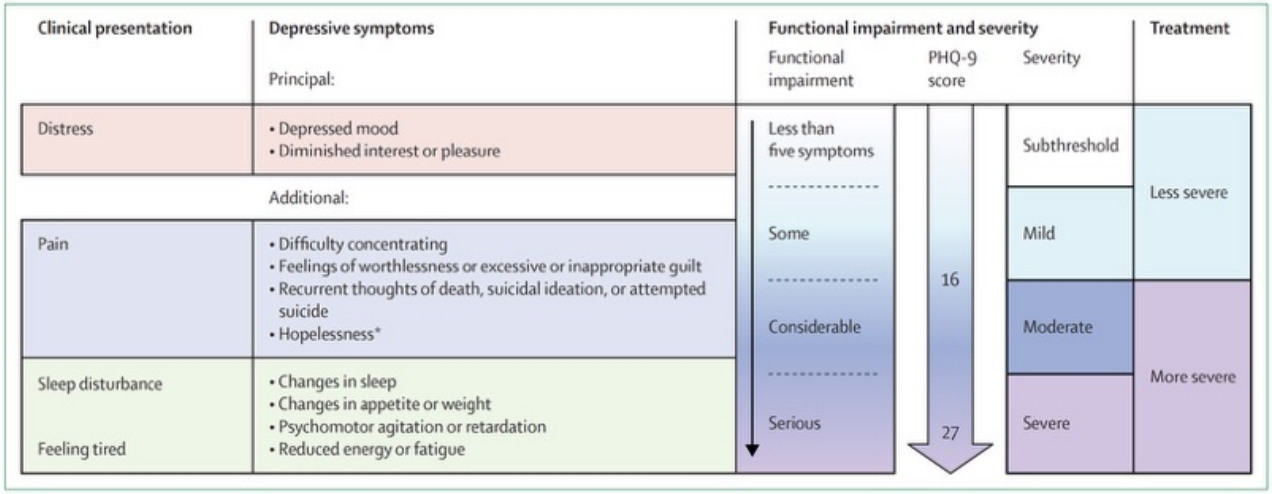


Figure 1: **Diagnosing depression**

The diagnosis of depression involves three components: (1) eliciting the symptoms that form a depressive episode; (2) determining their severity and the functional impairment that they cause; and (3) mapping their longitudinal course over the duration of an episode, as well as the illness as a whole. Depressive episodes usually last several weeks and can last several months if untreated. After remission, symptoms can re-emerge (relapse) before functional recovery and even then, further long-term episodes of depression (recurrence) remain likely. Scores and categories drawn from UK National Institute for Health and Care Excellence.[25] PHQ-9=Patient Health Questionnaire-9. *Hopelessness is only specified in ICD-11 and not in DSM-5-TR.

Panel 1: Depression vulnerability factors

Biological and physical health factors

Immutable factors

- Family history of mental illness*
  - Mood disorder
  - Substance misuse
- Epilepsy
- Intellectual disability
- Head injury
  - Concussion
  - Traumatic brain injury

Modifiable factors

- Physical condition
  - Cardiovascular (eg, hypertension and cardiovascular disease)
  - Neurological (eg, dementia and Parkinson's disease)
  - Metabolic (eg, diabetes and hypothyroidism)
- Lifestyle
  - Unbalanced diet
  - Lack of or irregular exercise
  - Deprivation or non-restorative sleep
  - Poor sleep hygiene
  - Smoking and consumption of drugs and alcohol

Psychological and mental health factors

Immutable factors

- Personal history of mental illness
  - Mood disorders (eg, depression and bipolar disorder)
  - Substance misuse (eg, alcohol and cannabis)

Modifiable factors

- Mental condition
  - Anxiety
  - Psychosis
  - Eating disorders
  - Substance use
- Personality
  - Insecure attachment
  - Negative self-concept
  - Sensitivity to rejection
  - Negative emotionality
  - Perfectionism
  - Pessimism
  - Low resilience
- Maladaptive coping strategies
  - Rumination

Social and economic factors

Immutable factors

- Previous stressful life events
  - Loss (eg, death of parents, siblings, or spouse; financial loss; or loss of identity)
- Past experience of abuse
  - Childhood abuse (physical, emotional, or sexual)
  - Partner or parental abuse (verbal, physical, sexual, or financial)
  - Bullying at school by peers or teachers
  - Harassment and bullying by co-workers and managers

Modifiable factors

- Current experience of abuse
  - Parental or partner abuse (verbal, physical, sexual, or financial)
  - Workplace harassment and bullying by co-workers, line managers, or organisation
- Lack of social support
  - Social exclusion due to one's values, belief, or identity
- Low socioeconomic status
  - Unemployment
  - Low income
  - Unstable housing
- Threats to safety and security
  - Unsafe living conditions
  - Insecure housing
  - Persecution and war

*Family history of mental illness reflects not only biological vulnerabilities via genetics, but also environmental risk factors associated with mental illness (eg, effects on parenting) as well as contextual risk factors (eg, poverty).

Panel 2: Watchful waiting in primary care

Diagnosing depression requires a person-centred approach. General practitioners (GPs) are suitable for this approach as they provide whole person care in the context of a doctor-patient relationship.[45] Formulating depression requires skilful integration of biopsychosocial and biographical information and GPs are well positioned in this regard as the patient is usually well known to them. This familiarity also enables GPs to distinguish between situational crises and clinical depression and function as gatekeepers as they determine which pathway of care to pursue and when to refer to a specialist.[46] This process is sometimes called watchful waiting[47] as it takes time and entails careful appraisal. During this time, which can vary considerably from days to weeks, collateral information can be sought, and investigations that help exclude medical causes of depression, such as anaemia and hypothyroidism, can be conducted; this approach is also helpful because it lends further credence to the patient's distress. Hence, watchful waiting is in fact an active process that allows other sources of distress such as pain or infection to be treated, and its principal aim is to allow sufficient time to lapse so that a proper diagnosis of depression can be made and suitable management can be determined. However, watchful waiting is not always appropriate, for example, in crisis situations such as severe depression or suicidal risk, in which practical steps might need to be taken immediately to treat the patient and ensure their safety. In these cases, mood monitoring should be instituted.[47]

Panel 3: Mood monitoring

Once depression is being considered by a health-care professional, patients should record their clinical symptoms, sleep, and physical activity. Asking patients to monitor themselves helps them and the health-care professional to understand the nature of their symptoms and provides a longitudinal record that is less reliant solely on the patient's long-term recall.[48,49] Monitoring symptoms is also useful during management as it helps evaluate treatment outcomes.

Digital health technologies—any form of technology for health care, such as the use of smartphones to monitor health or provide guidance—could assist with mood monitoring.[50] The term also refers to messaging, digital phenotyping, and the use of wearables such as activity trackers, as well as the use of telehealth and videoconferencing.[51] Digital health technologies are used to provide psychoeducation, reminders, mood monitoring, and the delivery of psychological interventions.[52]

Panel 4: Suicidal thoughts and risk of suicide

Suicidal thoughts often occur in the context of depression and can be confusing as they are a diagnostic feature of the illness (figure 1) but also a cause for concern. Thoughts about suicide are usually driven by critical thoughts about oneself, one's relationships, and one's situation in life. Negative thinking and feelings such as guilt can fuel a sense of helplessness and lead to a loss of hope, which can prompt thoughts about ending one's life, especially to avoid continuing psychological pain.[53] Therefore, when assessing a patient with depression, it is important to enquire about thoughts of suicide or self-harm, and when formulating an individual's risk of self-harm or suicide, examining their specific needs and how best to ensure their safety is crucial. Regarding suicidal thoughts, it is important to assess their nature (frequency, duration, and content), as well as the process of suicidal ideation (the individual's conviction and intent and any plans they might have made). Ideally, a formulation of suicide risk should include consideration of historical factors (eg, previous suicide attempts), recent difficulties, and the availability of resources such as family support.[54] If there is serious concern regarding a person's safety or there is an ongoing risk of self-harm, a referral should be made to specialist or emergency services, and hospitalisation might be indicated.

Panel 5: Risky lifestyle habits

In most countries, it is legal to smoke tobacco and drink alcohol and therefore they are by far the most common risky lifestyle habits, and their use is well documented and researched.[64]

Alcohol misuse

Links between alcohol misuse and depression are both direct and indirect as alcohol is a depressant, and once dependent, individuals continue to misuse alcohol to transiently alleviate stress.[65–67] Managing depression in the context of alcohol misuse (dual diagnosis) is complicated and usually requires specialist services. Many specialist services treat the two disorders concurrently. However, in most cases, substance misuse must be tackled first before depression can be treated.[68] This is because addressing alcohol consumption often reduces depressive symptoms,[69] and implementing strategies to address problematic alcohol use early in the management of depression (eg, with psychological interventions) increases the chance of benefiting from depression treatments.[70]

Smoking tobacco

Smoking is linked to heart disease, cancer, and metabolic disorders; there are no health benefits from this habit even though the inhalation of nicotine is initially anxiolytic. This anti-anxiety effect soon diminishes with repeated use and gives way to nicotine craving. Such gradual habituation and dependence are also evident in those who vape, and this is particularly concerning as this habit is increasingly common in adolescents and young adults.[71] Contrary to the misconception that smoking cessation might increase anxiety and depression,[68] those who stop smoking usually experience an improvement in ensuing months for these symptoms.[72]

Exercise

International guidelines recommend exercise to treat the symptoms of less severe depression and improve sleep quality and cognitive function.[25,42,44,76] This recommendation is supported by meta-analyses of controlled treatment studies in adults with depression that show that exercise produces tangible benefits with an overall moderately large effect size.[77,78] Research examining the benefits of various types of exercise in adults with depression highlights some specificity according to age and gender (figure 2A). For instance, aerobic exercise, walking, and jogging, as well as strength exercises and yoga, are on par in terms of efficacy with cognitive behavioural therapy (CBT),[78] and evidence for each of these activities is strong, positioning them as more effective than selective serotonin reuptake inhibitors (SSRIs). Furthermore, although there is no clear age or gender specificity for general exercise (eg, walking, jogging, and aerobic exercise), strength exercises produce greater improvements in younger adults and women. Conversely, yoga is of greater benefit to men and older individuals. The reasons for certain exercises being efficacious are multifaceted and might include other factors such as social interaction and skill acquisition (figure 2). Additionally, exercise is more beneficial when structured (time of day and frequency) and undertaken in combination with psychological interventions and medications (eg, SSRIs) and its benefits extend into old age.[77] Thus, in addition to its general health benefits, exercise is particularly useful in the treatment of depression as it alleviates symptoms and can prevent onset and recurrence.[84,85]

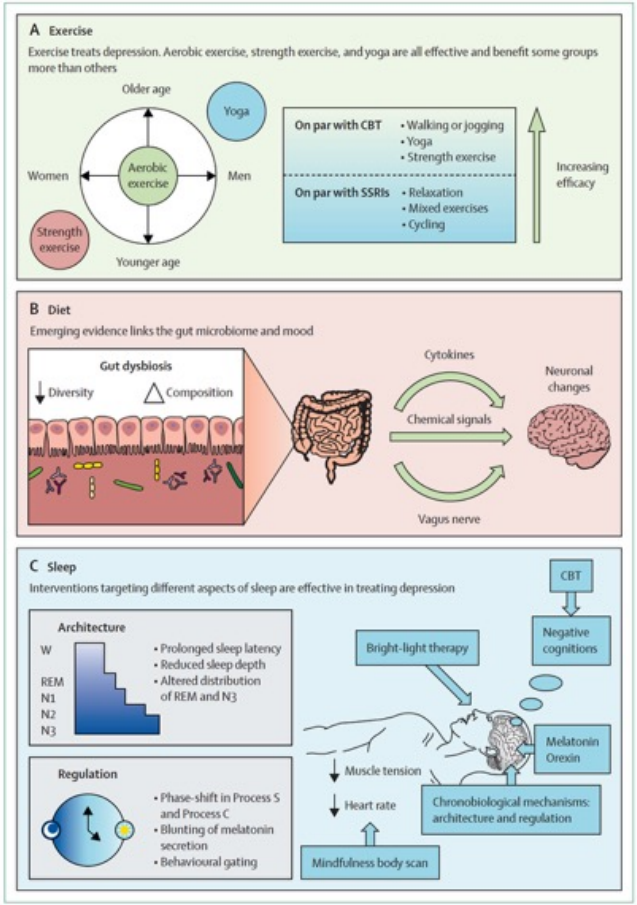


Figure 2: **Lifestyle modifications**
(A) Exercise is an effective treatment in depression and shows some specificity with respect to age and gender.[78] (B) The gut-brain axis is thought to be bidirectional and operate through a number of pathways in depression,[79] such as neural pathways (vagus nerve),[80] via inflammatory and immune signals, and through chemical signals,[81] all of which are inter-related.[82] Changes in the composition of gut bacteria (gut dysbiosis), as well as a lower overall diversity of gut flora, have been associated with depression.[83] (C) Sleep dysfunction is strongly implicated in depression, and both the architecture of sleep and its regulation are impacted. Sleep architecture typically involves four stages: after waking (W), rapid-eye-movement sleep (REM), light sleep (N1), deeper sleep (N2), and slow-wave sleep (N3). In individuals with depression, the regulation of sleep can be affected through a phase-shift in both homoeostatic sleep (Process S) and circadian sleep (Process C), as well as an insufficient Process S. This results in insomnia and sleep that is non-restorative, which can affect mood and functioning. The various interventions for sleep act via different mechanisms. CBT=cognitive behavioural therapy. SSRIs=selective serotonin reuptake inhibitors.

Panel 6: Sleep pharmacotherapy

Benzodiazepines and related medications can be effective sedatives if used in the short term (<4 weeks), but their use to modify sleep to treat depression is less well mapped and their prescription (both as monotherapy and adjunctive treatment to antidepressants) does not show sustained benefits. These medications should therefore be prescribed with caution and only for a limited time, after which they should be discontinued with gradual dose reduction.[109] Tricyclics have long been used to aid sleep and treat depression,[110] and more recently, antipsychotics that are sedating (eg, quetiapine) have been prescribed for similar reasons[110,111] as they help with initial insomnia and short-term relief of anxiety.[112] However, the adverse effects of these medications limit their benefit in the long term. Other medications that are used for sleep (eg, melatonin and orexin) appear to be effective in instituting normal sleep cycles, but again, specific benefits in the context of depression have not yet been established.[113–116] Notably, melatonin supplementation has only shown significant efficacy at higher doses and after 12 weeks of treatment,[114] and orexin antagonists have not shown consistent effectiveness in the treatment of depression.[113]

	Focus and core elements
Cognitive behavioural therapy	Identifies, challenges, and interrupts negative cognitions
Behaviour therapies, including behavioural activation	Increases engagement in activities that provide pleasure, and a sense of accomplishment
Interpersonal therapy	Improves unhelpful relationship patterns or situations
Psychodynamic psychotherapy	Explores unconscious motivations and unresolved conflicts and how these affect emotions, cognitions, and behaviours
Problem-solving therapy	Identifies problems and develops strategies and skills to successfully manage them
Schema-focused therapy	Changes long-held, self-defeating thought patterns and beliefs
Metacognitive therapy	Decreases perseverative thinking processes and metacognitions such as worrying, rumination, and uncontrollability of thoughts
Acceptance and commitment therapy	Acceptance of undesirable life experiences and difficulties and development of psychological flexibility to adapt to them
Dialectical behavioural therapy	Developing mindfulness, distress tolerance, interpersonal effectiveness, and adaptive emotion regulation
Rational emotive behaviour therapy	Replaces irrational beliefs with rational beliefs to reduce distress and increase functioning
Mindfulness-based therapies, including cognitive therapy	Enhances awareness of feelings, thoughts, and situations to reduce automatic responses
Positive psychotherapy	Increases positive emotions, engagement, and personal strengths
Counselling or non-directive support (non-manualised approaches)	Helps people find their own solutions by listening and empathising

An overview of psychological interventions for depression, highlighting their distinctive core elements.[25,150] For further information, including detailed definitions and specific examples of each of these therapies and evidence supporting these interventions, see the appendix (pp 8–11).

Table 1: **Major psychological interventions for depression**

	Features
Relapse	Recrudescence of same disorder episode due to loss of pharmacological effect
Recurrence	New episode of depression following previous recovery (remission over 6–9 months) due to loss of pharmacological effect
Rebound	Re-emergence of primary disorder symptoms to a greater extent than before taking medication; greater risk of relapse compared with patients not receiving antidepressants
Acute discontinuation syndrome	Non-specific symptoms (influenza-like, insomnia, nausea, imbalance, sensory disturbances, and hyperarousal); onset soon after discontinuation; transient and self-limiting in duration; quick improvement in symptoms upon resumption of medication

Adapted from Henssler et al (2019).[163]

Table 2: **Differential diagnosis of symptoms that follow antidepressant discontinuation or dose reduction**

	Preferred antidepressant(s)
Demographics	
Age	
Adolescents*	Fluoxetine or escitalopram[174,175]
Older adults	Trazodone[176]
Gender	
Pregnancy	SSRIs (citalopram, fluoxetine, sertraline, and escitalopram are most common)[177,177]
Menstrual disorders	Paroxetine, venlafaxine, or sertraline[178]
Clinical factors	
Symptoms	
Anxiety	SNRIs or SSRIs
Cognitive difficulties (eg, learning, memory, and decision making)	Duloxetine or vortioxetine
Sleep disturbances (eg, insomnia)	Agomelatine or mirtazapine
Fatigue	Bupropion
Pain	Duloxetine or tricyclics
Melancholia (eg, psychomotor slowing and diurnal mood variation)	Tricyclics
Psychotic symptoms (eg, mood congruent delusions)	Antipsychotic medication in addition to antidepressants
Atypical symptoms (eg, increased sleep and increased appetite)	Monoamine oxidase inhibitors
Loss of weight or anorexia	Mirtazapine[179]
Lifestyle factors	
Substance use	
Tobacco dependence	Bupropion
Opioid dependence	Doxepin

In addition to the two major classes (tricyclics and SSRIs), agents with broader monoaminergic actions than SSRIs but with better tolerability than tricyclics are available, in addition to those that are thought to act via different (ie, non-monoaminergic) pathways. These additional properties are thought to lend antidepressant medications suitability for different clinical profiles.[25,44,175] However, evidence to support differential efficacy according to clinical profile is absent, and in practice, management decisions should be based on tolerability and safety as well as efficacy. Nevertheless, by virtue of their properties, some agents have additional uses, and antidepressant effects that are seemingly adverse might at times be desirable. For example, sedation and weight gain might be helpful in patients with insomnia and those who are underweight because of depression. Many antidepressants also have anxiolytic effects (eg, SSRIs), although when first prescribed they can worsen anxiety. SSRIs=selective serotonin reuptake inhibitors. SNRIs=serotonin–norepinephrine reuptake inhibitors. *For important advice regarding prescription of antidepressants in adolescents, see panel 7.

Table 3: **Pharmacotherapy of depression based on clinical profile**

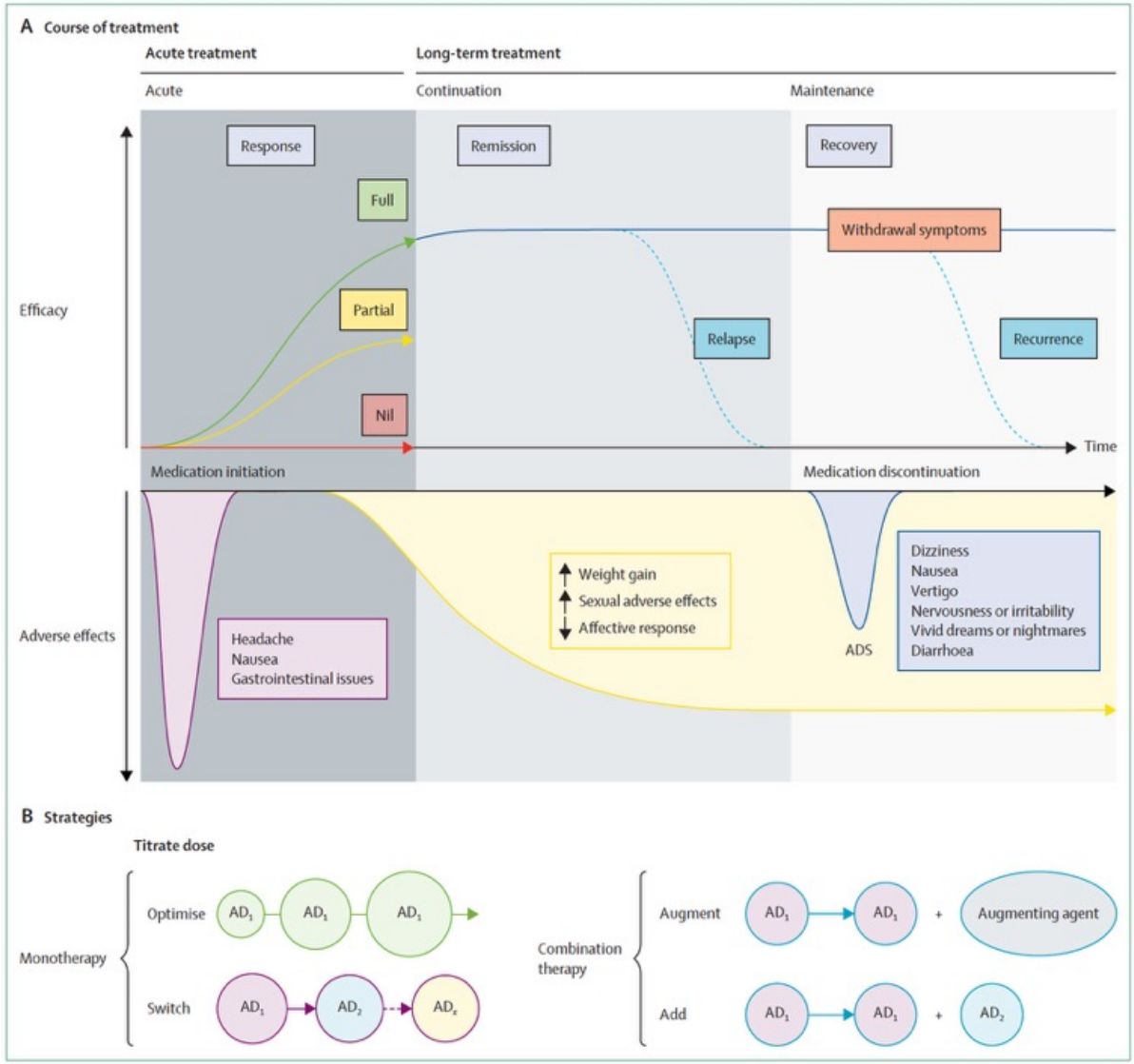


Figure 3: Framework for pharmacotherapy of depression

(A) Course of treatment. The treatment of depression comprises three phases: acute, continuation, and maintenance. These are demarcated by remission and recovery. Medication initiation: when initiating an antidepressant, potential acute and chronic adverse effects should be discussed. Medication discontinuation: the withdrawal of medication has a risk of both ADS[90] and relapse or recurrence (table 2; panel 2).[84] If symptoms recur on withdrawal of an antidepressant and ADS is ruled out, further ongoing treatment might be needed and medication could be reintroduced. (B) Strategies for ongoing treatment. Beginning with initiation and then optimising and combining or switching as necessary. Overall, there are two approaches—monotherapy or combination therapy. Monotherapy is preferable as it simplifies management and it is clearer which agent is responsible for a response or adverse effects. Prescribing only one agent also minimises adverse effects. If a response is only partial then combination treatment can be considered: several strategies can be used to enhance a partial response to AD_1, including augmenting with lithium or atypical antipsychotics such as quetiapine or aripiprazole,[91,92] or adding another antidepressant (eg, combining mirtazapine with venlafaxine). Combination therapies are only indicated if AD_1 has produced a reasonable partial response.[84] In real-world practice, most clinicians tend to switch to another antidepressant and this has the advantage of maintaining monotherapy.[93] Furthermore, the pattern of switching varies considerably but over a series of three antidepressant switches, the general trend seems to be switching from SSRIs to other medications such as mirtazapine, SNRIs, and tricyclics. SSRIs remain the most popular option throughout, despite a decrease in their overall use across successive trials. In contrast, mirtazapine use appears to remain steady and the use of other agents such as SNRIs and tricyclics gradually increases.[93] When switching antidepressants, within-class switching is recommended because of poor tolerability. However, if switching because of inefficacy, then trialling an altogether different molecule (from a different class with a different mechanism of action) is perhaps advantageous.[94] The STAR*D study,[84] a prospective trial of more than 4000 patients with depression reported that the cumulative remission rate after up to four antidepressant treatment trials was 67%, although this has been challenged recently by a re-analysis, which suggested that the rate should be 35%.[95] Either way, there are a substantial number of patients that do not respond to pharmacotherapy, underscoring the need for a multifaceted approach that combines antidepressant treatment with psychological interventions and includes foundational lifestyle modifications. AD_1=antidepressant 1. AD_2=antidepressant 2. AD_x=antidepressant x. ADS=acute discontinuation syndrome. SNRIs=serotonin–norepinephrine reuptake inhibitors. SSRIs=selective serotonin reuptake inhibitors.

Panel 7: Risk of suicide and antidepressants

The risk of suicidality (suicidal thinking or behaviour) is increased in adolescents and young people. Therefore, in the USA, many agents carry a US Food & Drug Administration black-box warning. In the UK, the safety warning from the Medicine and Healthcare products Regulatory Agency states that suicidal acts and behaviour are increased with the use of selective serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors in people younger than 25 years, and that the risks for specific antidepressants outweigh the benefits. Therefore, these antidepressants should not be used in this patient age group.

Consequently, routine monitoring of suicide is recommended in patients receiving antidepressant treatment, particularly at the outset (for the first 4 weeks or so) following the initiation of a new medication, and also after stopping treatment, and this message should also be included in any psychoeducation that is provided.[20,51]

Panel 8: Antidepressant discontinuation syndrome

Symptoms

- Mainly mild, reversible, non-specific, and physical in nature
- Peak: 36–96 hours
- Rapid onset within 1 week of discontinuation (3–5 half-lines)
- Resolve
  - Spontaneously (usually within 2 weeks), but might take longer (up to 6 weeks) depending on half-life
  - If medication is resumed

Risk for individual antidepressants

- Very high: phenelzine and tranylcypromine
- High: tricyclic antidepressants, venlafaxine, desvenlafaxine, and paroxetine
- Moderate: sertraline, citalopram, escitalopram, duloxetine, and vortioxetine
- Low: fluoxetine and milnacipran
- No risk: agomelatine
- Unclear or unknown: mirtazapine and bupropion

Adapted from Henssler et al (2019).[163]

Panel 9: Complementary treatments and emerging therapies

Complementary treatments

Complementary treatments include herbal compounds and nutraceuticals. Inconsistency of therapeutic dose ranges for most complementary treatments and lack of sufficient evidence, which is on par with that for antidepressants and psychological interventions, means that they are only recommended for treating less severe depression, but can be used adjunctively for more severe depression.

Herbal compounds include St John's Wort, saffron, lavender, and roseroot. Of these, only St John's Wort has evidence of efficacy in less severe depression. Hence, they are positioned as third-line treatments in the Canadian Network for Mood and Anxiety Treatments' guidelines.[47] Similarly, nutraceuticals (unregulated substances derived from natural sources), including dietary supplements and food additives such as omega-3 fatty acids and dehydroepiandrosterone, are regarded as second-line or third-line treatments for depression.

Emerging therapies

In recent years, renewed interest in developing novel treatments for depression has been fuelled by increasing frustration with existing therapies. Almost a third of patients with depression have a poor response to at least two adequate courses of currently available antidepressants and are referred to as treatment-resistant. As most antidepressants act on monoaminergic pathways, alternative mechanisms of action have been sought, often with the additional aim of having more immediate impact.

Ketamine and esketamine

Ketamine is an established dissociative anaesthetic that has been found to have psychoactive properties at subanaesthetic doses.[193] Binding to glutamate receptors, ketamine and its s-enantiomer (esketamine) reduce the symptoms of depression and suicide thoughts.[194,195] As such, intravenous ketamine is already used in the UK National Health Service to treat severe depression as an alternative to electroconvulsive therapy (appendix p 19).[196] However, even though the administration of intranasal esketamine and oral ketamine is easier, their use is limited partly due to limited long-term effects and the risk of dependence, but also due to the high cost of esketamine.[197] Hence, the National Institute for Health and Care Excellence does not endorse its use, and the US Food & Drug Administration has only approved esketamine as an adjunctive therapy to be administered alongside an oral antidepressant. A similar combination of ketamine with psychotherapy for depression is also available in the USA and the UK but this is not evidence-based.

Brexanolone

Brexanolone is a neurosteroid that structurally resembles endogenous allopregnanolone. It is a GABAergic system neuromodulator that enhances GABA signalling, a reduction in which has been found in women at risk for postpartum depression. Clinical trials have found it to be effective in this population and therefore it has an indication for postpartum depression (appendix pp 12–13).[198] Zuranolone—an allosteric GABA receptor modulator—is also showing antidepressant potential in early clinical trials.[199]

Medicinal cannabis

Components of *Cannabis sativa* are thought to have therapeutic potential and, in jurisdictions where medicinal cannabis products are licensed,[200] these are increasingly being self-administered to treat a range of medical and psychiatric conditions.[201] Although the main use of medicinal cannabis is for chronic pain, anxiety, sleep disorders, and post-traumatic stress disorder, individuals with depression are also taking specific formulations.[201] However, although there is some preliminary evidence regarding the use of medicinal cannabis in anxiety,[202] the evidence for its use specifically in depression is scarce (ie, its use to treat depression is not evidence-based). This is probably because, of the several hundred compounds within cannabis, tetrahydrocannabinol and cannabidiol are the most common, and while tetrahydrocannabinol is psychoactive (ie, causes a high), cannabidiol is not. However, in practice and especially in jurisdictions where there is no regulation of medicinal cannabis-containing products, those that are labelled as cannabidiol might contain tetrahydrocannabinol and might not be accurately labelled. Hence there is potential for substantial misuse of medicinal cannabis (appendix pp 12–13).[203,204]

Psychedelics

Psychedelics have a long history of use in healing as well as in ceremonies of religious and spiritual importance. A resurgence of interest in the past two decades has brought several agents to the fore, many of which are administered alongside psychotherapeutic interventions.[205,206]

Psilocybin is found in specific species of fungi and is consumed orally in the treatment of depression alongside psychological support.[207] Recent research suggests it might have some benefit in select cases, but emerging evidence also points to a potential increase in suicidality.[208] Hence, it is only available under supervision in approved health-care settings (appendix pp 12–13).

Ayahuasca is a traditional Amazonian plant medicine that is brewed to extract the hallucinogen dimethyltryptamine. Preliminary randomised controlled trials suggest a rapid but very short-lived antidepressant effect, with the majority of those injecting ayahuasca vomiting and many having severe nausea (appendix pp 12–13). Other molecules currently being investigated for their use in psychiatric disorders include 3,4-methylenedioxymethamphetamine (MDMA; also known as ecstasy). Currently MDMA has only been licensed for use in the

(Continues on next page)

(Panel 9 continued from previous page)

context of MDMA-assisted therapy for the treatment of post-traumatic stress disorder, and there is currently no evidence for its use in the treatment of depression.[219]

Anti-inflammatory medications and agents

Minocycline is an established tetracycline antibiotic that treats a broad spectrum of bacterial infections, including acne. It has been trialled in the treatment of depression (treatment-resistant and comorbid) both as monotherapy and adjunctive to antidepressants, and has been found to have variable benefit.[220–222] It is well tolerated but further research to establish its therapeutic profile as an antidepressant is under way.

Neuropeptide Y is produced in neurons and is involved in physiological regulatory processes including inflammatory mechanisms implicated in depression. When administered intranasally alongside an antidepressant, it appears to produce a rapid antidepressant effect that is short-lived.[223] Although promising, as it builds on the inflammatory hypothesis of depression, further research is needed.

Celecoxib—a non-steroidal anti-inflammatory drug used commonly for arthritic pain—has been found to have an antidepressant effect when prescribed adjunctively.[224]

Omega-3 fatty acid and cholesterol-lowering statins have been found to be effective when administered alongside antidepressants in treating depression, and omega-3 fatty acids are also useful as monotherapy; however long-term benefits need further research.[224]

Probiotics that contain live microorganisms have been investigated for antidepressant effects based on the hypothesis that gut alterations in microbiota can affect mental illnesses via gut–brain communication. Specific probiotic strains appear promising and might work by modifying the production of neurotransmitter precursors in the gut and countering inflammatory processes.[225] Similarly, prebiotics that consist of non-digestible fibre that stimulate gut bacteria selectively might also be of benefit in treating depression; however further research is needed.

Microbiome-targeted therapies

Faecal microbiota transplantation involves the transfer of faecal matter from a healthy person into the digestive system of a patient with depression. The aim is to restore the microbial composition of the gut. The process of faecal microbiota transplantation has shown encouraging results but further research is needed to understand the relationship between gut bacteria and depression and how altering the gut microbiota can alter mood.[226–228]

Conclusion

Depression is common throughout adulthood, and psychoeducation, lifestyle modifications, and psychological interventions might help anticipate acute exacerbations and limit illness duration. Treatments for depression are as multifaceted as the illness itself. A large proportion of patients will require multiple treatments to regain normal functioning, some will require referral to specialists and hospitalisation, and a few might never fully recover. Therefore, research into the development of new medications remains crucial alongside improving diagnosis and management using existing knowledge and treatments.

OpenAI o1-preview ist eine Reihe fortschrittlicher KI-Modelle, die speziell für komplexes logisches Denken (Reasoning) in Wissenschaft, Programmierung und Mathematik entwickelt wurden. Im Gegensatz zu GPT-4o „denken“ diese Modelle vor der Antwort länger nach und lösen Aufgaben schrittweise. Es ist als Vorschauversion verfügbar.

Wichtige Merkmale von o1-preview:

•**Verbessertes Reasoning:** o1-preview ist darauf ausgelegt, schwierige Probleme zu durchdenken, anstatt nur schnell zu antworten.

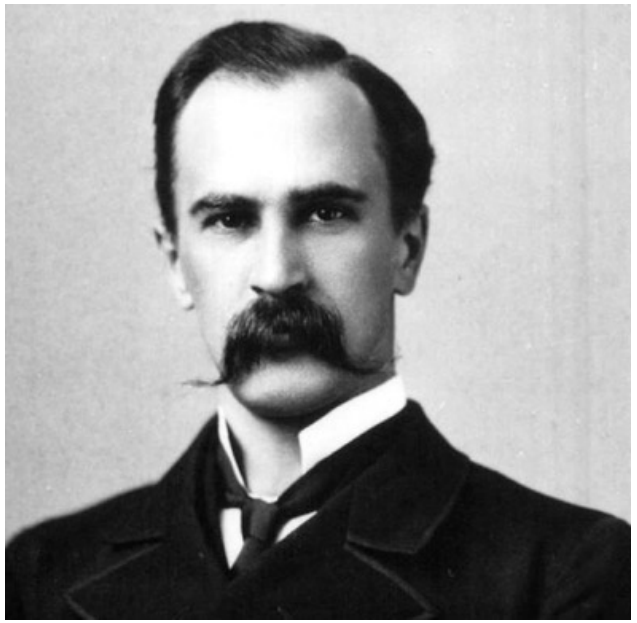
•**Chain of Thought (Gedankenkette):** Die Modelle generieren intern eine lange Kette von Überlegungen, bevor sie eine finale Antwort ausgeben.

•**Anwendungsgebiete:** Besonders stark in den MINT-Fächern (Mathematik, Informatik, Naturwissenschaft, Technik).

•**Verfügbarkeit:** Für ChatGPT Plus/Team-Nutzer sowie Entwickler (via API) zugänglich, mit aktuellen Ratenbegrenzungen (Stand September 2024: 50 Abfragen/Woche für o1-preview).

•**Unterschied zu o1-mini:** o1-preview bietet ein breiteres Weltwissen, während o1-mini schneller und kosteneffizienter, besonders beim Programmieren ist.

versus



AI can reason like a physician—what comes next?

Large language models (LLMs) are artificial intelligence (AI) algorithms that are trained on vast amounts of data to learn patterns that enable them to generate human-like responses. Reasoning models are LLMs with the added capability of working through problems step by step before responding, thus mirroring structured thinking. Such AI systems have performed well in assessing medical knowledge, but whether they can match physician-level clinical reasoning on authentic diagnostic tasks remains largely unknown. Brodeur *et al.* demonstrate that AI can now seemingly match or exceed physician-level clinical diagnostic reasoning on text-based scenarios by measuring against human physician performances on clinical vignettes and real-world emergency cases. The findings indicate an urgent need to understand how these tools can be safely integrated into clinical workflows, and a readiness for prospective evaluation alongside clinicians.

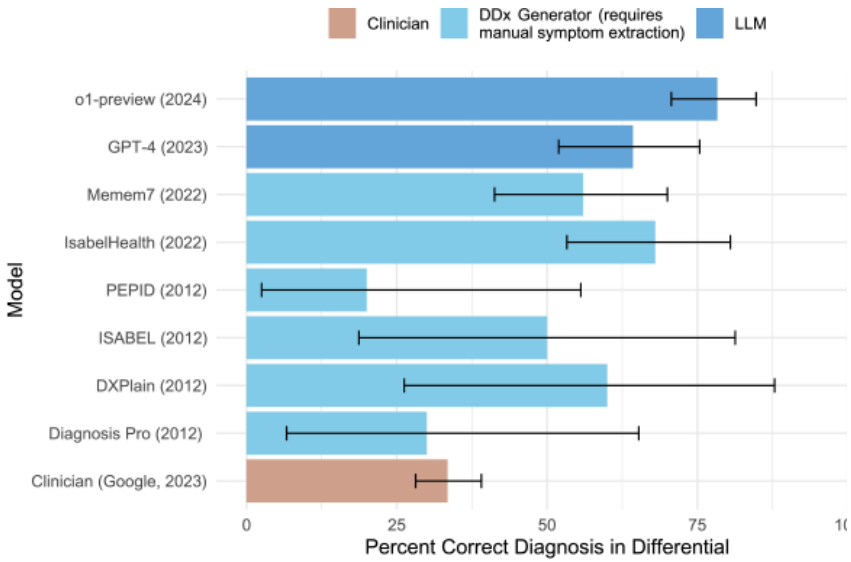
Performance of a large language model on the reasoning tasks of a physician

More than 65 years ago, complex clinical diagnostic reasoning cases were introduced as the gold standard for the evaluation of expert medical computing systems, a standard that has held ever since. in this study, we report the results of a physician evaluation of a large language model (llM) on challenging clinical cases across five experiments with a baseline of hundreds of physicians. We then report a real-world study comparing human expert and artificial intelligence (Ai) second opinions in randomly selected patients in the emergency room of a major tertiary academic medical center. in all experiments, the llM outperformed physician baselines and displayed continued improvement from prior generations of Ai clinical decision support. Our study suggests that llMs have eclipsed most benchmarks of clinical reasoning, motivating the urgent need for prospective trials.

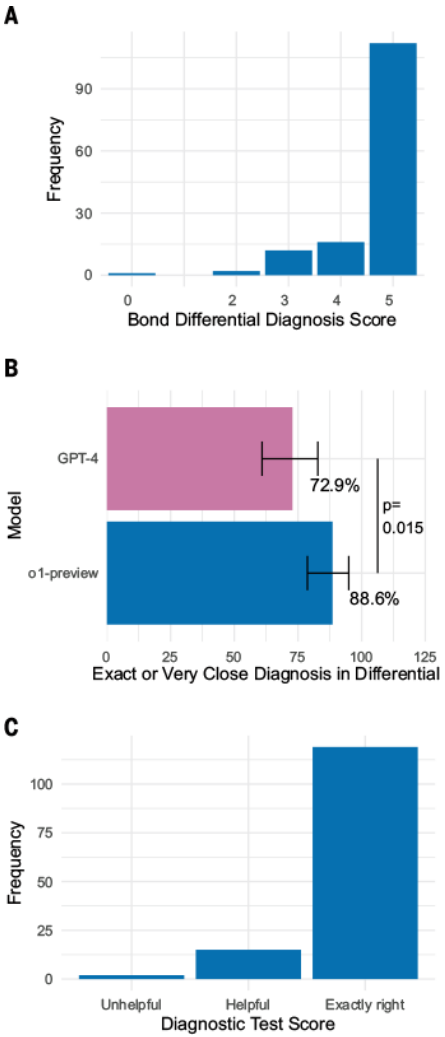
Quality of differential diagnoses and testing plans on NEJM clinicopathological conferences

We first evaluated o1-preview using the clinicopathologic conferences (CPCs) published by the *NEJM*, a standard for the evaluation of differential generators since the 1950s. There was substantial agreement between the two physicians evaluating the quality of o1-preview's differential diagnosis [agreement on 120/143 cases (84%), inter-rater reliability (K) = 0.66]. o1-preview included the correct diagnosis in its differential in 78.3% of cases [95% confidence interval (CI), 70.7 to 84.8%]. The first diagnosis suggested was the correct diagnosis in 52% of cases (95% CI, 44 to 61%). When expanding to also include potentially helpful or very close diagnoses, o1-preview was accurate on 97.9% (95% CI, 94.0 to 99.6%) of cases. We did not find evidence of a significant difference in performance before and after the pretraining cutoff date for o1-preview (79.8% accuracy before, 73.5% accuracy after, $P = 0.59$).

In a subset of 101 cases from a prior study, o1-preview outperformed a human physician baseline in both top-1 and top-10 accuracy. On 70 cases used to evaluate GPT-4 in a prior study, o1-preview produced a response with the exact or a very close diagnosis in 88.6% of cases, compared with 72.9% of cases by GPT-4 (*P* = 0.015; Fig. 2B). Overall, o1-preview and GPT-4 performed identically on 48/70 (68.6%) of cases, o1-preview outperformed GPT-4 on 17/70 (24.3%) of cases, and GPT-4 outperformed o1-preview on 5/70 (7.1%) of cases.



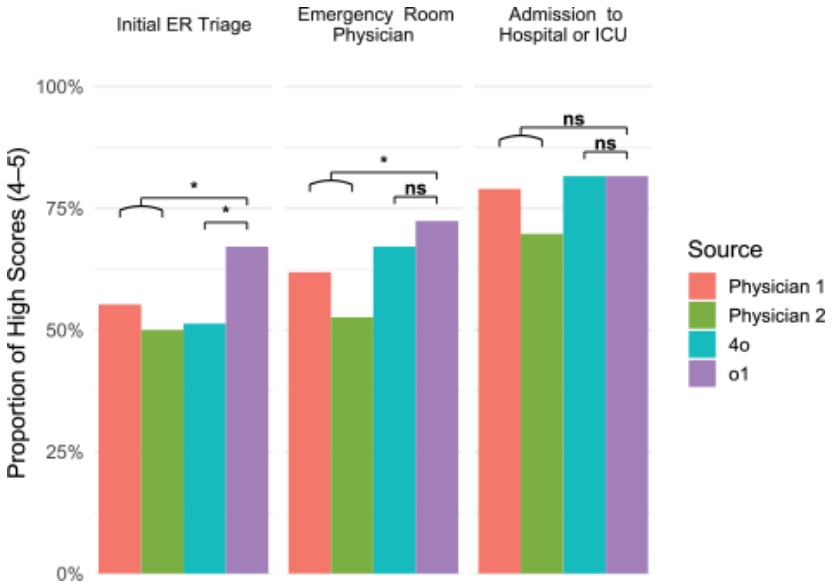
Performance of differential diagnosis generators and LLMs on *NEJM* clinico pathologic conferences (CPCs), 2012 to 2024. Bar plot showing the accuracy of including the correct diagnosis in the differential for differential diagnosis (DDx) generators and LLMs on the *NEJM* CPCs, sorted by year. Data for other LLMs or DDx generators were obtained from the literature (materials and methods). The 95% CIs were computed with a one-sample binomial test.



Quality of differential diagnosis and diagnostic test selection in *NEJM* clinicopathologic conferences (CPCs). (**A**) Histogram of o1-preview performance as measured by the Bond score on the complete set of 143 cases from 2021 to 2024. (**B**) Comparison of o1-preview with a previous evaluation of GPT-4 in providing the exact or very close diagnosis (Bond scores 4 to 5) on the same 70 cases. Bars are annotated with the accuracy of each model; 95% CIs were computed with a one-sample binomial test. The *P* value was com puted with McNemar's test. (**C**) Per formance of o1-preview in predicting the next diagnostic tests that should be ordered. Performance was measured by two physicians using a Likert scale of "Unhelpful," "Helpful," and "Exactly right." We excluded seven cases from the total case set in which it did not make sense to ask for the next test from the total case set (supplementary text 1C).

Discussion

We systematically evaluated the medical reasoning abilities of an LLM across six diverse experiments, comparing the model with hundreds of expert physicians. Overall, the model outperformed physicians across experiments, including in cases utilizing real and unstructured clinical data taken directly from the health record in an emergency department. These diagnostic touchpoints mirror the high-stakes decisions taken in emergency medicine departments, where nurses and clinicians make time-sensitive choices with limited information. Our results showed that humans, GPT-4o, and o1 all improved their diagnostic abilities as more information was available; o1 outperformed humans at multiple touchpoints, with the widest gap at initial ER triage, where there is the least information available.

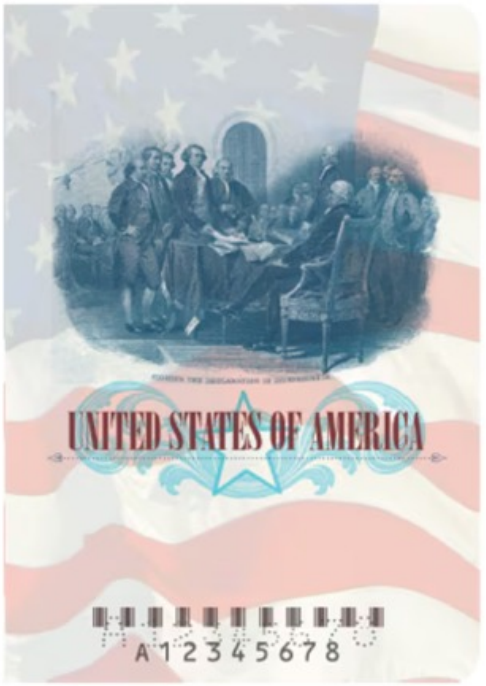


Blinded assessment of AI and human expert second opinions on real ER cases. Bar plot comparing two internal medicine attending physicians, o1, and GPT-4o diagnostic performance on 76 clinical cases at three diagnostic touchpoints (triage in the ER, initial evaluation by a physician, and admission to the hospital or ICU). Differential diagnoses were capped at five diagnoses for all participants. The source of the differential diagnosis was blinded and scored by two separate attending internal medicine physicians using the Bond scale. The proportion of responses scored 4 or 5 are shown, indicating a response that contains something exact or very close to the true diagnosis. *P* values were computed with a mixed-effects logistic regression model (materials and methods). $* P \leq 0.05$.

Overall, our findings show that LLMs now demonstrate substantial performance in differential diagnosis, diagnostic clinical reasoning, and management reasoning, and exceed both prior model generations and even human clinicians across multiple domains. These same performance gains are seen in providing second opinions in real, unstructured medical cases in the emergency department, where clinicians must act quickly with limited and often missing information.

More than 65 years ago, Ledley and Lusted described the standard for evaluating the diagnostic abilities of AI. The broad challenge they laid out of reasoning over complex clinical case vignettes has guided the development and evaluation of computational systems for much of the past century. Our findings suggest that LLMs have now eclipsed most benchmarks of clinical reasoning, motivating the urgent need for human-computer interaction studies and prospective clinical trials to rigorously assess the potential of AI systems to improve clinical practice and patient outcomes.

Image of Trump to be featured inside new passports to mark America's 250th



Fortunately, I renewed my passport in 2025