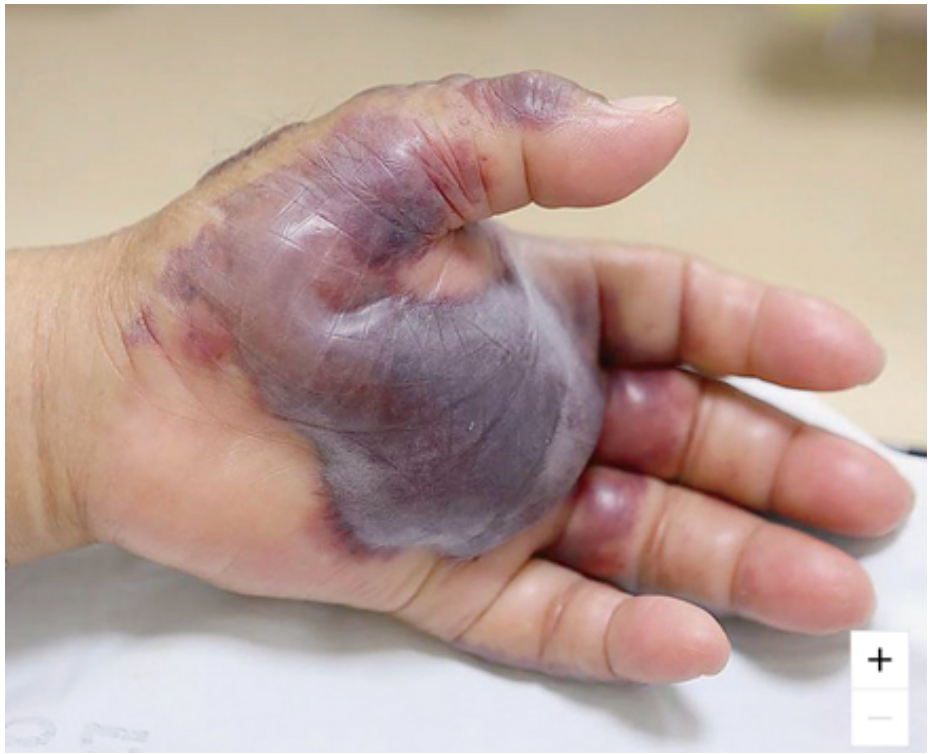
A 71-year-old man presented with fever and excruciating left-hand pain that developed 12 hours after eating raw seafood. His past medical history was significant for type 2 diabetes mellitus, hypertension, and end-stage renal disease. At time of presentation, a hemorrhagic bullae measuring 3.5 by 4.5 cm had developed in the palm of his left hand. Surgical intervention was performed and a causative organism was isolated. What is the most likely organism?



Staphylococcus aureus

Streptococcus pyogenes

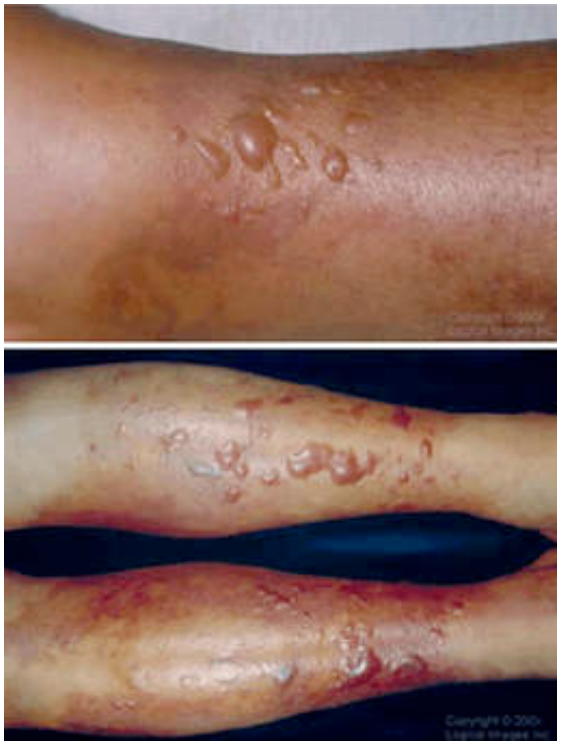
Haemophilus influenza

Vibrio vulnificus

Pseudomonas aeruginosa

The correct answer is Vibrio vulnificus infection. V. vulnificus can cause skin infections after wound exposure to contaminated seawater as well as primary septicemia through the consumption of contaminated raw or undercooked seafood. Patients with immunocompromising conditions, which include chronic liver disease and cancer, are at increased risk for infection and complications.

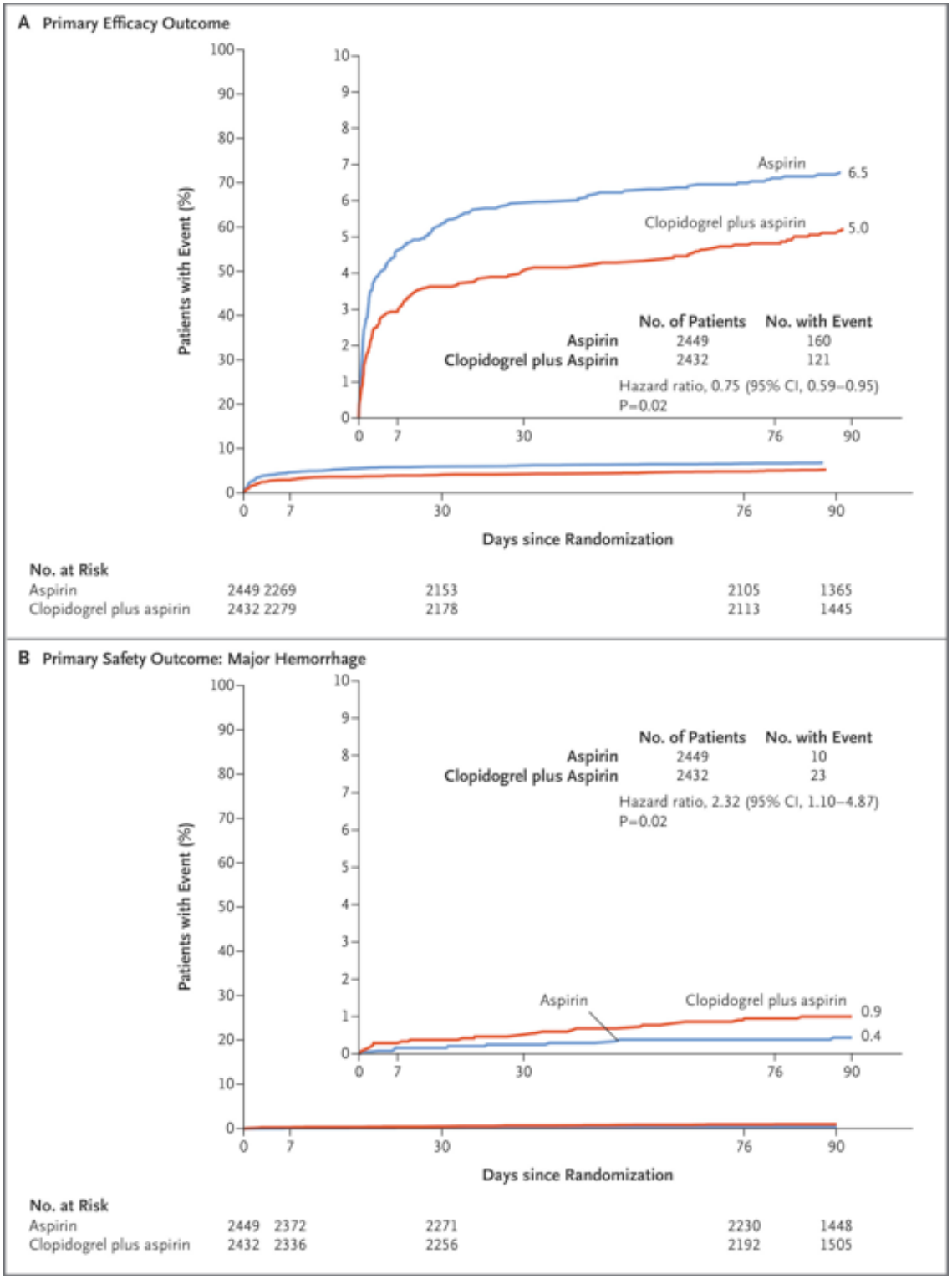
Vibrio vulnificus ist eine Art gram-negativer, gekrümmter Stäbchen-Bakterien der Gattung Vibrio. Sie kommen vor in marinen Umgebungen wie Flussmündungen, Brackwasser-Tümpeln oder Küstengebieten. V. vulnificus ist eng verwandt mit V. cholerae, dem Auslöser der Cholera. Eine Infektion mit V. vulnificus führt zu sich rasch ausdehnender Cellulitis oder Sepsis. Vibrio vulnificus verursacht eine Infektion, die häufig nach dem Verzehr von Meeresfrüchten, insbesondere Austern, auftritt; die Bakterien können auch durch offene Wunden (dazu zählen auch frische, d. h. noch nicht vollständig verheilte Tätowierungen) in den Körper eindringen beim Schwimmen oder Waten in verseuchten Gewässern, oder über Stichwunden durch Dornen von Fischen wie den Tilapia. Zu den Symptomen gehören Erbrechen, Diarrhö, Leibschmerzen und eine Blasen werfende Dermatitis, die manchmal fälschlicherweise für Pemphigus vulgaris oder Pemphigus gehalten wird.
Bei Menschen mit geschwächtem Immunsystem wie chronischer Leberkrankheit kann sich ein mit Vibrio-Bakterien infizierter Schnitt rasch verschlimmern und auf den Blutkreislauf übergreifen. Schwere Symptome können auftreten, sogar Tod.



Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA

Combination antiplatelet therapy with clopidogrel and aspirin may reduce the rate of recurrent stroke during the first 3 months after a minor ischemic stroke or transient ischemic attack (TIA). A trial of combination antiplatelet therapy in a Chinese population has shown a reduction in the risk of recurrent stroke. We tested this combination in an international population. In a randomized trial, we assigned patients with minor ischemic stroke or high-risk TIA to receive either clopidogrel at a loading dose of 600 mg on day 1, followed by 75 mg per day, plus aspirin (at a dose of 50 to 325 mg per day) or the same range of doses of aspirin alone. The dose of aspirin in each group was selected by the site investigator. The primary efficacy outcome in a time-to-event analysis was the risk of a composite of major ischemic events, which was defined as ischemic stroke, myocardial infarction, or death from an ischemic vascular event, at 90 days. Patients who were at least 18 years of age were enrolled if they could undergo randomization within 12 hours after having an acute ischemic stroke with a score of 3 or less on the National Institutes of Health Stroke Scale (NIHSS) (scores range from 0 to 42, with higher scores indicating greater stroke severity) or a high-risk TIA with a score of 4 or more on the ABCD^2 scale

Characteristic	Clopidogrel plus Aspirin (N=2432)	Aspirin (N=2449)
Median age (IQR) — yr	65.0 (55.0–74.0)	65.0 (56.0–74.0)
Female sex — no. (%)	1097 (45.1)	1098 (44.8)
Race — no./total no. (%)†		
White	1774/2360 (75.2)	1781/2378 (74.9)
Black	473/2360 (20.0)	493/2378 (20.7)
Asian	77/2360 (3.3)	67/2378 (2.8)
Other	36/2360 (1.5)	37/2378 (1.6)
Hispanic ethnic group — no./total no. (%)†	144/2320 (6.2)	146/2328 (6.3)
Region — no. (%)		
United States	2014 (82.8)	2029 (82.9)
Other countries	418 (17.2)	420 (17.1)
Medical history — no./total no. (%)		
Ischemic heart disease	257/2426 (10.6)	240/2443 (9.8)
Hypertension	1693/2423 (69.9)	1680/2437 (68.9)
Diabetes mellitus	678/2425 (28.0)	662/2447 (27.1)
Medication use at presentation — no. (%)		
Aspirin	1417 (58.3)	1397 (57.0)
Clopidogrel	48 (2.0)	42 (1.7)
Time from presentation to randomization		
Mean time (±SD) — hr	7.4±3.0	7.3±2.9
Interval — no./total no. (%)		
<6 hr	755/2431 (31.1)	789/2449 (32.2)
≥6 hr	1676/2431 (68.9)	1660/2449 (67.8)
Qualifying event — no. (%)		
TIA	1056 (43.4)	1052 (43.0)
Ischemic stroke	1376 (56.6)	1397 (57.0)
Median qualifying neurologic score (IQR)		
ABCD^2 for TIA‡	5.0 (4.0–6.0)	5.0 (4.0–5.0)
NIHSS for ischemic stroke§	2.0 (1.0–2.0)	2.0 (1.0–2.0)



Shown are the percentages of patients with the primary efficacy outcome (a composite of ischemic stroke, myocardial infarction, or death from ischemic vascular causes) (Panel A) and the primary safety outcome of major hemorrhage (Panel B). Inset graphs show the same data on an expanded y axis.

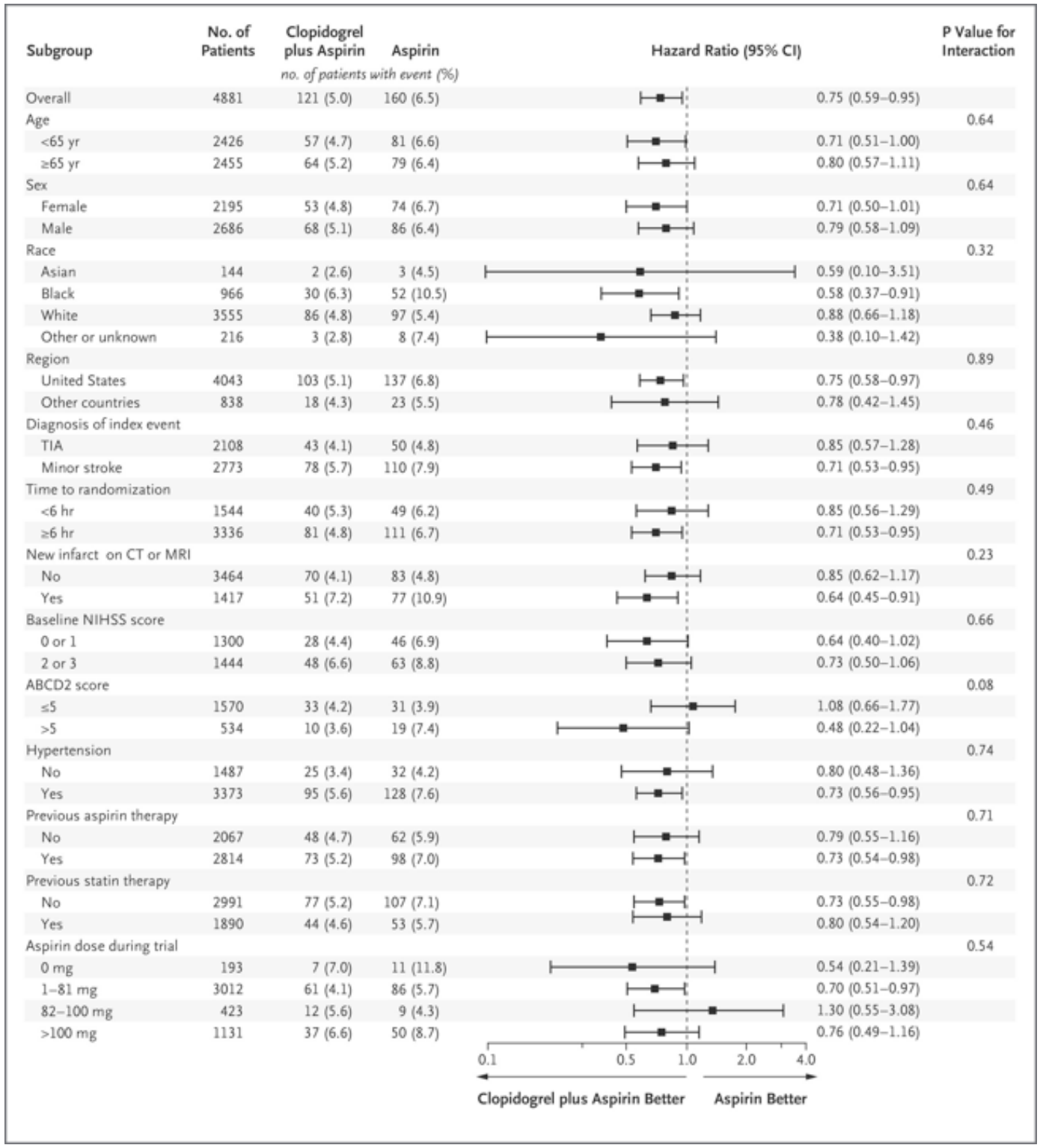

Subgroup
No. of Patients
Clopidogrel plus Aspirin
Aspirin
no. of patients with event (%)
Hazard Ratio (95% CI)
P Value for Interaction
Overall 4881 121 (5.0) 160 (6.5) 0.75 (0.59–0.95)
Age 0.64
<65 yr 2426 57 (4.7) 81 (6.6) 0.71 (0.51–1.00)
≥65 yr 2455 64 (5.2) 79 (6.4) 0.80 (0.57–1.11)
Sex 0.64
Female 2195 53 (4.8) 74 (6.7) 0.71 (0.50–1.01)
Male 2686 68 (5.1) 86 (6.4) 0.79 (0.58–1.09)
Race 0.32
Asian 144 2 (2.6) 3 (4.5) 0.59 (0.10–3.51)
Black 966 30 (6.3) 52 (10.5) 0.58 (0.37–0.91)
White 3555 86 (4.8) 97 (5.4) 0.88 (0.66–1.18)
Other or unknown 216 3 (2.8) 8 (7.4) 0.38 (0.10–1.42)
Region 0.89
United States 4043 103 (5.1) 137 (6.8) 0.75 (0.58–0.97)
Other countries 838 18 (4.3) 23 (5.5) 0.78 (0.42–1.45)
Diagnosis of index event 0.46
TIA 2108 43 (4.1) 50 (4.8) 0.85 (0.57–1.28)
Minor stroke 2773 78 (5.7) 110 (7.9) 0.71 (0.53–0.95)
Time to randomization 0.49
<6 hr 1544 40 (5.3) 49 (6.2) 0.85 (0.56–1.29)
≥6 hr 3336 81 (4.8) 111 (6.7) 0.71 (0.53–0.95)
New infarct on CT or MRI 0.23
No 3464 70 (4.1) 83 (4.8) 0.85 (0.62–1.17)
Yes 1417 51 (7.2) 77 (10.9) 0.64 (0.45–0.91)
Baseline NIHSS score 0.66
0 or 1 1300 28 (4.4) 46 (6.9) 0.64 (0.40–1.02)
2 or 3 1444 48 (6.6) 63 (8.8) 0.73 (0.50–1.06)
ABCD2 score 0.08
≤5 1570 33 (4.2) 31 (3.9) 1.08 (0.66–1.77)
>5 534 10 (3.6) 19 (7.4) 0.48 (0.22–1.04)
Hypertension 0.74
No 1487 25 (3.4) 32 (4.2) 0.80 (0.48–1.36)
Yes 3373 95 (5.6) 128 (7.6) 0.73 (0.56–0.95)
Previous aspirin therapy 0.71
No 2067 48 (4.7) 62 (5.9) 0.79 (0.55–1.16)
Yes 2814 73 (5.2) 98 (7.0) 0.73 (0.54–0.98)
Previous statin therapy 0.72
No 2991 77 (5.2) 107 (7.1) 0.73 (0.55–0.98)
Yes 1890 44 (4.6) 53 (5.7) 0.80 (0.54–1.20)
Aspirin dose during trial 0.54
0 mg 193 7 (7.0) 11 (11.8) 0.54 (0.21–1.39)
1–81 mg 3012 61 (4.1) 86 (5.7) 0.70 (0.51–0.97)
82–100 mg 423 12 (5.6) 9 (4.3) 1.30 (0.55–3.08)
>100 mg 1131 37 (6.6) 50 (8.7) 0.76 (0.49–1.16)
0.1
0.5
1.0
2.0
4.0
Clopidogrel plus Aspirin Better
Aspirin Better

Table 2. Efficacy and Safety Outcomes.

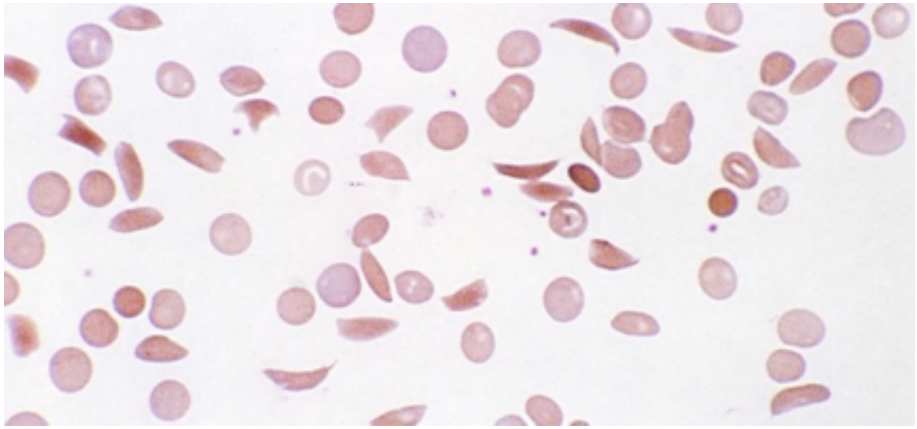
Outcome	Clopidogrel plus Aspirin (N=2432)	Aspirin (N=2449)	Hazard Ratio (95% CI)	P Value
	number (percent)			
Primary efficacy outcome				
Composite of ischemic stroke, myocardial infarction, or death from ischemic vascular causes	121 (5.0)	160 (6.5)	0.75 (0.59–0.95)	0.02
Secondary efficacy outcomes				
Ischemic stroke	112 (4.6)	155 (6.3)	0.72 (0.56–0.92)	0.01*
Myocardial infarction	10 (0.4)	7 (0.3)	1.44 (0.55–3.78)	0.46*
Death from ischemic vascular causes	6 (0.2)	4 (0.2)	1.51 (0.43–5.35)	0.52*
Ischemic or hemorrhagic stroke	116 (4.8)	156 (6.4)	0.74 (0.58–0.94)	0.01*
Composite of ischemic stroke, myocardial infarction, death from ischemic vascular causes, or major hemorrhage	141 (5.8)	167 (6.8)	0.84 (0.67–1.05)	0.13*
Primary safety outcome				
Major hemorrhage	23 (0.9)	10 (0.4)	2.32 (1.10–4.87)	0.02
Other safety outcomes				
Hemorrhagic stroke	5 (0.2)	3 (0.1)	1.68 (0.40–7.03)	0.47
Symptomatic intracerebral hemorrhage	2 (0.1)	2 (0.1)	1.01 (0.14–7.14)	0.99
Other symptomatic intracranial hemorrhage	2 (0.1)	0		0.16
Major hemorrhage other than intracranial hemorrhage	17 (0.7)	7 (0.3)	2.45 (1.01–5.90)	0.04
Minor hemorrhage	40 (1.6)	13 (0.5)	3.12 (1.67–5.83)	<0.001
Death from any cause	18 (0.7)	12 (0.5)	1.51 (0.73–3.13)	0.27

* Post hoc correction for multiple testing of five secondary end points by the Bonferroni method resulted in a P value of 0.01 to indicate a significant difference between groups.

In this international, multicenter, randomized trial, we found that patients with minor ischemic stroke or high-risk TIA who received a combination of clopidogrel and aspirin had a lower risk of major ischemic events but a higher risk of major and minor hemorrhage than did those receiving aspirin alone. Ischemic stroke accounted for most of the composite events of the primary efficacy outcome, and the effect of dual antiplatelet treatment was attributable to a reduction in the rate of these strokes. It is not possible to make direct comparisons between clinical and safety outcomes because disability due to each of the outcomes cannot be ascertained, but we estimate that for every 1000 patients who are treated with clopidogrel plus aspirin during a period of 90 days, such treatment would prevent approximately 15 ischemic events and would cause 5 major hemorrhages. The aspirin dose varied in the two treatment groups, which reflected the clinical practices of local investigators; however, in a potentially underpowered analysis, no difference in treatment effect was shown across aspirin doses.

In conclusion, in patients from diverse countries with minor ischemic stroke or high-risk TIA, those who received a combination of clopidogrel and aspirin had a lower risk of a composite of ischemic stroke, myocardial infarction, or death from ischemic vascular causes but had a higher risk of major hemorrhage than patients who received aspirin alone during the 90-day trial period.

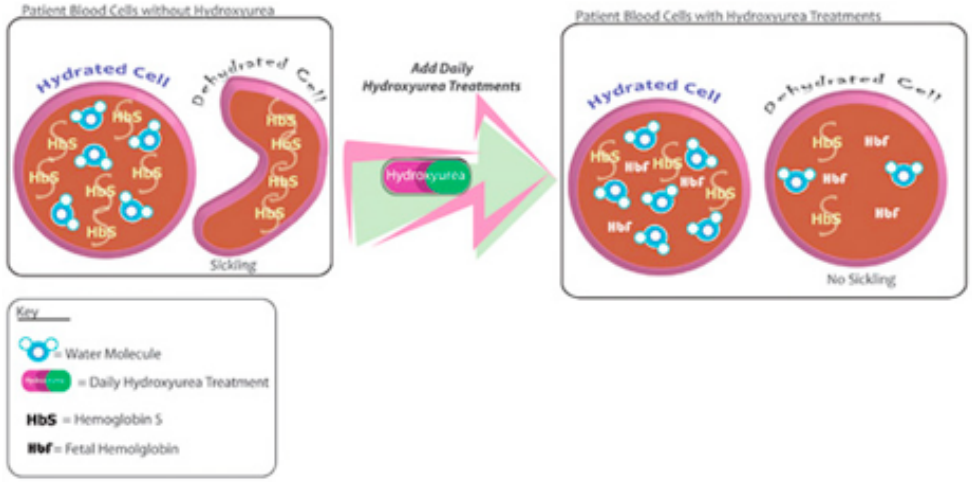
Die Sichelzellanämie ist eine Erbkrankheit, die zu den hämolytischen Anämien bzw. Hämoglobinopathien gehört. Sie wird durch einen genetischen Defekt (Punktmutation) ausgelöst, der zur Bildung von irregulärem Hämoglobin, dem so genannten Sichelzellhämoglobin (Hämoglobin S, HbS) führt. Die Sichelzellanämie folgt einem autosomal-rezessiven Erbgang. Es besteht eine Punktmutation der ß-Globinkette, wobei an Position 6 hydrophiles Glutamat gegen hydrophobes Valin substituiert wurde. Im desoxygenierten Zustand des HbS bilden sich Aggregate und es kommt zur Hämolyse.

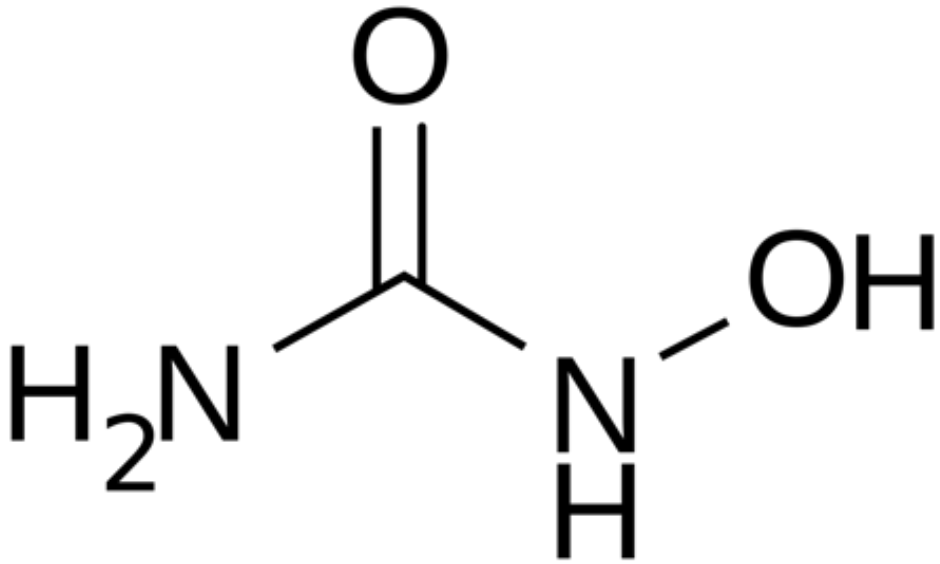


Es erkranken nur homozygote Merkmalsträger, bei denen das mütterliche und väterliche Gen verändert ist. Heterozygote Merkmalsträger sind weitgehend symptomfrei, da beide Allele kodominant sind, d.h. die Merkmalsträger produzieren sowohl normales als auch defektes Hämoglobin. Allerdings wird auch bei ihnen unter starkem Sauerstoffmangel, wie zum Beispiel während einer Narkose, die Sichelform der Erythrozyten ausgebildet, so dass es zu einer Beeinträchtigung der Organdurchblutung kommen kann.

Das akute Krankheitsgeschehen der Sichelzellanämie findet während einer sogenannten Sichelzellkrise statt. Auslöser einer Sichelzellkrise sind beispielsweise: Die Mikrozirkulation wird eingeschränkt und Organschädigungen resultieren. Nach längerer Krankheitsdauer können sich bedrohliche Komplikationen entwickeln, darunter Infarkte von Organen (z.B. Milz, Lunge). Zusätzlich kann sich ein akutes Thorax-Syndrom (ATS), ein Hand-Fuß-Syndrom (v.a. im Kindesalter) oder ein Priapismus klinisch manifestieren.

Hydroxycarbamid (oder hydroxyurea) ist ein zytostatisch wirkender Arzneistoff, dessen Einsatzschwerpunkt die Therapie der chronisch lymphatischen Leukämie (CLL) darstellt. Seltener wird der Wirkstoff auch gegen die Sichelzellenanämie oder die Thalassämia major verwendet. Hydroxycarbamid wirkt hemmend auf die Mitose und die DNA-Synthese.
Hydroxycarbamid hemmt zunächst einmal die Synthese von DNA, was eine Zellteilung unmöglich macht. Der genaue Wirkungsmechanismus ist noch nicht gänzlich geklärt. Als wahrscheinlich gilt, dass das Zytostatikum das Enzym Ribonukleotidreduktase hemmt. Dieses katalysiert die Umwandlung von Ribose in Desoxyribose. Letztere ist ein wichtiger Baustein der DNA. Steht nicht genug Desoxyribose zur Verfügung, ist DNA-Synthese blockiert. Gleiches gilt folglich für die Zellteilung.
Hydroxycarbamid verhindert weiterhin eine Integration von Thymin-Nukleotiden in den DNA-Strang.





Fetales Hämoglobin stoppt das Entstehen dieser Polymere im Sichelhämoglobin innerhalb der roten Blutkörperchen. Das Medikament Hydroxyurea wird verwendet, um fetales Hämoglobin zu erhöhen und dadurch die Auswirkungen der Erkrankung zu reduzieren. Dies ist eine Aktualisierung eines zuvor veröffentlichten Cochrane Review.

A Phase 3 Trial of l-Glutamine in Sickle Cell Disease

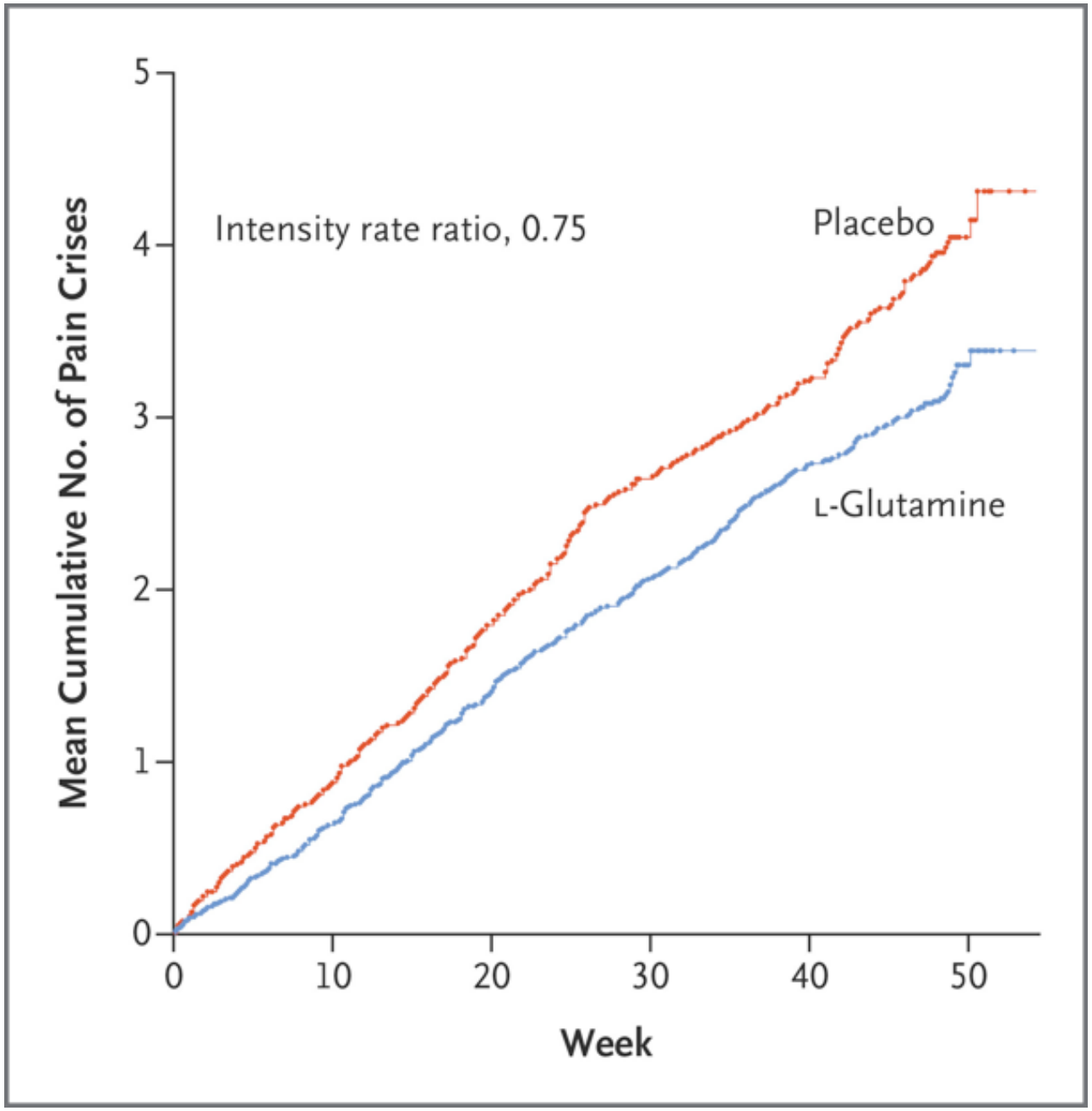
Oxidative stress contributes to the complex pathophysiology of sickle cell disease. Oral therapy with pharmaceutical-grade l-glutamine (USAN, glutamine) has been shown to increase the proportion of the reduced form of nicotinamide adenine dinucleotides in sickle cell erythrocytes, which probably reduces oxidative stress and could result in fewer episodes of sickle cell–related pain. In a multicenter, randomized, placebo-controlled, double-blind, phase 3 trial, we tested the efficacy of pharmaceutical-grade l-glutamine (0.3 g per kilogram of body weight per dose) administered twice daily by mouth, as compared with placebo, in reducing the incidence of pain crises among patients with sickle cell anemia or sickle β0-thalassemia and a history of two or more pain crises during the previous year. Patients who were receiving hydroxyurea at a dose that had been stable for at least 3 months before screening continued that therapy through the 48-week treatment period.

Oxidative stress contributes to the complex pathophysiology of sickle cell disease. Nicotinamide adenine dinucleotide (NAD^+) is a ubiquitous oxidation–reduction (redox) cofactor in red cells. NAD^+ and its reduced form, NADH, play major roles in maintaining redox balance. Sickle red cells have a lower redox ratio ([NADH]:[NAD^++NADH]) than normal red cells.

Table 1. Baseline Characteristics in the Intention-to-Treat Population.*

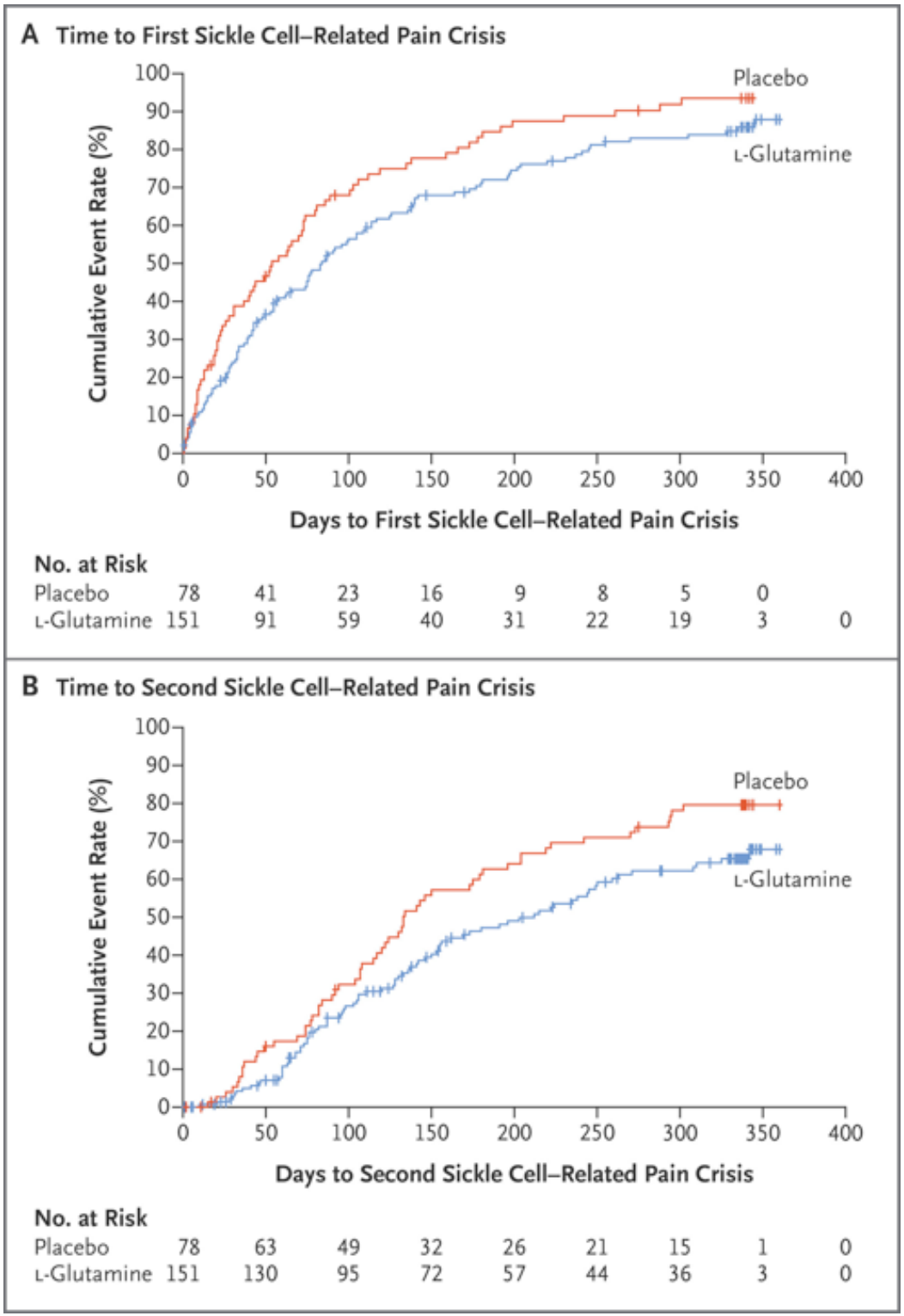
Characteristic	L-Glutamine (N=152)	Placebo (N=78)
Age — yr		
Mean	22.4±12.32	21.4±12.42
Median (range)	19.0 (5 to 57)	17.0 (5 to 58)
Age group — no. (%)		
5–12 yr	34 (22.4)	17(21.8)
13–18 yr	41 (27.0)	26 (33.3)
>18 yr	77 (50.7)	35 (44.9)
Hydroxyurea use — no. (%)	101 (66.4)	52 (66.7)
Sex — no. (%)		
Male	73 (48.0)	33 (42.3)
Female	79 (52. 0)	45 (57.7)
Race or ethnic group — no. (%)†		
Black	144 (94.7)	73 (93.6)
Hispanic	4 (2.6)	3 (3.8)
Other	4 (2.6)	2 (2.6)
Diagnosis — no. (%)		
Sickle cell anemia	136 (89.5)	71 (91.0)
Sickle β^0-thalassemia	14 (9.2)	7 (9.0)
Sickle β^+-thalassemia	2 (1.3)	0
Sickle cell pain crises in the year before trial entry — no. (%)		
0–1	1 (0.7)	1 (1.3)
2–5	128 (84.2)	61 (78.2)
6–9	15 (9.9)	14 (17.9)
≥10	8 (5.3)	2 (2.6)
Hemoglobin level at baseline — g/dl	8.8±1.4	8.7±1.2
Hematocrit level at baseline — %	27.7±4.4	27.5±3.6
No. of reticulocytes at baseline — per mm^3	284,000±129,000	295,000±142,000

* Plus–minus values are means ±SD. Percentages may not sum to 100 because of rounding.
† Race and ethnic group were reported by the patients.



Recurrent Events of Sickle Cell–Related Pain Crisis over Time, According to Trial Group.

An analysis of sickle cell–related pain crisis over time yielded an intensity rate ratio (i.e., the ratio of the recurrent event rates in each trial group) of 0.75 (95% CI, 0.62 to 0.90, according to the Andersen–Gill model; and 95% CI, 0.55 to 1.01, according to the Lin–Wei–Yang–Ying modification of the Andersen–Gill model), which indicates that the cumulative number of painful crises was 25% lower in the l-glutamine group than in the placebo group over the entire 48-week treatment period.



Time to Sickle Cell–Related Pain Crisis.

Panel A shows the Kaplan–Meier curves for time to the first sickle cell–related pain crisis. The median time to the first pain crisis was 84 days (95% CI, 62 to 109) in the l-glutamine group, as compared with 54 days (95% CI, 31 to 73) in the placebo group (hazard ratio, 0.69; 95% CI, 0.52 to 0.93; P=0.02). Panel B shows the Kaplan–Meier curves for time to the second sickle cell–related pain crisis. The median time to the second pain crisis was 212 days (95% CI, 153 to 250) in the l-glutamine group, as compared with 133 days (95% CI, 115 to 179) in the placebo group (hazard ratio, 0.68; 95% CI, 0.49 to 0.96; P=0.03).

Table 2. End-Point and Additional Analyses.

Through Week 48	L-Glutamine (N=152)	Placebo (N=78)	P Value
Primary end point			
No. of pain crises			0.005*
Mean	3.2±2.24	3.9±2.54	
Median (range)	3 (0–15)	4 (0–15)	
Secondary end points			
No. of hospitalizations for sickle cell–related pain			0.005*
Mean	2.3±1.99	3.0±2.33	
Median (range)	2 (0–14)	3 (0–13)	
Cumulative no. of days in hospital			0.02†
Mean	12.1±16.6	18.1± 27.4	
Median (range)	6.5 (0–94)	11 (0–187)	
No. of emergency department visits for sickle cell–related pain			0.09*
Mean	1.1±1.49	1.5±2.29	
Median (range)	1 (0–12)	1 (0–15)	
Additional analyses			
Median no. of days to first pain crisis (95% CI)	84 (62–109)	54 (31–73)	0.02‡
Median no. of days to second pain crisis (95% CI)	212 (153–250)	133 (115–179)	0.03‡
Episodes of acute chest syndrome — no. (%)			0.003*
0	139 (91.4)	60 (76.9)	
≥1	13 (8.6)	18 (23.1)	
1	10 (6.6)	13 (16.7)	
2	3 (2.0)	4 (5.1)	
3	0	1 (1.3)	

* The P value was calculated with the use of the Cochran–Mantel–Haenszel test with modified ridit scores, with adjustment for region and hydroxyurea use
† The P value was calculated with the use of the Wilcoxon rank-sum test.
‡ The P value was calculated with the use of the log-rank test of the Kaplan–Meier survival curve.

The rate of adverse events was higher in the placebo group than in the l-glutamine group (100% vs. 98.0%), as was the rate of serious adverse events (87.1% vs. 78.2%). Adverse events with a higher incidence in the l-glutamine group than in the placebo group and with at least a 5% incidence in the l-glutamine group are listed.

Table 3. Adverse Events (Safety Population).*

Adverse Event	L-Glutamine (N=151)	Placebo (N=78)
	no. of patients (%)	
Cardiac disorders		
Tachycardia	8 (5.3)	4 (5.1)
Gastrointestinal disorders		
Constipation	38 (25.2)	19 (24.4)
Nausea	34 (22.5)	13 (16.7)
Vomiting	22 (14.6)	10 (12.8)
Abdominal pain upper	16 (10.6)	6 (7.7)
Diarrhea	12 (7.9)	5 (6.4)
General disorders and administration site conditions		
Chest pain (noncardiac)	21 (13.9)	7 (9.0)
Fatigue	9 (6.0)	1 (1.3)
Infections and infestations		
Urinary tract infection	10 (6.6)	3 (3.8)
Musculoskeletal and connective tissue disorders		
Pain in extremity	24 (15.9)	6 (7.7)
Back pain	20 (13.2)	5 (6.4)
Nervous system disorders		
Headache	32 (21.2)	14 (17.9)
Dizziness	8 (5.3)	4 (5.1)
Respiratory, thoracic, and mediastinal disorders		
Nasal congestion	11 (7.3)	5 (6.4)

* The table shows adverse events with a higher incidence in the L-glutamine group than in the placebo group and with at least a 5% incidence in the L-glutamine group. Adverse events are categorized by system organ class and preferred terms according to the *Medical Dictionary for Regulatory Activities*, version 12.0.

In the current trial, in which the majority of patients received concomitant hydroxyurea, the number of pain crises per patient was significantly lower in the l-glutamine group than in the placebo group and differed between trial groups by a median of one event over 48 weeks. The time to the first pain crisis began to diverge within 2 weeks after the start of the treatment period, with sustained separation of curves over the duration of the trial. The analysis of recurrent pain crises over time reinforced the observation that over the entire trial period, the median number of pain crises was 25% lower with l-glutamine than with placebo. The exact mechanisms by which l-glutamine reduces the frequency of pain crises have not been fully elucidated.

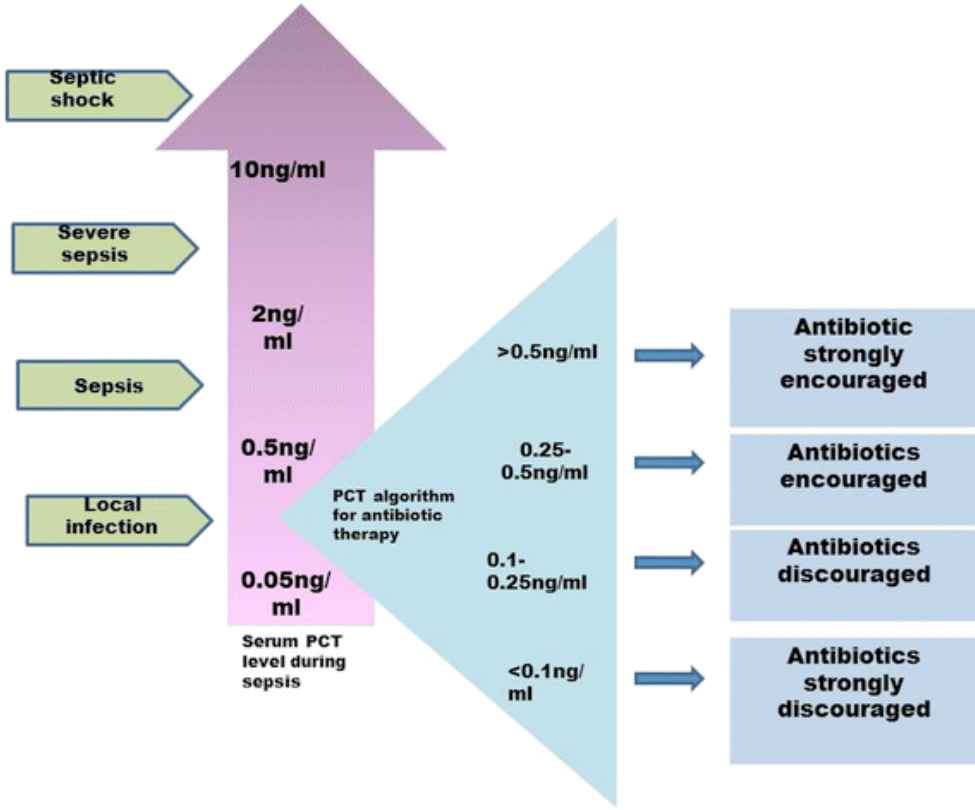
The 33% between-group difference in the median number of hospitalizations is notable because hospitalization can be very costly. The mean number of ED visits was lower in the l-glutamine group than in the placebo group, but the difference was not significant.

In 2017, the U.S. Food and Drug Administration approved l-glutamine (USAN, glutamine) for the prevention of acute vaso-occlusive pain events in persons with sickle cell disease who are older than 5 years of age — only the first drug to be approved for this indication in the 20 years since the approval of hydroxyurea.

The price of l-glutamine is much higher than that of hydroxyurea; 1 year of treatment with Endari (Emmaus Medical) for an average adult is estimated at $40,515, as compared with approximately $1700 for hydroxyurea. Whether the cost will be a hindrance to its use has yet to be determined. This agent certainly has been slow to enter the market because prescribing l-glutamine for patients requires many steps, which may dissuade busy practitioners from actively prescribing it. Because l-glutamine has a putatively different mechanism (or mechanisms) of action and toxicity profile than hydroxyurea, concomitant use is possible and most likely advantageous.

Therefore, caution may be warranted in prescribing l-glutamine to patients with sickle cell disease who have clinically significant renal and hepatic dysfunction. Of note, in the two randomized trials of l-glutamine involving patients with sickle cell disease, three deaths occurred in the l-glutamine groups, as compared with none in the placebo groups.

Procalcitonin ist das Prohormon des Calcitonins. Unter physiologischen Bedingungen wird Procalcitonin in den C-Zellen der Schilddrüse als Vorläuferprotein gebildet und proteolytisch zum funktionsfähigen Hormon prozessiert. Bei einem generalisiert-entzündlichen Geschehen wird Procalcitonin aus bisher nicht verstandenen Gründen vermehrt gebildet. Anders als unter physiologischen Bedingungen erfolgt die Synthese dann aber vermutlich in der Leber. Freisetzungsreiz sind hierbei u.a. bakterielle Endotoxine, z.B. das Lipopolysaccharid.
Procalcitonin erlangt dadurch eine hohe Spezifität für bakterielle Infektionen, insbesondere bei Vorliegen einer Sepsis oder systemisch verlaufenden Erkrankungen. In diesen Fällen kann es auf Werte von 10-1000 µg/l ansteigen. Es kann jedoch auch zu einem Anstieg des Procalcitonin-Wertes bei Pilzinfektionen und protozoenbedingten Infektionen kommen.
Bei Virus- oder Autoimmunerkrankungen hingegen steigt es nicht oder nur marginal an. Durch dieses Verhalten leistet das Procalcitonin wertvolle Dienste hinsichtlich der Diskriminierung von bakteriellen und viralen Entzündungen.
Serumspiegel < *0,5 µg/ll*

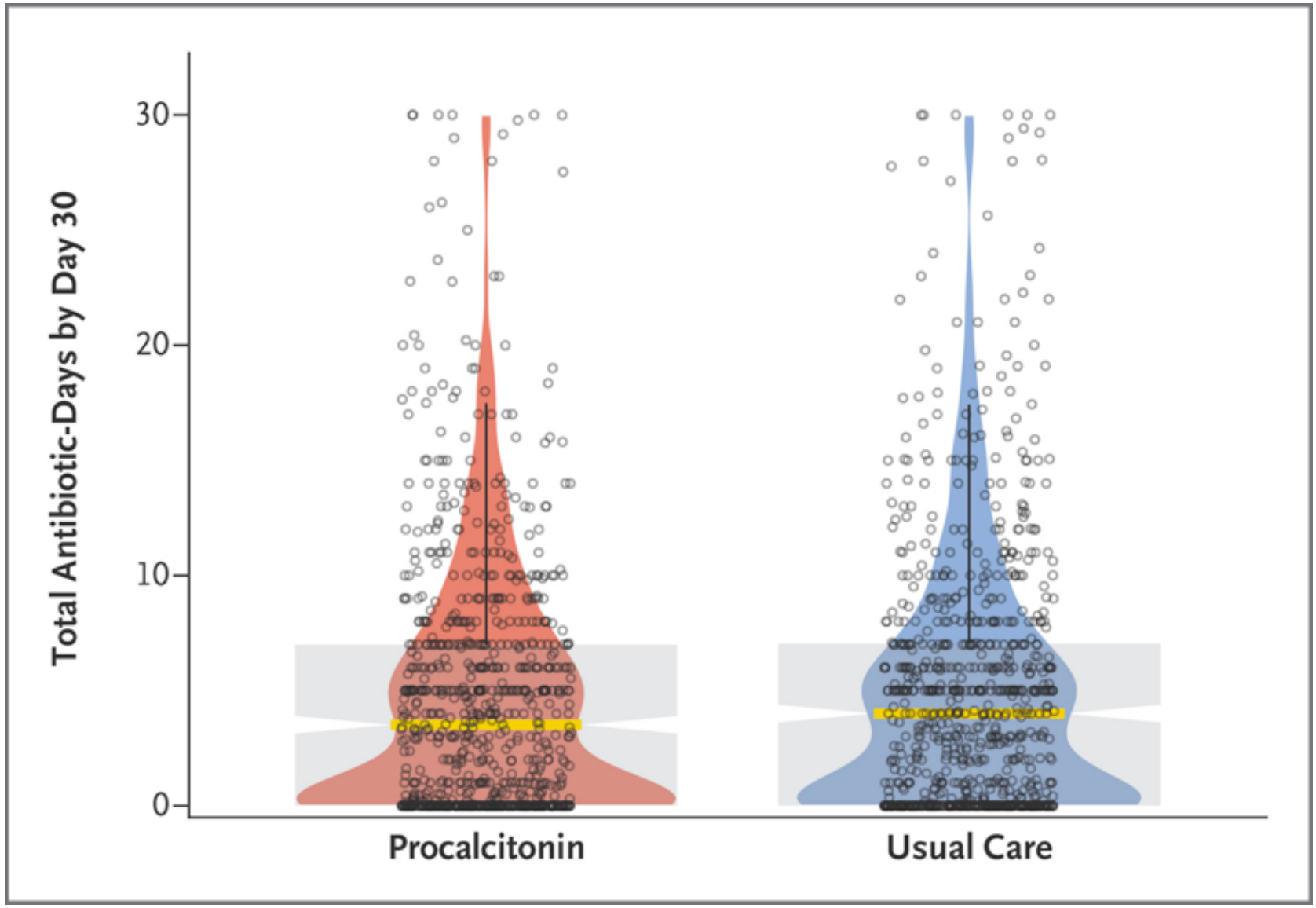


Procalcitonin-Guided Use of Antibiotics for Lower Respiratory Tract Infection

The effect of procalcitonin-guided use of antibiotics on treatment for suspected lower respiratory tract infection is unclear. In 14 U.S. hospitals with high adherence to quality measures for the treatment of pneumonia, we provided guidance for clinicians about national clinical practice recommendations for the treatment of lower respiratory tract infections and the interpretation of procalcitonin assays. We then randomly assigned patients who presented to the emergency department with a suspected lower respiratory tract infection and for whom the treating physician was uncertain whether antibiotic therapy was indicated to one of two groups: the procalcitonin group, in which the treating clinicians were provided with real-time initial (and serial, if the patient was hospitalized) procalcitonin assay results and an antibiotic use guideline with graded recommendations based on four tiers of procalcitonin levels, or the usual-care group.

We hypothesized that within 30 days after enrollment the total antibiotic-days would be lower — and the percentage of patients with adverse outcomes would not be more than 4.5 percentage points higher — in the procalcitonin group than in the usual-care group.

Characteristic	Procalcitonin (N=826)	Usual Care (N=830)
Age — yr	52.9±18.4	53.2±18.7
Male sex — no. (%)	357 (43.2)	354 (42.7)
Race or ethnic group†		
White — no. (%)	455 (55.1)	470 (56.6)
Black — no. (%)	296 (35.8)	297 (35.8)
Hispanic — no./total no. (%)	108/815 (13.3)	104/812 (12.8)
Coexisting conditions and risk factors		
Charlson comorbidity score‡	1.4±1.6	1.4±1.4
Current smoker — no./total no. (%)	263/804 (32.7)	256/813 (31.5)
COPD — no./total no. (%)	267/822 (32.5)	262/823 (31.8)
Asthma — no./total no. (%)	312/822 (38.0)	337/823 (40.9)
Home medications — no./total no. (%)§		
Home oxygen	89/820 (10.9)	87/823 (10.6)
Oral glucocorticoids	107/820 (13.0)	108/823 (13.1)
Inhaled glucocorticoids	211/820 (25.7)	225/822 (27.4)
Inhaled long-acting bronchodilators	225/820 (27.4)	243/822 (29.6)
Leukotriene-receptor antagonists	43/820 (5.2)	59/823 (7.2)
Symptoms		
Duration — days	5.5±5.1	5.5±5.1
Type — no./total no. (%)		
Cough	734/822 (89.3)	714/823 (86.8)
Dyspnea	683/822 (83.1)	715/823 (86.9)
Sputum production	495/822 (60.2)	443/823 (53.8)
Chest discomfort	423/822 (51.5)	454/823 (55.2)
Chills	279/822 (33.9)	256/823 (31.1)
Clinical findings¶		
Temperature — °C	36.9±0.6	36.8±0.6
Heart rate — beats/min	90.3±17.9	91.9±18.5
Respiratory rate — breaths/min	19.9±5.2	20.0±5.8
Arterial pressure — mm Hg	96.0±15.1	96.4±15.0
Oxygen saturation — %	96.4±4.8	96.4±2.9
Rhonchi — no./total no. (%)	111/822 (13.5)	117/823 (14.2)
Wheezing — no./total no. (%)	440/822 (53.5)	456/823 (55.4)
Median white-cell count (IQR) — cells/mm^3‖	8.8 (6.8–11.4)	8.9 (6.8–12.1)
Procalcitonin level**		
Median level (IQR) — μg/liter	0.05 (0.05–0.10)	0.05 (0.05–0.06)
Category — no./total no. (%)		
<0.1 μg/liter	588/808 (72.8)	648/788 (82.2)
0.1–0.25 μg/liter	158/808 (19.6)	72/788 (9.1)
>0.25–0.5 μg/liter	27/808 (3.3)	23/788 (2.9)
>0.5 μg/liter	35/808 (4.3)	45/788 (5.7)
Final diagnosis — no./total no. (%)††		
Asthma	310/822 (37.7)	336/823 (40.8)
COPD	265/822 (32.2)	259/823 (31.5)
Acute bronchitis	208/822 (25.3)	190/823 (23.1)
Community-acquired pneumonia	167/822 (20.3)	161/823 (19.6)
PSI class I	48/167 (28.7)	34/161 (21.1)
PSI class II	52/167 (31.1)	52/161 (32.3)
PSI class III	30/167 (18.0)	33/161 (20.5)
PSI class IV	29/167 (17.4)	38/161 (23.6)
PSI class V	7/167 (4.2)	3/161 (1.9)
Other lower respiratory tract infection	42/822 (5.1)	42/823 (5.1)
Non–lower respiratory tract infection	20/822 (2.4)	21/823 (2.6)
Hospitalized — no. (%)‡‡	378 (45.8)	404 (48.7)

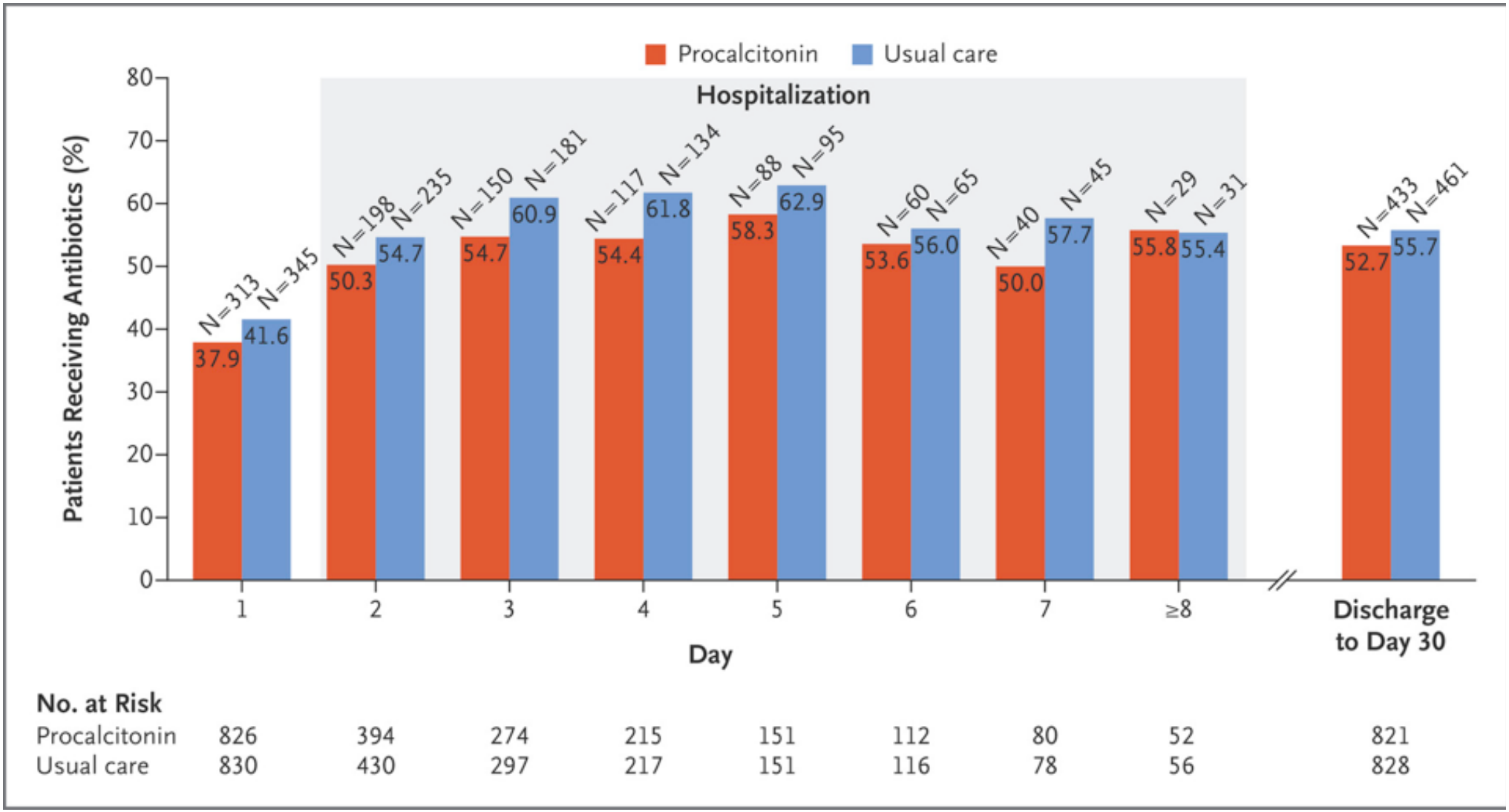


Violin plots for the primary outcome of antibiotic-days by day 30 are shown. The width of the colored shape indicates the probability density of patients with a given result. The gray notched box plots represent the median (yellow horizontal line), 95% confidence interval of the median (notch), interquartile range (25th to 75th percentile) (box), and the upper 1.5 times the interquartile range (solid vertical line).

Antibiotic Exposure.

In the intention-to-treat analysis, there was no significant difference in antibiotic exposure during the first 30 days between the procalcitonin group and the usual-care group (mean antibiotic-days, 4.2 and 4.3 days, respectively; difference, −0.05 day; 95% confidence interval [CI], −0.6 to 0.5; P=0.87). The results were similar in the per-protocol analysis (difference, −0.1 day; 95% CI, −0.7 to 0.6), per-guideline analysis (−0.1 day; 95% CI, −1.0 to 0.8), complete-case analysis (−0.1 day; 95% CI, −0.7 to 0.5), and missing-not-at-random analysis (−0.1 day; 95% CI, −0.7 to 0.5). There was no significant difference in antibiotic-days by day 30 in any prespecified subgroup analysis.

Outcome	Procalcitonin (N=826)	Usual Care (N=830)	Difference (95% or 99.86% CI)†
Intention-to-treat population‡			
Antibiotic-days by day 30§	4.2±5.8	4.3±5.6	−0.05 (−0.6 to 0.5)
Received any antibiotics by day 30 — estimated no. (%)¶	471 (57.0)	513 (61.8)	−4.8 (−12.7 to 3.0)
Antibiotic prescription in ED — estimated no. (%)¶‖	282 (34.1)	321 (38.7)	−4.6 (−12.2 to 3.0)
Antibiotic-days during hospital stay	2.6±3.3	2.7±3.0	−0.1 (−0.8 to 0.6)
Hospital length of stay — days	5.0±4.4	4.7±3.5	0.3 (−0.2 to 0.9)
Per-protocol population**			
No. of patients	696	830	
Antibiotic-days by day 30	4.2±5.7	4.3±5.7	−0.1 (−0.7 to 0.6)
Per-guideline population††			
No. of patients	513	830	
Antibiotic-days by day 30	4.2±5.7	4.3±5.7	−0.1 (−1.0 to 0.8)
Complete-case population‡‡			
No. of patients	658	645	
Antibiotic-days by day 30	4.5±5.8	4.6±5.7	−0.1 (−0.7 to 0.5)
Missing-not-at-random population‡‡			
No. of patients	826	830	
Antibiotic-days by day 30§	4.3±5.8	4.4±5.7	−0.1 (−0.7 to 0.5)
Patients with final diagnosis of asthma			
No. of patients	310	336	
Antibiotic-days by day 30	3.7±5.2	3.6±4.9	0.1 (−1.2 to 1.4)
Received any antibiotics by day 30 — estimated no./total no. (%)¶	169/310 (54.6)	182/336 (54.1)	0.5 (−12.3 to 13.3)
Antibiotic prescription in ED — estimated no./total no. (%)¶‖	90/310 (28.9)	104/336 (30.8)	−1.9 (−13.5 to 9.6)
Antibiotic-days during hospital stay	1.8±2.4	2.3±2.9	−0.4 (−1.4 to 0.6)
Hospital length of stay — days	4.0±3.0	4.2±3.0	−0.1 (−0.8 to 0.6)
Patients with final diagnosis of COPD			
No. of patients	265	259	
Antibiotic-days by day 30	5.3±6.1	5.2±5.3	0.1 (−1.6 to 1.7)
Received any antibiotics by day 30 — estimated no./total no. (%)¶	191/265 (71.9)	200/259 (77.4)	−5.5 (−17.7 to 6.8)
Antibiotic prescription in ED — estimated no./total no. (%)¶‖	108/265 (40.6)	115/259 (44.3)	−3.7 (−17.5 to 10.1)
Antibiotic-days during hospital stay	3.0±3.9	2.8±2.4	0.2 (−0.8 to 1.3)
Hospital length of stay — days	5.4±4.8	4.6±3.1	0.8 (−0.0 to 1.6)
Patients with final diagnosis of acute bronchitis			
No. of patients	208	190	
Antibiotic-days by day 30	2.7±5.1	3.6±5.5	−0.9 (−2.6 to 0.9)
Received any antibiotics by day 30 — estimated no./total no. (%)¶	77/208 (37.0)	100/190 (52.8)	−15.8 (−31.9 to 0.4)
Antibiotic prescription in ED — estimated no./total no. (%)¶‖	36/208 (17.3)	61/190 (32.1)	−14.8 (−28.5 to −1.1)
Antibiotic-days during hospital stay	1.6±2.3	1.9±3.4	−0.3 (−2.1 to 1.6)
Hospital length of stay — days	5.4±5.7	4.4±3.8	1.0 (−0.9 to 3.0)
Patients with final diagnosis of community-acquired pneumonia			
No. of patients	167	161	
Antibiotic-days by day 30	7.8±7.0	7.2±6.0	0.7 (−1.7 to 3.1)
Received any antibiotics by day 30 — estimated no./total no. (%)¶	148/167 (88.6)	154/161 (95.9)	−7.3 (−16.8 to 2.2)
Antibiotic prescription in ED — estimated no./total no. (%)¶‖	120/167 (71.9)	123/161 (76.3)	−4.4 (−19.9 to 11.0)
Antibiotic-days during hospital stay	3.9±3.0	4.1±3.1	−0.2 (−1.5 to 1.1)
Hospital length of stay — days	5.8±4.9	5.9±4.2	−0.1 (−1.2 to 1.1)
Patients with final diagnosis of other lower respiratory tract infection			
No. of patients	42	42	
Antibiotic-days by day 30	2.5±4.4	4.4±6.4	−2.0 (−4.4 to 0.5)
Received any antibiotics by day 30 — estimated no./total no. (%)¶	17/42 (39.6)	24/42 (56.9)	−17.4 (−39.2 to 4.5)
Antibiotic prescription in ED — estimated no./total no. (%)¶‖	11/42 (26.2)	18/42 (42.4)	−16.2 (−36.3 to 3.9)
Antibiotic-days during hospital stay	1.0±2.0	2.2±2.3	−1.2 (−2.6 to 0.3)
Hospital length of stay — days	5.0±4.0	5.7±2.6	−0.6 (−2.9 to 1.6)
Patients with final diagnosis of non–lower respiratory tract infection			
No. of patients	20	21	
Antibiotic-days by day 30	2.1±3.2	1.4±2.8	0.7 (−1.3 to 2.6)
Received any antibiotics by day 30 — estimated no./total no. (%)¶	7/20 (37.2)	6/20 (30.2)	7.0 (−23.1 to 37.2)
Antibiotic prescription in ED — estimated no./total no. (%)¶‖	3/20 (15.0)	5/21 (23.8)	−8.8 (−32.8 to 15.2)
Antibiotic-days during hospital stay	2.6±3.0	0.8±1.5	1.9 (−1.4 to 5.1)
Hospital length of stay — days	6.0±3.8	2.8±1.0	3.3 (−0.6 to 7.1)



Antibiotic Exposure over Time.

Day 1 is from the time of enrollment to midnight. Day 2 and beyond are from midnight to midnight. Serial procalcitonin levels were obtained from hospitalized patients through day 7. Data on post-discharge antibiotic exposure were derived from the intention-to-treat analysis of the primary outcome.

In this multicenter trial, the use of a procalcitonin-guided antibiotic prescription guideline did not result in less exposure to antibiotics than did usual care among patients presenting to the emergency department with suspected lower respiratory tract infection. There are several possible explanations for this finding. In the usual-care group, even when clinicians did not know the procalcitonin assay result, they prescribed antibiotics less frequently to patients in the lower procalcitonin-level tiers than to those in the higher tiers. Patients with lower procalcitonin levels also had fewer clinical features of infection, and in that context, procalcitonin probably provided a modest amount of additional information to guide decisions. There was some suggestion of heterogeneity of the effect of the intervention, such as lower antibiotic prescription rates for patients with acute bronchitis than for those with other final diagnoses and a possible interaction between treatment effect and procalcitonin tier. However, these secondary analyses were exploratory, and the differences were largely nonsignificant.

We did not directly address whether antibiotics can be safely withheld on the basis of a low procalcitonin level alone but rather tested the effect of a deployment strategy to promote the recommended use of the assay in clinical practice (in a patient population in which the likelihood of antimicrobial use was intermediate). In our strategy, procalcitonin assay results were provided to the clinical team before decision making in most but not all instances. A lack of knowledge about the prescribing practices used by individual physicians limits the insights we can make. The potential effect of emerging technology that may improve the rapid identification of infectious agents — technology that was largely unavailable during the course of this trial — is unclear. Finally, we did not achieve follow-up for all the patients in our trial, but our results were robust to complete-case and missing-not-at-random sensitivity analyses.

Physiologisch ist die Koronare Flussreserve (CFR von coronary flow reserve) der Quotient des maximalen Blut-Volumenstroms in den Koronararterien unter Belastung und des Blut-Volumenstroms in den Koronararterien in Ruhe. Es ist also der maximale zusätzliche Volumenstrom, der den Herzmuskel versorgen kann, wenn es belastet wird und einen erhöhten Bedarf an Blutversorgung hat.

Sie wird üblicherweise als Quotient von maximalem Belastungs- und Ruhe-Volumenstrom angegeben.

Beim Gesunden kann die CFR den Wert 6 oder höher betragen; als normal werden Werte oberhalb von 3,5 angesehen. Die CFR ist unter anderem erniedrigt bei Stenosen in den Koronararterien, bei Bluthochdruck, beim Kardialen Syndrom X und bei der Hypertrophen Kardiomyopathie.

Goldstandard zur Bestimmung der Koronaren Flussreserve ist die Untersuchung mit einem intrakoronaren Doppler-Draht im Rahmen einer Herzkatheteruntersuchung. Des Weiteren werden PET sowie die transthorakale Echokardiografie bei der LAD eingesetzt. Allen Methoden gemeinsam ist, dass zunächst eine Untersuchung in Ruhe durchgeführt wird und dann unter medikamentöser Belastung wiederholt wird, zumeist mit Adenosin.

Five-Year Outcomes with PCI Guided by Fractional Flow Reserve

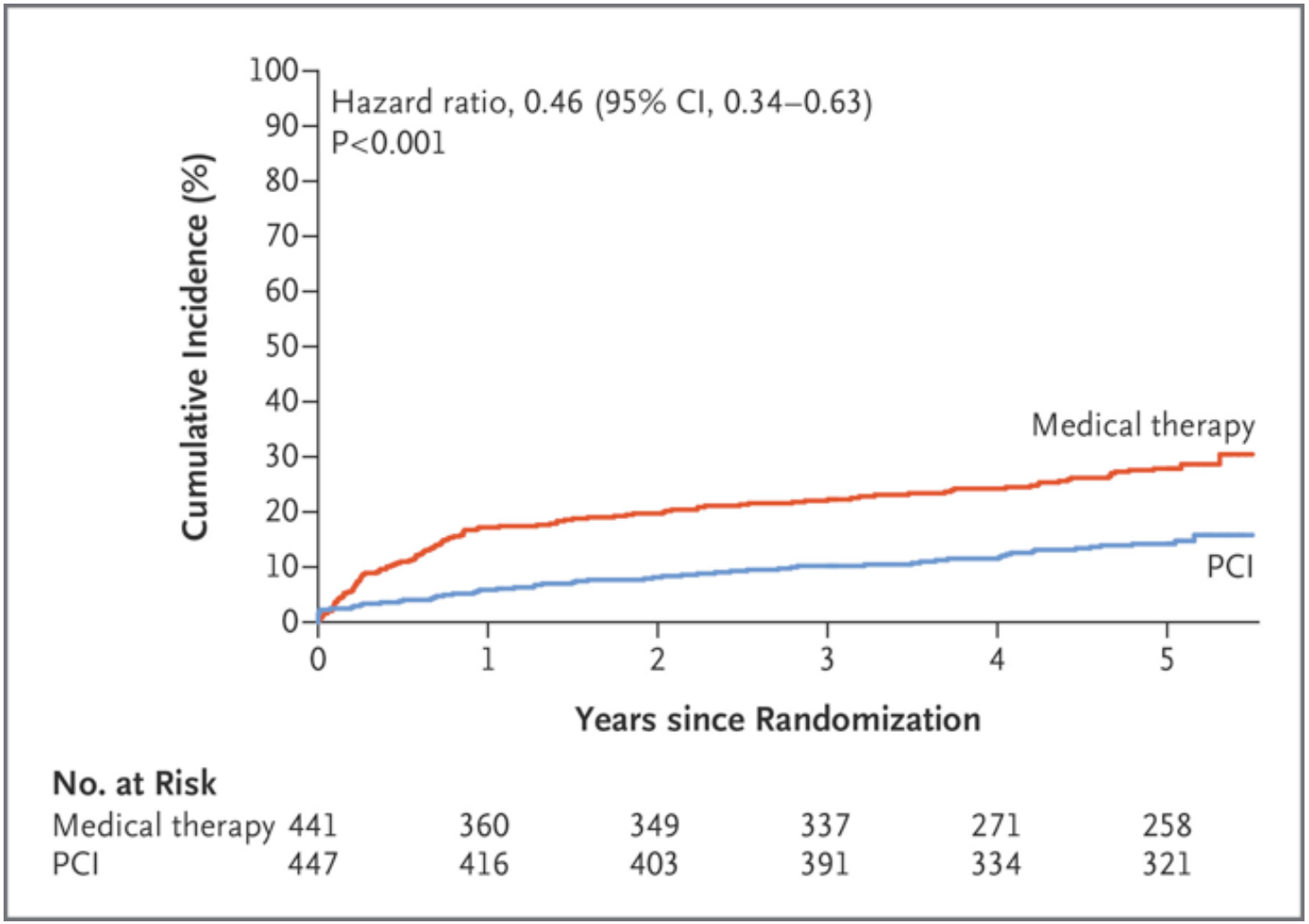
We hypothesized that fractional flow reserve (FFR)–guided percutaneous coronary intervention (PCI) would be superior to medical therapy as initial treatment in patients with stable coronary artery disease. Among 1220 patients with angiographically significant stenoses, those in whom at least one stenosis was hemodynamically significant (FFR, ≤0.80) were randomly assigned to FFR-guided PCI plus medical therapy or to medical therapy alone. Patients in whom all stenoses had an FFR of more than 0.80 received medical therapy and were entered into a registry. The primary end point was a composite of death, myocardial infarction, or urgent revascularization.

Characteristic	PCI Group (N=447)	Medical-Therapy Group (N=441)
Age — yr	63.5±9.4	63.9±9.6
Age >60 yr — no. (%)	282 (63.1)	279 (63.3)
Male sex — no. (%)	356 (79.6)	338 (76.6)
Body-mass index†	28.3±4.3	28.4±4.5
Family history of coronary artery disease — no./total no. (%)	216/446 (48.4)	207/441 (46.9)
Current smoking — no. (%)	89 (19.9)	90 (20.4)
Hypertension — no. (%)	347 (77.6)	343 (77.8)
Hypercholesterolemia — no. (%)	330 (73.8)	348 (78.9)
Diabetes mellitus — no. (%)		
Any	123 (27.5)	117 (26.5)
Insulin-dependent	39 (8.7)	39 (8.8)
Renal insufficiency — no. (%)‡	8 (1.8)	12 (2.7)
Peripheral vascular disease — no. (%)	43 (9.6)	47 (10.7)
History of stroke or TIA — no. (%)	33 (7.4)	28 (6.3)
History of myocardial infarction — no. (%)	164 (36.7)	165 (37.4)
History of PCI in target vessel — no. (%)	80 (17.9)	76 (17.2)
Angina — no./total no. (%)§		
No angina or asymptomatic	53/447 (11.9)	46/440 (10.5)
CCS class I	82/447 (18.3)	98/440 (22.3)
CCS class II	204/447 (45.6)	197/440 (44.8)
CCS class III	80/447 (17.9)	65/440 (14.8)
CCS class IV	28/447 (6.3)	34/440 (7.7)
Silent ischemia — no. (%)	73 (16.3)	73 (16.6)
Left ventricular ejection fraction <50% — no. (%)	83 (18.6)	56 (12.7)

Table 2. Clinical End Points at 5-Year Follow-up.*

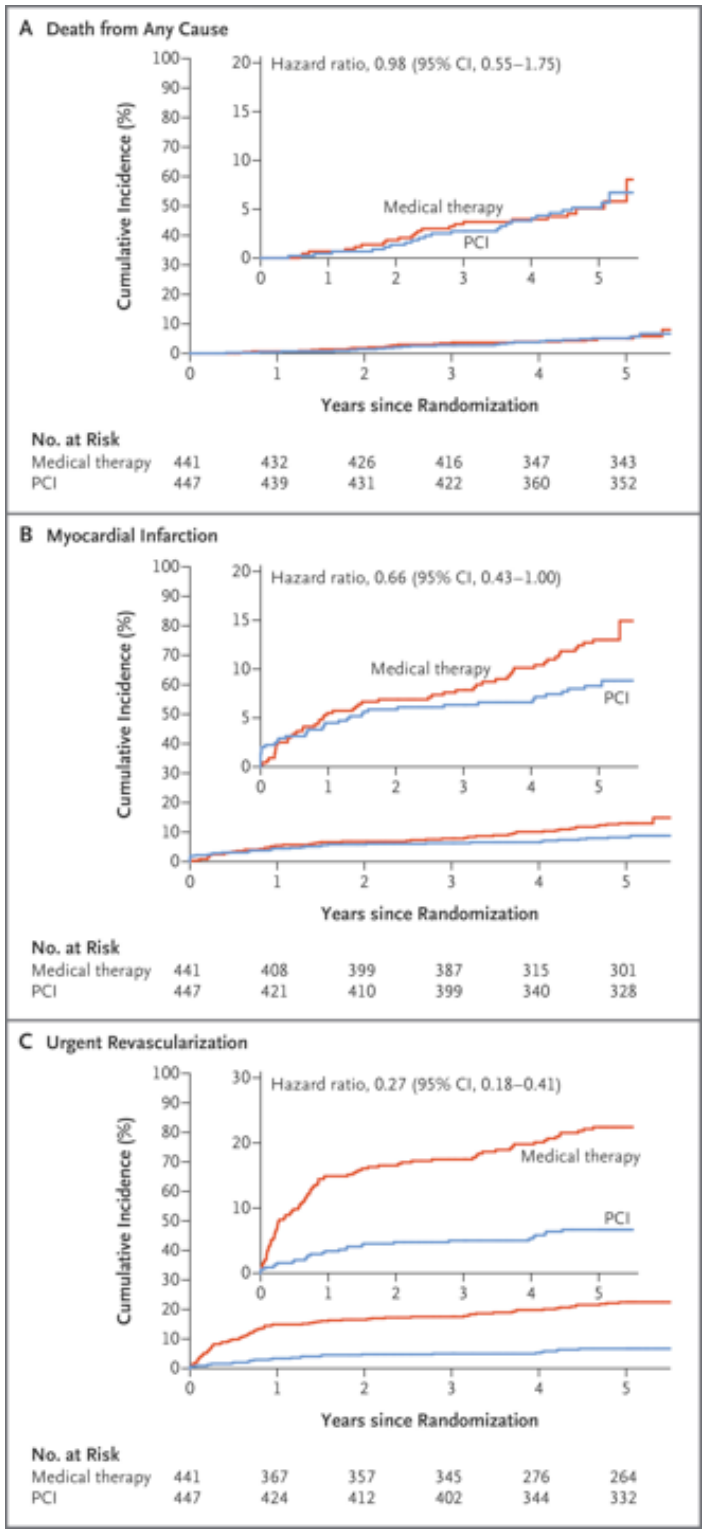
End Points	PCI Group (N=447)	Medical-Therapy Group (N=441)	Hazard Ratio (95% CI)	Registry Cohort (N=166)
	no. of patients (%)			*no. of patients (%)*
Primary composite end point	62 (13.9)	119 (27.0)	0.46 (0.34–0.63)	26 (15.7)
Components of primary end point				
Death from any cause	23 (5.1)	23 (5.2)	0.98 (0.55–1.75)	7 (4.2)
Myocardial infarction	36 (8.1)	53 (12.0)	0.66 (0.43–1.00)	14 (8.4)
Urgent revascularization	28 (6.3)	93 (21.1)	0.27 (0.18–0.41)	14 (8.4)
Death or myocardial infarction	53 (11.9)	71 (16.1)	0.72 (0.50–1.03)	20 (12.0)
Death from cardiac causes	11 (2.5)	7 (1.6)	1.54 (0.60–3.98)	3 (1.8)
Death from cardiac causes or myocardial infarction	43 (9.6)	59 (13.4)	0.70 (0.48–1.04)	16 (9.6)
Revascularization				
Any revascularization	60 (13.4)	225 (51.0)	0.19 (0.14–0.26)	29 (17.5)
Nonurgent revascularization	34 (7.6)	155 (35.1)	0.18 (0.12–0.26)	17 (10.2)
Stroke	12 (2.7)	7 (1.6)	1.69 (0.67–4.31)	1 (0.6)
Definite or probable stent thrombosis	7 (1.6)	2 (0.5)	3.46 (0.72–16.70)	1 (0.6)

* The primary end point was a composite of death from any cause, myocardial infarction, or urgent revascularization. The 95% confidence intervals for secondary end points were not adjusted for multiple testing, and any inferences drawn from the intervals as reported may not be reproducible.



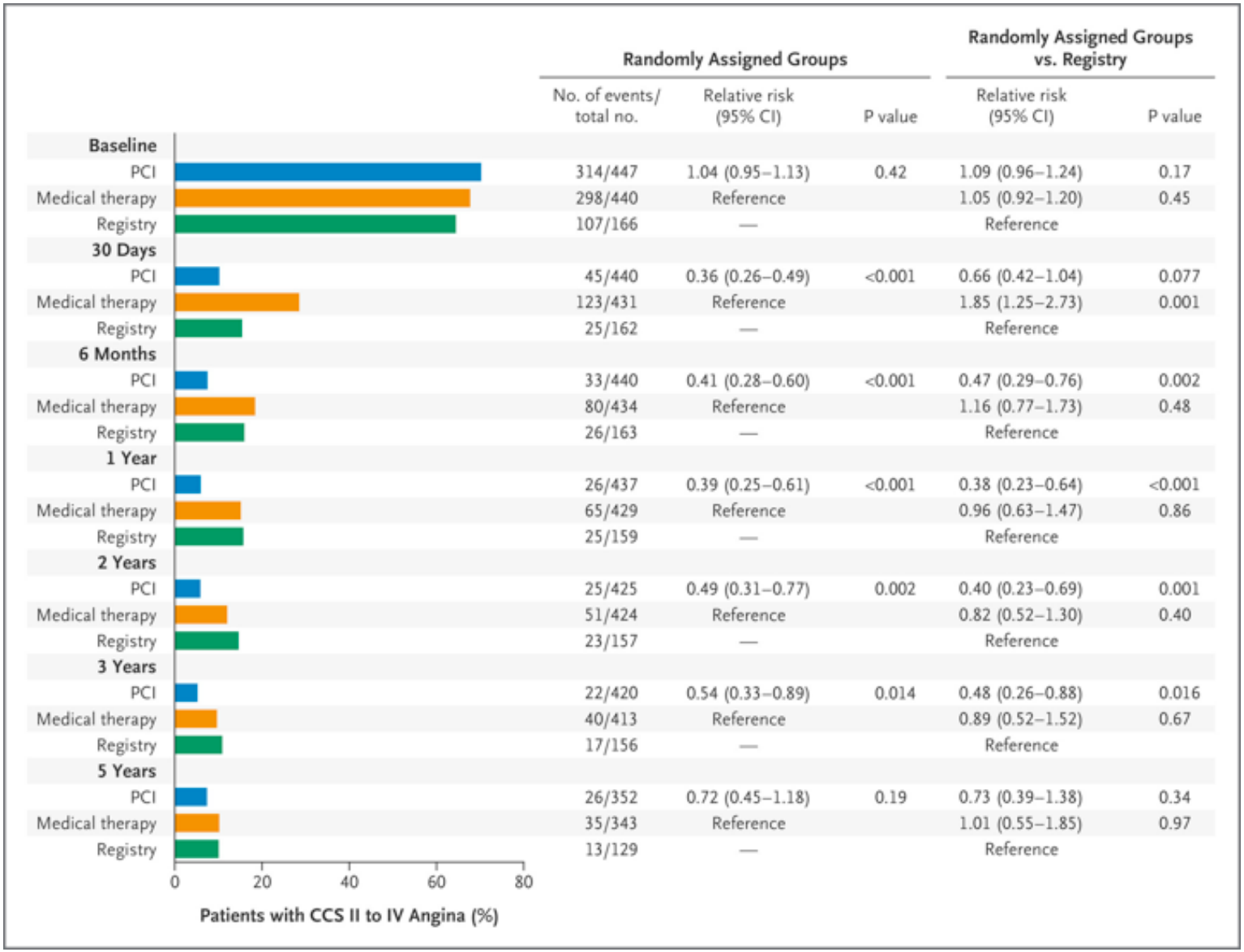
Kaplan–Meier Curves for the Primary End Point.

Shown is the cumulative incidence of the primary end point (a composite of death from any cause, myocardial infarction, or urgent revascularization) in the two groups in the trial. A hazard ratio below 1.00 denotes a lower incidence of the primary end point in the group that underwent fractional flow reserve–guided percutaneous coronary intervention (PCI) than in the medical-therapy group.



Kaplan–Meier Curves for Death from Any Cause, Myocardial Infarction, and Urgent Revascularization.

Hazard ratios below 1.00 denote a lower incidence of events in the PCI group than in the medical-therapy group. The 95% confidence intervals for secondary end points were not adjusted for multiple testing, and any inferences drawn from the intervals as reported may not be reproducible. Insets show the same data on an enlarged y axis.

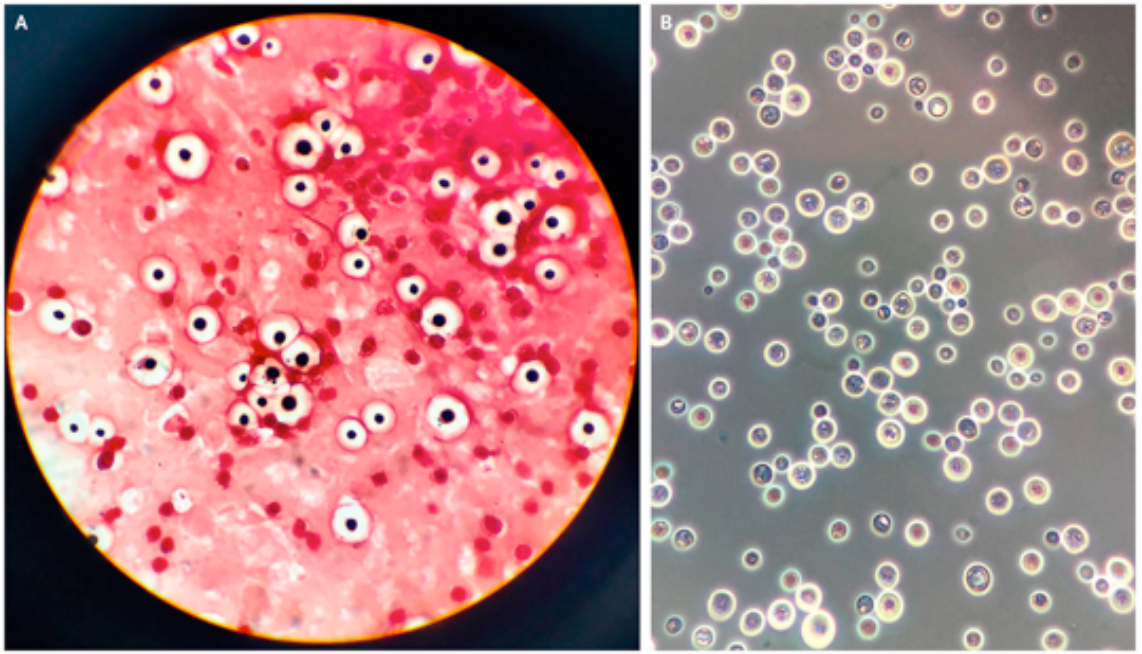


Angina Class in Patients in the Trial Groups and Registry Cohort over Time.

Shown are the numbers of patients in the two trial groups and the registry cohort who had angina of class II to IV on the Canadian Cardiovascular Society (CCS) scale (which ranges from I to IV, with higher classes indicating greater limitations on physical activity owing to angina) at various time points. The 95% confidence intervals for secondary end points were not adjusted for multiple testing, and any inferences drawn from the intervals as reported may not be reproducible.

This 5-year follow-up of the FAME 2 trial showed that, among patients with stable angina, FFR-guided PCI led to a significantly lower rate of the prespecified primary composite end point of death, myocardial infarction, or urgent revascularization than medical therapy alone. This difference was driven by a significantly lower rate of urgent revascularization in the PCI group than in the medical-therapy group. Patients in whom all coronary stenoses were hemodynamically nonsignificant had an event rate with medical therapy alone that did not differ significantly from the rate among patients with hemodynamically significant stenoses who underwent FFR-guided PCI. There was no evidence of convergence of event rates between groups in the long term. Patients who had originally been assigned to undergo FFR-guided PCI reported significantly less angina up to 3 years after randomization than did patients who had been assigned to receive medical therapy alone. However, this difference was no longer significant at 5 years, by which time 51% of the patients who had been initially assigned to medical therapy alone had undergone revascularization. Some limitations must be taken into account. First, enrollment was stopped prematurely by the data and safety monitoring board because of a large excess of primary end-point events in the medical-therapy group. The early termination of clinical trials has been shown to exaggerate treatment effects.

In conclusion, in patients with stable coronary artery disease, an initial FFR-guided PCI strategy resulted in a sustained clinical benefit, as compared with medical therapy alone, with regard to the composite primary end point of death, myocardial infarction, or urgent revascularization at 5 years. Patients without hemodynamically significant stenoses had a favorable long-term outcome with medical therapy alone.



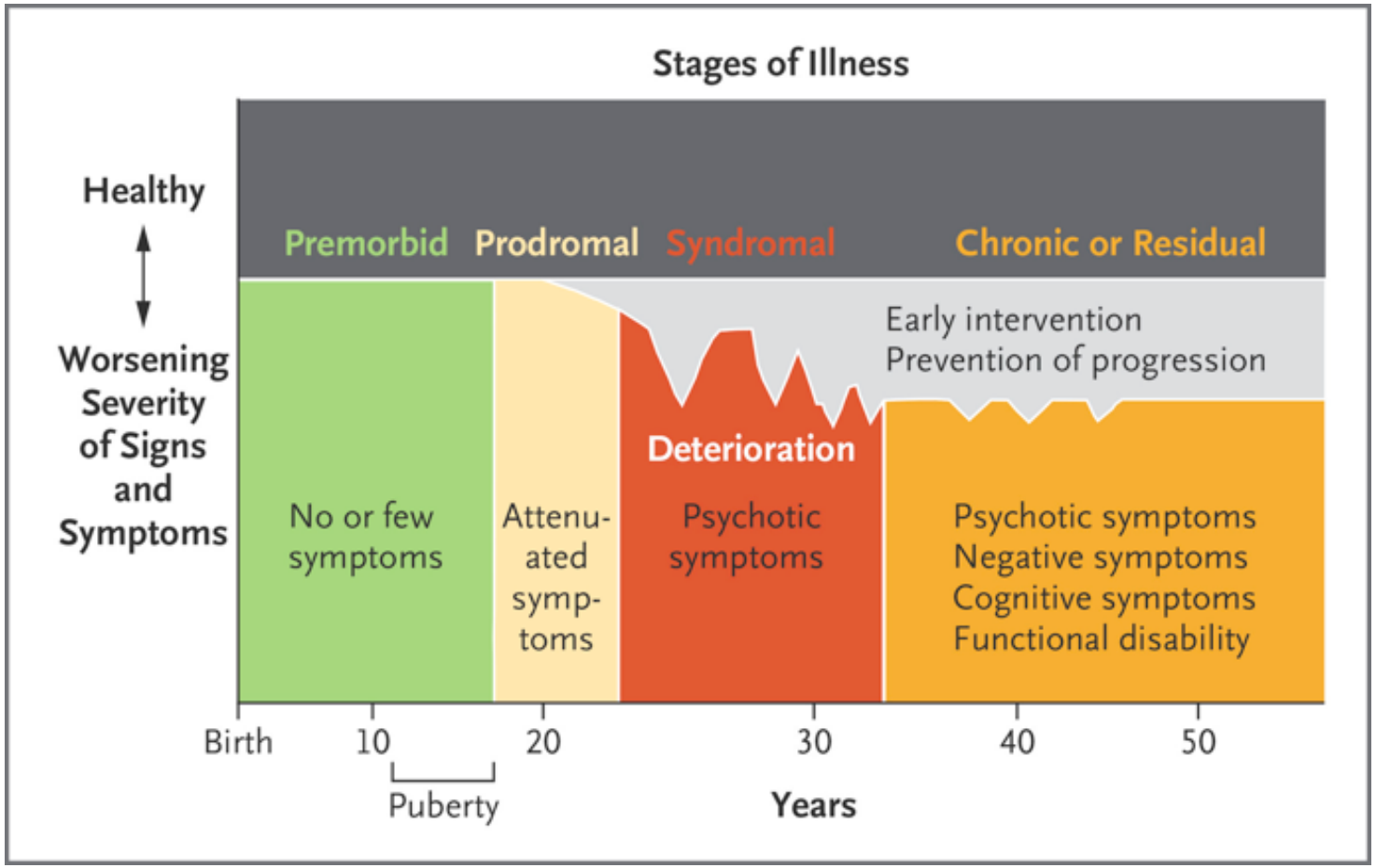
A 36-year-old man presented to the emergency department with a 2-week history of fever, headache, drowsiness, and photophobia. He was previously healthy and was sexually active with men. The physical examination was notable for a temperature of 38.3° C and neck stiffness. Computed tomography of the head was normal. The opening pressure on lumbar puncture was 29 cm of water (reference range, <20 cm). The cerebrospinal fluid (CSF) cell count was 340 cells per microliter (reference range, 0 to 10), with 90% mononuclear cells, which were predominantly lymphocytes. The glucose level was 46 mg per deciliter (2.6 mmol per liter; reference range, 40 to 70 mg per deciliter [2.2 to 3.8 mmol per liter]), and the protein level was 0.80 g per liter (reference range, 0.15 to 0.45). Gram's stain (Panel A) and India ink stain (Panel B) revealed abundant encapsulated, round yeasts, with some budding forms. The cryptococcal antigen titer was 1:128, and the CSF culture grew Cryptococcus neoformans. No other pathogen was detected. A test for the human immunodeficiency virus antibody was positive; the viral load was 300,000 copies per milliliter, and the CD4+ count was 7 cells per microliter (reference range, 500 to 1450). Induction therapy with liposomal amphotericin B and flucytosine was started, and resolution of symptoms and negative results on CSF culture were noted after 2 weeks of treatment. Consolidation therapy with fluconazole was started, and antiretroviral therapy was later prescribed.

Psychotic Disorders

The term “psychosis,” which is derived from the Greek word for abnormal condition of the mind, has been used in many different ways in clinical medicine. Before 1980, the term “psychotic” was applied generically to persons whose mental functioning was sufficiently impaired to interfere with their capacity to meet the ordinary demands of life. Starting in 1980 with the publication of the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III), the term indicated gross impairment in reality testing — that is, disruption of the ability to distinguish between the internal experience of the mind and the external reality of the environment.

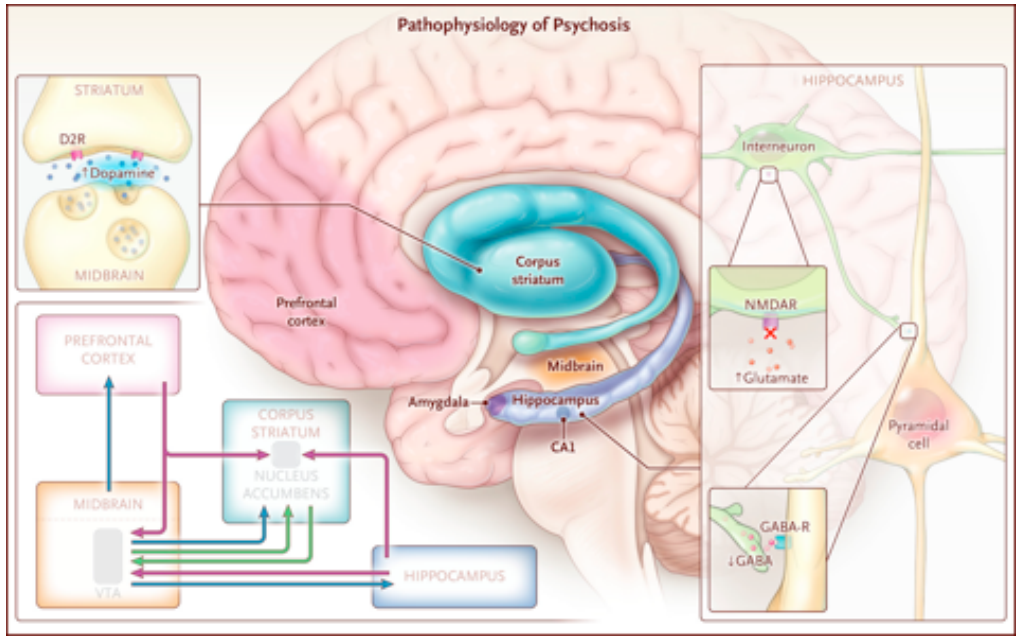
To achieve greater diagnostic precision, DSM-IV, published in 1994, defined psychosis more specifically to apply to mental disorders characterized by symptoms such as fixed false beliefs (delusions, such as the belief that one is being poisoned by neighbors who are piping gas through the walls), hallucinations, disorganized thoughts (illogical and incoherent speech, neologisms, and made-up words), clang associations (rhymed words), word salad (nonsensical sentences), echolalia (repetition of spoken words), and abnormal motor behavior (bizarre postures, stereotypy, and waxy flexibility).

Psychotic Disorder	Psychotic Symptoms	Distinguishing Features	Lifetime Prevalence (%)	Basis for Diagnosis
Idiopathic primary psychoses				
Schizophrenia	Delusions, hallucinations (mostly auditory), disorganized thinking, disorganized or abnormal psychomotor behavior	Active-phase psychotic symptoms with prodromal and residual-phase symptoms, ≥6-mo duration, decline in functioning†	0.30–0.87	Clinical
Schizoaffective disorder	Delusions, hallucinations (mostly auditory), disorganized thinking, disorganized or abnormal psychomotor behavior	Psychotic symptoms (delusions and hallucinations) and mood symptoms occurring concurrently or independently	0.32	Clinical
Bipolar disorder with psychotic features	Delusions, hallucinations	Psychotic symptoms during manic episodes	0.12	Clinical
Major depressive disorder with psychotic features	Delusions, hallucinations	Psychotic symptoms only during depressive episodes	0.33	Clinical
Delusional disorder	Delusions	Functioning not impaired apart from impact of delusions	0.18	Clinical
Schizophreniform disorder	Delusions, hallucinations, disorganized thinking, disorganized or abnormal psychomotor behavior	Psychotic symptoms lasting 1–6 mo	0.07	Clinical
Brief psychotic disorder	Delusions, hallucinations, disorganized thinking, disorganized or abnormal psychomotor behavior	Psychotic symptoms lasting <1 mo	0.05	Clinical
Postpartum psychosis	Delusions, hallucinations	Psychotic symptoms within 6 wk after delivery	0.07‡	Clinical
Toxic psychoses				
Psychosis induced by recreational substances§	Delusions, hallucinations	Psychotic symptoms temporally related to substance intoxication or withdrawal	0.42	Toxicologic assays for drugs
Psychosis induced by toxins¶	Delusions, hallucinations	Psychotic symptoms temporally associated with toxin exposure		Toxicologic assay
Iatrogenic psychosis‖	Delusions, hallucinations	Psychotic symptoms as a medication side effect		Temporal association with a medication known to cause psychotic symptoms
Psychoses due to medical conditions				
Neurologic, endocrine, metabolic, and other conditions**	Delusions, hallucinations	Psychotic symptoms temporally related to medical condition		Temporal association with a medical condition known to cause psychosis



Natural History of Schizophrenia and the Rationale for Preventing Chronic Disease.

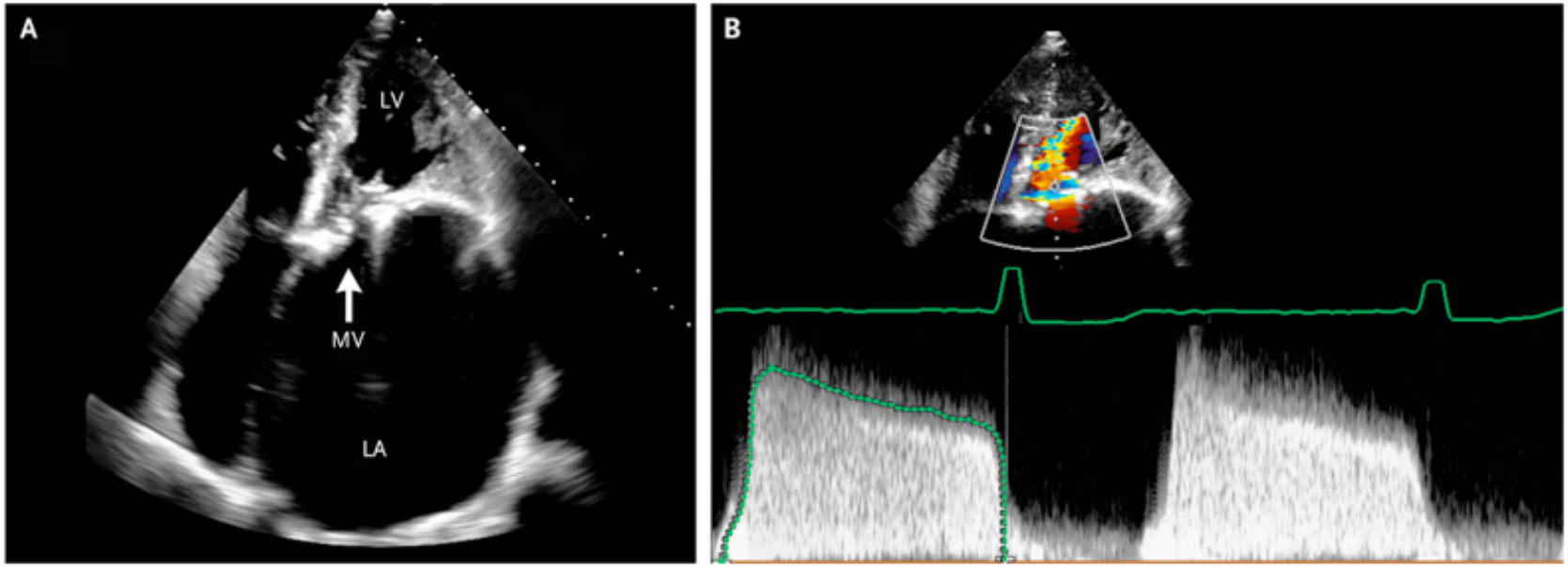
Shown are the stages of illness in schizophrenia, the prototypical idiopathic psychotic disorder. Detection and treatment in the early stages of illness, ideally close to the onset of the first episode of psychosis, shorten the duration of psychotic episodes, reduce recurrences, and limit the progressive decline in functioning (deterioration) that occurs in the syndromal stage and leads to the chronic effects of the disease. The syndromal stage begins with the first episode of psychosis and continues through the progressive stage.



A sagittal view of the brain through the midline depicts the hippocampus, midbrain, corpus striatum, and prefrontal cortex, all regions that are implicated in psychotic symptoms and disorders. The affected neurotransmitters include dopamine (blue arrows), glutamate (purple arrows), and γ-aminobutyric acid (GABA) (green arrows). Idiopathic psychoses (e.g., schizophrenia and mood disorders with psychotic symptoms) are believed to arise from overactivity of neurons that release glutamate onto cells located in and projecting from the CA1 region of the hippocampus. Deficits in hippocampal GABAergic interneurons and hypofunctioning *N*-methyl-D-aspartate glutamate receptors (NMDARs) (the red X denotes hypofunction) are the main molecules that are thought to be responsible for these disturbances. Shown in the hippocampus is a glutamate-expressing pyramidal cell and a GABA interneuron. Despite the increase in synaptic glutamate, there is underactivation of the interneuron. Also shown is the interneuron axon forming a synapse with the apical dendrite of the pyramidal cell. Because of understimulation, the interneuron releases less GABA, which in turn disinhibits the pyramidal cell and causes it to release more glutamate from hippocampal projections to the midbrain (ventral tegmental area [VTA]) and the corpus striatum (nucleus accumbens). Hippocampal overactivity augments dopamine release in the striatum either directly (at the level of the nucleus accumbens) or by stimulation of midbrain dopamine neurons, which project to the nucleus accumbens and the prefrontal cortex. Dopamine neurons in the midbrain further promulgate the dysregulation of dopamine and glutamate through a projection back to the hippocampus. Psychotic symptoms can be induced in nonidiopathic disorders that affect these pathways at various locations. For example, in autoimmune or toxic psychoses (e.g., psychoses due to PCP), the exogenous drug or antibody acts as an NMDAR antagonist, thus mimicking a constitutionally hypofunctioning NMDAR. In Alzheimer's disease, the cholinergic system is compromised and cholinergic inhibitory inputs to glutamateric cells in the hippocampus and dopaminergic cells in the midbrain are diminished. D2R denotes D2 receptor.

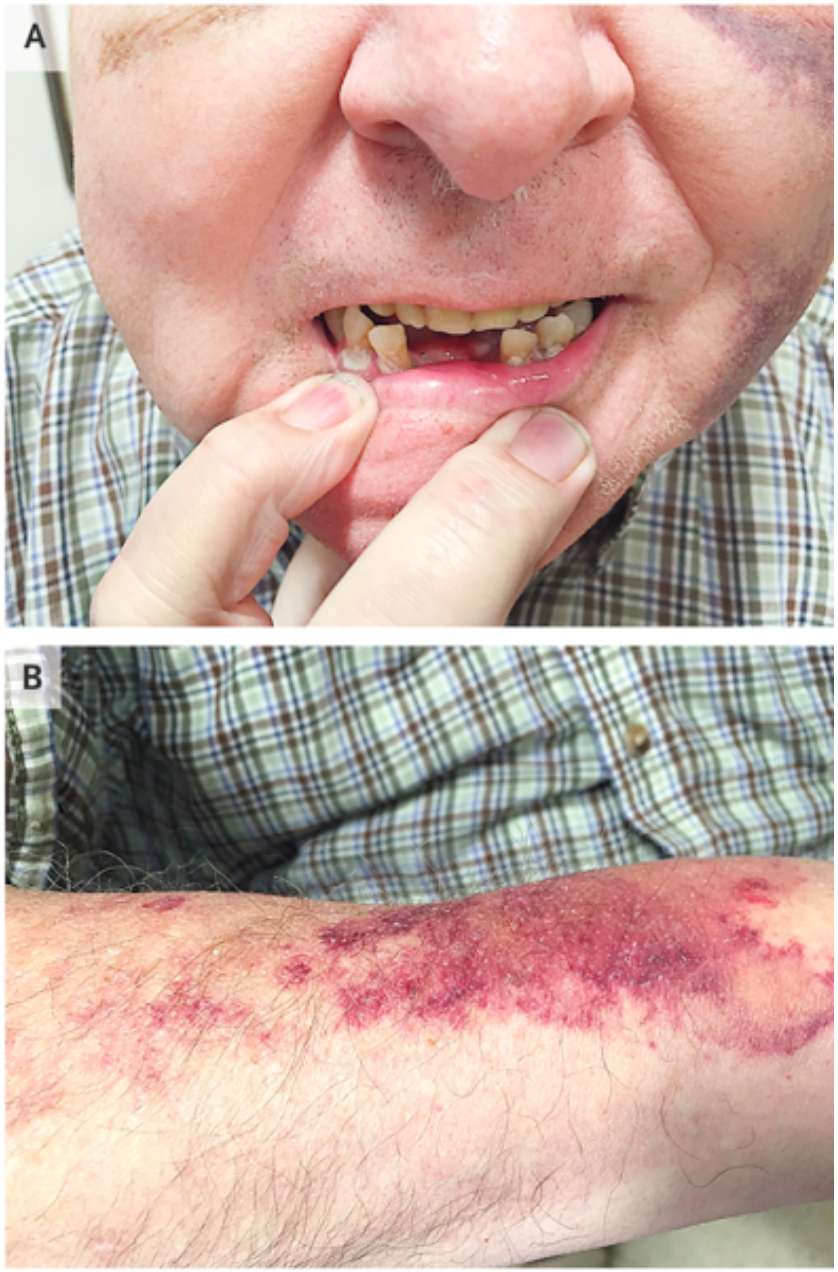
Approximately 20 antipsychotic medications are currently marketed in the United States, all of which work largely by blocking or mitigating the activity of dopamine at D2 receptors. These medications are effective in treating psychotic symptoms in patients with various disorders, although their effectiveness depends on their safety profile, which varies with the drug's pharmacology and the nature of the underlying cause of the condition (e.g., dementia vs. drug-induced psychosis). The older — typical, or first-generation — medications have a propensity to cause extrapyramidal neurologic side effects, whereas the atypical, or second-generation, drugs are more likely to induce weight gain and disturbances in glucose and lipid metabolism. An exception is clozapine, which produces few extrapyramidal effects and has therapeutic efficacy in patients with a partial response or no response to other antipsychotic agents.32 However, clozapine can be associated with serious side effects, including seizures (in approximately 4% of patients), myocarditis (in 1%), and agranulocytosis (in 0.8%), and is therefore indicated mainly for the treatment of refractory psychotic symptoms.

Enthusiasm for early intervention in and prevention of idiopathic psychotic disorders has led investigators and the National Institute of Mental Health to determine how to extend this approach to patients in the prodromal stage of illness in order to prevent the onset of a more disturbing psychotic disorder. Before this approach can be applied, better diagnostic methods must be developed, because the current criteria for identifying persons with attenuated psychotic symptoms who are believed to have a high clinical risk of conversion to a syndromal form of psychosis have a false positive rate that is higher than 50%. Consequently, a diagnostic test is needed that can identify psychotic episodes that will progress to a syndromal psychosis, as well as episodes that are stable or transient and those that can be attenuated. Treatments so far have been shown to be effective for alleviation of symptoms but not for prevention of conversion to syndromal psychosis.



A 47-year-old man presented to the emergency department with a 6-month history of worsening exertional dyspnea. He had recently emigrated from Honduras and had a history of cardiac surgery as a child, but the initial diagnosis and specific procedure that had been performed were not known. The physical examination revealed a right parasternal heave, a loud S1, a midpeaking systolic ejection murmur (grade 2/6) at the upper sternal border, and a low-pitched diastolic rumble at the apex. An electrocardiogram showed atrial flutter with variable atrioventricular conduction. Transthoracic echocardiography revealed moderate aortic stenosis (calculated valve area, 1.3 cm2) and very severe mitral stenosis (calculated valve area, 0.5 cm2) (see video and Panel A; LA denotes left atrium, LV left ventricle, and MV mitral valve). The left atrium was enlarged, with an indexed atrial volume of 364 ml per square meter (normal value, <35). Color-flow Doppler images (Panel B, upper half) and a continuous-wave Doppler flow pattern (Panel B, lower half) showed the stenotic mitral valve during diastole. The continuous-wave Doppler flow pattern depicts flow velocity (vertical axis) and time (horizontal axis). The slow decline in transmitral flow velocity reflects the very slow decrease in left atrial pressure and slow increase in left ventricular diastolic pressure that occur in mitral stenosis. The mean transmitral gradient was 14 mm Hg (normal value, <3). The patient underwent replacement of the mitral and aortic valves with mechanical prostheses. At a 6-month follow-up visit, he had only slight limitations on physical activity (New York Heart Association class II).

A 64-year-old man was admitted to this hospital because of progressive leg weakness, recurrent falls, and anemia. Four months before this admission, the patient fell in his garage and attributed the fall to tripping over an object on the ground. He did not hit his head, lose consciousness, or need assistance to stand or walk after the fall. He was evaluated by his primary care provider. On evaluation, he reported 3 months of increased alcohol consumption (up to 6 or 7 glasses of wine each night) and several months of voluntarily restricted food intake to achieve weight loss. On physical examination, the vital signs were normal. The height was 166.6 cm, and the weight was 128.4 kg (6 months earlier, the weight had been 140.6 kg); the body-mass index (the weight in kilograms divided by the square of the height in meters) was 46. On evaluation in the clinic, the patient reported mild pain above the left eye but no headache, neck pain, back pain, urinary retention, fecal incontinence, fever, chills, morning stiffness, muscle pain, muscle swelling, dark stools, melena, or hematemesis. He had a history of atrial fibrillation, hypertension, gout, osteoarthritis of the knees, gastroesophageal reflux disease, and Barrett's esophagus, which had been diagnosed by means of biopsy 7 years before this admission. Roux-en-Y gastric bypass had been performed 6 years before this admission. Medications were allopurinol, amlodipine, furosemide, indomethacin, losartan, metoprolol, omeprazole, rivaroxaban, bupropion, cyanocobalamin, ergocalciferol, and a thiamine supplement. The patient was divorced, lived alone, and worked as a store manager. He did not smoke tobacco. His father and brother had both died of esophageal cancer.



The first and second heart sounds were normal, without murmurs. The breath sounds were normal bilaterally, without wheezing or rhonchi. Bowelsounds were present, and the abdomen was soft, nondistended, and nontender on palpation. The edge of the liver was not palpable, and the spleen was not enlarged. Motor strength was 3 out of 5 bilaterally on hip flexion and 4 out of 5 bilaterally on hip extension; the patient could not rise from a seated position, even when he used his arms for assistance. The remainder of the motor examination was normal. There was no muscle atrophy, swelling, or tenderness on palpation. Perception of pinprick was diminished in the legs from the toes to above the knees. Perception of light touch was diminished on the plantar surface of the feet. Proprioception was decreased in the big toes. Reflexes were normal, as were the results of finger–nose–finger testing. An evaluation for the Babinski sign and a Romberg test were not performed. Hair was thin and fragile on the arms and absent on the legs. The stool was brown and negative for occult blood. The remainder of the physical examination was normal. The patient was referred to the emergency department of this hospital for further evaluation.

Table 1. Laboratory Data.*

Variable	Reference Range, Adults†	On Presentation
Hematocrit (%)	41–53	36.1
Hemoglobin (g/dl)	13.5–17.5	12.7
White-cell count (per mm^3)	4500–11,000	6090
Differential count (%)		
Neutrophils	40–70	69
Lymphocytes	22–44	18
Monocytes	4–11	12
Eosinophils	0–8	0.5
Basophils	0–3	0.3
Platelet count (per mm^3)	150,000–400,000	236,000
Red-cell count (per mm^3)	4,500,000–5,900,000	3,970,000
Mean corpuscular volume (fl)	80–100	90.9
Mean corpuscular hemoglobin (pg)	26–34	32
Mean corpuscular hemoglobin level (g/dl)	31–37	35.2
Red-cell distribution width (%)	11.5–14.5	14.5
Reticulocyte count (%)	0.5–2.5	2.1
Erythrocyte sedimentation rate (mm/hr)	0–13	36
Sodium (mmol/liter)	135–145	126
Potassium (mmol/liter)	3.4–5.0	3.9
Chloride (mmol/liter)	98–108	83
Carbon dioxide (mmol/liter)	23–32	23
Glucose (mg/dl)	70–110	95
Urea nitrogen (mg/dl)	8–25	14
Creatinine (mg/dl)	0.6–1.5	1.1
Prothrombin time (sec)	11–14	15.2
Prothrombin-time international normalized ratio	0.9–1.1	1.2
Alkaline phosphatase (U/liter)	45–115	142
Bilirubin (mg/dl)		
Total	0–1.0	1.3
Direct	0–0.4	0.5
Alanine aminotransferase (U/liter)	10–55	58
Aspartate aminotransferase (U/liter)	10–40	79
Osmolality in blood (mOsm/kg of water)	280–296	263
Osmolality in random urine (mOsm/kg of water)	150–1150	153
Sodium in random urine (mmol/liter)	NA	<10

* To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for bilirubin to micromoles per liter, multiply by 17.1. NA denotes not available.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

The patient was admitted to the hospital, and a high-dose thiamine infusion, a folate supplement, and a multivitamin were administered, in addition to his usual medications. One hour after admission, the blood pressure was 89/47 mm Hg and the heart rate was 90 beats per minute while the patient was sitting; after he stood up, the blood pressure was 75/40 mm Hg and the heart rate was 100 beats per minute. Amlodipine, furosemide, losartan, and metoprolol were discontinued, and fluids were administered intravenously. Two days later, the blood pressure was 124/72 and the heart rate was 91 beats per minute while the patient was sitting; after he stood up, the blood pressure was 80/50 mm Hg and the heart rate was 89 beats per minute. He could rise from a seated position with minimal use of his arms. An area of bruising (10 cm in diameter) developed on the right forearm, where a peripheral intravenous catheter had been placed.

Falls in Older Patients

This patient attributed his fall to tripping over an object in his garage. After a fall, many patients develop a narrative or explanation to normalize the event. Falling is always a surprise to a person with a lifetime of experience remaining upright, despite tripping or walking on slippery surfaces. Maintaining balance after tripping is dependent on strength in the hip flexor and gluteal muscles, and such strength decreases gradually with aging. When patients describe a fall as “just tripping,” I ask whether they think they would have fallen if the same event had occurred 10 or 20 years earlier.

Orthostatic Hypotension

Could this patient’s recurrent falls have been due to orthostatic (postural) hypotension? An assessment for orthostatic hypotension would be useful, since he was receiving antihypertensives and diuretics, and medication side effects such as orthostatic hypotension are another common cause of falls in older adults. On admission to the hospital, he was given his usual medications, as well as a standard multivitamin, a folate supplement, and a thiamine infusion. Rapid intravenous infusion of thiamine can cause hypotension, but such hypotension is transient. However, although this patient had potential age-related risk factors for falling, his alcohol use was the most worrisome risk factor.

Falls in Patients with Alcohol Use

If I had seen this patient in the clinic, I would have strongly suspected that his first fall had been related to alcohol intoxication, since he had reported drinking up to 6 or 7 glasses of wine daily during the 3 months before the evaluation. Alcohol-use disorder can occur after Roux-en-Y gastric bypass in patients who have no history of excessive drinking.

Falls in Patients with Nutritional Deficiencies

When the patient returned to the clinic 4 months after the initial fall, he reported falling multiple times, with injuries, and had rented a wheelchair in order to safely negotiate his activities of daily living. His primary care physician performed a detailed neurologic examination that revealed weakness on hip flexion and hip extension and changes in sensation and proprioception, findings that raised concerns about subacute combined degeneration related to a nutritional deficiency, such as vitamin B12 deficiency. The patient was at high risk for nutritional deficiencies resulting from both decreased intake of vitamins and minerals in the context of alcohol use and decreased absorption of vitamins and minerals in the context of previous gastric bypass. He reported taking prescribed vitamin B12 and vitamin D supplements daily, and he had normal levels of those vitamins. However, he was not taking the daily multivitamin that is recommended after bariatric surgery, and he could have had other nutritional deficiencies. Ingested copper is stabilized by gastric acid and absorbed by the stomach and proximal small intestine. Copper deficiency after Roux-en-Y gastric bypass is increasingly recognized as a cause of myeloneuropathy that is similar to vitamin B12 deficiency.

Scurvy

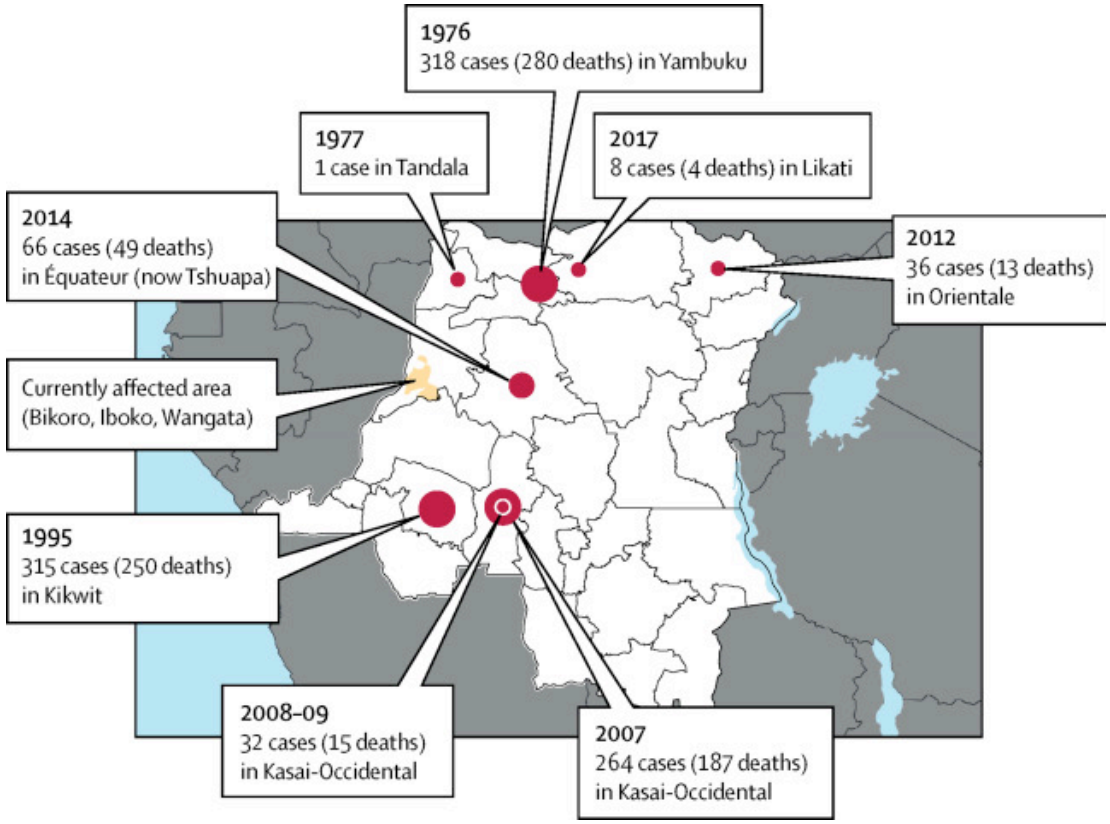
Vitamin C is present in many fruits and vegetables, but proper food preparation is necessary to avoid degrading the vitamin C content. This patient is the prototypical person who is at risk for the development of “bachelor scurvy,” a condition that occurs among unpartnered men who prepare their own meals or eat out frequently, drink heavily, and eat virtually no fruits or vegetables.

Diagnosis

Laboratory testing revealed deficiencies in multiple vitamins and minerals. The patient had markedly low blood levels of folate (2 ng per milliliter; normal range, >4.7), vitamin B_6 (<2 μg per liter; normal range, 5 to 50), and vitamin C (<0.1 mg per deciliter [<6 μmol per liter]; normal range, 0.4 to 2.0 mg per deciliter [23 to 114 μmol per liter]). The zinc level was mildly low, and the copper and selenium levels were at the low end of the normal range. The levels of vitamin B_1 (thiamine), vitamin A, vitamin E, and 25-hydroxyvitamin D were not obtained. Taken together, the final pathologic diagnoses in this case were vitamin C deficiency (scurvy), as well as folate, vitamin B_6, and zinc deficiencies.

Outbreak of Ebola virus disease in the Democratic Republic of the Congo, April–May, 2018: an epidemiological study

On May 8, 2018, the Government of the Democratic Republic of the Congo reported an outbreak of Ebola virus disease in Équateur Province in the northwest of the country. The remoteness of most affected communities and the involvement of an urban centre connected to the capital city and neighbouring countries makes this outbreak the most complex and high risk ever experienced by the Democratic Republic of the Congo. We provide early epidemiological information arising from the ongoing investigation of this outbreak. We classified cases as suspected, probable, or confirmed using national case definitions of the Democratic Republic of the Congo Ministère de la Santé Publique. We investigated all cases to obtain demographic characteristics, determine possible exposures, describe signs and symptoms, and identify contacts to be followed up for 21 days. We also estimated the reproduction number and projected number of cases for the 4-week period from May 25, to June 21, 2018.



Ebola virus disease case and contact definitions

Suspected case

- Any living person having or having had a high fever with a sudden onset, with an epidemiological link to:
  - a suspected, probable or confirmed case
  - a dead or sick animal, or
- Any deceased person having or having had a high fever with a sudden onset, and who has been in contact with:
  - a person with suspected or probable Ebola virus disease
  - a dead or sick animal, or
- Anyone with a high fever with a sudden onset and at least three of the following symptoms: headache, severe fatigue, anorexia or loss of appetite, difficulty swallowing, abdominal pain, difficulty breathing, vomiting, hiccups, diarrhoea, muscle or joint pain, or
- Anyone with unexplained bleeding, or
- Anyone with sudden and unexplained death

Probable case

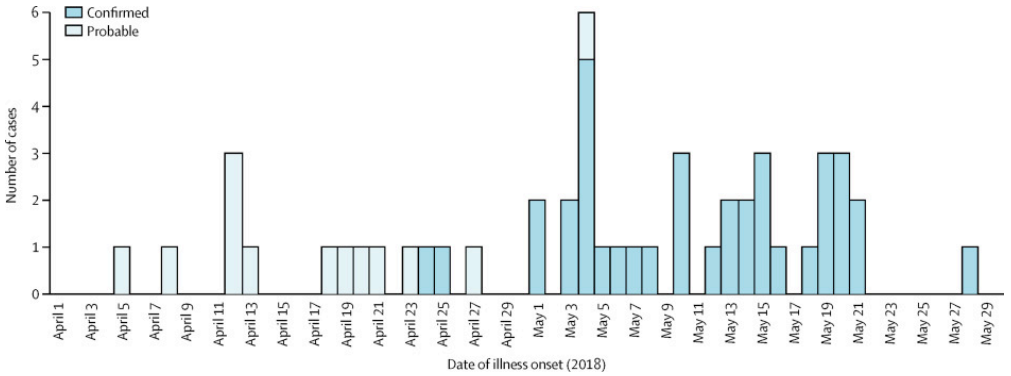
- Any suspected case as evaluated by a clinician, or
- Any suspected case that has died (and for which it has not been possible to obtain biological samples for laboratory confirmation) with an epidemiological link to a confirmed case

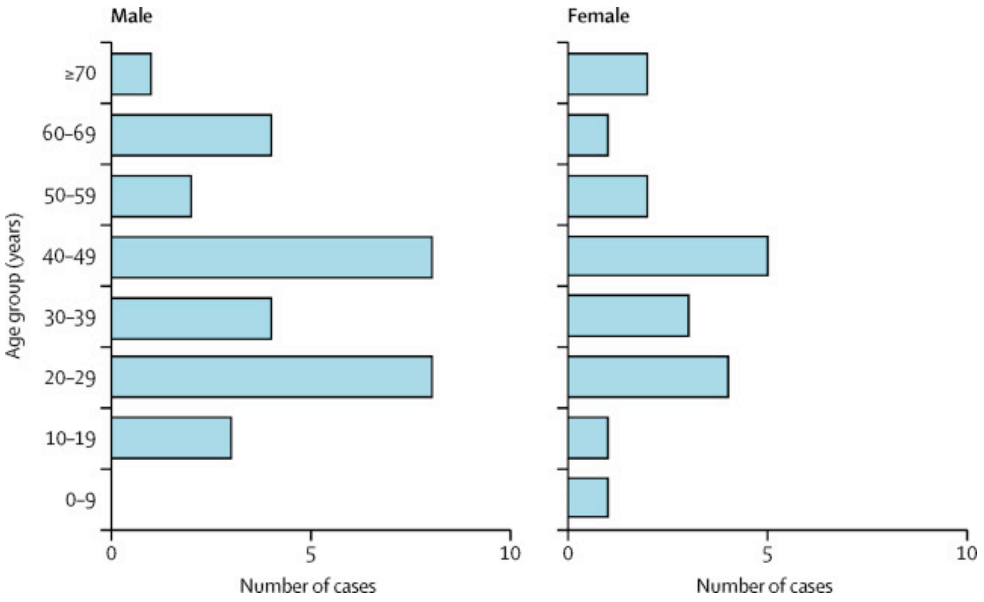
Confirmed case

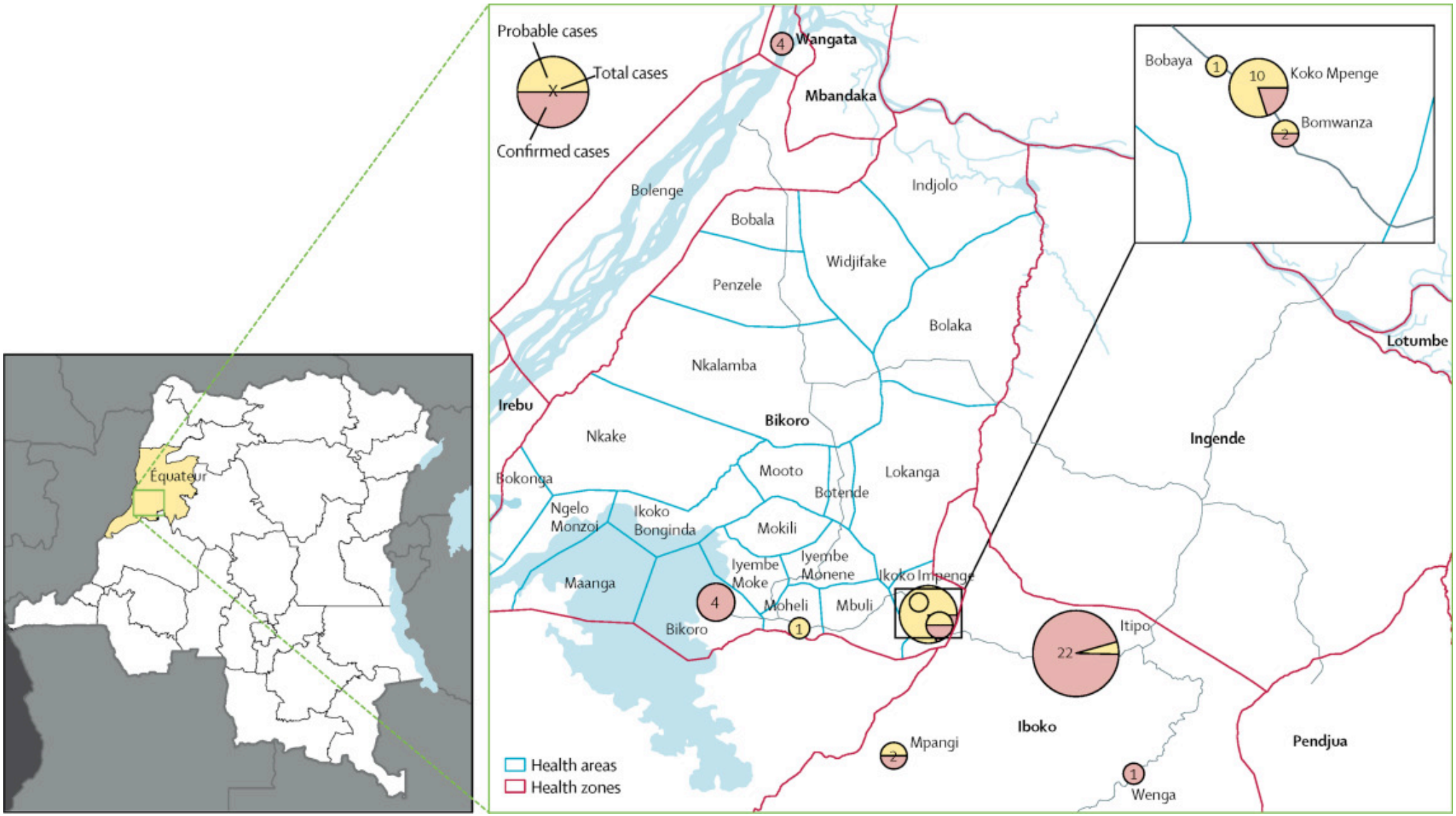
- Any suspected or probable case with a positive laboratory result for viral RNA by reverse transcription PCR, or, for retrospective diagnosis, antibodies against Ebola virus

Contacts

- Any person having had contact with a confirmed, probable or suspected Ebola virus disease case by:
  - Sleeping in the same house as the case in the month before illness onset
  - Having direct physical contact during the case's illness or with the body of a deceased case
  - Having shared the same transport vehicle as a case during their illness
  - Having touched any body fluids of a case during their illness
  - Having handled any clothes or linen of a case during their illness
  - Having been breastfed by a case



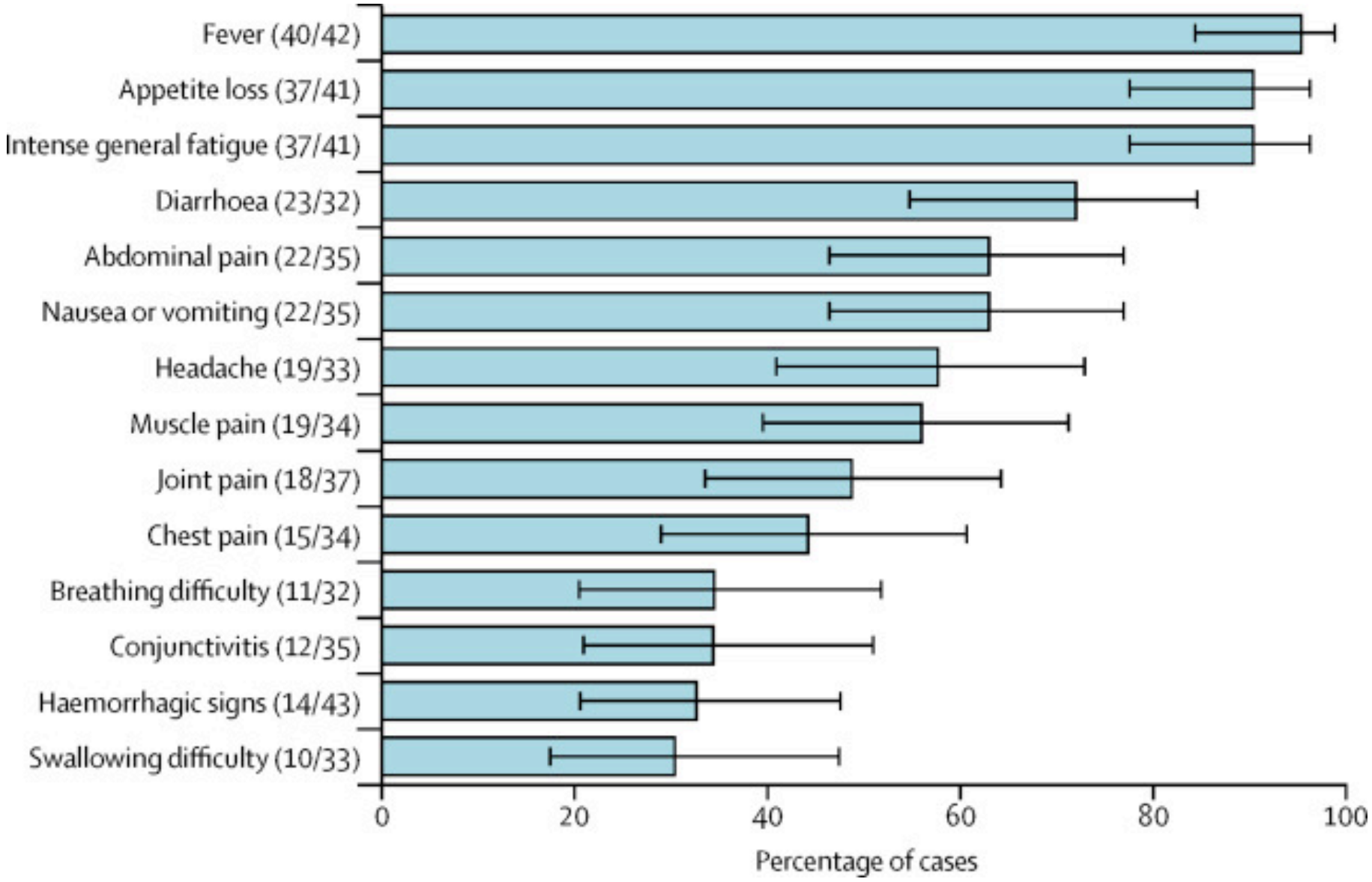




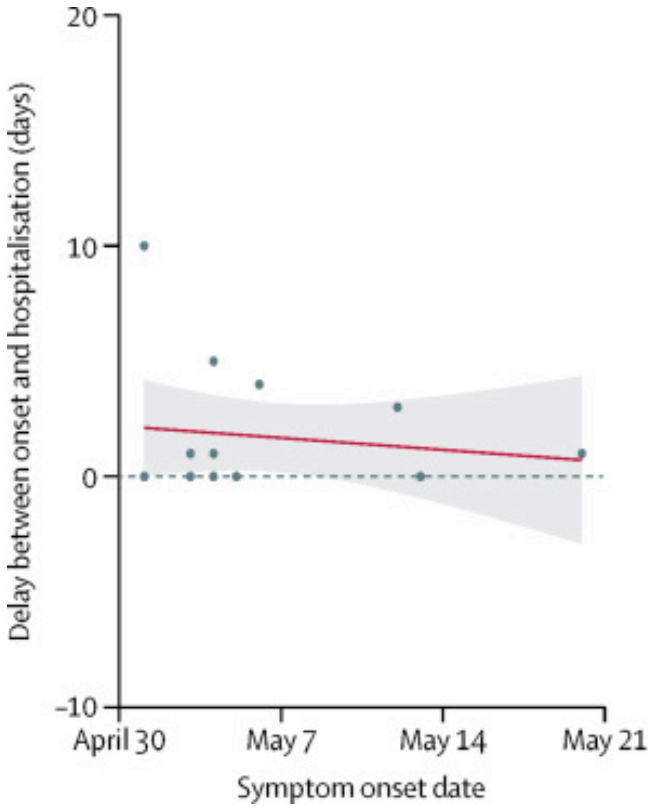
Confirmed and probable cases (n=47) by approximate place of residence

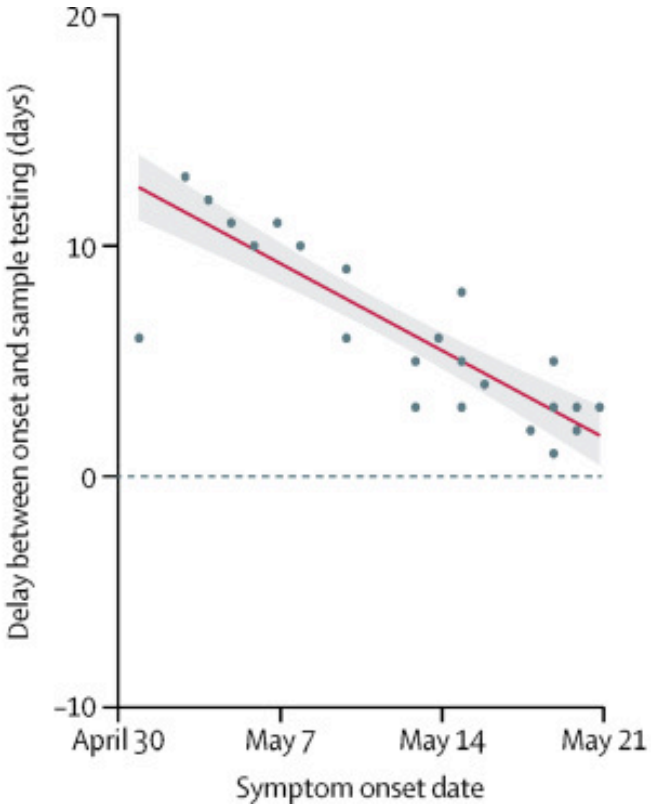
Data are as of May 30, 2018; three cases from Bikoro health zone not shown because of unavailability of location information. Cases only displayed where location can be determined at the scale of this map. Other cases not indicated. Boundaries are subject to confirmation and locations are approximate. The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Health zones are indicated in bold font.

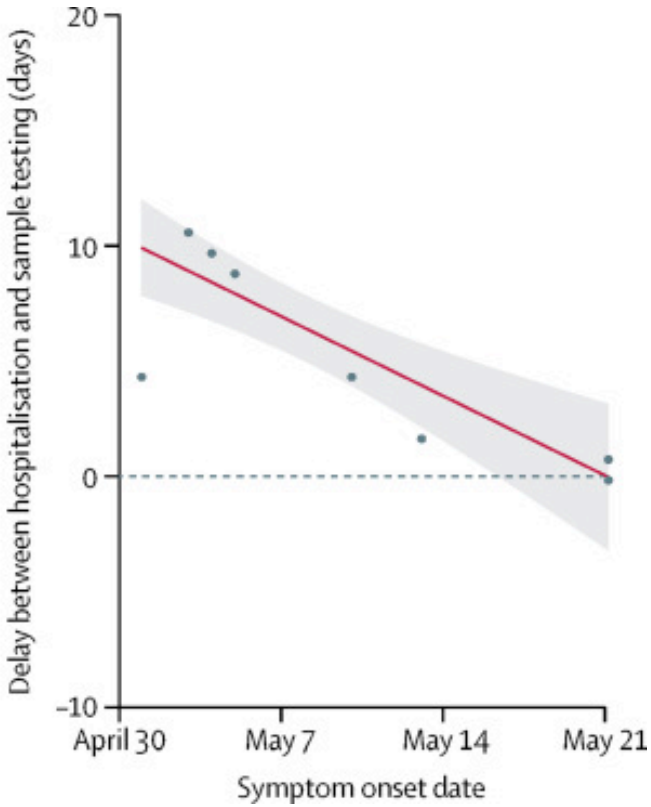
Frequency distribution of the most common symptoms reported for confirmed and probable cases



Delays between illness onset and first reported hospitalisation (n=16) and sample testing (n=30), and between hospitalisation and sample testing (n=12)







Exposures before onset of illness reported for confirmed and probable cases

	Confirmed cases reporting exposure	Probable cases reporting exposure	Confirmed and probable cases reporting exposure
Contact with other confirmed or probable cases, or sick people, in the month before illness	22/31 (71%)	7/10 (70%)	29/41 (71%)
Funeral participant	18/31 (58%)	6/9 (67%)	24/40 (60%)
Travel outside of home village or town	11/27 (41%)	1/8 (13%)	12/35 (34%)
Previous hospitalisation	11/28 (39%)	2/7 (29%)	13/35 (37%)
Visited traditional healer	2/26 (8%)	1/7 (14%)	3/33 (9%)
Direct contact with animals or raw meat	1/21 (5%)	0/5 (0%)	1/26 (4%)

Data are as of May 30, 2018. Missing and inconclusive responses excluded.

Confirmation of cases required detection of Ebola virus RNA in blood or body fluids by reverse transcription PCR. We investigated all notified suspected, probable, and confirmed cases to record demographic characteristics, determine possible exposures, document information about illness onset and signs and symptoms, and to identify potentially exposed contacts. These data were collected by trained field investigators and health professionals attending to cases, using a standardised case investigation form, which was subsequently entered into an electronic database. For people who had recovered or died before May 5, 2018, we did retrospective case classification by reviewing medical records at health facilities in the affected locations. For cases who were alive or for whom disease onset was after the declaration of the outbreak on May 8, 2018, information was collected prospectively at the time of case investigation. Our analysis included probable and confirmed cases as of May 30, 2018. Suspected cases reported throughout the study period were systemically investigated, sampled, and reclassified on the basis of laboratory results to confirm or exclude them as non-cases. We excluded suspected cases pending further investigation as of May 30, 2018.

Added value of this study

By publishing evidence as it emerges, we aim to ensure transparency and availability of information from this ongoing event in near real-time. To our knowledge, this is the most rapid scientific publication of preliminary data and analyses from an ongoing Ebola virus disease outbreak. While highlighting the ongoing efforts of the Ministry of Health of the Democratic Republic of the Congo and supporting partner agencies to investigate and control the current Ebola virus disease outbreak, we present emerging descriptive epidemiological characteristics of cases detected by the time of publication, and draw inferences about the case fatality ratio, the reproduction number, and case incidence projected from these data. Our results are informing response strategies.

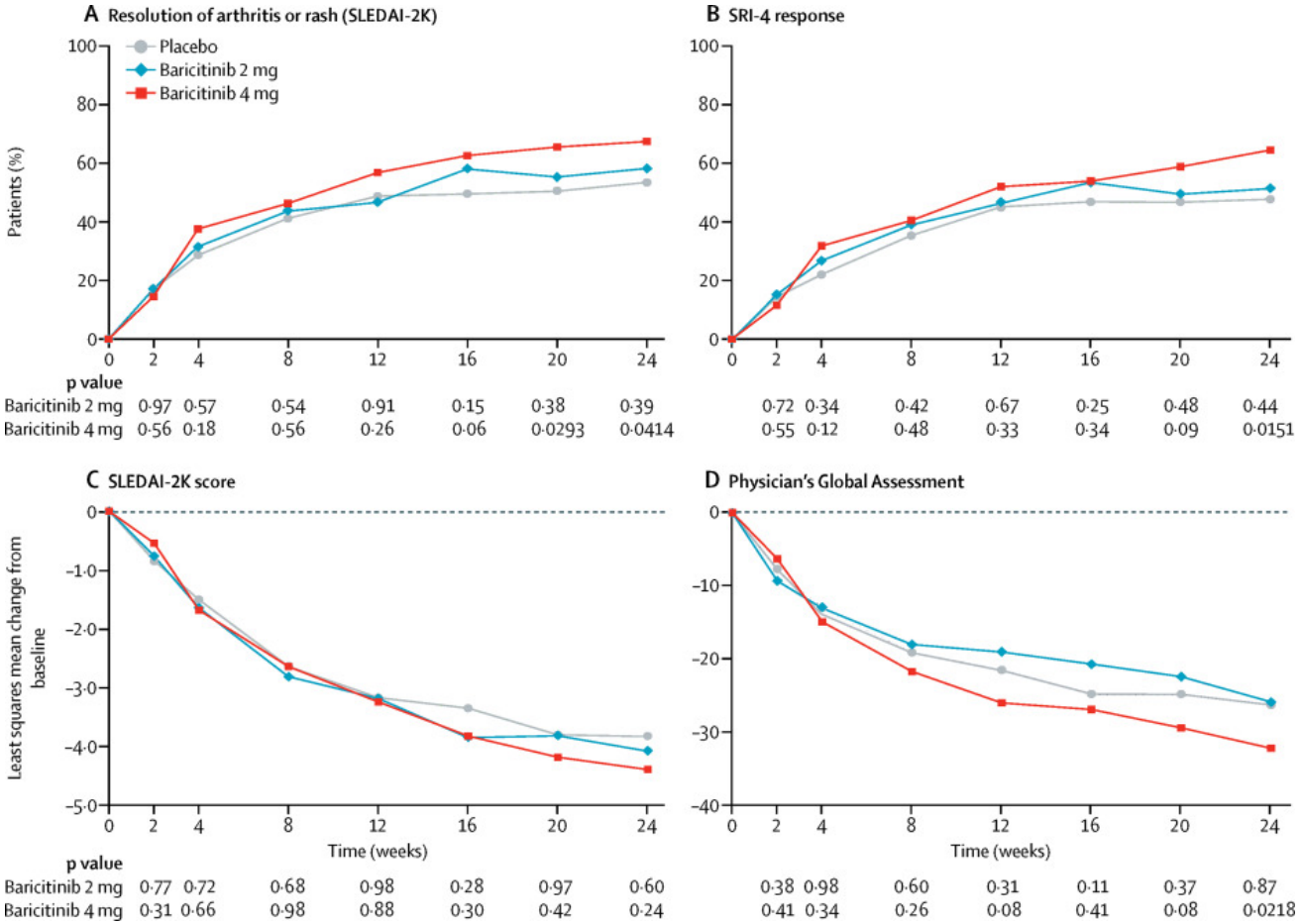
Implications of all the available evidence

The nature and context of this Ebola virus disease outbreak present a formidable challenge to public health authorities. The presence of Ebola virus disease in three locations makes this response particularly challenging, and proximity to an urban centre with connections to Kinshasa and regional borders infers a substantially higher risk of national and regional spread than previous outbreaks of Ebola virus disease in the Democratic Republic of the Congo. Evidence emerging from this ongoing event suggests a similar epidemiological presentation to past outbreaks, with current capacity adequate to respond if recent trends continue. Our results, combined with past experiences, provide a strong evidence base to guide and further strengthen response measures, and, following this event, remain useful in informing the early evolution of Ebola virus disease outbreaks.

Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 2 trial

Patients with systemic lupus erythematosus have substantial unmet medical need. Baricitinib is an oral selective Janus kinase (JAK)1 and JAK2 inhibitor that we hypothesised might have therapeutic benefit in patients with systemic lupus erythematosus. In this double-blind, multicentre, randomised, placebo-controlled, 24-week phase 2 study, patients were recruited from 78 centres in 11 countries. Eligible patients were aged 18 years or older, had a diagnosis of systemic lupus erythematosus, and had active disease involving skin or joints. We randomly assigned patients (1:1:1) to receive once-daily baricitinib 2 mg, baricitinib 4 mg, or placebo for 24 weeks. The primary endpoint was the proportion of patients achieving resolution of arthritis or rash at week 24, as defined by Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2K).

	Placebo (n=105)	Baricitinib 2 mg (n=105)	Baricitinib 4 mg (n=104)
Mean age, years	44·9 (12·8)	43·2 (11·0)	45·0 (12·4)
Mean time since onset of systemic lupus erythematosus, years	9·7 (7·7)	11·8 (9·1)	11·5 (10·3)
Concomitant medications			
Corticosteroids	77 (73%)	79 (75%)	74 (71%)
Mean prednisone dose (or equivalent), mg/day	7·9 (4·6)	8·7 (5·8)	10·5 (17·4)
Prednisone dose (or equivalent), ≥7·5 mg/day	36/77 (47%)	40/79 (51%)	41/74 (55%)
Antimalarials	75 (71%)	71 (68%)	76 (73%)
Immunosuppressants	45 (43%)	47 (45%)	50 (48%)
Methotrexate	13 (12%)	17 (16%)	13 (13%)
Azathioprine	15 (14%)	10 (10%)	11 (11%)
Mycophenolate mofetil	11 (10%)	10 (10%)	16 (15%)
Non-steroidal anti-inflammatory drug	27 (26%)	29 (28%)	32 (31%)
Mean SLEDAI-2K score*	8·9 (2·9)	8·8 (3·4)	9·0 (3·3)
SLEDAI-2K score ≥10	43 (41%)	35 (33%)	44 (42%)
SLEDAI-2K organ system involvement			
CNS	3 (3%)	1 (1%)	2 (2%)
Vascular	1 (1%)	4 (4%)	3 (3%)
Musculoskeletal	93 (89%)	93 (89%)	96 (92%)
Renal	9 (9%)	9 (9%)	7 (7%)
Mucocutaneous	90 (86%)	82 (78%)	92 (88%)
Cardiovascular and respiratory	2 (2%)	1 (1%)	1 (1%)
Immunological	62 (59%)	63 (60%)	64 (62%)
Constitutional	2 (2%)	2 (2%)	0
Haematological	13 (12%)	9 (9%)	5 (5%)
≥1 A or ≥2 B BILAG scores†	62 (59%)	56 (53%)	69 (66%)
Mean Physician's Global Assessment score‡	49·5 (16·9)	48·8 (15·8)	51·7 (16·0)
Mean CLASI activity score§	4·9 (5·7)	3·8 (5·4)	4·0 (3·4)
Mean tender joint count	7·7 (5·8)	8·7 (6·6)	8·5 (6·2)
Mean swollen joint count	5·3 (4·7)	5·2 (4·7)	5·5 (4·2)
Mean SLICC/ACR Damage Index score¶	0·59 (0·97)	0·44 (0·68)	0·40 (0·88)

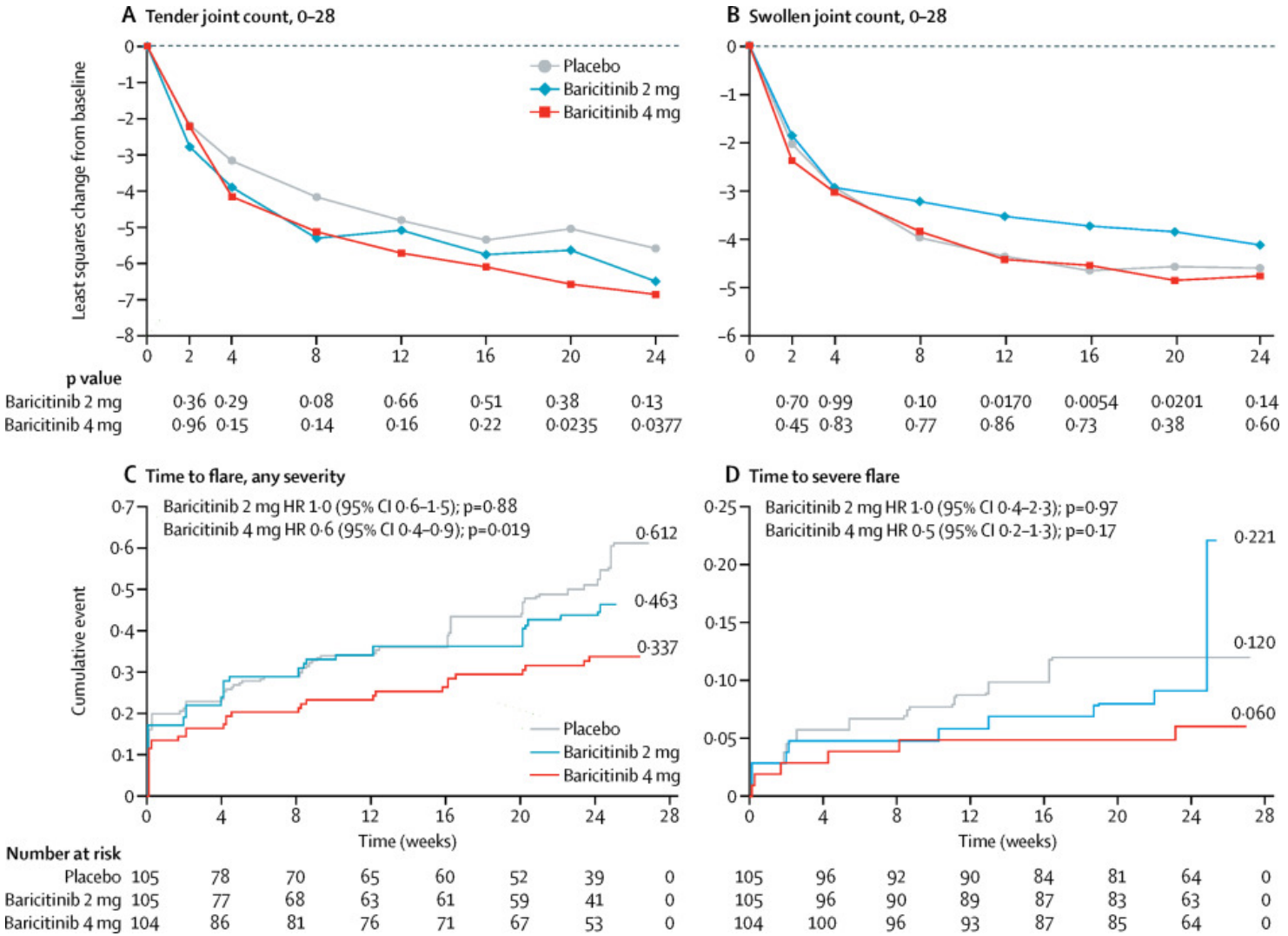


Primary and secondary efficacy analyses

(A) Proportion of patients achieving resolution of arthritis or rash, as determined by SLEDAI-2K. (B) Proportion of patients achieving an SRI-4 response. (C) Least squares mean change from baseline in the SLEDAI-2K score (scores ranging from 0 to 105, higher scores indicate more severe disease). (D) Least squares mean change from baseline in the Physician's Global Assessment of Disease Activity, with scores ranging from 0 (0 mm) to 3 (100 mm; visual analogue scale, higher scores indicate more severe disease). The figure includes all patients in the modified intention-to-treat analysis (n=314). p values are for comparisons of baricitinib 2 mg and 4 mg with placebo. SLEDAI-2K=Systemic Lupus Erythematosus Disease Activity Index-2000. SRI-4=Systemic Lupus Erythematosus Responder Index-4.

Clinical and biomarker outcomes at week 24 in the intention-to-treat population

	Placebo (n=105)	Baricitinib 2 mg (n=105)		Baricitinib 4 mg (n=104)	
	Week 24	Week 24	Comparison with placebo (95% CI); p value	Week 24	Comparison with placebo (95% CI); p value
Primary outcome					
Resolution of arthritis/rash (SLEDAI-2K)*	56 (53%)	61 (58%)	1·3 (0·7 to 2·3); p=0·39	70 (67%)	1·8 (1·0 to 3·3); p=0·0414
Secondary and exploratory outcomes					
SRI-4*	50 (48%)	54 (51%)	1·3 (0·7 to 2·2); p=0·44	67 (64%)	2·0 (1·2 to 3·6); p=0·0151
≥4 point improvement in SLEDAI-2K*	51 (49%)	55 (52%)	1·2 (0·7 to 2·2); p=0·45	67 (64%)	2·0 (1·1 to 3·5); p=0·0220
No worsening (≥1A/2B) by BILAG*	80 (76%)	82 (78%)	1·2 (0·6 to 2·2); p=0·67	85 (82%)	1·4 (0·7 to 2·8); p=0·31
No worsening by PGA*	78 (74%)	82 (78%)	1·3 (0·7 to 2·5); p=0·45	84 (81%)	1·5 (0·8 to 2·9); p=0·26
LLDAS*	27 (26%)	35 (33%)	1·4 (0·8 to 2·7); p=0·25	40 (38%)	1·9 (1·0 to 3·5); p=0·0391
Flares (any severity) on the SELENA-SLEDAI Flare Index†	54 (51%)	45 (43%)	1·0 (0·6 to 1·5); p=0·88	34 (33%)	0·6 (0·4 to 0·9); p=0·0193
Severe flares on the SELENA-SLEDAI Flare Index†	12 (11%)	10 (10%)	1·0 (0·4 to 2·3); p=0·98	6 (6%)	0·5 (0·2 to 1·3); p=0·17
Least squares mean change from baseline‡					
SLEDAI-2K	−3·8 (0·4)	−4·1 (0·4)	−0·3 (−1·2 to 0·7); p=0·60	−4·4 (0·4)	−0·6 (−1·6 to 0·4); p=0·24
PGA	−26·3 (1·8)	−25·9 (1·8)	0·4 (−4·6 to 5·4); p=0·87	−32·2 (1·8)	−5·9 (−10·9 to −0·9); p=0·0218
CLASI activity score	−2·8 (0·4)	−1·7 (0·4)	1·1 (0·1 to 2·2); p=0·0371	−2·3 (0·4)	0·5 (−0·5 to 1·6); p=0·33
28-tender joint count	−5·6 (0·4)	−6·5 (0·4)	−0·9 (−2·1 to 0·3); p=0·13	−6·9 (0·4)	−1·3 (−2·5 to −0·1); p=0·0377
28-swollen joint count	−4·6 (0·2)	−4·1 (0·2)	0·5 (−0·2 to 1·1); p=0·14	−4·8 (0·2)	−0·2 (−0·8 to 0·5); p=0·60
SLICC/ACR Damage Index score	0·05 (0·03)	0·07 (0·03)	0·03 (−0·05 to 0·10); p=0·53	0·07 (0·03)	0·03 (−0·05 to 0·10); p=0·52
Worst Joint Pain NRS	−0·9 (0·3)	−1·6 (0·3)	−0·6 (1·3 to 0·1); p=0·07	−1·8 (0·3)	−0·9 (−1·6 to −0·2); p=0·0157
Worst Pain NRS	−0·6 (0·3)	−1·2 (0·3)	−0·6 (−1·3 to 0·1); p=0·10	−1·3 (0·3)	−0·8 (−1·5 to 0); p=0·0403
Worst Fatigue NRS	−1·2 (0·2)	−1·1 (0·2)	0·1 (−0·6 to 0·7); p=0·89	−1·5 (0·2)	−0·3 (−1·0 to 0·3); p=0·32
Anti-dsDNA, IU/mL	55·4 (26·8)	1·0 (27·1)	−54·4 (−128·0 to 19·2); p=0·15	48·5 (26·9)	−6·8 (−80·6 to 66·9); p=0·86
Complement C3, g/L	0 (0·02)	0 (0·02)	−0·01 (−0·06 to 0·04); p=0·75	−0·02 (0·02)	−0·02 (−0·07 to 0·02); p=0·31
Complement C4, g/L	0·01 (0·01)	−0·01 (0·01)	−0·01 (−0·03 to 0); p=0·18	−0·01 (0·01)	−0·02 (−0·03 to 0); p=0·0314



Improvements in systemic lupus erythematosus disease activity, weeks 0–24
The least squares mean change from baseline in tender joint count (A) and swollen joint count (B). Time to first flare of any severity (C) and time to first severe flare (D), as defined by the SSFI. p values are for comparisons of baricitinib 2 mg and 4 mg with placebo. HR=hazard ratio. SSFI=Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index Flare Index.

Serious adverse events were reported in five (5%) patients receiving placebo, 11 (10%) patients receiving baricitinib 2 mg, and ten (10%) patients receiving baricitinib 4 mg. There were no deaths, malignancies, or major adverse cardiovascular events in the study. One serious adverse event of deep-vein thrombosis was reported in the baricitinib 4 mg group, 46 days after the patient's first dose of baricitinib, in a patient with antiphospholipid antibodies (table 3). There were more serious infections reported in the baricitinib 4 mg group (six [6%] patients) than in the 2 mg group (two [2%] patients) or placebo group (one [1%] patient. There were no cases of serious or multidermatomal herpes zoster virus infection or opportunistic infection, and no reports of tuberculosis. There was one occurrence of non-serious herpes zoster virus infection in the placebo group, none in the baricitinib 2 mg group, and one in the baricitinib 4 mg group.

Adverse events

	Placebo (n=105)	Baricitinib 2 mg (n=105)	Baricitinib 4 mg (n=104)
Discontinuation from study treatment because of an adverse event	4 (4%)	10 (10%)	11 (11%)
Any adverse event after the start of therapy	68 (65%)	75 (71%)	76 (73%)
Infections	41 (39%)	47 (45%)	47 (45%)
Serious infections	1 (1%)	2 (2%)	6 (6%)
Herpes zoster virus infection	1 (1%)	0	1 (1%)
Deep-vein thrombosis	0	0	1 (1%)
Serious adverse events	5 (5%)	11 (10%)	10 (10%)

Data are n (%). Adverse events that occurred between baseline and week 24, and up to 30 days after treatment, are shown.

Added value of this study

In this phase 2 trial, baricitinib improved the signs and symptoms of active disease in patients with systemic lupus erythematosus who were receiving standard background therapy. Baricitinib 4 mg treatment resulted in a greater proportion of patients achieving resolution of arthritis, as defined by Systemic Lupus Erythematosus Disease Activity Index-2000, than with placebo. The safety profile of baricitinib was consistent with other drugs used to treat active systemic lupus erythematosus.

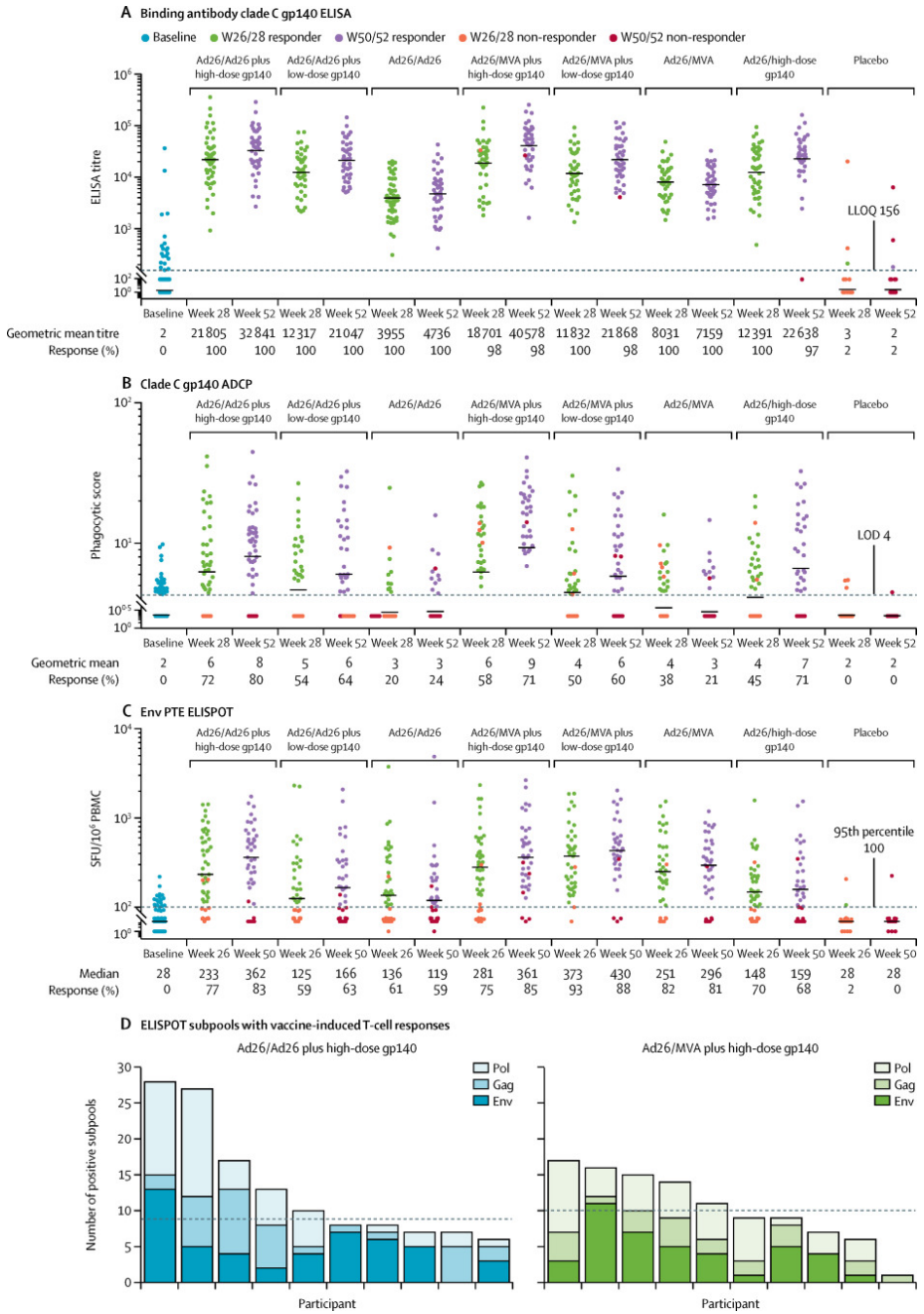
Implications of all the available evidence

These findings support the evidence that JAK/STAT signalling could have a central role in the pathogenesis of systemic lupus erythematosus. To our knowledge, this is the first study to show clinical benefit of JAK inhibition in the treatment of systemic lupus erythematosus. This work provides the foundation for additional study of JAK1/2 inhibition with baricitinib as a potentially effective oral treatment option for active systemic lupus erythematosus in patients who have not achieved adequate disease control with available standard of care therapies.

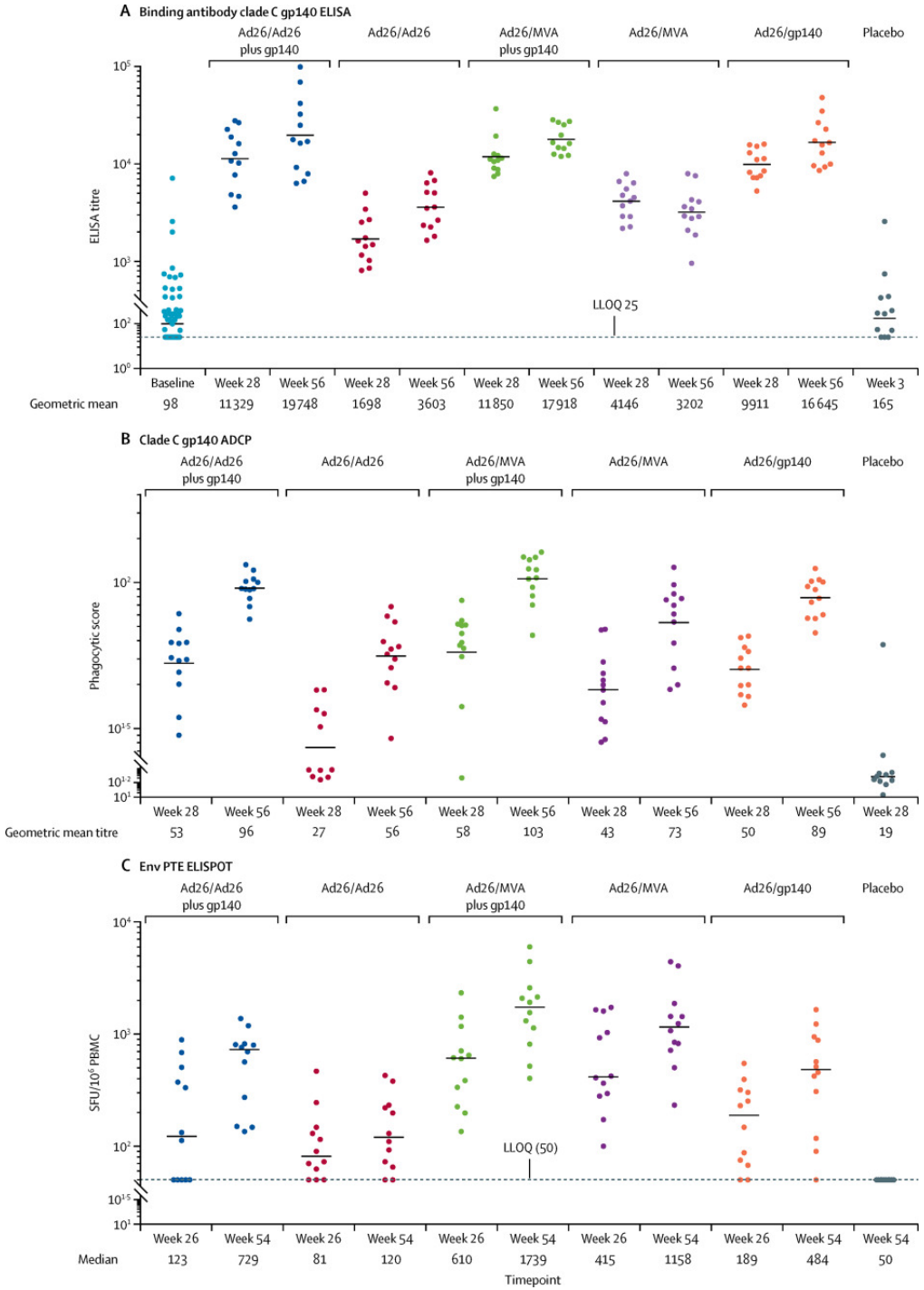
Evaluation of a mosaic HIV-1 vaccine in a multicentre, randomised, double-blind, placebo-controlled, phase 1/2a clinical trial (APPROACH) and in rhesus monkeys (NHP 13-19)

More than 1·8 million new cases of HIV-1 infection were diagnosed worldwide in 2016. No licensed prophylactic HIV-1 vaccine exists. A major limitation to date has been the lack of direct comparability between clinical trials and preclinical studies. We aimed to evaluate mosaic adenovirus serotype 26 (Ad26)-based HIV-1 vaccine candidates in parallel studies in humans and rhesus monkeys to define the optimal vaccine regimen to advance into clinical efficacy trials. We randomly assigned participants to one of eight study groups, stratified by region. Participants and investigators were blinded to the treatment allocation throughout the study. We primed participants at weeks 0 and 12 with Ad26.Mos.HIV (5×10^{10} viral particles per 0·5 mL) expressing mosaic HIV-1 envelope (Env)/Gag/Pol antigens and gave boosters at weeks 24 and 48 with Ad26.Mos.HIV or modified vaccinia Ankara (MVA; 10^8 plaque-forming units per 0·5 mL) vectors with or without high-dose (250 μg) or low-dose (50 μg) aluminium adjuvanted clade C Env gp140 protein. Those in the control group received 0·9% saline. All study interventions were administered intramuscularly. Primary endpoints were safety and tolerability of the vaccine regimens and Env-specific binding antibody responses at week 28. Safety and immunogenicity were also assessed at week 52.

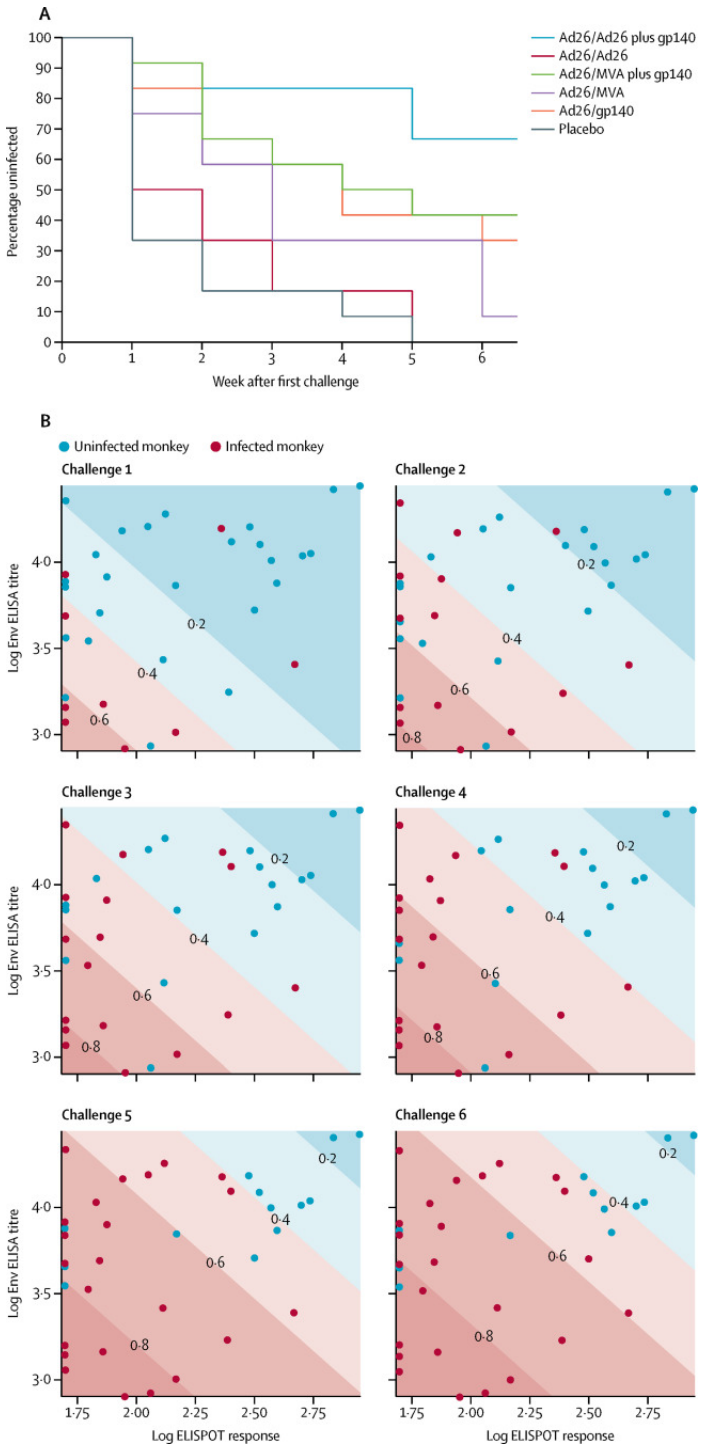
The rhesus macaque (Macaca mulatta) is one of the best-known species of Old World monkeys. It is listed as Least Concern in the IUCN Red List of Threatened Species in view of its wide distribution, presumed large population, and its tolerance of a broad range of habitats. Native to South, Central, and Southeast Asia, rhesus macaque have the widest geographic ranges of any nonhuman primate, occupying a great diversity of altitudes and a great variety of habitats, from grasslands to arid and forested areas, but also close to human settlements



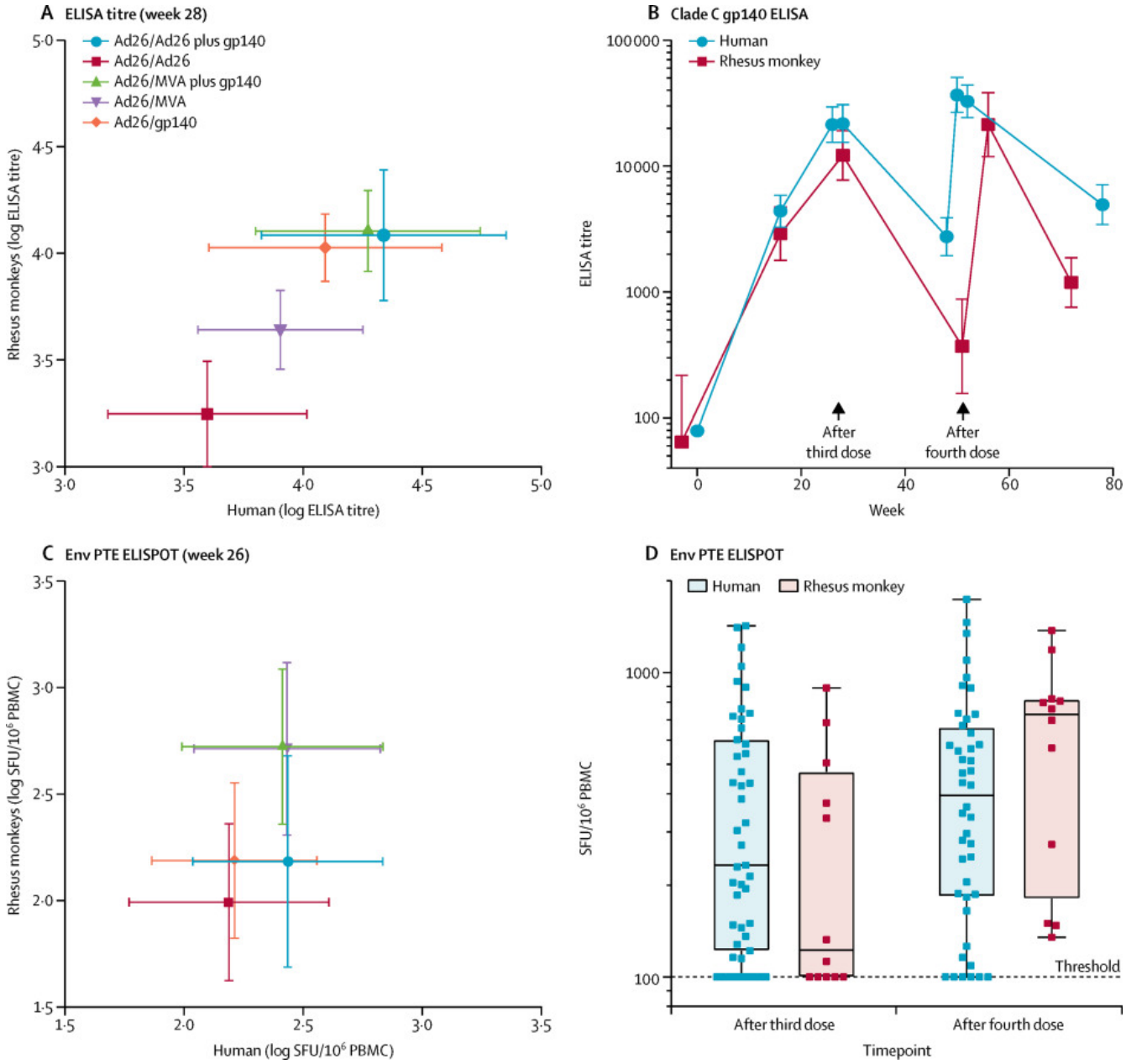
Immune response to vaccination regimens in humans Responder rates are shown for each vaccine group at baseline, after the third vaccination at weeks 26 or 28, and fourth vaccination at weeks 50 or 52. Vaccine response was defined as value more than threshold (if baseline is <threshold or is missing); otherwise, it was defined as value with a three-time increase from baseline (if baseline is ≥threshold). (A) The dotted line is the LLOQ threshold. (B) The dotted line is the LOD threshold. (C) The dotted line is the 95th percentile of the overall baseline values. (D) Number of ELISPOT subpools with vaccine-induced T-cell responses for a subset of participants in Ad26/Ad26 plus high-dose gp140 and Ad26/MVA plus high-dose gp140 vaccine groups. The dotted line is the median number of subpools recognised. W26/28=weeks 26 or 28. W50/52=weeks 50 or 52. Ad26=adenovirus serotype 26. MVA=modified vaccinia Ankara. LLOQ=lower limit of quantification. ADCP=antibody-dependent cellular phagocytosis. LOD=limit of detection. ELISPOT=enzyme-linked immunospot. Env=envelope. PTE=potential T-cell epitope. PBMC=peripheral blood mononuclear cells. SFU=spot forming units.



Immune response to vaccination regimens in rhesus monkeys Responses are shown for each vaccine group at baseline, after the third vaccination at weeks 26 or 28, and fourth vaccination at weeks 54 or 56. Vaccine response was defined as value more than threshold (if baseline is <threshold or is missing); otherwise, it was defined as value with a three-time increase from baseline (if baseline is ≥threshold). The dotted lines are the LLOQ thresholds. Ad26=adenovirus serotype 26. MVA=modified vaccinia Ankara. LLOQ=lower limit of quantification. ADCP=antibody-dependent cellular phagocytosis. Env=envelope. PTE=potential T-cell epitope. ELISPOT=enzyme-linked immunospot. PBMC=peripheral blood mononuclear cells. SFU=spot forming units.



Protection and correlates in rhesus monkeys (A) Kaplan-Meier plot of the protection of each vaccine regimen in rhesus monkeys, assessed 1 week after each challenge. No animals were censored. (B) Humoral and cellular immune response measured by clade C ELISA at week 28 and PTE_g Env ELISPOT at week 26, and the infection status the week following each of six challenges (at weeks 77–84) of rhesus monkeys from the following groups: Ad26/Ad26, Ad26/gp140, Ad26/Ad26 plus gp140. The diagonal lines display model-derived probabilities of infection, modelled on ELISA and ELISPOT responses. Ad26=adenovirus serotype 26. MVA=modified vaccinia Ankara. Env=envelope.



Data comparison of humans and rhesus monkeys
Data are geometric mean titres or SFU per million PBMC. Panels (B) and (D) compare the Ad26/Ad26 plus high-dose gp140 regimen. Error bars are SDs in panels (A), (C), and (D), and 95% CIs in panel (B). Comparisons of the magnitude of immunological responses between rhesus monkey and human studies are shown. Rhesus monkey ELISA data in (A) and (B) have been transformed to human ELISA units. Ad26=adenovirus serotype 26. MVA=modified vaccinia Ankara. PBMC=peripheral blood mononuclear cells. SFU=spot forming units. Env=envelope. PTE=potential T-cell epitope. ELISPOT=enzyme-linked immunospot.

Added value of this study

All vaccines that were tested in this study showed favourable safety and tolerability profiles in humans. The mosaic Ad26/Ad26 plus gp140 HIV-1 vaccine induced robust humoral and cellular immune responses in both humans and rhesus monkeys. Immune responses in humans and rhesus monkeys were similar in magnitude, durability, and phenotype. This vaccine provided 67% protection against acquisition of six intrarectal simian-human immunodeficiency virus (SHIV)-SF162P3 challenges in rhesus monkeys.

Implications of all the available evidence

The mosaic Ad26/Ad26 plus gp140 HIV-1 vaccine met pre-established safety and immunogenicity criteria to advance into a phase 2b clinical efficacy study in sub-Saharan Africa, which is now underway (NCT03060629).

Time to deliver: report of the WHO Independent High-Level Commission on NCDs (Nicht-übertragbare Krankheiten)

The 2030 Agenda for Sustainable Development, with its pledge to leave no one behind, is our boldest agenda for humanity. It will require equally bold actions from Heads of State and Government. They must deliver on their time-bound promise to reduce, by one-third, premature mortality from NCDs through prevention and treatment and promote mental health and wellbeing.

Because many policy commitments are not being implemented, countries are not on track to achieve this target. Country actions against NCDs are uneven at best. National investments remain woefully small and not enough funds are being mobilised internationally. There is still a sense of business-as-usual rather than the urgency that is required. Plenty of policies have been drafted, but structures and resources to implement them are scarce.

The challenge is not only to gain political support, but also to guarantee implementation, whether through legislation, norms and standards setting, or investment. We need to keep arguing for NCDs and mental health to have greater priority, but countries must also take responsibility for delivery on agreed outputs and outcomes, as stated in endorsed documents. There is no excuse for inaction, as we have evidence-based solutions.

The WHO Independent High-level Commission on NCDs was convened by the WHO Director-General to advise him on bold recommendations on how countries can accelerate progress towards SDG target 3.4 on the prevention and treatment NCDs and the promotion of mental health and wellbeing.

Start from the top: political leadership and responsibility, from capitals to villages

Recommendation 1: (a) Heads of State and Government, not Ministers of Health only, should oversee the process of creating ownership at national level of NCDs and mental health. (b) Political leaders at all levels, including the subnational level, for example, city mayors, should take responsibility for comprehensive local actions, together with the health sector, that can advance action against NCDs and mental disorders.

Embed and expand: NCDs within health systems and UHC

Recommendation 3: Governments should reorient health systems to include health promotion and the prevention and control of NCDs and mental health services in their UHC policies and plans, according to national contexts and needs.

(a) Governments should ensure that the national UHC public benefit package includes NCD and mental health services, including health promotion and prevention and priority health care interventions as well as access to essential medicines and technologies.

(b) Primary health services should be strengthened to ensure equitable coverage, including essential public health functions, with an adequate and well-equipped multi-disciplinary health workforce, especially including community health workers and nurses.

(c) Synergies should be identified in existing chronic-care platforms, such as HIV and TB, to jumpstart NCD and mental health services.

Collaborate and regulate

Recommendation 4: Governments should increase effective regulation, appropriate engagement with the private sector, academia, civil society, and communities, building on a whole-of-society approach to NCDs, and share experiences and challenges, including policy models that work.

Governments

(a) Governments must take the lead in creating health-protecting environments through robust laws, where and when necessary, and through dialogue, where appropriate, based on the "health is the priority" principle, including clear objectives, transparency, and agreed targets. Dialogue must not, however, replace regulation in cases where regulation is the most or the only effective measure. Any dialogue platform should include transparency and a mechanism for accountability and evaluation as well as a timeframe.

Private sector

(b) Governments should be encouraged to engage constructively with the private sector—with the exception of the tobacco industry and with due attention to the management of commercial and other vested interests, while protecting against any undue influence, to seek ways to strengthen commitments and contributions to achieving public health goals, in accordance with the mandate of the SDGs.

(c) Taking into account and managing possible commercial and other vested interests, in order to contribute to accelerated progress towards SDG target 3.4, governments should work with: food and non-alcoholic beverage companies in areas such as reformulation, labelling, and regulating marketing; the leisure and sports industries to promote physical activity; the transportation industry to ensure safe, clean, and sustainable mobility; the pharmaceutical industry and vaccine manufacturers to ensure access to affordable, quality-assured essential medicines and vaccines; and with technology companies to harness emerging technologies for NCD action. Governments could also encourage economic operators in the area of alcohol production and trade to consider ways in which they could contribute to reducing the harmful use of alcohol in their core areas, as appropriate, depending on national, religious, and cultural contexts.

(d) Governments should give priority to restricting the marketing of unhealthy products (those containing excessive amounts of sugars, sodium, saturated fats and trans fats) to children. WHO should explore the possibility of establishing an international code of conduct on this issue, along with an accountability mechanism, while acknowledging the need for partnerships based on alignment of interests.

(e) Both fiscal incentives and disincentives should be considered to encourage healthy lifestyles by promoting the consumption of healthy products and by decreasing the marketing, availability, and consumption of unhealthy products.

Act for accountability

Recommendation 6: Governments should strengthen accountability to their citizens for action on NCDs.

(a) Governments should create or strengthen national accountability mechanisms, taking into account the global NCD accountability mechanism and health-impact assessments.

(b) WHO should simplify the existing NCD accountability mechanism and establish clear tracking and accountability for the highest impact programmes that can lead to achievement of SDG target 3.4, including a harmonised Countdown 2030 for NCDs and mental health.

If we wait for politics to solve these matters, we will have died

- A 23-year-old man, born in the UK, and a non-smoker
- No history of asthma in childhood
- Referred from local hospital to the Royal Brompton respiratory outpatients department
- Presented with a 4-year history of episodic shortness of breath, wheeze and hypoxia, and had more than ten previous emergency department attendances and three admissions to hospital
- He had received numerous short-burst courses of prednisolone, which resulted in rapid improvement in his hypoxia (within 24 h of taking prednisolone)
- Working diagnosis: difficult asthma, managed with inhaled corticosteroids (ICS) and long-acting beta-agonists (LABA)
- Past medical history: hayfever and mild childhood eczema
- Family history: nil
- Occupation: call centre supervisor; no relevant exposures

Which of these factors should be considered when presented with a diagnosis of 'difficult asthma'?

- ○ Misdiagnosis (eg, structural lung disease/cardiac disease)
- ○ Treatment adherence
- ○ Exacerbating factors (eg, gastro-oesophageal reflux disease or rhinitis)
- ○ Triggers (eg, pets or occupation)
- ○ All of the above

Which of these factors should be considered when presented with a diagnosis of 'difficult asthma'?

Correct
The correct answer is all of the above

- Misdiagnosis (eg, structural lung disease/cardiac disease)
- Treatment adherence
- Exacerbating factors (eg, gastro-oesophageal reflux disease or rhinitis)
- Triggers (eg, pets or occupation)
- (•) All of the above

- All these factors should be considered when assessing a patient with difficult asthma before determining that they have severe asthma.
- Published cross-sectional studies suggest that up to 20% of patients referred to a difficult asthma service do not have severe asthma following a systematic assessment process.

Parameter	Result
IgE (IU/mL)	381 (normal range <70)
Eosinophils (x10^9/L)	6·3–8·9 (normal range 0·0–0·5)
Antinuclear antibodies (ANA)	Negative
Anti-neutrophil cytoplasmic antibody (ANCA)	Negative
Aspergillus precipitins	Negative
CT chest scan	Small volume right paratracheal node (<1 cm), a few areas of patchy consolidation in the left lower lobe, and lingula. Focal bronchiectasis in the anterior segment of the right upper lobe
Bronchoscopy	Structurally normal large airways
Bronchoalveolar lavage (microscopy, culture, and sensitivities [MC&S]; acid-fast bacilli [AFB])	No growth

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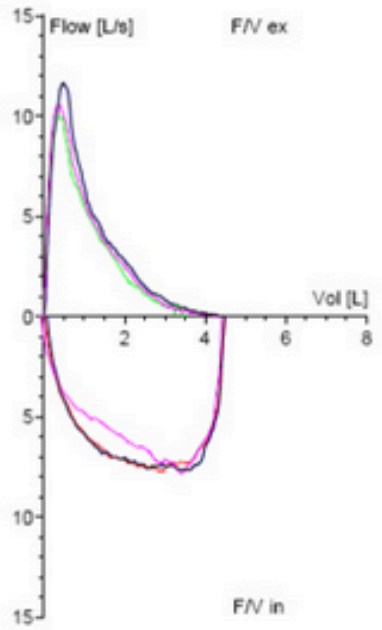
Serology	Result
Strongyloides	Negative
Filaria	Negative
Schistosoma	Negative

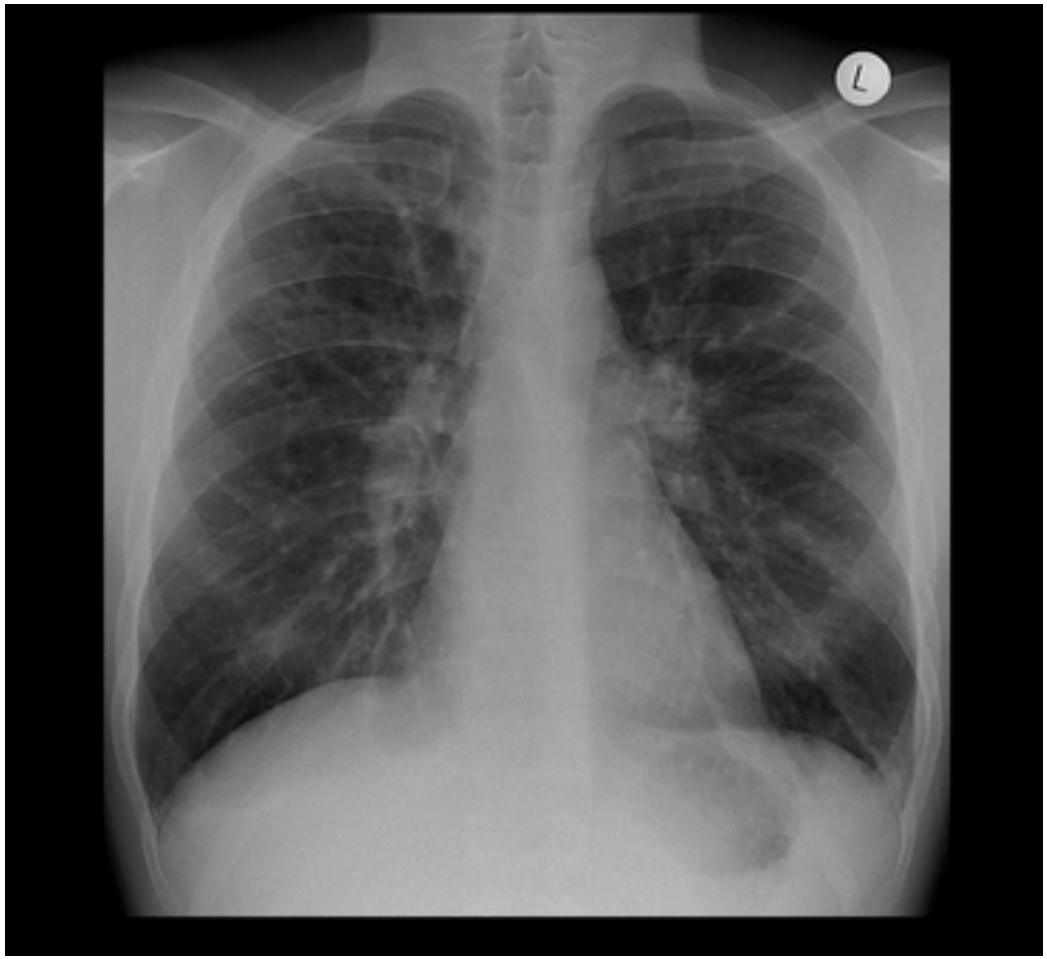
- Sputum: No growth. Eosinophils +++

Date of tests: Jan 23, 2009

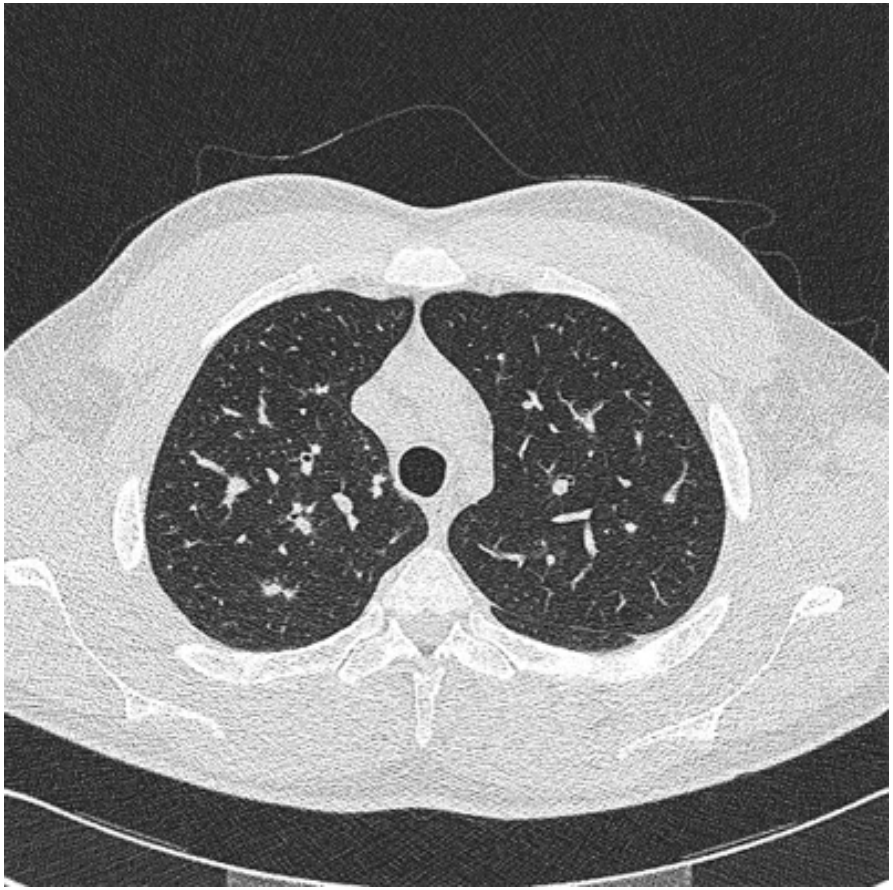
	Pred LL	Pred UL	Test 1	% Pred	SR
FEV_1	3·39	5·06	2·94	69·5	−2·53
Forced vital capacity (FVC)	4·05	6·05	4·45	88·2	−0·97
Vital capacity max	4·37	6·21	4·45	84·2	−1·49
FEV_1%M	70·91	94·51	65·93	79·7	−2·33
Peak expiratory flow (PEF)	8·39	12·36	11·63	112·1	1·04
MEF 75	6·04	11·66	5·56	62·8	−1·92
MEF 50	3·68	8·02	2·15	36·7	−2·80
MEF 25	2·81	2·81	0·44	15·5	..
FET	..	..	12·70	..	..
Peak inspiratory flow (PIF)	7·78	7·78	7·70	99·0	..



The patient's hypoxia on arterial blood gas (PaO_2 8·53 kPa (10·00–13·50)) is out of keeping with his formal pulmonary function tests, which demonstrate obstructive airways disease. There was no evidence of reversibility to salbutamol. However, the FEV_1 improved with oral corticosteroids.



- Given the significant hypoxia and eosinophilia, the patient was started on prednisolone 40 mg daily.
- Within 48 h oxygen saturation levels were 97% on air and the blood eosinophil count had fallen to zero.



What abnormality is shown on the CT images?

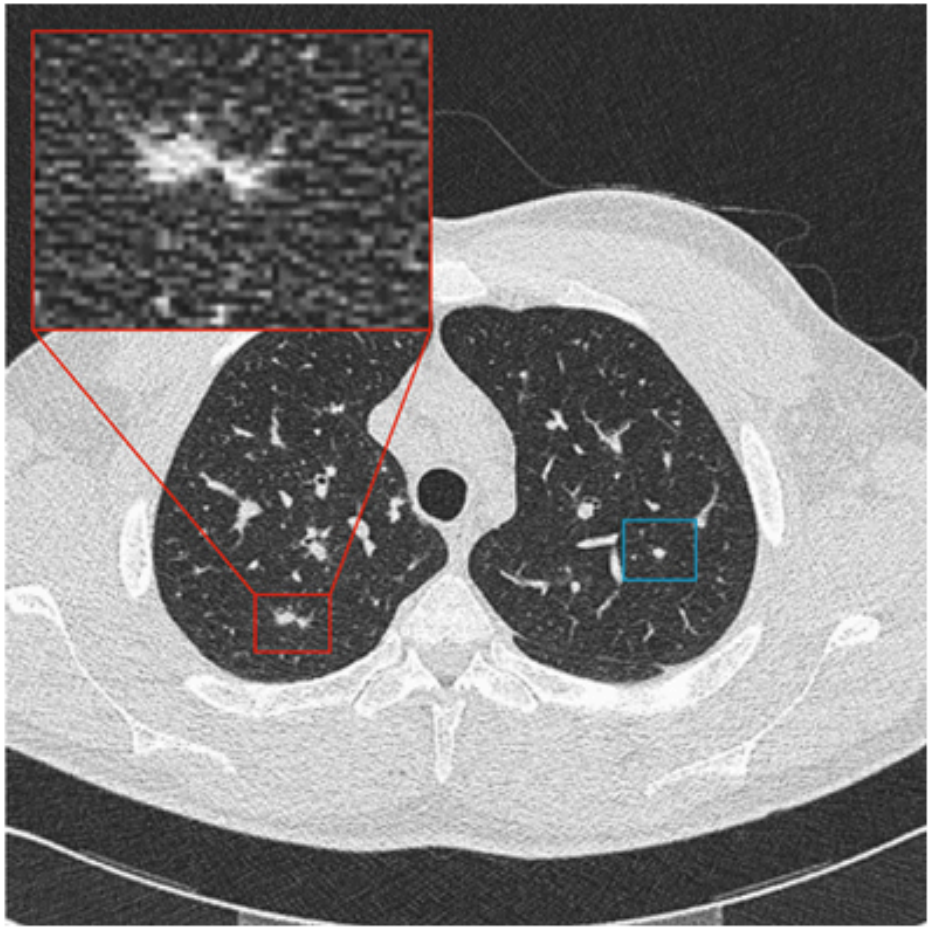
- ○ Bronchial wall thickening
- ○ Bronchiectasis
- ○ Irregular pulmonary vasculature
- ○ Ground glass shadowing
- ○ Pleural thickening

Correct

The correct answer is irregular pulmonary vasculature

- ○ Bronchial wall thickening
- ○ Bronchiectasis
- ◉ Irregular pulmonary vasculature
- ○ Ground glass shadowing
- ○ Pleural thickening

- Some of the vessels in the right hemithorax are irregular in outline.



Dr Anand Devaraj discusses the appearance of the CT chest scan.

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A representative section is shown. The red box highlights an example of the irregular vasculature, whereas the vessel in the blue box appears normal.

What would you do next?

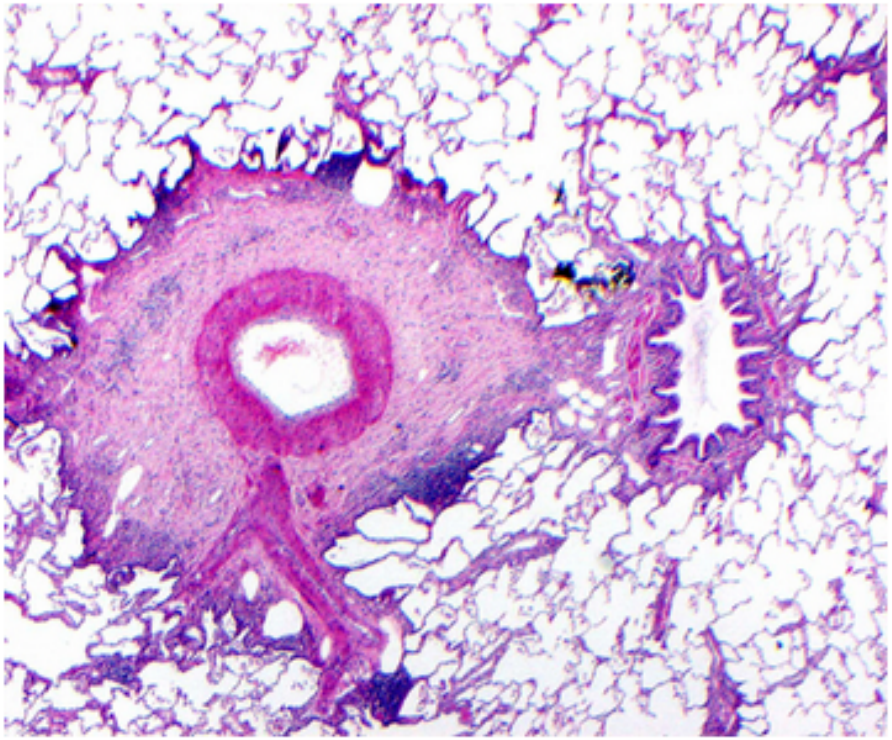
- ○ Fibre optic bronchoscopy
- ○ PET scan
- ○ Lung MRI
- ○ Biopsy with video-assisted thoracoscopic surgery (VATS)
- ○ Repeat surveillance CT in 3 months

What would you do next?

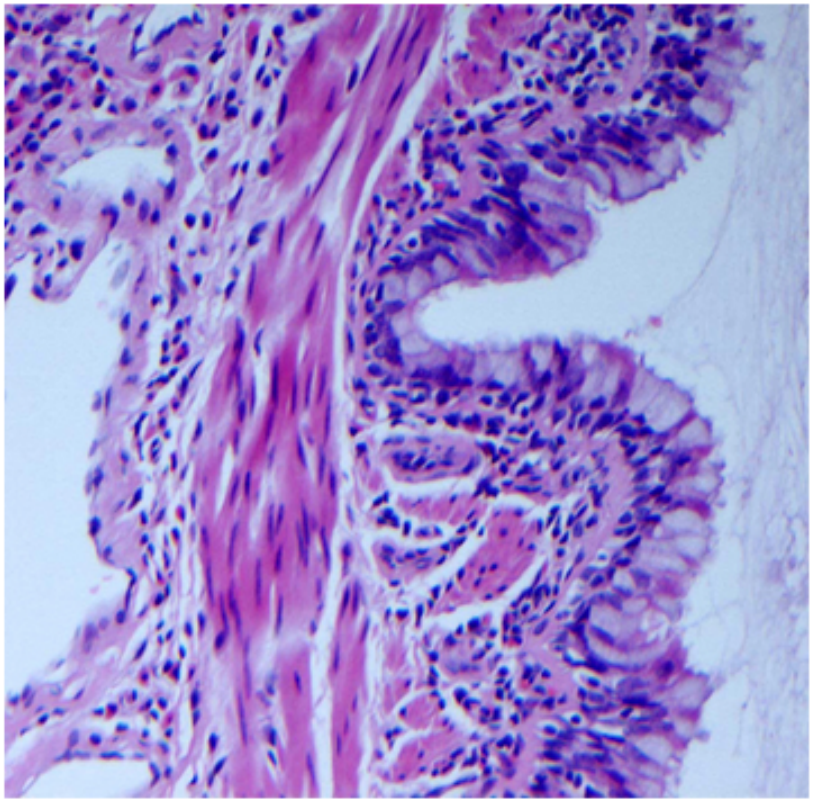
Correct
The correct answer is biopsy with video-assisted thoracoscopic surgery (VATS)

- ○ Fibre optic bronchoscopy
- ○ PET scan
- ○ Lung MRI
- ◉ Biopsy with video-assisted thoracoscopic surgery (VATS)
- ○ Repeat surveillance CT in 3 months

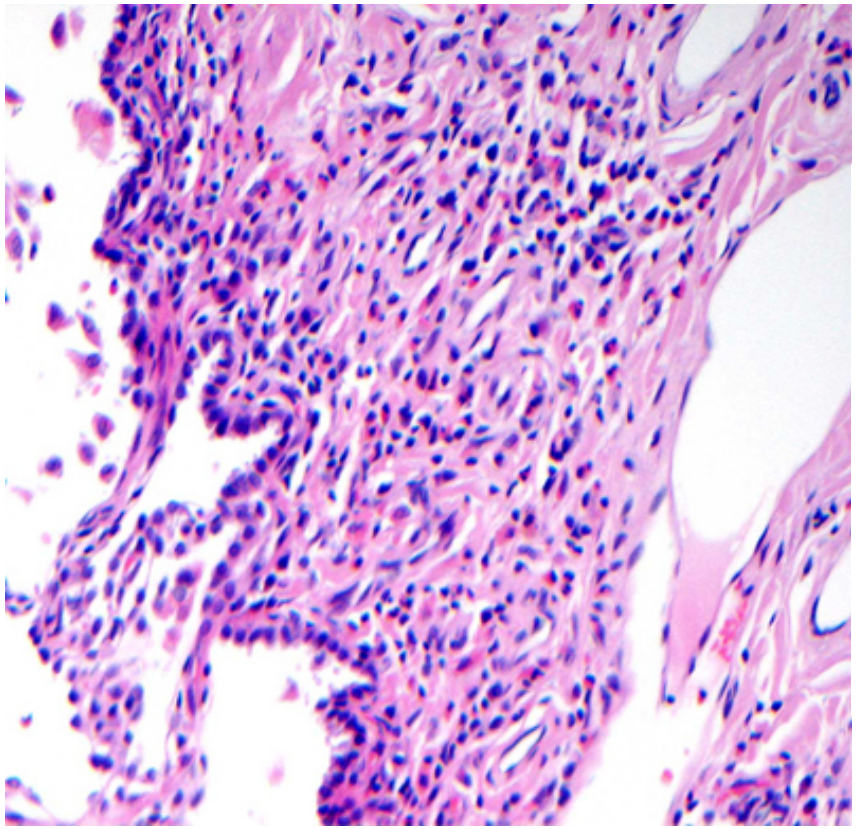
- The aetiology of this clinical presentation is uncertain and before proceeding to treatment it is logical to obtain tissue in an attempt to establish a firm diagnosis.



Haematoxylin and eosin stain (magnification × 40)



Haematoxylin and eosin stain (magnification × 200)



What abnormalities do the VATS biopsy specimens show?

- [ ] Goblet cell hyperplasia
- [ ] Active vasculitis
- [ ] Basement membrane thickening
- [ ] Granulomas
- [ ] Tissue eosinophilia

What abnormalities do the VATS biopsy specimens show? (please select all answers that apply)

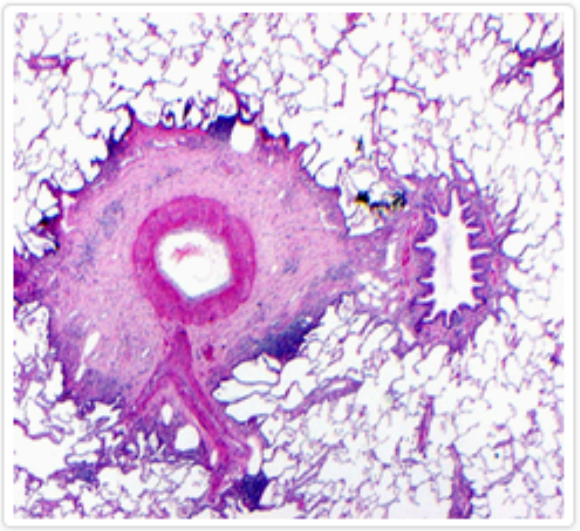
Correct
The correct answers are goblet cell hyperplasia, basement membrane thickening and tissue eosinophilia

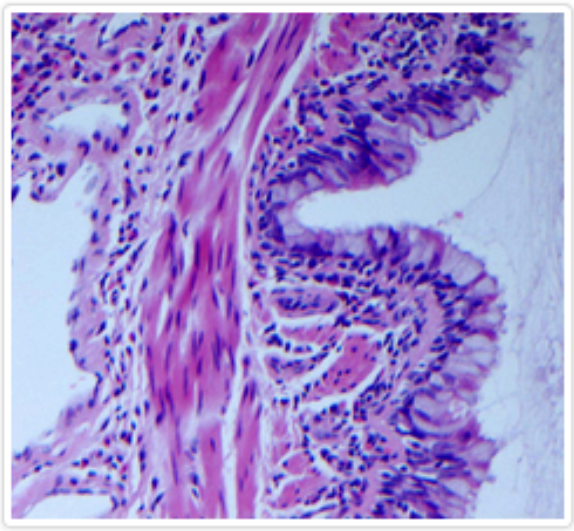
- [x] Goblet cell hyperplasia
- [ ] Active vasculitis
- [x] Basement membrane thickening
- [ ] Granulomas
- [x] Tissue eosinophilia

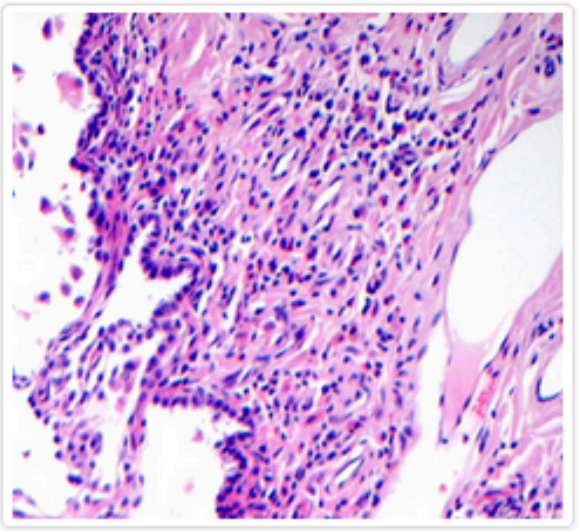
- Features of asthma, namely goblet cell hyperplasia, basement membrane thickening, and tissue eosinophilia are evident.
- Although there is marked thickening of the adventitia, specific features of vasculitis and granulomata are not evident, which likely relates to the high-dose prednisolone the patient was receiving at the time of the VATS biopsy. With eosinophilic asthma alone, it would be highly unusual to see a persistence of tissue eosinophilia following prolonged high-dose oral corticosteroids.

Hypoxia and eosinophilia in a patient with 'difficult asthma'

View other Interactive Grand Rounds







Prof Andrew Nicholson discusses the VATS lung biopsy specimens.

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Which of these diagnoses is most likely?

- ○ Allergic bronchopulmonary aspergillosis (ABPA)
- ○ Tropical pulmonary eosinophilia
- ○ Idiopathic hypereosinophilic syndrome
- ○ Eosinophilic granulomatosis with polyangiitis (EGPA)
- ○ Severe atopic asthma

Which of these diagnoses is most likely?

Correct
The correct answer is eosinophilic granulomatosis with polyangiitis (EGPA)

- ○ Allergic bronchopulmonary aspergillosis (ABPA)
- ○ Tropical pulmonary eosinophilia
- ○ Idiopathic hypereosinophilic syndrome
- ◉ Eosinophilic granulomatosis with polyangiitis (EGPA)
- ○ Severe atopic asthma

Discussion of the other options:

- Although patients with ABPA frequently have peripheral eosinophilia, it is usually not as marked as in this case and the aspergillus serology is negative
- The patient has too long a history for tropical pulmonary eosinophilia—although it should certainly be considered, and a travel history should be checked. In this case the parasite serology was negative
- Idiopathic hypereosinophilic syndrome is a diagnosis of exclusion, made only when secondary and clonal causes of hypereosinophilia have been fully investigated
- Severe atopic asthma is not usually associated with this degree of peripheral eosinophilia

- We present the second published case report of this rare manifestation of EGPA. The initial presentation with significant blood eosinophilia and hypoxia out of proportion to pulmonary function tests highlighted the need for further investigation as this was an unusual presentation for a patient with severe eosinophilic asthma. The combination of continuing tissue eosinophilia despite high-dose oral corticosteroids, with CT abnormalities of the pulmonary vasculature, and the previously stated clinical presentation led to the diagnosis of EGPA pulmonary vasculitis.
- In a previously published case report,[1] irregular stellate-shaped arteries were also noted.

1. Buschman DL, Waldron JA Jr, King TE Jr. Churg-Strauss pulmonary vasculitis. High-resolution computed tomography scanning and pathologic findings. *Am Rev Respir Dis* 1990; **142:** 458–61.

What is the most appropriate first-line treatment for this patient?

- ○ Intravenous cyclophosphamide
- ○ Subcutaneous mepolizumab
- ○ Oral prednisolone
- ○ Oral azathioprine
- ○ Intravenous rituximab

What is the most appropriate first-line treatment for this patient?

Correct
The correct answer is oral prednisolone

- ○ Intravenous cyclophosphamide
- ○ Subcutaneous mepolizumab
- ◉ Oral prednisolone
- ○ Oral azathioprine
- ○ Intravenous rituximab

- Published evidence suggests using high-dose prednisolone first line in the treatment of EGPA.

Discussion of the other options:

- Cyclophosphamide should be used if the presentation includes cardiac, CNS, or gastroenterological involvement
- Mepolizumab is still being investigated in EGPA (see later in the presentation)
- Azathioprine can be used as a steroid sparing agent in EGPA if required
- Rituximab has been used anecdotally as rescue therapy in treatment refractory EGPA

- Swift control of eosinophilia with high-dose prednisolone, weaned to 10 mg over 3 months
- Spirometry improvement: FEV_1 of 4·25 and FVC of 5·15
- Stable for 1 year on 7·5 mg prednisolone daily
- The patient also takes a high-dose combination inhaler (ICS–LABA).
- The patient's symptoms are well controlled. He has had no further disease flares or emergency department attendances. He has returned to work and attends for outpatient follow-up appointments every 3 months.

- Vasculitis of small-to-medium sized vessels
- Previously known as Churg-Strauss syndrome. First described in 1951 by Churg and Strauss[1] in 13 patients with:
  - asthma
  - tissue eosinophilia
  - systemic vasculitis
  - extravascular granulomas
  - fibrinoid necrosis of connective tissue
- No diagnostic test
- pANCA (perinuclear) positive in 50%
- Biopsy to demonstrate eosinophilic infiltrate with granuloma formation. Necrotising vasculitis of small-to-medium sized vessels

1. Churg J, Strauss L. Allergic granulomatosis, allergic angiitis, and periarteritis nodosa*. *Am J Pathol* 1951; **27:** 277–301.

- In the context of histological evidence of necrotising vasculitis:
  - asthma
  - >10% blood eosinophilia
  - paranasal sinusitis
  - pulmonary infiltrates
  - extravascular eosinophils
  - mononeuritis multiplex or polyneuropathy
- The presence of four or more of these criteria yielded a 85% sensitivity and 99·7% specificity.[1]

1. Masi AT, Hunder GG, Lie JT, et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). *Arthritis Rheum* 1990; **33:** 1094–100.

Upper and lower respiratory tract:

- Asthma (96–100%)
- Eosinophilic pulmonary infiltrates
- 75% have allergic rhinitis

Neurological:

- Peripheral neuropathy (65–75%)
- Cranial nerve palsies
- Cerebral haemorrhage/infarction

Cardiac:

- Eosinophilic endomyocarditis (CMR)
- Coronary vasculitis
- Valvular heart disease
- Pericarditis

Gastroenterological:

- Eosinophilic gastroenteritis

Renal:

- Mild renal involvement (proteinuria) (26–63%)

- 81–92% remission with therapy
- 26–28% relapse rate (40% relapse in first year)
- 40% require oral corticosteroids only
- Predictors of poor outcome:
  - Cardiac involvement
  - Severe gastrointestinal disease
  - Proteinuria >1g/day

1. Guillevin L, Cohen P, Gayraud M, Lhote F, Jarrousse B, Casassus P. Churg-Strauss syndrome. Clinical study and long-term follow-up of 96 patients. *Medicine (Baltimore)* 1999; **78:** 26–37.
2. Solans R, Bosch JA, Pérez-Bocanegra C, et al. Churg-Strauss syndrome: outcome and long-term follow-up of 32 patients. *Rheumatology* 2001; **40:** 763–71.

- Corticosteroids
  - High-dose initiation and taper over 12 months
  - Long-term steroids are often required
- Cyclophosphamide (consider in the following scenarios):
  - Glomerulonephritis
  - Cardiac involvement
  - CNS involvement
- Steroid-sparing agents:
  - Methotrexate
  - Azathioprine
  - Mycophenolate mofetil
  - Cyclosporin
- Alternatives (unproven):
  - Intravenous immunoglobulin
  - Interferon alfa-2b
  - Rituximab

1. Guillevin L, Cohen P, Gayraud M, Lhote F, Jarrousse B, Casassus P. Churg-Strauss syndrome. Clinical study and long-term follow-up of 96 patients. *Medicine (Baltimore)* 1999; **78:** 26–37.
2. Fauci AS, Katz P, Haynes BF, Wolff SM. Cyclophosphamide therapy of severe systemic necrotizing vasculitis. *N Engl J Med* 1979; **301:** 235–38.

Mepolizumab is a monoclonal antibody against interleukin-5 (IL-5). IL-5 is the key cytokine in eosinophil maturation, survival, and priming.

Mepolizumab has been extensively studied in patients with severe eosinophilic asthma. The first randomised controlled trial examining the use of mepolizumab in EGPA was by Wechsler and colleagues.[1]

- Mepolizumab treatment led to significantly more accrued weeks of remission than placebo (28% vs 3% of participants had ≥24 weeks of accrued remission; odds ratio [OR], 5·91, 95% CI 2·68–13·03, p<0·001), and a higher percentage of participants in remission at both week 36 and week 48 (32% vs 3%; OR 16·74, 95% CI 3·61–77·56, p<0·001).
- Remission did not occur in 47% participants in the mepolizumab group versus 81% of those in the placebo group.
- The annualised relapse rate was 1·14 in the mepolizumab group compared with 2·27 in the placebo group (rate ratio 0·50, 95% CI 0·36–0·70, p<0·001).

1. Wechsler ME, Akuthota P, Jayne D. Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis. *N Engl J Med* 2017; **376:** 1921–32.

- EGPA is a multisystem vasculitic disorder, which should be considered in a patient presenting with 'difficult asthma', especially in the context of significant peripheral eosinophilia.
- In cases of diagnostic uncertainty, a biopsy is recommended.
- Current first-line treatment consists of high-dose corticosteroids. Cyclophosphamide should be considered in cases of renal, cardiac, or CNS involvement. Once disease activity has been controlled, steroid-sparing agents may subsequently be used.
- Future treatment options may include monoclonal antibody therapy, although longer-term studies are required.